Received: 16 April 2020 | Revised: 1 December 2020 | Accepted: 18 December 2020

DOI: 10.1002/ijc.33455

CANCER EPIDEMIOLOGY

IJC International Journal of Cancer

Association between changes in mammographic density category and the risk of breast cancer: A nationwide cohort study in East-Asian women

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Funding information
Korea Association of Health Promotion, Grant/Award Number: 2020; the Korean Foundation for cancer research, Grant/Award Number: 1; Hanyang University

Abstract

Breast density is strongly associated with breast cancer risk; however, studies on the association between density changes and breast cancer risk have controversial results. The aim of our study was to determine the association between breast density changes and breast cancer risk in East-Asian women. We included 3 301 279 women aged ≥40 years screened for breast cancer twice during 2009 to 2010 and 2011 to 2012. Data were obtained from the National Health Insurance Service (NHIS) database. Breast density was evaluated using the Breast Imaging-Reporting and Data System (BI-RADS). Relative risk (RR) and 5-year risk of developing breast cancer according to density category changes were calculated. Overall, 23.0% of the women had a higher breast density and 22.2% of the women had a lower breast density in second screening compared to the first. An increase in the BI-RADS density category between two subsequent mammographic screenings was associated with an increase in breast cancer risk and vice versa in terms of RR. The 5-year breast cancer risk was affected by the initial BI-RADS density category, changes in density category and patients' characteristics such as age, menopausal status and family history of breast cancer. In patients with breast cancer family history, the 5-year breast cancer risk was prominent, at a maximum of 2.39% (95% CI = 1.23-3.55) in women with breast density category of 2 to 4. Changes in the BI-RADS density category were associated with breast cancer risk. Longitudinal measures of BI-RADS density may be helpful in identifying high-risk women, especially those with a breast cancer family history.

KEYWORDS
BI-RADS, breast cancer, density, risk, screening mammography

1 | INTRODUCTION

Breast cancer is the most common cancer in women. In 2018, it constituted 25% of cancers among women worldwide, and 2.8 million new cases were recorded. Despite the relatively low incidence in East Asian countries compared to that in European countries, the incidence of breast cancer has rapidly increased in East Asian countries.[1]

Breast density is one of the most important risk factors of breast cancer.[2,3] Women with dense breasts have a four- or five-time higher risk of breast cancer.[3,4] This association has also been observed in Asian women.[5,6] Breast density changes over time and has an inverse association with age.[7] Despite the lower breast cancer incidence in

Abbreviations: BI-RADS, Breast Imaging-Reporting and Data System; CI, confidence interval; DCIS, ductal carcinoma in situ; IBC, invasive breast cancer; IRB, The Institutional Review Board; NHIS, The National Health Insurance Service; RR, relative risk.

Asian women, dense breasts are common among Asian women than Western women.[8,9] In previous studies comparing breast density by age between Caucasian and Korean women aged <50 years, >90% had dense breasts, which was much higher than that among the Western women. However, in women aged ≥60 years, the prevalence of dense breasts decreased to approximately 40%, which was comparable with that in Western women.[10,11] Researchers suggested that the breast density pattern by age may explain the unique age-specific breast cancer incidence rate in women from Asian countries,[12] where the breast cancer incidence peaks around 50 years of age and then decreases.[13,14] In Western countries where breast cancer incidence increases with age, despite the lower breast density, the cumulative exposure to high breast density may be a cause of breast cancer.[15] Numerous studies in Western countries have focused on the association between breast density and breast cancer. However, studies on the relationship between changes in breast density and the risk of breast cancer are few and report controversial results.[16-22] With the higher prevalence of dense breasts in Asian countries, recent studies on the association between breast density and the risk of breast cancer have been carried out,[5,6] although these studies did not focus on the association between longitudinal breast density changes and the risk of breast cancer. In Korea, the national breast cancer screening program offers biennial mammographic screening, which assesses breast density for all women aged ≥40 years. Therefore, we investigated the association between breast density changes and breast cancer in Korean women using data from the national breast cancer screening program.

What's new?

Breast density is strongly associated with breast cancer risk. However, in Western countries, the association between density changes and breast cancer risk remains controversial, and no such studies have been reported in East Asia. This Korean study found an association between changes in the BI-RADS density category and the risk of breast cancer. In East-Asian women with a breast cancer family history and high-density category in either the first or second screening mammography, the 5-year risk of developing breast cancer was >1.67%. Longitudinal measures of BI-RADS density may help identify high-risk women, especially those with a breast cancer family history.

2 | MATERIALS AND METHODS

2.1 | Data sources and population

Data were sourced from the health screening database of the National Health Insurance Service (NHIS), which includes data related to regular health check-ups for cardiovascular diseases and malignancies such as gastric, hepatic, colon, breast and cervical cancer in Korea. For breast cancer screening, women aged ≥40 years receive biennial mammographic screening as part of the NHIS cancer screening program. During screening, standardized questionnaires on health behavioral factors, family history and reproductive factors were filled by the women themselves. Breast density was evaluated using the Breast Imaging-Reporting and Data System (BI-RAD) classification. Screening-related information including screening results and questionnaires was transferred to the NHIS database after obtaining informed consent from the women. By linkage with the screening database and medical usage of NHIS, breast cancer incidence was identified together with disease code and catastrophic illnesses code up to December 2017. Our study was approved by the Institutional Review Board (IRB) of Hanyang University College of Medicine (IRB No. HYI-18-175-1). We then obtained permission to access the NHIS database from the National Health Insurance Sharing Service.

The BI-RADS has been used to classify breast density in the Korean National Breast Cancer Screening Program since 2009. Therefore, we used data from the screening database since 2009. We identified 3 429 324 cancer-free women who were screened for breast cancer using mammography in both 2009 to 2010 and 2011 to 2012. Among them, 107 816 women without breast density information in either of the two examinations and 20 229 women with breast cancer or any other cancer within 90 days of the second examination were excluded. Therefore, we included 3 301 279 women. Among these women, 18 064 women with invasive breast cancer (IBC) and 4717 women with ductal carcinoma in situ (DCIS) were identified.

2.2 | Variables related to mammographic density and risk factors for breast cancer

The BI-RADS classifies breast density in four categories. BI-RADS Category 1 refers to almost entirely fat (parenchyma proportion, 0%-25%); Category 2 refers to scattered fibroglandular densities (parenchyma proportion, 25%-50%); Category 3 refers to heterogeneously dense (parenchyma proportion, 50%-75%); and Category 4 refers to extremely dense (parenchyma proportion, 75%-100%). Changes in the BI-RADS category between the first and second mammography were considered.

Participants' age, age at menarche, menopausal status, age at menopause, number of children, breastfeeding duration, hormone replacement therapy among menopausal women, oral contraceptive use, family history in first-degree relatives, body-mass index, smoking status, drinking status during the past year and physical activity per week, which were measured using a self-administered questionnaire, were considered as adjusted variables.

2.3 | Statistical analysis

Basic characteristics of the study population at the first and second mammographic screenings and the distribution of the first and second

TABLE 1 Baseline characteristics of the study population

Risk factor	No breast cancer	Total breast cancer
Age, mean (SD) (years)	54.41 (9.8)	51.87 (8.6)
40 to 44	592 050 (18.1)	5731 (25.2)
45 to 49	483 402 (14.7)	4220 (18.5)
50 to 54	719 851 (22.0)	5008 (22.0)
55 to 59	447 921 (13.7)	2855 (12.5)
60 to 64	488 362 (15.0)	2842 (12.5)
65 to 69	306 432 (9.4)	1341 (5.9)
70 to 74	240 480 (7.3)	784 (3.4)
Age at menarche (years)		
≤15	1 423 780 (43.4)	11 989 (52.6)
16 to 17	1 127 530 (34.4)	6985 (30.7)
>17	616 928 (18.8)	3084 (13.5)
Missing	110 260 (3.4)	723 (3.2)
Menopausal status		
First mammography		
Premenopause	1 371 893 (41.9)	12 343 (54.2)
Postmenopause	1 851 143 (56.5)	10 068 (44.2)
Unknown	55 462 (1.7)	370 (1.6)
Second mammography		
Premenopause	1 106 048 (33.7)	10 485 (46.0)
Postmenopause	2 167 999 (66.1)	12 255 (53.8)
Unknown	4451 (0.1)	41 (0.2)
Age at menopause (years)		
Premenopause	1 106 048 (33.7)	10 485 (46.0)
≤49	687 190 (21.0)	3317 (14.6)
50 to 51	618 785 (18.9)	3416 (15.0)
>51	788 144 (24.0)	5053 (22.2)
Unknown	78 331 (2.4)	510 (2.2)
Number of children (baseline)		
0	52 148 (1.6)	331 (1.5)
1	300 200 (9.2)	2872 (12.6)
2	2 808 200 (85.7)	18 332 (80.5)
≥3	116 053 (3.5)	1234 (5.4)
Unknown	1897 (0.7)	12 (0.1)
Breastfeeding duration (Baseline)		
0	488 817 (14.9)	4309 (18.9)
<1 year	2 405 476 (73.4)	14 607 (64.1)
≥1 year	369 850 (11.3)	3734 (16.4)
Unknown	14 355 (0.4)	131 (0.6)
Hormone replacement therapy among menopaused women		
First mammography		
Never	1 456 708 (44.4)	7419 (32.6)
Ever	384 844 (11.7)	2592 (11.4)
Premenopause	1 371 893 (41.9)	12 343 (54.2)
Unknown	65 053 (2.0)	427 (1.9)

TABLE 1 (Continued)

Risk factor	No breast cancer	Total breast cancer
Second mammography		
Never	1 575 313 (48.1)	8339 (36.6)
Ever	584 696 (17.8)	3879 (17.0)
Premenopause	1 106 048 (33.7)	10 485 (46.0)
Unknown	12 441 (0.4)	78 (0.3)
Oral contraceptive use		
First mammography		
Never	2 587 462 (78.9)	18 012 (79.1)
Ever	631 181 (19.3)	4382 (19.2)
Unknown	59 855 (1.8)	387 (1.7)
Second mammography		
Never	2 326 613 (71.0)	16 328 (71.7)
Ever	941 577 (28.7)	6379 (28)
Unknown	10 308 (0.3)	74 (0.3)
Family history (in first degree relative)		
No	3 226 645 (98.4)	22 029 (96.7)
Yes	51 853 (1.6)	752 (3.3)
BMI (kg/m^2)		
First mammography		
<23	1 350 442 (41.2)	9802 (43.0)
24 to 25	843 962 (25.7)	5612 (24.6)
>25	1 083 454 (33.1)	7361 (32.3)
Unknown	640 (0.0)	6 (0.0)
Second mammography		
<23	1 346 786 (41.1)	9640 (42.3)
24 to 25	842 662 (25.7)	5755 (25.3)
>25	1 088 772 (33.2)	7385 (32.4)
Unknown	278 (0.0)	1 (0.0)
Smoking status		
First mammography		
Never smoked	3 134 254 (95.6)	21 642 (95.0)
Ever smoked	128 107 (3.9)	1029 (4.5)
Missing	16 137 (0.5)	110 (0.5)
Second mammography		
Never smoked	3 116 805 (95.1)	21 497 (94.4)
Ever smoked	158 695 (4.8)	1267 (5.6)
Missing	2998 (0.1)	17 (0.1)
Drinking status during the last 1 year		
First mammography		
No drinking	2 623 492 (80.0)	17 691 (77.7)
Drinking	628 933 (19.2)	4920 (21.6)
Missing	26 073 (0.8)	170 (0.8)
Second mammography		
No drinking	2 671 137 (81.5)	17 942 (78.8)
Drinking	604 349 (18.4)	4824 (21.2)
Missing	3012 (0.1)	15 (0.1)

(Continues)

TABLE 1 (Continued)

Risk factor	No breast cancer	Total breast cancer
Physical activity per week		
First mammography		
No activity	1 811 921 (55.3)	12 082 (53.0)
≥1 day	1 451 403 (44.3)	10 598 (46.5)
Unknown	15 174 (0.5)	101 (0.4)
Second mammography		
No activity	1 755 889 (53.6)	11 285 (49.6)
≥1 day	1 520 751 (46.4)	11 486 (50.4)
Unknown	1858 (0.7)	10 (0.0)

mammographic breast density between breast cancer cases and controls with respect to age, menopausal status and breast cancer family history were presented.

The association between changes in breast density and the risk of breast cancer was presented as relative risk (RR) and 95% confidence interval (CI) based on the Poisson distribution, considering the rare events of breast cancer in our study population.[23,24] The association was compared between both groups and adjusted for the abovementioned variables. The 5-year risk of developing breast cancer with respect to density changes was also estimated. RRs and 5-year risks were also estimated with respect to age, menopausal status and breast cancer family history and were subdivided according to breast cancer type (IBC and DCIS). These calculations were performed using SAS (version 9.4; SAS Institute, Cary, NC).

3 | RESULTS

Table 1 shows the general characteristics of the participants with respect to the development of breast cancer. The mean age of women who developed breast cancer was 51.87 years and that of women who did not develop breast cancer was 54.41 years. Most women who developed breast cancer were premenopausal and had a relevant family history of breast cancer compared to those who did not develop breast cancer.

Table 2 shows the distribution of the BI-RADS categories by age in the two screening mammograms. For women who developed breast cancer, the first and second BI-RADS densities were stratified by IBC and DCIS. Women with breast cancer had a higher proportion of dense breasts than those without cancer in both screening sessions and in all the age groups. The BI-RADS density was lower in older women who were older, menopausal women and women with no breast cancer family history in both screening sessions (Table 2 and Supplementary Table 1).

The association between changes in BI-RADS density categories with 16 possible combinations and the risk of developing breast cancer is presented in Table 3. Overall, 23.0% of the women had a higher density category, and 22.2% had a lower density category in the second screening compared to the first screening. As the breast density category increased between the first and second mammographic screenings, the RRs of developing breast cancer increased. As the breast density category decreased, the RRs decreased, as compared to women without change in density category. The RR pattern according to changes in the breast density category was similar irrespective of the age (<50 and ≥50 years), menopausal status (premenopause and postmenopause) and breast cancer family history (Table 3 and Supplementary Table 2).

As the BI-RADS density category increased between the first and second mammographic screenings, the 5-year risk of developing breast cancer increased and vice versa, compared to women with the same density category. For women with BI-RADS Category 4 during both screenings, the 5-year risk was 1.24% (95% CI, 1.19-1.28), which was the highest risk among the 16 combinations. The absolute 5-year risks were higher in all density category combinations in women with a breast cancer family history, compared to women without a family history. Especially among women with a breast cancer family history, women whose density category changed from 1 to 4, 2 to 4, 3 to 2 or 4, and 4 to 1 or 3 and those whose category remained as 3 and 4, the 5-year risks of developing breast cancer were >1.67%, reaching a maximum of 2.39% (95% CI = 1.23-3.55) in women with breast density category from 2 to 4. In addition, the absolute 5-year risks were higher in most density category combinations in women aged <50 years and premenopausal women than in women aged ≥50 years and postmenopausal women (Supplementary Table 2).

When stratified by IBC and DCIS, the absolute 5-year risk was lower in DCIS than in IBC, and the adjusted RR was comparable between the two breast cancer groups (Supplementary Table 3).

4 | DISCUSSION

An increase in the BI-RADS density category between two subsequent mammographic screenings was associated with an increased breast cancer risk, and a decrease in the BI-RADS category decreased the breast cancer risk in terms of RR in East-Asian women. Regarding absolute risk, the 5-year breast cancer risk was affected by the initial

TABLE 2 Breast density on first and second screening mammography examinations with respect to age and breast cancer type

Characteristics	BI-RADS density	No breast cancer		Total breast cancer		Invasive breast cancer		Ductal carcinoma in situ	
		First screen	Second screen	First screen	Second screen	First screen	Second screen	First screen	Second screen
Total									
	1	924 140 (28.2)	858 906 (26.2)	3451 (15.2)	3027 (13.3)	2844 (15.7)	2487 (13.8)	607 (12.9)	540 (11.5)
	2	920 787 (28.1)	979 941 (29.9)	5565 (24.4)	5846 (25.7)	4401 (24.4)	4680 (25.9)	1164 (24.7)	1166 (24.7)
	3	967 920 (29.5)	996 658 (30.4)	8558 (37.6)	8850 (38.9)	6686 (37.0)	6919 (38.3)	1872 (39.7)	1931 (40.9)
	4	465 651 (14.2)	442 993 (13.5)	5207 (22.9)	5058 (22.2)	4133 (22.9)	3978 (22.0)	1074 (22.8)	1080 (22.9)
Age 40 to 49									
	1	97 842 (9.1)	79 325 (7.4)	553 (5.6)	408 (4.1)	432 (5.6)	325 (4.2)	121 (5.5)	83 (3.8)
	2	213 504 (19.9)	214 984 (20.0)	1431 (14.4)	1300 (13.1)	1123 (14.5)	1035 (13.4)	308 (13.9)	265 (12.0)
	3	454 063 (42.2)	474 598 (44.1)	4291 (43.1)	4552 (45.7)	3297 (42.6)	3501 (45.2)	994 (45.0)	1051 (47.6)
	4	310 043 (28.8)	306 545 (28.5)	3676 (36.9)	3691 (37.1)	2890 (37.3)	2881 (37.2)	786 (35.6)	810 (36.7)
Age 50 to 59									
	1	281 828 (24.1)	267 014 (22.9)	1153 (14.7)	1045 (13.3)	959 (15.2)	855 (13.5)	194 (12.6)	190 (12.3)
	2	384 040 (32.9)	413 612 (35.4)	2301 (29.3)	2545 (32.4)	1844 (29.2)	2053 (32.5)	457 (29.6)	492 (31.8)
	3	372 639 (31.9)	374 982 (32.1)	3119 (39.7)	3123 (39.7)	2469 (39.1)	2481 (39.3)	650 (42.1)	642 (41.6)
	4	129 265 (11.1)	112 164 (9.6)	1290 (16.4)	1150 (14.6)	1046 (16.6)	929 (14.7)	244 (15.8)	221 (14.3)
Age 60 to 69									
	1	383 804 (48.3)	359 723 (45.3)	1360 (32.5)	1207 (28.9)	1122 (33.7)	1000 (30.0)	238 (28.0)	207 (24.4)
	2	263 310 (33.1)	284 410 (35.8)	1578 (37.7)	1721 (41.1)	1218 (36.5)	1348 (40.4)	360 (42.4)	373 (43.9)
	3	124 139 (15.6)	128 998 (16.2)	1028 (24.6)	1059 (25.3)	817 (24.5)	832 (25.0)	211 (24.9)	227 (26.7)
	4	23 541 (3.0)	21 663 (2.7)	217 (5.2)	196 (4.7)	177 (5.3)	154 (4.6)	40 (4.7)	42 (5.0)
Age 70 to 74									
	1	160 666 (66.8)	152 844 (63.6)	385 (49.1)	367 (46.8)	331 (49.4)	307 (45.8)	54 (47.4)	60 (52.6)
	2	59 933 (24.9)	66 935 (27.8)	255 (32.5)	280 (35.7)	216 (32.2)	244 (36.4)	39 (34.2)	36 (31.6)
	3	17 079 (7.1)	18 080 (7.5)	120 (15.3)	116 (14.8)	103 (15.4)	105 (15.7)	17 (14.9)	11 (9.7)
	4	2802 (1.2)	2621 (1.1)	24 (3.1)	21 (2.7)	20 (3.0)	14 (2.1)	4 (3.5)	7 (6.1)

Note: P value <.0001 by using chi-square.

TABLE 3 Breast cancer risk with respect to change in density categories between the first and second mammography for total breast cancer by presence of family history of breast cancer

First screen	Second screen	Total breast cancer N[a]	Person-year[b]	No of cases[c]	Adjusted RR (95% CI)[d]	*P* value	5-year risk% for total breast cancer (95% CI)
Total							
BI-RADS 1							
	BI-RADS 1	570 106	2 784 045.2	1634	1		0.30 (0.29-0.32)
	BI-RADS 2	259 002	1 266 713.3	1161	1.48 (1.37-1.60)	<.0001	0.47 (0.44-0.49)
	BI-RADS 3	80 688	395 577.5	522	2.01 (1.81-2.23)	<.0001	0.67 (0.61-0.73)
	BI-RADS 4	17 795	87 461.2	134	2.22 (1.84-2.67)	<.0001	0.77 (0.64-0.90)
BI-RADS 2							
	BI-RADS 1	212 849	1 041 715.9	877	0.73 (0.67-0.79)	<.0001	0.43 (0.40-0.46)
	BI-RADS 2	466 028	2 285 321.3	2707	1		0.60 (0.58-0.62)
	BI-RADS 3	209 198	1 026 535.5	1594	1.31 (1.23-1.40)	<.0001	0.79 (0.75-0.82)
	BI-RADS 4	38 277	187 943.8	387	1.76 (1.57-1.96)	<.0001	1.04 (0.94-1.14)
BI-RADS 3							
	BI-RADS 1	64 449	315 970.7	386	0.69 (0.62-0.77)	<.0001	0.62 (0.56-0.68)
	BI-RADS 2	220 262	1 081 362.5	1621	0.83 (0.78-0.88)	<.0001	0.76 (0.72-0.80)
	BI-RADS 3	536 339	2 634 260.8	4873	1		0.93 (0.91-0.96)
	BI-RADS 4	155 428	763 756.8	1678	1.18 (1.11-1.24)	<.0001	1.11 (1.05-1.16)
BI-RADS 4							
	BI-RADS 1	14 529	71 305.4	130	0.80 (0.67-0.96)	.0150	0.92 (0.76-1.08)
	BI-RADS 2	40 495	198 792.1	357	0.78 (0.69-0.87)	<.0001	0.91 (0.81-1.00)
	BI-RADS 3	179 283	881 014.3	1861	0.88 (0.83-0.93)	<.0001	1.06 (1.02-1.11)
	BI-RADS 4	236 551	1 162 747.9	2859	1		1.24 (1.19–1.28)
Family history of breast cancer (–)							
BI-RADS 1							
	BI-RADS 1	564 464	2 756 548.6	1592	1		0.30 (0.28-0.31)
	BI-RADS 2	255 785	1 250 999.5	1133	1.48 (1.37–1.60)	<.0001	0.46 (0.44-0.49)
	BI-RADS 3	79 553	390 036.0	509	2.02 (1.81-2.25)	<.0001	0.66 (0.61-0.72)
	BI-RADS 4	17 531	86 162.0	129	2.21 (1.83-2.67)	<.0001	0.76 (0.63-0.89)
BI-RADS 2							
	BI-RADS 1	210 269	1 029 106.1	864	0.73 (0.68-0.79)	<.0001	0.43 (0.40–0.46)
	BI-RADS 2	458 568	2 248 729.9	2639	1		0.60 (0.57-0.62)
	BI-RADS 3	205 599	1 008 991.8	1548	1.31 (1.23–1.40)	<.0001	0.78 (0.74-0.81)
	BI-RADS 4	37 589	184 588.7	371	1.73 (1.55-1.94)	<.0001	1.01 (0.91-1.12)
BI-RADS 3							
	BI-RADS 1	63 537	311 509.9	378	0.70 (0.63-0.78)	<.0001	0.62 (0.55-0.68)
	BI-RADS 2	216 400	1 062 472.8	1551	0.82 (0.77-0.87)	<.0001	0.74 (0.70-0.78)
	BI-RADS 3	525 636	2 581 930.4	4695	1		0.92 (0.89-0.94)
	BI-RADS 4	152 335	748 587.9	1619	1.18 (1.11-1.25)	<.0001	1.09 (1.04-1.14)
BI-RADS 4							
	BI-RADS 1	14 314	70 257.8	125	0.80 (0.67–0.96)	.0169	0.90 (0.74-1.06)
	BI-RADS 2	39 791	195 336.2	348	0.79 (0.70-0.88)	<.0001	0.90 (0.81-0.99)
	BI-RADS 3	175 743	863 786.7	1782	0.88 (0.83–0.93)	<.0001	1.04 (0.99-1.09)
	BI-RADS 4	231 560	1 138 399.4	2746	1		1.21 (1.17-1.26)
Family history of breast cancer (+)							
BI-RADS 1							
	BI-RADS 1	5642	27 496.6	42	1		0.78 (0.54-1.01)
	BI-RADS 2	3217	15 713.8	28	1.16 (0.71-1.88)	.5597	0.91 (0.57-1.24)
	BI-RADS 3	1135	5541.5	13	1.40 (0.72-2.74)	.3238	1.19 (0.55-1.83)
	BI-RADS 4	264	1299.2	5	2.25 (0.83-6.13)	.1115	1.94 (0.26-3.62)

TABLE 3 (Continued)

First screen	Second screen	Total breast cancer N[a]	Person-year[b]	No of cases[c]	Adjusted RR (95% CI)[d]	*P* value	5-year risk% for total breast cancer (95% CI)
BI-RADS 2							
	BI-RADS 1	2580	12 609.7	13	0.56 (0.31-1.01)	.0546	0.53 (0.24-0.81)
	BI-RADS 2	7460	36 591.4	68	1		0.94 (0.72-1.17)
	BI-RADS 3	3599	17 543.7	46	1.42 (0.96-2.08)	.0765	1.32 (0.94-1.70)
	BI-RADS 4	688	3355.1	16	2.62 (1.48-4.65)	.0010	2.39 (1.23–3.55)
BI-RADS 3							
	BI-RADS 1	912	4460.8	8	0.53 (0.26-1.08)	.0783	0.91 (0.28-1.54)
	BI-RADS 2	3862	18 889.7	70	1.11 (0.84-1.48)	.4510	1.87 (1.43-2.30)
	BI-RADS 3	10 703	52 330.5	178	1		1.71 (1.46-1.96)
	BI-RADS 4	3093	15 168.8	59	1.14 (0.85-1.54)	.3858	1.95 (1.46-2.45)
BI-RADS 4							
	BI-RADS 1	215	1047.6	5	0.97 (0.39-2.40)	.9513	2.38 (0.32-4.44)
	BI-RADS 2	704	3456.0	9	0.54 (0.27-1.07)	.0780	1.32 (0.46-2.17)
	BI-RADS 3	3540	17 227.7	79	0.96 (0.72-1.29)	.7944	2.31 (1.81-2.81)
	BI-RADS 4	4991	24 348.5	113	1		2.32 (1.90-2.75)

[a]Total study sample including normal, breast cancer incidence and other cancer incidence.

[b]Corresponding to 1 to 4 after the second health check-up (1) breast cancer incidence, (2) death, (3) other cancers incidence and (4) 5 years after the second health check-up.

[c]Limited to breast cancer within 5 years of the second health check-up.

[d]Adjusted for age at first mammography, age at menarche, changes in menopausal status (pre-pre, pre-post, post-post), age at menopause, number of children, breast feeding duration, hormone replacement therapy use, oral contraceptive use, body-mass index at first and second mammography, smoking status at first mammography, drinking status at first mammography and physical activity at first mammography.

BI-RADS density category; changes in density category; the patients' characteristics such as age, menopausal status and family history of breast cancer. In patients with a breast cancer family history, the 5-year breast cancer risk was prominent, showing a maximum of 2.39% (95% CI, 1.23-3.55) in women with a breast density category from 2 to 4.

Several studies have reported a strong association between high breast density and increased risks of breast cancer.[20] However, studies on the association between changes in breast density and breast cancer have shown inconsistent results. Studies considering breast density as a continuous variable did not show a significant association between breast density changes and the risk of breast cancer.[13,16,19,20,22] However, when breast density was categorized, the risk of breast cancer increased with an increase in the breast density and vice versa between the two measurements.[16-18] When the BI-RADS density category was used, a prominent association between breast cancer risk and changed density category was observed not only in our study but also in other studies.[17,18] Changes in the density category would be sufficiently large and would indicate the risk of breast cancer better than mean difference or per percent change would. This could explain the inconsistent results between continuous and categorical measurement. Lokate et al reported no differences in the average density change between breast cancer cases and controls, but showed associations between categorical density changes and breast cancer risk, supporting the explanation.[16]

Unlike the study by Kerlikowske et al who found the association between changes in BI-RADS density category and breast cancer risk only in women with an initial BI-RADS category of 1, 2 and 3, we observed an association in all initial BI-RADS categories. The higher breast cancer incidence rate in young Asian women,[25] and higher breast density in young women[16,17,26] could explain the significant association in women with BI-RADS Category 4. In addition, based on the previous results[17,18] and result of our study, it could be suggested that both density change and initial breast density are important predictors of breast cancer.

Regarding the absence/presence of breast cancer family history, despite comparable RRs of changes in density categories, women with a breast cancer family history had higher absolute breast cancer risks, similar to a previous study.[18] Both single measure and changes in breast density are independent risk factors of breast cancer, especially in women with a breast cancer family history.[22,27-29] In our study, the 5-year risk of developing breast cancer in women with both family history and rapid density increment or a high initial density category was >1.67%. In Western countries, women with a 5-year risk >1.67% of developing breast cancer are considered to be the high-risk group, and interventions such as lifestyle modification or chemoprevention are recommended to reduce this risk.[30] Considering the lower breast cancer incidence in Korea than that in Western countries,[31] more intensive preventive interventions or screening could be helpful for these high-risk women.

There are several methods to measure breast density, including percent density, percentage homogeneous densities and absolute density measures.[32] Although the BI-RADS density classification aims to identify women with cancers that may be masked by dense tissue and cannot exactly quantify the breast density,[33] it is the most widely used method for assessing density and the standard reporting method in the Korean National Breast Cancer Screening Program. Thus, risk assessment based on the changes in the BI-RADS category may be easily performed and incorporated into risk assessment in the screening setting.

Our study had several limitations. A major limitation of our study was the subjective interpretation of breast density, followed by possible disagreement in the BI-RADS density assessment among the radiologists at the screening units. However, previous studies suggested a substantial interobserver and intraobserver agreement regarding BI-RADS categories.[34-37] A mammography education program in Korea to standardize the performance of radiologists[38] may increase the reproducibility of the density measures. In a previous study conducted as a quality assurance of the Korean National Breast Cancer Screening Program, the interradiologist variability in the assessment of the BI-RADS density category of the randomly selected film was 0.83, suggesting a very high agreement.[39] If a measurement error in the density category existed, the misclassification would be nondifferential, therefore providing conservative results regarding the association between density change and the risk of breast cancer.[40,41] In addition, the large study population reduced the effect of bias on our results.[42] Second, the BI-RADS was updated in 2013, and the breast density composition scale was modified.[43] Studies have shown that the percentage of women with dense breasts when classified using the fifth edition was slightly higher than when using the fourth edition.[37,44,45] However, women who underwent mammographic screening in both 2019 to 2010 and 2011 to 2012 were included in our study. Thus, we used the BI-RADS fourth edition in our study for breast classification. This might have caused an underestimation of the proportion of women with dense breasts. However, our results were affected minimally, given that we used this classification consistently throughout the study period. Additionally, to reduce masking associations owing to dense breasts,[46] we excluded people diagnosed with breast cancer within 90 days after the second screening. Third, although various automated quantitative density measurements have been applied, we used the BI-RADS system, which is based on the reporting system of the NHIS. However, irrespective of the method of density measurement, their association with the risk of breast cancer was similar,[47,48] supporting robust association with density. Fourth, information on confounders was collected using a self-reported questionnaire, which could have a possible information bias. Unmeasured factors could not be adjusted. For identification of the high-risk group, that is, those whose 5-year risk was above the threshold, we did not present the adjusted risk because the crude risk reflects the true risk of the population.[49] Despite these limitations, to the best of our knowledge, this is the first study to assess the association between changes in mammographic density and the risk of breast cancer in East-Asian women. Our study also included the largest number of subjects with two breast density measurements among all existent studies to date and includes approximately 45% of the eligible women in Korea.[50]

In summary, breast cancer risk tends to increase with higher BI-RADS density category, vice versa. Therefore, two longitudinal measures of BI-RADS breast density may be helpful in predicting an individual's breast cancer risk alone or together with other risk factors or prediction models.[18] Together with breast cancer family history, changes in BI-RADS breast density measures may be helpful in identifying women with a high risk of breast cancer. Physicians should consider changes in BI-RADS density categories during mammographic screening when assessing the risk of breast cancer in women.

ACKNOWLEDGEMENTS

The present study was supported by a grant from the Korea Association of Health Promotion (2020-05), Hanyang University (Research No. HY-201900000003243) and the Korean Foundation for Cancer Research in 2019, Seoul, the Republic of Korea.

CONFLICT OF INTEREST

All the authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on the website of the National Health Insurance Sharing Service (https://nhiss.nhis.or.kr/). We accessed the database after submitting the study protocol, the IRB approval document, and the reviewed request form by the committee. Further information is available from the corresponding author upon request.

ETHICS STATEMENT

This study was approved by the institutional review board (IRB) of the Hanyang University in Korea (HYI-18-175-5) and complied with the Declaration of Helsinki.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Kim S, Park B. Association between changes in mammographic density category and the risk of breast cancer: A nationwide cohort study in East-Asian women. *Int. J. Cancer*. 2021;148:2674–2684. https://doi.org/10.1002/ijc.33455