



Mammographic breast density and cardiovascular disease risk in women

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ABSTRACT

Aims: We aimed to determine the predictive role of mammographic breast density in addition to the Framingham Risk Score (FRS) on subsequent CVD events in women.

Methods and Results: This cohort study included 4,268,579 women aged ≥ 40 years who underwent mammography screening between 2009 and 2010 with follow-up until 2020. Breast density was reported following the Breast Imaging Reporting and Data System. Primary outcomes included coronary heart disease, cerebrovascular disease, peripheral arterial disease, and heart failure. The incremental predictive ability of breast density added to the FRS model was assessed using the ROC and net reclassification index (NRI) among all women and strata based on FRS risk categories ($< 5\%$ as low-risk, $5\%–10\%$ as moderate-risk, and $\geq 10\%$ as high-risk). In total, 135,475 CVD events were recorded after a median follow-up of 10.9 years. A lower category of breast density was associated with a higher risk of CVD. Compared to the extremely dense breast group, the hazard ratios (95% CI) for CVDs were 1.12 (1.09–1.14), 1.19 (1.17–1.22), and 1.29 (1.26–1.32) in women with heterogeneously dense, scattered fibroglandular densities, and almost entirely fat breast density, respectively. Adding breast density to the FRS showed a slight improvement in AUROC but a modest improvement in NRI; the C-statistic difference was 0.083% (95% CI 0.069–0.096) with a 7.15% (6.85–7.69) increase in NRI, with the strongest improvement observed in the low-risk group.

Conclusions: Mammographic breast density is an independent predictor of incident CVD among women. The addition of mammographic breast density to FRS improves the prediction of CVDs, especially in low-risk individuals.

1. Introduction

Cardiovascular diseases (CVDs) and neoplasms, especially breast cancer, mainly contribute to morbidity and mortality among women [1, 2]. CVDs prevention is important through the early identification of high-risk groups based on CVD risk prediction and using targeted interventions (lifestyle modification and lipid-lowering drugs) [3]. Several countries have implemented population-based mammography screening

to reduce breast cancer mortality [4]. Recently, some mammographic features have been associated with breast cancer risk as well as extra-breast morbidities, such as CVD [5,6]. Breast density is one of the most important breast cancer risk factors, with a 4- to 6-fold elevated risk in women with dense breasts than in those with fatty breasts [7–12]. However, previous studies have shown an inverse association between breast density and CVDs, in contrast to a positive association between breast density and breast cancer risk; women with dense breasts have a

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lower CVDs risk than women with fatty breasts [5,6]. Although the association between mammographic breast features and CVDs has been evaluated [5,13–16], the role of breast density in predicting CVD risk has not been addressed.

We hypothesized that adding breast density to the conventional CVD risk factors would improve the CVD prediction in women. Thus, we aimed to determine whether adding mammographic breast density to the Framingham Risk Score (FRS), one of the most validated CVD prediction models, improves the prediction of CVD events in women who participate in population-based breast cancer screening.

2. Patients and methods

2.1. Study settings and study population

The data for this retrospective cohort study were obtained from the National Health Insurance Service-National Health Information Database (NHIS-NHID) in Korea. In Korea, NHIS is a mandatory health insurance system for the entire population. The NHIS-NHID contains information on demographics, healthcare utilization, deaths, and national health screening results for the Korean population [17]. As part of national health screening programs, biennial mammographic breast cancer screening is offered to women aged ≥ 40 years. This study population included women who underwent mammographic breast cancer screening between January 1, 2009, and December 31, 2010.

This study was approved by the Institutional Review Board of the Hanyang University College of Medicine (approval no. HYUIRB-202106-003-1). Based on their 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 NHIS database was constructed after the anonymization of individual identities.

2.2. Inclusion and exclusion criteria

In this study, women aged 40–70 years were included, based on the recommended ages for breast cancer screening in Korea and the age range used in FRS prediction [18]. Participants with missing information on breast density or FRS components were further excluded. Women who reported a history of cancer, stroke, or ischemic heart disease were excluded from the analysis. If women underwent

mammographic screening more than once between 2009 and 2010, data from the first screening were used. After applying the aforementioned exclusion criteria to the 5,105,128 women who underwent mammography screening between 2009 and 2010, the final study sample included 4,268,579 individuals (Fig. 1).

During health and breast cancer screening, the following data were collected and recorded in the database: (1) demographic variables, including age at screening; (2) self-reported health behaviors and medical history using a standardized questionnaire used for health screening; (3) clinical measurements, including anthropometric (weight and height) data and blood pressure; and (4) laboratory test results from blood and urine samples.

2.3. Measurements of Framingham Risk Score components

Age, total cholesterol, HDL-C, systolic blood pressure, antihypertensive medication, smoking status, and type 2 diabetes status were risk factors included in the FRS [18]. Smoking status from the standardized questionnaire during health screening was assessed as a categorical variable with three values: “never,” “former,” and “current smokers.” Blood pressure was measured using digital or automatic monitors after participants rested for at least 2 min in a sitting position. Serum total cholesterol and HDL-C levels were extracted from the laboratory test results. To define type 2 diabetes status, we used fasting plasma glucose measurements (FPG) during health screening and self-reported questionnaires (for antidiabetic medication usage). Glucose levels were measured after at least 8 h of fasting. During the health examination, all participants were asked whether they had ever received a diagnosis of diabetes by a physician and if they were on antidiabetic medication. Following the American Diabetes Association criteria [19], we defined diabetes as either 1) fasting plasma glucose (FPG) ≥ 126 mg/dL or 2) a history of diabetes diagnosis with current use of antidiabetic medications. Information on antihypertensive medication use was assessed using a self-reported questionnaire.

2.4. Measurements of mammographic breast density and other variables

Mammographic breast density was reported a result of mammographic breast cancer screening. Currently, under the National Cancer Screening Program in Korea, breast density is reported using the fourth edition of the Breast Imaging and Reporting Data System (BI-RADS)

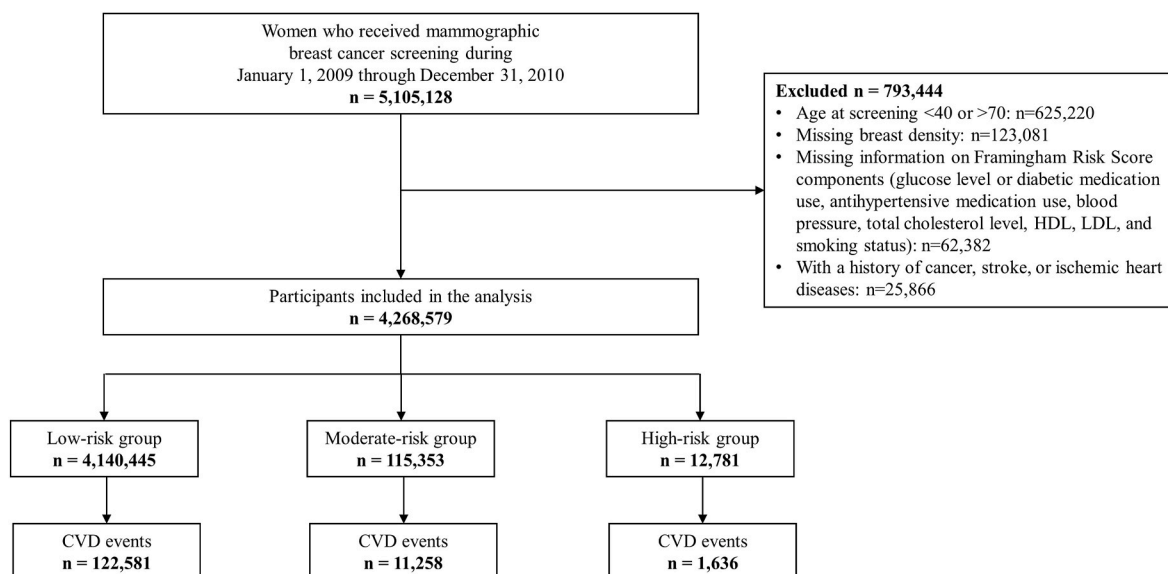


Fig. 1. Flow diagram used for selection of the eligible population.

density categories, which includes four categories (1–4) [20]. BI-RADS category 1 indicates almost entirely fat (parenchyma <25%); category 2, scattered fibroglandular density (parenchyma is 25–50%); category 3, heterogeneously dense (parenchyma is 51–75%); and category 4, extremely dense (parenchyma >75%).

At breast cancer screening, participants were requested to report their current menopausal status by answering the question: "What is your present menopausal condition?" They could select one of the following responses: still experiencing menstruation, having undergone a hysterectomy, or having reached menopause. Using these data, we categorized menopausal status as either premenopausal or postmenopausal, encompassing individuals who had undergone a hysterectomy or had experienced natural menopause.

2.5. Measures of CVDs outcome

The primary outcome in this study was the CVD incidence included in the FRS prediction, including coronary heart disease, cerebrovascular disease, peripheral arterial disease, and heart failure [18]. The incidence of CVDs until December 31, 2020, was ascertained by linking the screening database to the healthcare utilization database of the NHIS-NHID, whose records were classified according to the 10th Revision of the International Classification of Diseases and Related Health Problems (ICD-10). CVD events were defined as inpatient hospitalizations for at least 2 days with a CVD diagnosis [21]. For our analysis, the specific ICD-10 codes used for CVD were as follows: ischaemic heart diseases (IHD, I20–I25), cerebrovascular diseases (I60–I69), peripheral artery disease (I708, I709, I743, I744, I745, and I771), and heart failure (I50).

2.6. Statistical analysis

In the present study, originally developed and validated predictors and coefficients were used to calculate the CVD risk, and the equation for the female population was applied [18]. The following components were used to calculate the risk score: age, systolic blood pressure, total

cholesterol level, HDL-C level, smoking status, history of diabetes, and antihypertensive medication use. CVD risk was classified into three categories based on the calculated risk score: <5%, low risk; between 5% and 10%, moderate risk; and $\geq 10\%$, high risk [22].

Descriptive statistics of the baseline characteristics of all participants and their CVD risk level were presented. We calculated the cumulative CVD incidence by mammographic breast density categories using non-parametric methods to account for the competing risk, and the Gray test was used to statistically compare the cumulative incidence functions [23]. The Cox proportional hazard model was used to evaluate the association between mammographic breast density and risk of CVDs and stratified by CVD risk categories. The following Cox models were fitted: 1) a univariate model for FRS components and breast density was applied to assess the crude hazard ratio (HR) of each factor with CVD risk; 2) a multivariate model including only FRS components; and 3) a multivariate model including FRS components with breast density. Breast density was entered into the models as an ordinal variable with four levels, from 1 (fatty breast) to 4 (extremely dense breast).

Model performance was assessed using discrimination and calibration to compare the two multivariate models. Discrimination is the ability to categorize individuals with and without CVDs based on predictive values, and calibration is a measure of how accurately the predicted risk matches the observed risk. The C-statistics of the two models were compared to measure the enhancement in discrimination of the FRS. We further calculated the net reclassification improvement (NRI) to quantify the improvement of the new model over the original Framingham model. C-statistics and NRI statistics were calculated using the SAS macro [24]. Calibration was assessed statistically using a chi-square goodness-of-fit test to determine whether the observed CVD risk differed significantly from the expected values at the end of the study. Model performance was evaluated in the total study population and in each CVD risk group separately. All reported p-values were two sided with a type I error ($\alpha < 0.05$) and were considered statistically significant. Statistical analyses were performed using the SAS statistical software (version 9.4, SAS Institute, Cary, NC, USA).

Table 1
Baseline characteristics of the participants according to Framingham risk score categories.

Variable	Total n = 4,268,579	Low-risk n = 4,140,445	Moderate risk n = 115,353	High risk n = 12,781
Age, y, mean (SD)	52.5 (8.3)	52.1 (8.2)	63.2 (4.9)	64.5 (4.3)
BMI (kg/m ²), mean (SD)	23.8 (3.2)	23.7 (3.1)	25.9 (3.4)	26.2 (3.4)
SBP (mmHg), mean (SD)	121.1 (15.5)	120.3 (14.8)	145.6 (16.4)	159.2 (18)
DBP (mmHg), mean (SD)	75 (10.2)	74.7 (9.9)	85.5 (10.9)	90.5 (11.9)
TC (mg/dL), mean (SD)	11.2 (2.1)	11.2 (2.1)	12.6 (2.5)	13.8 (3.3)
HDL-cholesterol, (mg/dL), mean (SD)	3.3 (1.7)	3.3 (1.8)	2.8 (0.7)	3.3 (1.8)
Fasting glucose, (mg/dL), mean (SD)	96.8 (21.3)	95.8 (19.4)	127.8 (42.2)	174.6 (216.1)
Antihypertensive use (yes)	701,237 (16.4)	606,122 (14.6)	84,219 (73)	10,896 (85.3)
Lipid lowering drug use (yes)	133,217 (3.1)	123,221 (3.0)	9105 (7.9)	891 (7.0)
Glucose-lowering drug use (yes)	209,737 (4.9)	148,019 (3.6)	53,558 (46.4)	8160 (63.8)
Smoking status				
Never	4,068,962 (95.3)	3,951,948 (95.5)	105,925 (91.8)	11,089 (86.8)
Former	61,397 (1.4)	60,225 (1.5)	1058 (0.9)	114 (0.9)
Current	138,220 (3.2)	128,272 (3.1)	8370 (7.3)	1578 (12.4)
Menopausal status				
Premenopausal	2,036,953 (47.7)	2,023,159 (48.9)	12,520 (10.9)	1274 (10)
Postmenopausal	2,159,009 (50.6)	2,046,577 (49.4)	101,075 (87.6)	11,357 (88.9)
Missing	72,617 (1.7)	70,709 (1.7)	1758 (1.5)	150 (1.2)
Breast density				
Almost entirely fat (1)	1,024,421 (24.0)	961,182 (23.2)	56,721 (49.2)	6518 (51.0)
Scattered fibroglandular densities (2)	1,179,141 (27.6)	1,137,224 (27.5)	37,757 (32.7)	4160 (32.6)
Heterogeneously dense (3)	1,365,819 (32.0)	1,346,828 (32.5)	17,261 (15.0)	1730 (13.5)
Extremely dense (4)	699,198 (16.4)	695,211 (16.8)	3614 (3.1)	373 (2.9)

SD, standard deviation; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein cholesterol; TC, total cholesterol; BI-RADS, Breast Imaging Reporting and Data System.

^a Almost entirely fat was categorized as BI-RADS a, scattered fibroglandular densities as BI-RADS b, and heterogeneously or extremely dense as BI-RADS c and d.

3. Results

3.1. Characteristics of the study population

Among the 4,268,579 women who were included in the final analysis, 135,475 CVD events were recorded during a median follow-up of 10.9 years (interquartile range, 10.3–11.4 years, maximum 12 years). Of those, 4,140,445 (97.0%) women were included in the low-risk group, 115,353 (2.7%) in the moderate-risk group, and 12,781 (0.3%) in the high-risk group (Fig. 1). The mean age at screening was 52.5 ± 8.3 years, while the mean BMI was 23.7 ± 3.1 for all participants (Table 1). The low-risk group was younger mean age than those in moderate- and high-risk groups (mean ages of 52.1, 63.2 and 64.5 years, respectively). Higher mean values of body mass index, systolic blood pressure, diastolic blood pressure, total cholesterol level, low-density lipoprotein level, and FPG were observed in the moderate- and high-risk groups than in the low-risk group. Among the total population, 24% had almost entirely fat breasts (BI-RADS 1), 27.6% had scattered fibroglandular densities, 32.0% had heterogeneously dense breasts, and 16.4% had extremely dense breasts (BI-RADS 4). The proportion of women with dense breasts (heterogeneous or extremely dense) was lower in the moderate- and high-risk groups than that in the low-risk group (18.1%, 16.1%, and 49.3%, respectively).

3.2. Association between breast density and risk of CVDs

The cumulative CVD incidences according to BI-RADS breast density are shown in Fig. 2. In the total population, we observed that women with a lower breast density had a higher risk of CVD development during the study period (p -value from Gray's test <0.001) (Fig. 2A). A consistent pattern was observed in the low-risk group, with a p -value <0.001 (Fig. 2B). In the moderate-risk group, the lower breast density group also had a higher cumulative incidence of CVD development ($p < .001$) despite the difference between the breast density categories not being as large as that observed in the low-risk group (Fig. 2C). In the high-risk

group, there was no difference in the cumulative CVD incidences across breast density categories ($p = 0.580$) (Fig. 2D).

The univariate model assessing the association between breast density and CVD risk yielded a significant increase in HR in women with lower levels of breast density relative to that in those with extremely dense breasts (Supplementary Table 1 and Table 2). Compared with women with extremely dense breasts, those with heterogenous dense breasts had a 1.50-fold increase CVDs risk (95% confidence interval [CI], 1.47–1.53); scattered fibroglandular densities, a 2.38-fold increase (95% CI, 2.33–2.43); and almost entirely fat, a 3.39-fold increase (95% CI, 3.36–3.42) (Supplementary Table 1). After adding breast density to the regression model with other FRS components, the HR values decreased; however, the results remained statistically significant. Compared to the women with BI-RADS density category 4, the adjusted HR in categories 3, 2, and 1 were 1.12 (95% CI, 1.09–1.14), 1.19 (95% CI, 1.17–1.22), and 1.29 (95% CI, 1.26–1.32), respectively (Table 2). In women with low-risk group, the aHR in BI-RADS density categories 3, 2, and 1 were 1.11 (95% CI, 1.08–1.13), 1.18 (95% CI, 1.16–1.21), and 1.29 (95% CI, 1.26–1.32), respectively. Similar findings were observed in the moderate-risk group with lower HR values, but the results in the high-risk group were not significant.

3.3. Model performance of Framingham Risk Score prediction after adding breast density

A significant improvement in the AUC was observed in the model with breast density compared to the traditional model without breast density: 71.62% vs. 71.70% (difference in AUC 0.083, $p < 0.0001$) (Table 3). The NRI statistics also showed a significant improvement of 7.15% (95% CI, 6.85–7.69, $p < 0.0001$) in the total population. Consistent findings were observed in the low-risk group, with a difference in AUC of 0.1 ($p < 0.0001$) and an increase in NRI of 7.11% (95% CI, 6.66–7.68, $p < 0.0001$). In the moderate group, the difference in AUC was not statistically significant, and a 2.15% improvement was observed in the NRI statistics with statistical significance ($p = 0.007$). No

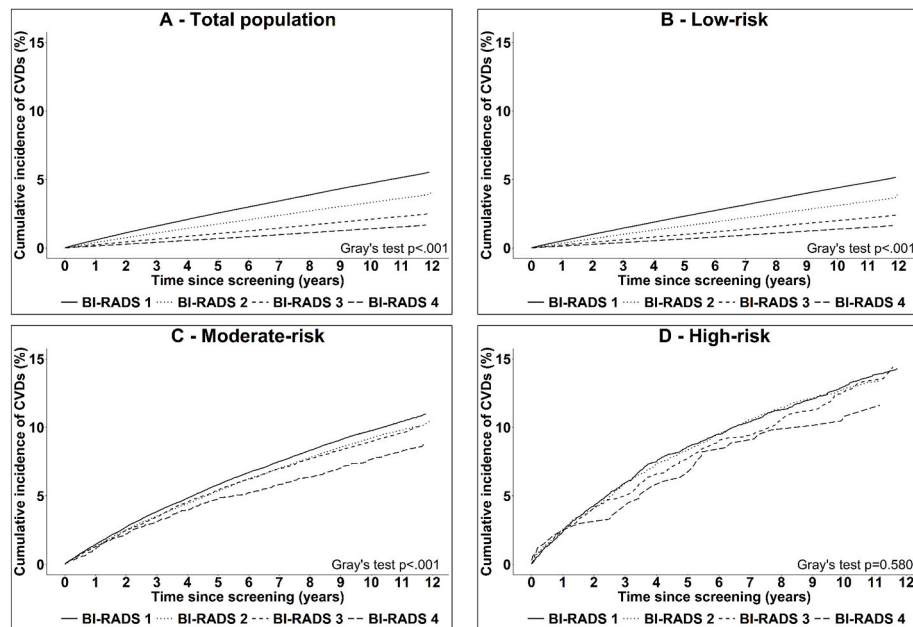


Fig. 2. Cumulative incidence functions of cardiovascular diseases risk by breast density classification.

(A) Cumulative incidence in total study population. (B) Cumulative incidence in the low-risk group. (C) Cumulative incidence in the moderate-risk group. (D) Cumulative incidence in the high-risk group. Solid lines indicate cumulative incidence function in women with breast density category a (almost entirely fat), dotted lines indicate cumulative incidence function in women with breast density category b (scattered fibroglandular densities), dashed lines indicate cumulative incidence function in women with breast density category c (heterogeneously dense) and long-dashed lines indicate cumulative incidence function in women with breast density category d (extremely dense). p -values were obtained from Gray's test for equality of cumulative incidence functions of the four breast density categories. The cumulative CVD incidence was higher in those with lower category of dense breast density, especially in the low-risk group.

Table 2

Absolute and relative risk for developing cardiovascular disease according to mammographic breast density in the overall and CVD risk strata.

BI-RADS breast density	Total cases	Person-years	Incidence rate per 100,000 person-years	Age-adjusted	Multivariable-adjusted
				HR (95% CI)	HR (95% CI)
Total					
Extremely dense (4)	10,568	7,501,921	141 (138–144)	Reference	Reference
Heterogeneously dense (3)	30,830	14,606,233	211 (209–213)	1.14 (1.11–1.17)	1.12 (1.09–1.14)
Scattered fibroglandular densities (2)	42,035	12,525,773	336 (332–339)	1.25 (1.22–1.28)	1.19 (1.17–1.22)
Almost entirely fat (1)	52,042	10,795,998	482 (478–486)	1.37 (1.34–1.40)	1.29 (1.26–1.32)
Low risk					
Extremely dense (4)	10,247	7,461,637	137 (135–140)	Reference	Reference
Heterogeneously dense (3)	29,010	14,415,644	201 (199–204)	1.14 (1.11–1.16)	1.11 (1.08–1.13)
Scattered fibroglandular densities (2)	37,914	12,105,693	313 (310–316)	1.25 (1.22–1.28)	1.18 (1.16–1.21)
Almost entirely fat (1)	45,410	10,162,940	447 (443–451)	1.37 (1.34–1.41)	1.29 (1.26–1.32)
Moderate risk					
Extremely dense (4)	280	36,649	764 (675–853)	Reference	Reference
Heterogeneously dense (3)	1599	173,896	920 (874–965)	1.16 (1.02–1.31)	1.16 (1.02–1.31)
Scattered fibroglandular densities (2)	3603	380,185	948 (917–979)	1.14 (1.01–1.29)	1.14 (1.01–1.29)
Almost entirely fat (1)	5776	570,244	1013 (987–1039)	1.17 (1.04–1.32)	1.18 (1.04–1.33)
High risk					
Extremely dense (4)	41	3635	1128 (783–1473)	Reference	Reference
Heterogeneously dense (3)	221	16,693	1324 (1149–1498)	1.15 (0.82–1.60)	1.15 (0.82–1.60)
Scattered fibroglandular densities (2)	518	39,896	1298 (1187–1410)	1.09 (0.79–1.50)	1.08 (0.79–1.49)
Almost entirely fat (1)	856	62,814	1363 (1271–1454)	1.13 (0.82–1.55)	1.13 (0.82–1.55)

HR, hazard ratio; CI, confidence interval; FRS, Framingham risk score; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; TC, total cholesterol; BI-RADS, Breast Imaging Reporting and Data System.

Table 3

Model prediction performance of the Framingham risk score after adding mammographic breast density.

Indicators	Total population	Low-risk	Moderate-risk	High-risk
AUC analysis				
Model 1 AUC ^a	71.62	70.74	55.73	55.35
Model 2 AUC ^b	71.70	70.84	55.78	55.39
Difference in AUC	0.083	0.1	0.0459	0.0414
95% CI of difference in AUC	0.069–0.096	0.079–0.011	–0.039–0.131	–0.227–0.310
p-value of AUC difference	<0.0001	<0.0001	0.289	0.7629
Net reclassification improvement analysis				
NRI	7.15%	7.11%	2.15%	2.98%
NRI SE	0.027	0.029	0.987	2.515
NRI 95% CI	6.85–7.69	6.66–7.68	0.22–4.09	–1.95–7.91
NRI p-value	<0.0001	<0.0001	0.0067	0.2608
Percent of events correctly reclassified	8%	5%	10%	32%
p-value	<0.0001	<0.0001	<0.0001	<0.0001
Percent of non-events correctly reclassified	–1%	2%	–8%	–29%
p-value	<0.0001	<0.0001	<0.0001	<0.0001

AUC, area under the ROC curve (AUC); Net reclassification improvement, NRI.

^a Model 1 was a multivariate model for FRS components only.

^b Model 2 was a multivariate model for the FRS component and mammographic breast density.

significant improvement in both the AUC and NRI statistics was observed in the high-risk group. In terms of calibration, the original FRS and the updated model with breast density produced similar results (Supplemental Fig. 1).

4. Discussion

In this population-based cohort study, we found that a decreased level of breast density was associated with increased CVD risk, and adding breast density resulted in a slight but significant improvement in CVD risk prediction, especially among low-risk group (Fig. 3). In particular, the increase in CVDs in women with lower breast density remained significant after adjusting for other traditional CVD risk factors in the FRS. To the best of our knowledge, few studies has assessed the association between mammographic density and CVD development in combination with FRS, as well as the potential value of adding breast density to CVD risk prediction.

Prior to this study, two recent studies reported the association between breast density and the risk of CVD development: the Karolinska

Mammography Project for Risk Prediction of Breast Cancer (KARMA) cohort in Sweden [5] and the multicentre BRECARD study in Italy [6]. Consistent with our findings, these two studies also reported an inverse association between dense breasts and CVD [5,6]. The KARMA study reported that in women without cardiometabolic diseases, higher breast density was associated with a lower risk of CVDs, including hypertension, chest pain, and peripheral vascular disease [5]. In the BRECARD Study [6], breast density was assessed using the BI-RADS density category, similar to our study, but the study only included premenopausal women. The authors reported a 3.23-fold (95 % CI, 1.25–7.89) increase in the risk of major adverse cardiac events in premenopausal women with BI-RADS breast density category 1 compared to women with breast density categories 2 to 4 [6]. Despite the differences in the study population, measurement of breast density, and CVD outcomes, these two studies and our findings suggest that there is a significant association between breast fat accumulation and an increased risk of cardiovascular events. These findings suggest that breast fat accumulation, assessed by breast density, is an important pathogenic factor for CVD prediction and might have potential value in risk prediction in women.

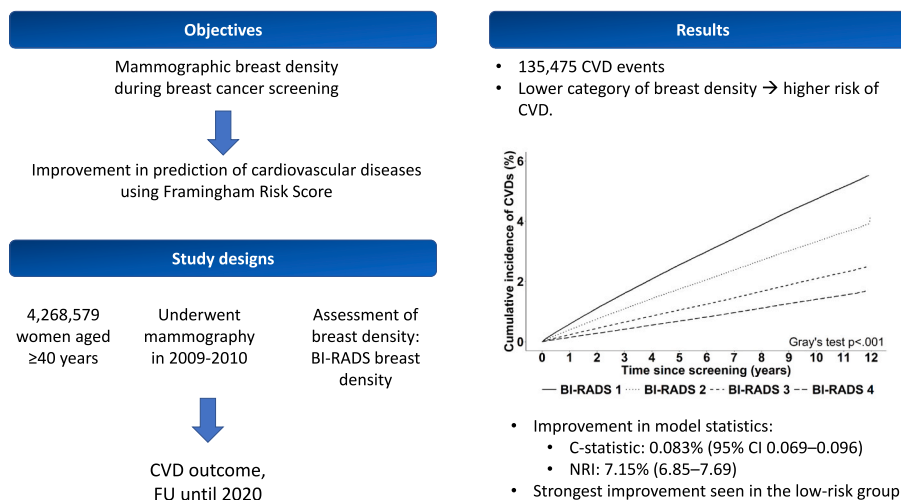


Fig. 3. Graphical abstract.

The decreased risk of CVDs in women with dense breasts may be attributable to the combined impact of adiposity and aging. The percentage of dense breast tissue decreases with increasing age [25], and women with denser breasts are relatively older than those with fatty breasts. Although age was adjusted for in our analysis, the impact of age cannot be fully eliminated, which might explain the lower CVD risk observed in women with denser breasts. Percent breast density and adiposity are negatively associated with each other [26,27]. Thus, the biological relationship between breast density and CVD risk may be related to the aromatase activity of body fat, which is a significant source of endogenous estrogens that promote breast tissue proliferation [26]. Even though women with dense breasts are generally at a reduced risk for CVDs, their concomitant medications and hormonal exposure should be considered when including breast density in predicting CVDs [6]. The increased risk of CVDs after menopause, followed by a decline in estrogen levels [28] suggests that estrogen plays an important role in CVD development among women. However, the effects of exogenous versus endogenous estrogen levels, as well as the effects of different estrogen types, could also lead to differences in CVD risk [29,30]. Both increased exposure to endogenous and exogenous estrogen and its responsiveness are associated with increased breast density [31,32]. Although we did not compare the estrogen levels in women with dense or fatty breasts, the possible higher estrogen levels among women with dense breasts, after adjusting for covariates such as age and menopausal status, could explain the protective association with CVDs.

Our findings revealed that adding mammographic breast density to the current FRS might help with the better prediction of CVD risk in women. After adding breast density to the FRS model, despite minimal improvement in C-statistics, the NRI improved (>7%), especially in women with low CVD risk. The NRI quantifies the correctness of upward and downward reclassifications of predicted probabilities as a result of adding a new marker, and it has been recommended to assess the model performance comparison [33,34]. Our findings indicate that adding breast density through mammography might present a potential benefit in predicting CVD risk in women, as well as in the early detection of breast cancer. It is worth noting that the breast density-included model improves model performance in women with low CVD risk in both C-statistics and NRI.

The limitations of this study include the assessment of breast density. In the Korean National Breast Cancer Screening Program, double reading, which is the interpretation of screening mammograms by at least two radiologists, is not obligatory, as in European guidelines [35]. Thus, the BI-RADS breast densities were interpreted by a single radiologist at several screening centers. Although the BI-RADS classification has been widely employed, the results may vary depending on the ability

and experience of radiologists. Inter-radiologist variability was assessed in randomly selected films from the Korean National Breast Cancer Screening Program, and an inter-radiologist variability of 0.83 was reported, indicating a very high agreement [36]. Thus, BI-RADS breast density has been used widely in recent years. Another limitation was the duration of our study, with a median follow-up period of 10.9 years, which was relatively short and insufficient for comprehensively evaluating the CVD risk. Additionally, our dataset could have been influenced by a selection bias since women who participate in breast cancer screening may represent a health-conscious subset of the population.

CVDs remain the most common cause of mortality in women [1] and optimal prevention requires more accurate assessment of CVD risk factors in women. Several risk prediction tools have been developed and validated to predict CVD risk, and several studies have added other elements to improve these tools [22,37]. In this context, determining female-specific risk factors, such as breast density, and applying them in risk prediction tools could enhance preventive approaches. Our study included >4 million women from population-based breast cancer screening, broadly representing the demographic composition of women in Korea and other East Asian populations. Hence, this large national cohort study with prospective ascertainment of CVD cases provides new evidence of the potential value of breast density in CVD prediction. We believe that the present investigation is the largest study to examine the potential benefits of breast density in CVD risk prediction, particularly in East Asian women.

Herein, our results revealed that a lower level of dense breast tissue, in other words, a higher deposition of adipose tissue in the breast, was associated with an increased risk of CVD. Furthermore, the addition of mammographic breast density improved the prediction of CVDs during the 10-year follow-up, especially in low-risk group. Findings from this study suggest the potential for collaboration between cardiologists and breast imagers to enhance the benefits of screening mammography in predicting both breast malignancy and CVDs.

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CRedit authorship contribution statement

Thi Xuan Mai Tran: Formal analysis, Data curation, Conceptualization, Software, Writing - original draft, Writing - review & editing. **Yoo-soo Chang:** Supervision, Conceptualization, Methodology, Writing - review & editing. **Soyeoun Kim:** Data curation, Project administration, Writing - review & editing. **Seungho Ryu:** Supervision, Conceptualization, Methodology, Writing - review & editing. **Boyoung Park:** Supervision, Conceptualization, Data curation, Formal analysis, Methodology, Resources, Writing - original draft, Writing - review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.atherosclerosis.2023.117392>.

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