Title

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Clinical significance of background parenchymal enhancement in breast cancer risk stratification

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ABSTRACT (Maximum 300 words)

BACKGROUND

Background parenchymal enhancement (BPE) is an established breast cancer risk factor. However, the relationship between BPE levels and breast cancer risk stratification remains unclear.

PURPOSE

To evaluate the clinical relationship between BPE levels and breast cancer risk with covariate adjustments for age, ethnicity, and hormonal status.

STUDY TYPE

Retrospective

POPULATION

954 screening breast MRI datasets representing 721 women divided into four cohorts: women with pathogenic germline BReast CAncer (*BRCA*) mutations (Group 1, N=211), women with non-*BRCA* germline mutations (Group 2, N=60), women without high-risk germline mutations but with a lifetime breast cancer risk of ≥ 20% using the Tyrer-Cuzick model (Group 3, N=362), and women with <20% lifetime risk (Group 4, N=88).

FIELD STRENGTH/SEQUENCE

3 T/ axial non-fat-saturated T1, short tau inversion recovery (STIR), fat-saturated pre-contrast, and post-contrast T1-weighted images.

ASSESSMENT

Data on age, body mass index, ethnicity, menopausal status, genetic predisposition, and hormonal therapy use were collected. BPE levels were evaluated by two breast fellowship-trained radiologists independently in accordance with BI-RADS, with a third breast fellowship-trained radiologist resolving any discordance.

STATISTICAL TESTS

Propensity score matching (PSM) was utilized to adjust covariates, including age, ethnicity, menopausal status, hormonal treatments, and prior bilateral oophorectomy. The Mann-Whitney U test, chi-squared test, and univariate and multiple logistic regression analysis were performed, with an odds ratio (OR) and corresponding 95% confidence interval. Weighted Kappa statistic was used to assess inter-reader variation. A P value less than 0.05 indicated a significant result.

RESULTS

In the assessment of BPE, there was substantial agreement between the two interpreting radiologists ($\kappa = 0.74$). Patient demographics were not significantly different between patient groups after PSM. The BPE of Group 1 was significantly lower than that of Group 4 and Group 3 among premenopausal women. In estimating the BPE level, the OR of gene mutations was 0.35.

DATA CONCLUSION

Adjusting for potential confounders, the BPE level of premenopausal women with *BRCA* mutations was significantly lower than that of non-high-risk women.

Keywords

Breast MRI, High-risk screening, BRCA, Background Parenchymal Enhancement (BPE), Lifetime risk

Introduction

Approximately 10% of breast cancers are likely related to a hereditary cause (1). In fact, Beitsch *et al*. demonstrated that 7.9% of patients with breast cancer who did not meet National Comprehensive Cancer Network (NCCN) criteria for genetic testing were found to have a pathogenic or likely pathogenic variant and recommended expanded panel testing for all patients (2). High-risk patients should be surveilled with "quality-assured MRI screening" according to the Evaluation of Imaging Methods for Secondary Prevention of Familial Breast Cancer (EVA) trial, which investigated the diagnostic accuracy of different breast imaging modalities in screening women with elevated familial risk (3).

Background parenchymal enhancement (BPE) is the enhancement degree of normal fibroglandular tissue on breast MRI. In the breast imaging reporting and data system (BI-RADS) lexicon, BPE can be categorized into four levels: minimal, mild, moderate, and marked. The level of BPE is hormone-sensitive, particularly to serum estrogen concentrations, and is affected by menopausal status, hormonal treatment, and prior breast radiation therapy. BPE could affect MRI interpretations with both false-positive and false-negative results (4). The clinical impact of BPE in screening breast MRI has been widely debated, particularly its potential association with an increased risk for breast cancer (5–7). A recent study analyzing BPE in the presence of breast lesions suggested that moderate and marked BPE could correlate with the risk of breast cancer (7). Among high-risk patients, those with higher levels of BPE have been shown to have 2.1-2.5 times the risk of developing breast cancer compared to those with low BPE levels (8,9). It has been proposed that these findings are due to possible differences in molecular and vascular

properties of BPE in women with germline pathogenic mutations such as BReast CAncer (*BRCA*) *1* or *BRCA2* (*BRCA1/2*) compared with non-carriers (10).

In this study, we sought to compare qualitative BPE levels between women at high risk for breast and non-high-risk women and to identify breast BPE characteristics of high-risk women with covariate adjustments for age, ethnicity, and hormonal status.

Materials and Methods

Study population and MRI protocol

This retrospective study was approved by our institutional review board and compliant with the Health Insurance Portability and Accountability Act. The requirement to obtain informed consent was waived. We retrospectively reviewed all breast MRI examinations performed between January 2017 and December 2019 at a single institution. The following MRI scans were excluded: those with non-contrast, with Multihance contrast, acquired at 1.5T MRI, incomplete exams (e.g., the case that the examination had to discontinue since patients vomited during the exam), exams on male patients, exams on patients with breast cancer or a history of breast cancer, exams on patients with a history of breast surgery for unknown indication, and follow-up examinations for prior imaging abnormalities. We also excluded cases of women on hormonal medications within the last six months during the patient selection, including chemoprevention with tamoxifen or aromatase inhibitors for high-risk women, and adjusted for potential confounders of endogenous hormonal status for analysis in this study. MRI scans performed on 1.5T scanners were excluded for the purpose of standardization. Of note, this only consisted of 34 cases out of 5,489 breast MRI scans.

Exclusion criteria were applied to yield a sample of 1,199 screening breast MRIs, which were then divided into four groups as follows: Group 1 with known *BRCA* mutation carriers, Group 2 with non-*BRCA* pathogenic germline variants (*TP53, ATM, CHEK2, PALB2, PTEN, STK11, CDH1, NBN, BARD1,* and *NF1*), Group 3 with MRIs for all other women with ≥ 20% or more lifetime risk of breast cancer not due to a known *BRCA* mutation using the Tyrer-Cuzick model (11), and Group 4 with MRIs for women with <20% lifetime risk or unknown risk. The Tyrer-Cuzick model takes into account age, body mass index, menarche, age at first childbirth, menopause age, hormone replacement therapy use, radiologic breast density (A: almost entirely fat, B: scattered fibroglandular tissue, C: heterogeneous fibroglandular tissue, and D: extreme fibroglandular tissue), personal and family history of *BRCA* mutations, personal history of ovarian cancer with age at diagnosis, personal history of high-risk lesions (lobular carcinoma in situ (LCIS), atypical lobular hyperplasia (ALH), and atypical ductal hyperplasia (ADH)), family history of breast and ovarian cancers with age at the time of MRI diagnosis, and Ashkenazi Jewish descent. From Group 4, 31 women with high-risk lesions and 11 women with a history of mantle field irradiation due to Hodgkin's lymphoma were subsequently excluded. Patients who had not received genetic testing, but a result of a variant of uncertain significance, or a negative result for limited *BRCA* testing, were assigned to Group 3 or 4, depending on their level of lifetime risk. The lifetime risk score was documented in a formal evaluation by breast oncology physicians in High-Risk Clinic (HRC) medical notes using the Tyrer-Cuzick model (11). If not available, the lifetime risk score automatically generated was used. This automatic score was based on the Tyrer-Cuzick model of the patient's Breast Radiology intake questionnaire at the time of the MRI service. The flowchart for the study inclusion is presented in **Figure 1**.

Although breast MRI for screening purposes is not recommended for non-high-risk women, the MRI scans were ordered and performed under the direction of the patient's primary care providers, who may not have had a thorough understanding of the screening guidelines.

MRIs were performed in the prone position without breast compression on a 3 Tesla (T) scanner (Siemens Verio, Erlangen, Germany) using a dedicated eight-channel breast coil (Invivo Sentinelle, Gainesville, FL). The institution's MRI protocol limited MRI dates on pre-menopausal women to 7-14 days from the onset of the self-reported last menstrual period to minimize BPE levels due to the effects of estrogen.

The following MRI sequences were performed: three-plane localizer, axial non-fat-saturated T1, short tau inversion recovery (STIR), fat-saturated pre-contrast, and post-contrast T1-weighted images. The detailed MRI scan parameters are listed in **Table 1**. Post-contrast sequences were obtained at 90-second intervals after intravenous injection of gadolinium-based contrast dosed by weight (0.1 mmol/kg) using a power injector at a rate of 2 mL/sec, followed by a 20 mL saline flush. Post-processed maximum-intensity projection (MIP) and subtraction sequences were generated automatically on the Picture Archiving and Communication System (PACS). The total imaging time of the entire MRI protocol was approximately 16 to 17 minutes.

Clinical and imaging analysis

The following patient features were recorded at the time of the MRI exam: age, body mass index (BMI), ethnicity, menopausal status, personal history of bilateral oophorectomy, hormonal therapy within six months prior to MRI, type of hormonal therapy, genetic test results, and fibroglandular tissue (FGT) level on the MRI report (Density A: almost entirely fat, Density B:

scattered fibroglandular tissue, Density C: heterogeneous fibroglandular tissue, and Density D: extreme fibroglandular tissue). Menopausal status was determined based on patient-submitted questionnaires. The most recent genetic testing result was reviewed and used in the dataset, even if it was after the MRI.

Evaluation of qualitative BPE levels for both breasts was performed by three independent breast fellowship-trained radiologists (1: S.L-F., 2: W.M. and 3: S. M.), with eleven, eight and seven years of experience, respectively. BPE evaluation was conducted in accordance with the 5th edition of the American College of Radiology (ACR) Breast Imaging Reporting and Data System (BI-RADS) (12) (BPE: minimal, mild, moderate, and marked). We evaluated BPE with the earliest post-contrast phase of DCE MR images. All three radiologists were blinded to the patient's clinical information and other modality images. The BPE evaluation for each case was chosen from the breast with a higher BPE level. For logistic regression analysis, the BPE threshold was regarded as a mild threshold at the first time point (k_0 = 90s), which means that we regard as the dependent variable "1" when the level of BPE is mild or greater, as described in prior studies (12, 13). Other dichotomized categories, such as moderate or marked BPE compared with minimal or mild BPE, were not considered because of the relatively small number of patients with moderate or marked BPE by minimizing estrogen-dependent BPE level changes. "Dense breast tissue" includes cases with heterogeneous fibroglandular tissue (density C) and extreme fibroglandular tissue (density D). For subjects with multiple MRI exams, the latest exam was included.

Statistical analysis

The Mann-Whitney U test and chi-squared test were used to compare patient demographic information and BPE level. Weighted Kappa statistic was used to assess inter-reader agreement. The propensity score matching (PSM) (14) technique, which attempts to reduce the bias due to confounding variables, was used for analyzing comparisons to adjust covariates, including age, ethnicity, menopausal status, hormonal treatments, and history of bilateral oophorectomy. These covariates were balanced between any two groups to be compared within the strata of the propensity score. Univariate and multiple logistic regression analysis was used to evaluate the relationship between clinical information and BPE levels along with odds ratio (OR) and corresponding 95% confidence interval (CI). For multiple comparisons, the Benjamini-Hochberg False Discovery Rate (FDR) correction (15) was applied within each comparison for overall, premenopausal, and postmenopausal cohorts. All statistical analyses were performed by using software R (version 3.6.3). A p-value of < 0.05 was considered statistically significant.

Results

The final study sample included 954 MRI datasets representing 721 women for Groups 1 – 4 collectively, with 302 MRI exams (211 women) in Group 1, 82 in Group 2 (60 women), 470 in Group 3 (362 women), and 100 in Group 4 (88 women). In Group 1 and Group 2, there were no cases with a history of chest radiation. Therefore, our final dataset was 211 MRIs in Group 1, 60 MRIs in Group 2, 362 MRIs in Group 3, and 88 MRIs in Group 4.

Patient demographic information is summarized in **Table 2** with unmatched and matched PSM. After PSM, patient characteristics (including age, BMI, menopausal status, hormonal

therapy, history of oophorectomy, and ethnicity) were not significantly different between patient groups (p-value = 0.246, 0.429, 0.893, 0.682, 0.973, and 0.268, respectively).

The BPE evaluation in this study exclusively used MRI scans performed for screening purposes rather than diagnostic examination since, for the latter group, MRI scans tend to be reported with higher BI-RADS categorization. In the assessment of BPE, there was substantial agreement among interpreting readers , with an agreement of 73.4% (readers 1 vs. 2;κ = 0.74, 95% confidence interval (CI) = 0.61, 0.88), 70.4% (readers 2 vs. 3; κ = 0.74, 95% confidence interval (CI): 0.71, 0.76), and 71.0% (readers 1 vs. 3; κ = 0.75, 95% confidence interval (CI): 0.62, 0.89).

Table 3 shows the results of the comparison between various combinations of BPE groups for all subjects, premenopausal and postmenopausal women, where the groups were matched by PSM. For all subjects, the BPE level in high-risk women (Groups 1, 2, and 3) and high-risk women without gene mutation (Group 3) was significantly higher compared with non-high-risk women. The BPE level of Group 1 was significantly lower than that of high-risk women without gene mutation (Group 3) and non-gene mutation groups (Group 3 and 4). Gene mutation groups (Groups 1 and 2) had a significantly lower level of BPE compared with non-gene mutation groups (Groups 3 and 4). For premenopausal women, the BPE levels in all gene mutation carriers and *BRCA* mutation carriers alone were significantly lower compared with non-high-risk women. After correcting for the multiple comparisons using Benjamini-Hochberg FDR, significant differences among all patients were found between high-risk women without gene mutation (Group 3) and non-high-risk women (Group 4), as well as between *BRCA* mutation carriers (Group 1) and Group 3, between *BRCA* mutation carriers (Group 1) and non-

gene mutation groups (Group 3 and 4), and between gene mutation groups (Group 1 and 2) and non-gene mutation groups (Group 3 and 4). Similarly, among premenopausal women, significant differences were observed between gene mutation groups (Group 1 and 2) and Group, as well as between Group 1 and Group 4, between Group 1 and Group 3, between Group 1 and non-gene mutation groups (Group 3 and 4), and between gene mutation groups (Group 1 and 2) and non-gene mutation groups (Group 3 and 4). Figure 2 shows representative MR images of two representative premenopausal women from Group 1 and Group 4. Compared with the BPE level of the case of Group 1, that of Group 4 is greater despite of similar patient demographic among them. In all subjects together and in premenopausal women, *BRCA* mutation carriers had significantly lower BPE levels than high-risk women without gene mutations. Figure 3 shows two representative women (Groups 1 and 3) with different BPE levels, both of which have extreme fibroglandular tissue and similar patient demographics. For postmenopausal women, the BPE level in high-risk women without gene mutations was significantly higher than that of non-high-risk women. Representative MR images of two postmenopausal women in Group 3 and Group 4 are shown in **Figure 4**.

Using logistic regression analysis to estimate a high level of BPE (**Table 4**), the univariate analysis demonstrated significant differences in age, menopausal status, history of oophorectomy, breast tissue density, and gene mutations. By multivariate analysis, the odds ratios of having higher BPE were lower in postmenopausal women (OR = 0.39, CI 0.23-0.67) and women with gene mutations (OR = 0.35, CI: 0.23-0.52) and higher in women with dense breast (OR = 2.05, CI:1.37-3.08). In addition, we illustrated logistic regression analysis using a BPE threshold of moderate (**Table 5**). There were less significant differences in both univariate

and multivariate analysis compared to the logistic regression analysis using a BPE threshold of mild.

Discussion

This study analyzed the relationship between BPE level by cancer risk stratification according to genetic testing and lifetime risk as calculated by the Tyrer-Cuzick model, with adjustment for age, hormonal status, BMI, and ethnicity. Our study shows that women with *BRCA* mutations had lower levels of BPE on MRI screening images compared to non-high-risk women. Among premenopausal women, the BPE level of *BRCA* carriers alone and combined with other mutation carriers were lower than that of non-high-risk women. Hence, high levels of BPE seen on MRI images in premenopausal BRCA mutation carriers should be analyzed with greater clinical suspicion of an abnormality. We reported the unadjusted and FDR-corrected p-values since there may be variation in reader opinions on what constitutes a family of hypotheses and the multiple comparison procedure needed.

Through logistic regression analysis, we demonstrated lower BPE levels in gene mutation carriers. This is consistent with a prior study by Grubstein *et al.* (16), which compared BPE levels in *BRCA* mutation carriers and age-matched non-mutation carriers. Differences in BPE levels were hypothesized to be affected by hormonal status. Factors affecting breast cancer subgroups, such as hormone-enriched cancers versus those associated with defective DNA damage repair by homologous recombination, certainly affect preventative strategies (16).

Women at high risk for breast cancer independent of gene mutations tend to have multiple risk factors contributing to a 20% or more lifetime risk per the Tyrer-Cuzick model (11). These factors could include a strong family history of breast or ovarian cancer, dense breast tissue on mammography, hormone exposures, a history of high-dose chest radiation, and a personal history of high-risk lesions (ADH, ALH, and/or LCIS). Given the mix of these various risk factors, a simple analysis of this group is challenging. With high-risk lesions, no prior studies were able to correlate specific morphologic, kinetic, or other imaging features of the lesions with BPE that could predict malignancy upgrade (17–19). Further research is needed to clarify the correlation between high-risk lesions and BPE levels in the future, but this was not the subject of our current project.

Regarding non-high-risk women, the indication for MRI screening varies from patient to patient based on their social background, including their personal preferences (e.g., to avoid radiation).

The peak incidence of breast cancer among women with *BRCA1* mutation is known to occur in women 30-50 years old (20). Based on our results, patients with *BRCA* mutations tend to have lower BPE levels than other risk categories at baseline. MRI images of premenopausal *BRCA* mutation carriers should be carefully considered as more likely to be clinically remarkable when non-mass enhancement is detected, as it is sometimes difficult to clinically distinguish between BPE and NME. Consideration to up-score to BI-RADS category 3 or higher may be warranted.

BPE level is correlated to the vascular supply and permeability of breast parenchyma (21). BPE may affect MRI interpretations, including a higher false-positive rate and higher

biopsy rate in women with elevated BPE (21–23). The level of BPE is affected by serum estrogen concentration (24), both endogenous fluctuations based on menopausal status and exogenous hormonal therapies, and prior breast radiation therapy (25). Tamoxifen, aromatase inhibitors, and a personal history of bilateral oophorectomies reduce the level of BPE (25–28). At our institution, MRI scheduling is advised to be 7-14 days after the onset of the most recent menstrual period in order to minimize increased BPE due to the effects of estrogen. A large study using data from the Breast Cancer Surveillance Consortium demonstrated that BPE is associated with future invasive breast cancer risk independent of breast density. Interestingly, this relationship was not seen between BPE and DCIS (29). In high-risk women, the OR of high BPE to low BPE is 2.1–9 (6,8,9,30). On the other hand, a prior study by Dontchos *et al.* (6) found no relationship between the BPE category and estrogen receptor positivity of breast cancers. In non-mutation carriers, breast tissue with potential malignant transformation is stimulated by a hormone-enriched environment. In *BRCA* mutation carriers, the primary risk for breast cancer is defective DNA damage-repair response. For patients who are in-between risk, the development of cancer is induced by both genetics and environmental factors (16).

There has been a trend in individualized approaches for breast cancer screening and treatment. As an imaging surrogate for the stratified individual risk as a reflection of breast activity, BPE can be a valuable tool for the clinical management of breast cancer. In order to fully realize how BPE fits into the broader picture of such individualized and targeted approaches, further research is warranted to determine the pathophysiological causes of BPE, along with the radiomic and radiogenomic analysis of BPE.

In this study, the OR of the dense breast is associated with a higher degree of BPE by multivariate logistic regression analysis, consistent with a previous study of the significant correlation between breast density and BPE (25). However, there are prior studies that conversely failed to show a significant correlation (31, 32). This conflicting result may be due to differences in study design and patient selection.

Limitations

First, the patient selection may contain a potential bias since not all patients pursued genetic testing, particularly for women with 20% or more lifetime risk (Group 3). Second, the disproportion between minimal or mild BPE (around 70-80%) and moderate and marked BPE (around 20-30%) hinders subgroup analyses due to the limited sample size. This could be related to the fact that the BPE evaluation was a qualitative assessment with a limited dynamic range because MRI for premenopausal women is scheduled during menstrual cycle days 7-14 to minimize the hormonal effects on BPE levels as an institutional guideline. In addition, when breast imaging with asymmetric BPE was observed, we chose a higher level of the breast for our evaluation. This can be further investigated in terms of the relationship between breast risk stratification and asymmetric BPE in future studies. Third, the inter-variation was evaluated by two breast radiologists, with a third breast radiologist resolving any discordance. Therefore, the degree of inter-reader variation may not be fully determined due to a lack of a third independent reader when evaluating BPE levels. Finally, *BRCA1* and *BRCA2* were not analyzed separately in order to focus on a more comprehensive evaluation, although significant differences between them have been reported (33–35).

Conclusion

This study demonstrates the relationship between BPE level and risk stratification. Among high-risk women, in particular premenopausal *BRCA* mutation carriers, BPE levels are typically lower when compared with non-high-risk women.

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Tables

Table 1 Scanning parameters of each breast MRI sequence

Name	Imaging Plane Orientation	Sequence	TR (ms)	TE (ms)	FA (degree)	FOV (mm)	Matrix (read × phase x slices)	Slice thickness (mm)	Spacing between slices (mm)	TA
T1WI	Axial	3D FLASH	6.62	2.91	20°	380	448x448x176	1.1	1.1	2:18
STIR	Axial	STIR-TSE	4000-4950	93	80°	380	384x384x40	4	5.2	3:44-4:37
Dyamic	Axial	3D FLASH	4.14	1.54	10°	380	448x448x176	1.1	1.1	1:35

TR, repetition time; TE, echo time; FA, flip angle; FOV, field of view; TA, acquision time; TSE, turbo spin echo; FLASH, fast low-angle shot; STIR, short tau inversion recovery

Table 2 Patient characteristics

	Original					Propensity Score Matching				
	Group 1+2+3		Group 4			Group 1+2+3		Group 4		
	High risk women (n = 633)		Non-high risk women (lifetime risk ≥ 20%) (n = 88)		*P* Value	High risk women (n = 264)		Non-high risk women (lifetime risk ≥ 20%) (n = 88)		*P* Value
Age (y), mean (range) †	46.1	(21 - 83)	55.3	(30 - 86)	**< 0.0001** *	53.9	(28 - 83)	55.3	(30 - 86)	0.246
BMI	25.2		24.8		0.429	25.6		24.8		0.429
Menopausal Status ‡					**< 0.0001** *					0.893
Pre-Menopausal	388	(61.3%)	25	(28.4%)		79	(29.9%)	25	(28.4%)	
Post-Menopausal	243	(38.4%)	63	(71.6%)		185	(70.1%)	63	(71.6%)	
Unknown	2	(0.3%)	0							
Hormonal Therapy (other than Tamoxifen) ‡					0.379					0.682
Yes	162	(25.6%)	27	(30.7%)		73	(27.7%)	27	(30.7%)	
No	470	(74.2%)	61	(69.3%)		191	(72.3%)	61	(69.3%)	
Unknown	1	(0.2%)	0							
History of Salpingo-oopholectomy ‡					0.745					0.973
Bilateral	101	(16.0%)	16	(18.2%)		51	(19.3%)	16	(18.2%)	
Unilateral	4	(0.6%)	1	(1.1%)		3	(1.1%)	1	(1.1%)	
No	528	(83.4%)	71	(80.7%)		210	(79.5%)	71	(80.7%)	
Ethnicity ‡					0.390					0.268
Ashkenazi Jewish/African American	143	(22.6%)	15	(17.0%)		47	(17.8%)	15	(17.0%)	
Not Above	251	(39.7%)	18	(20.5%)		94	(35.6%)	18	(20.5%)	
Unknown	239	(37.8%)	55	(62.5%)		132	(46.6%)	55	(62.5%)	
Gene mutation ‡					**< 0.0001** *					**< 0.0001** *
BRCA	211	(22.6%)	0	(0%)		76	(28.8%)	0	(0%)	
Other gene mutation	60	(39.7%)	0	(0%)		31	(11.7%)	0	(0%)	
Non-mutation carrier or not tested	362	(37.8%)	88	(100%)		157	(59.5%)	88	(100%)	

BMI, Body Mass Index

* Significant different.

† Mann–Whitney U test is used.

‡ Chi-square test is used.

The number between brackets describes percentage for each group.

Table 3 BPE level by group following Propensity score matching

A All subjects

	Group1+2+3 High-risk women (n = 264)	Group4 Non-high risk women (n = 88)	*P* Value	*Benjamini-Hochberg P* Value
BPE			**0.0462** *	0.0647
Minimal	94 (35.6)	39 (44.3)		
Mild	90 (34.1)	27 (30.7)		
Moderate	61 (23.1)	22 (25.0)		
Marked	19 (7.2)	0 (0.0)		

	Group1+2 Gene mutation carriers (n = 88)	Group4 Non-high risk women (n = 88)	*P* Value	*Benjamini-Hochberg P* Value
BPE			0.1844	0.1844
Minimal	49 (55.68)	39 (44.3)		
Mild	21 (23.86)	27 (30.7)		
Moderate	16 (18.18)	22 (25.0)		
Marked	2 (2.273)	0 (0.0)		

	Group1 BRCA mutation carriers (n = 77)	Group4 Non-high risk women (n = 77)	*P* Value	*Benjamini-Hochberg P* Value
BPE			0.1432	0.1671
Minimal	37 (48.05)	32 (41.56)		
Mild	21 (27.27)	25 (32.47)		
Moderate	15 (19.48)	20 (25.97)		
Marked	4 (5.195)	0 (0)		

	Group3 High-risk women without gene mutation (n = 88)	Group4 Non-high risk women (n = 88)	*P* Value	*Benjamini-Hochberg P* Value
BPE			**0.0157** *	**0.0275** *
Minimal	24 (27.3)	39 (44.3)		
Mild	33 (37.5)	27 (30.7)		
Moderate	25 (28.4)	22 (25.0)		
Marked	6 (6.8)	0 (0.0)		

	Group1 BRCA mutation carriers (n = 140)	Group3 High-risk women without gene mutation (n = 140)	*P* Value	*Benjamini-Hochberg P* Value
BPE			**0.0003** *	**0.0008** *
Minimal	54 (38.6)	26 (18.6)		
Mild	45 (32.1)	54 (38.6)		
Moderate	35 (25.0)	40 (28.6)		
Marked	6 (4.3)	20 (14.3)		

	Group1 BRCA mutation carriers (n = 155)	Group3+4 women without gene (n = 155)	*P* Value	*Benjamini-Hochberg P* Value
BPE			**0.0001** *	**0.0004** *
Minimal	68 (43.9)	33 (21.3)		
Mild	46 (29.7)	57 (36.8)		
Moderate	35 (22.6)	47 (30.3)		
Marked	6 (3.9)	18 (11.6)		

	Group1+2 gene mutation carriers (n = 208)	Group3+4 women without gene (n = 208)	*P* Value	*Benjamini-Hochberg P* Value
BPE			**0.0001** *	**0.0004** *
Minimal	89 (42.8)	49 (23.6)		

B Premenopausal women

	Group1+2+3 High-risk women (n = 79)	Group4 Non-high risk women (n = 25)	*P* Value	*Benjamini-Hochberg P* Value
BPE			0.1675	0.1954
Minimal	19 (24.05)	5 (20.0)		
Mild	24 (30.38)	8 (32.0)		
Moderate	25 (31.65)	12 (48.0)		
Marked	11 (13.92)	0 (0.0)		

	Group1+2 Gene mutation carriers (n = 29)	Group4 Non-high risk women (n = 25)	*P* Value	*Benjamini-Hochberg P* Value
BPE			**0.0307 ***	**0.0430 ***
Minimal	14 (48.28)	5 (20.0)		
Mild	8 (27.59)	8 (32.0)		
Moderate	5 (17.24)	12 (48.0)		
Marked	2 (6.897)	0 (0.0)		

	Group1 BRCA mutation carriers (n = 36)	Group4 Non-high risk women (n = 24)	*P* Value	*Benjamini-Hochberg P* Value
BPE			**0.0094 ***	**0.0164** *
Minimal	16 (44.44)	4 (16.67)		
Mild	10 (27.78)	8 (33.33)		
Moderate	6 (16.67)	12 (50)		
Marked	4 (11.11)	0 (0)		

	Group3 High-risk women without gene mutation (n = 25)	Group4 Non-high risk women (n = 25)	*P* Value	*Benjamini-Hochberg P* Value
BPE			0.3301	0.3301
Minimal	5 (20.0)	5 (20.0)		
Mild	8 (32.0)	8 (32.0)		
Moderate	9 (36.0)	12 (48.0)		
Marked	3 (12.0)	0 (0.0)		

	Group1 BRCA mutation carriers (n = 112)	Group3 High-risk women without gene mutation (n = 109)	*P* Value	*Benjamini-Hochberg P* Value
BPE			**0.0002** *	**0.0007** *
Minimal	41 (36.6)	14 (12.8)		
Mild	37 (33.0)	45 (41.3)		
Moderate	28 (25.0)	33 (30.3)		
Marked	6 (5.4)	17 (15.6)		

	Group1 BRCA mutation carriers (n = 105)	Group3+4 women without gene (n = 111)	*P* Value	*Benjamini-Hochberg P* Value
BPE			**0.0003 ***	**0.0007** *
Minimal	39 (37.1)	14 (12.6)		
Mild	34 (32.4)	45 (40.5)		
Moderate	26 (24.8)	37 (33.3)		
Marked	6 (5.7)	15 (13.5)		

	Group1+2 gene mutation carriers (n = 139)	Group3+4 women without gene (n = 138)	*P* Value	*Benjamini-Hochberg P* Value
BPE			**0.0001 ***	**0.0002** *
Minimal	50 (36.0)	17 (12.3)		

C Postmenopausal women

	Group1+2+3 High-risk women (n = 185)	Group4 Non-high risk women (n = 63)	*P* Value	*Benjamini-Hochberg P* Value
BPE			0.1450	0.3383
Minimal	75 (40.54)	34 (54.0)		
Mild	66 (35.68)	19 (30.2)		
Moderate	36 (19.46)	10 (15.9)		
Marked	8 (4.324)	0 (0.0)		

	Group1+2 Gene mutation carriers (n = 59)	Group4 Non-high risk women (n = 63)	*P* Value	*Benjamini-Hochberg P* Value
BPE			0.5895	0.6878
Minimal	35 (59.32)	34 (54.0)		
Mild	13 (22.03)	19 (30.2)		
Moderate	11 (18.64)	10 (15.9)		
Marked	0 (0)	0 (0.0)		

	Group1 BRCA mutation carriers (n = 41)	Group4 Non-high risk women (n = 53)	*P* Value	*Benjamini-Hochberg P* Value
BPE			0.6616	0.6616
Minimal	21 (51.22)	28 (52.83)		
Mild	11 (26.83)	17 (32.08)		
Moderate	9 (21.95)	8 (15.09)		
Marked	0 (0)	0 (0)		

	Group3 High-risk women without gene mutation (n = 63)	Group4 Non-high risk women (n = 63)	*P* Value	*Benjamini-Hochberg P* Value
BPE			**0.0239 ***	0.1672
Minimal	19 (30.2)	34 (54.0)		
Mild	25 (39.7)	19 (30.2)		
Moderate	16 (25.4)	10 (15.9)		
Marked	3 (4.8)	0 (0.0)		

	Group1 BRCA mutation carriers (n =28)	Group3 High-risk women without gene mutation (n = 30)	*P* Value	*Benjamini-Hochberg P* Value
BPE			0.3676	0.5146
Minimal	13 (46.4)	11 (36.7)		
Mild	8 (28.6)	9 (30.0)		
Moderate	7 (25.0)	7 (23.3)		
Marked	0 (0.0)	3 (10.0)		

	Group1 BRCA mutation carriers (n = 50)	Group3+4 women without gene (n = 44)	*P* Value	*Benjamini-Hochberg P* Value
BPE			0.1892	0.3311
Minimal	29 (58.0)	19 (43.2)		
Mild	12 (24.0)	12 (27.3)		
Moderate	9 (18.0)	10 (22.7)		
Marked	0 (0.0)	3 (6.8)		

	Group1+2 gene mutation carriers (n = 69)	Group3+4 women without gene (n = 70)	*P* Value	*Benjamini-Hochberg P* Value
BPE			0.1138	0.3983
Minimal	39 (56.5)	32 (45.7)		
Mild	15 (21.7)	18 (25.7)		

Table 4 Logistic regression analysis to predict BPE level using a BPE threshold of mild

Factors	Univariate analysis				Multivariate analysis			
	Coefficient	OR	(95% CI)	*P* value	Coefficient	OR	(95% CI)	*P* value
Age	-0.04	0.96	(0.95 - 0.97)	**<0.0001** *	-0.01	0.99	(0.97 - 1.01)	0.370
BMI	-0.02	0.98	(0.95 - 1.01)	0.192	0.04	1.04	(1.00 - 1.08)	0.045
Ashkenazi Jewish or African American	-0.01	1.01	(0.88 - 1.17)	0.855	-0.01	0.99	(0.85 - 1.15)	0.903
Menopause	-1.22	0.30	(0.21 - 0.41)	**<0.0001** *	-0.94	0.39	(0.23 - 0.67)	**<0.0001** *
Hormonal Therapy (other than tamoxifen)	0.27	1.31	(0.91 - 1.90)	0.155	0.02	1.02	(0.68 - 1.55)	0.913
No History of Bilateral Salpingo-oophorectomy	1.22	3.39	(2.28 - 5.08)	**<0.0001** *	0.02	1.02	(0.60 - 1.72)	0.944
Dense Breast	0.93	2.53	(1.83 - 3.51)	**<0.0001** *	0.72	2.05	(1.37 - 3.08)	**<0.0001** *
Gene mutation	-1.00	0.37	(0.26 - 0.51)	**<0.0001** *	-1.05	0.35	(0.23 - 0.52)	**<0.0001** *
BRCA gene mutation	-0.90	0.41	(0.30 - 0.57)	**<0.0001** *				
Other gene mutation	-0.57	0.57	(0.33 - 0.98)	**0.040** *				

BMI; body mass index, OR; odds ratio, BPE: background parenchymal enhancement, *BRCA*; BReast CAncer

BPE threshold $\geqq$ mild threshold at first timepoint ($k_0 = 90s$)

* Significantly different.

Table 5 Logistic Regression Analysis of Odds Ratio (OR) for Clinical Factors using a BPE threshold of moderate

Factors	Univariate analysis				Multivariate analysis			
	Coefficient	OR	(95% CI)	*P* value	Coefficient	OR	(95% CI)	*P* value
Age	-0.05	0.95	(0.9 - 0.97)	**<0.001** *	-0.02	0.98	(1 - 1.01)	0.22
Ashkenazi Jewish	-0.22	0.80	(0.5 - 1.31)	0.38	-0.29	0.75	(0.4 - 1.28)	0.30
Menopause	-1.34	0.26	(0.2 - 0.41)	**<0.001** *	-0.68	0.51	(0.2 - 1.10)	0.09
Hormonal Therapy (other than tamoxifen)	0.76	2.14	(1.38 - 3.32)	**<0.001** *	0.32	1.37	(0.8 - 2.23)	0.20
History of Bilateral Salpingo-oophorectomy	-1.22	0.30	(0.17 - 0.50)	**<0.001** *	-0.23	0.79	(0.4 - 1.64)	0.53
Dense Breast	1.03	2.79	(1.78 - 4.47)	**<0.001** *	0.62	1.85	(1.1 - 3.09)	**0.02** *
BRCA gene mutation	-0.34	0.71	(0.46 - 1.09)	0.12	-0.39	0.68	(0.4 - 1.31)	0.24
Other gene mutation	0.66	1.93	(1.14 - 3.22)	**0.01** *	0.42	1.53	(0.7 - 3.14)	0.25

BMI; body mass index, OR; odds ratio, BPE: background parenchymal enhancement, *BRCA* ; BReast CAncer

BPE threshold $\geqq$ moderate threshold at first timepoint ($k_0 = 90s$)

* Significantly different.

Figure Legends

Figure 1. Flowchart of the patient selection for the study.

Figure 2. Representative MR images of a premenopausal woman in Group 1 (top) and Group 3 (bottom). Early phase fat-suppressed T1-weighted contrast-enhanced breast MRI (A) and maximum intensity projection (MIP) image (B) in a 38-year-old *BRCA1* positive woman (Group 1) who is non-Ashkenazi Jewish, non-African American, premenopausal, without prior history of hormonal therapy, without prior bilateral oophorectomies, and with normal range BMI (20.08). BPE level is minimal, and FGT level is extreme fibroglandular tissue. Early phase fat-suppressed T1-weighted contrast-enhanced MRI (C) and MIP image (D) in a 34-year-old woman with a lifetime risk of 22.9% using the Tyrer-Cuzick model (Group 3) who is a non-Ashkenazi Jewish, non-African American, premenopausal, without prior history of hormonal therapy, without prior bilateral oophorectomies, and with normal range BMI (21.26). BPE level is marked and FGT level is extreme fibroglandular tissue, although the demographics of the two patients are similar to each other.

Figure 3. Representative MR images of a postmenopausal woman in Group 3 (top) and Group 4 (bottom). Early phase fat-suppressed T1-weighted contrast-enhanced breast MRI (A) and maximum intensity projection (MIP) image (B) in a 62-year-old woman with a lifetime risk of 36.0% using the Tyrer-Cuzick model (Group3), whose ethnicity is unknown, and who is postmenopausal, without prior history of hormonal therapy, without prior bilateral oophorectomies, and with overweight range BMI (27.76). BPE level is marked, and FGT level is heterogeneously dense fibroglandular tissue. Early phase fat-suppressed T1-weighted contrast-enhanced breast MRI (C) and MIP image (D) in a 59-year-old woman with a lifetime risk of 19.0% using the Tyrer-Cuzick model (Group4), whose ethnicity is unknown, and who is postmenopausal, without prior history of hormonal therapy, without prior bilateral oophorectomies, and with overweight range BMI (25.18). BPE level is minimal, and FGT level is heterogeneously dense fibroglandular tissue, although the demographics of the two patients are similar to each other.

Figure 4. Representative MR images of a premenopausal woman in Group 1 (top) and Group 4 (bottom). Early phase fat-suppressed T1-weighted contrast-enhanced breast MRI (A) and maximum intensity projection (MIP) image (B) in a 27 year-old BRCA1 positive woman (Group1), who is non-Ashkenazi Jewish, non-African American, premenopausal, without prior history of hormonal therapy, without prior bilateral oophorectomies, and with normal range BMI (19.31). BPE level is minimal, and FGT level is extreme fibroglandular tissue. Early phase fat-suppressed T1-weighted contrast-enhanced breast MRI (C) and MIP image (D) in a 39 year-old woman with a lifetime risk of 17.4 using the Tyrer-Cuzick model (Group4), who is non-Ashkenazi Jewish, non-African American, premenopausal, without prior history of hormonal therapy, without prior bilateral oophorectomies, and with normal range BMI (20.00). BPE level is moderate and FGT level is extreme fibroglandular tissue, although the demographics of the two patients are similar to each other.