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Original

Factors Influencing Background Parenchymal Enhancement on Breast MRI Classified by Mammographic Density

Natsuko Kunimatsu[1], Akira Kunimatsu[2], Yoshihiro Uchida[3], Sachiko Inano[4] and Shigeru Nawano[1]

1 Department of Radiology, International University of Health and Welfare, Mita Hospital, 1-4-3 Mita, Minato-ku, Tokyo 108-8329, Japan
2 Department of Radiology, Graduate School of Medicine, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8655, Japan
3 Breast Center, International University of Health and Welfare, Mita Hospital, 1-4-3 Mita, Minato-ku, Tokyo 108-8329, Japan
4 Department of Radiology, Sanno Hospital, 8-10-16 Akasaka, Minato-ku, Tokyo 107-0052, Japan

Abstract

Background: Mammographic dense breast or high background parenchymal enhancement (BPE) in magnetic resonance imaging (MRI) hinders diagnostic accuracy for breast tumor detection. We retrospectively investigated relationship between BPE on MRI and mammographic densities along with the influential factors.

Methods: Our study included 144 Japanese women who underwent both mammography and breast MRI using a 3T unit. The subjects were classified into either mammographically dense group or fatty group, then further categorized into 4 subgroups by the degree of BPE (minimal, moderate, mild, marked) on enhanced MRI. As influential factors, their ages, menopausal status, and experience of lactation were statistically investigated.

Results: 73.8% of mammographically dense group showed minimal or mild BPE on the breast MRI. Women with minimal BPE in the mammographically dense group were significantly older than those with mild and marked BPE. In the mammographically fatty group, women with minimal BPE were significantly older than those with moderate BPE. Also, significant differences of BPE were shown between menopausal and premenopausal women in both mammographic groups, but experience of lactation did not influence BPE.

Conclusion: BPE on MRI is considered to be affected by age and menopausal status, not by breast-feeding experience, regardless of the mammographic density.

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Corresponding author:
Natsuko Kunimatsu
Department of Radiology, International University of Health and Welfare, Mita Hospital, 1-4-3 Mita, Minato-ku, Tokyo 108-8329, Japan
Tel: +81-3-3451-8121
E-mail: idanatsu-tky@umin.ac.jp

Introduction

A dense breast not only reduces the sensitivity of mammography but also is a moderate independent risk factor for breast cancer.[1-3] Asian females have the tendency of presenting with dense breast tissue on mammography compared with other ethnic groups.[4-6] Consequently, with mammography, detection of a mass is difficult in some cases with dense breast tissue. In addition, the risk of breast cancer in women with mammographically dense breasts is three to five times higher than that in women with mammographically fatty breasts.[1,7-10] Magnetic resonance imaging (MRI) can differentiate tissues and visualize breast lesions largely based on the enhancement patterns after the intravenous administration of contrast materials. Background parenchymal enhancement (BPE) on MRI will markedly influence the accuracy of breast cancer diagnosis, as the density of fibroglandular tissue of the breast acts in the same way as in mammography.[11] Breast tissue density on mammograms is classified into four categories: almost entirely fatty, scattered fibroglandular tissue, heterogeneously dense, and extremely dense.[12] In a similar fashion, normal BPE of MRI is also categorized as minimal (<25% of glandular tissue demonstrating enhancement), mild (25-50% enhancement), moderate (50-75% enhancement), or marked (>75% enhancement).[12-16]

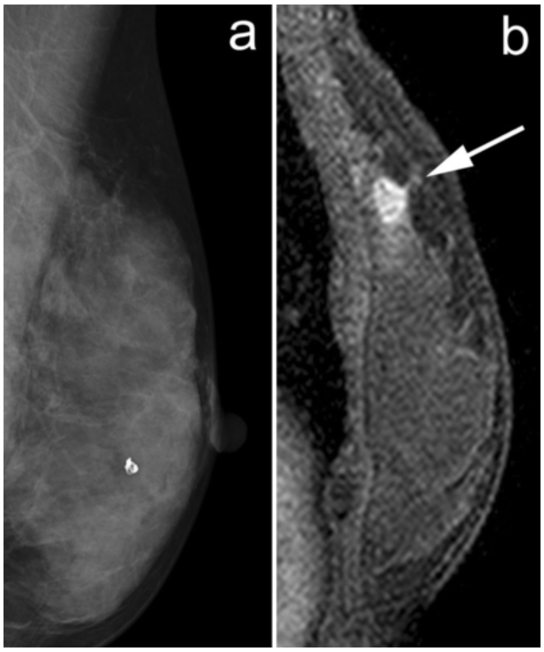

Fig. 1 Mammogram (a) and MRI (b) of a 73-year-old woman with a breast cancer
a. Mammogram of medio-lateral oblique view shows heterogeneously dense breast, but a mass is not detectable.
b. Sagittal MRI reveals a clearly-enhanced mass (arrow) in fibroglandular tissue because of the minimal background parenchymal enhancement.

Although both the mammographic density and BPE of MRI similarly influence the diagnostic accuracy, we often see patients who show dense breasts on mammography but their BPE on MRI is not so marked (Fig. 1). In such cases, breast MRI can be very effective to detect breast lesions. We considered that knowledge on factors that exert an influence on BPE of MRI in patients showing dense breasts on mammography will help select candidates for whom breast MRI should be recommended after mammography. It has been reported that the age, menstrual or menopausal status, and hormone replacement therapy may affect fibroglandular tissue enhancement in the breasts.[17] However, to our knowledge, few attempts have been made to clarify the correlation between BPE on MRI and the mammographic density, even though such information is necessary to reasonably choose the examination process for the detection of breast lesions.

In this study, we investigated factors influencing BPE on MRI in Japanese women with mammographic findings, by analyzing factors regarding the age, menopausal status, and lactation (breast-feeding) experience.

Materials and methods

Patients

This study was approved by the institutional review board of our hospital as a retrospective study.

We conducted a retrospective review of contrast-enhanced bilateral breast MRI findings of 180 consecutive female patients between January 2013 and March 2014. Among the 180 subjects, we selected 144 who underwent bilateral mammography and had records of the menopausal status and presence or absence of lactation experience, and had no history of chemotherapy or mammoplasty. MRI was conducted due to screening for high cancer-risk patients (n = 2), abnormal nipple discharge (n = 5), problem solving for category 3 of mammogram or ultrasound examination (n = 88), or disease extent evaluation of known malignancy (n = 49).

Mammography technique

Mammographic acquisition, practice, apparatus, and interpretation methods followed the guidelines of the Japan Central Organization on Quality Assurance of Breast Cancer Screening. We used a digital radiography system for mammography which incorporated a flat panel detector system (Selenia Dimensions, Hologic, MA, USA). All patients underwent mediolateral oblique imaging. In many subjects, craniocaudal imaging was also conducted. Mammograms were obtained irrespective of the patient menstrual cycles because information on the menstrual cycles was not available on the medical records.

Breast MRI technique

All breast MRI examinations were acquired with a 3.0T whole-body scanner (Achieva 3T TX, Philips, the Netherlands) with the patients in a prone position using a dedicated breast coil (SENSE-Breast 7 TX). The MR imaging protocols included the following: T2-weighted fat-suppressed imaging (TR/TE, 4095–4838/62–63 ms; slice thickness, 2.2 mm; interslice gap, 0.5 mm; reconstructed voxel size, 0.59 × 0.59 × 5.0 mm, field of view, 30 cm; acquisition matrix, 420 × 318), diffusion-weighted imaging (TR/TE, 6500/65 ms; slice thickness, 5 mm; interslice gap, 1 mm; acquisition matrix, 92 × 119; 0 and 1,000 s/mm^2 of b values), and coronal, dynamic, fat suppressed 3D T1-weighted imaging for the bilateral breasts with enhanced T1 high resolution isotropic volume excitation (eTHRIVE) (TR/TE, 3.1/ 1.1 ms; field of view, 30 cm; slice thickness, 1.0 mm; acquisition matrix, 384 × 288 or 408 × 286; reconstructed voxel size, 0.39 × 0.39 × 1.0 mm), before, 1 minute after, and 8 minutes after a rapid intravenous bolus injection of 0.1 mmol/L gadopentetate dimeglumine (Magnevist, Bayer Healthcare Pharmaceuticals, Montville, NJ, USA) per kilogram body weight. A postcontrast sagittal 3D T1-weighted turbo field echo imaging with fat-suppression for the bilateral breasts (TR/TE, 3.1–4.0/1.1–2.1 ms; field of view, 22 cm; slice thickness, 0.8 mm; acquisition matrix, 288 × 259; reconstructed voxel size, 0.43 × 0.43 × 0.8 mm) was also acquired at approximately 4 minutes (for the right breast) and 6 minutes (for the left breast) after intravenous injection of the contrast media. MR images were obtained irrespective of the patient menstrual cycles as were mammograms.

Image evaluation of breast MRI and mammography

We retrospectively reviewed mammograms and classified the density of the fibroglandular tissue into four categories (almost entirely fatty, scattered fibroglandular tissue, heterogeneously dense, and extremely dense) according to the Japan Central Organization of Quality Assurance of Breast Cancer Screening and Breast Imaging Reporting and Data System (BI-RADS) criteria,[12] and also classified BPE of breast MRI into four categories (minimal, mild, moderate, and marked) in accordance with BI-RADS and previous reports.[12,14,16,18] We used the coronal images and three-dementional images of maximum intensity projection on the arteral phase with the center of k-space at 1 minute after the initiation of contrast injection. Two experienced radiologists certified by the Japan Central Organization of Quality Assurance of Breast Cancer Screening (both radiologists) and by the Japanese Breast Cancer Society (one radiologist) independently assessed the imaging findings and categorized them.

The reproducibility of the inter-rater agreement of mammography and breast MRI was calculated by using kappa and weighted kappa statistics. The classification of BPE on breast MRI and mammography was determined by agreement when the diagnoses were inconsistent.

Study design and statistical measurements

First, we separated the patients into two groups by the mammographic density. The dense group (103 of 144 patients) showed either heterogeneously dense or extremely dense fibroglandular tissue on mammography. The fatty group (41 of 144 patients) showed either almost entirely fatty or scattered fibroglandular tissue. Second, the two mammographically separated groups were classified into four BPE types (minimal, mild, moderate, and marked) based on the interpreted findings on the enhanced MRI. To investigate factors of the age, menopausal status, and experience of lactation, both groups were statistically analyzed.

To assess the association between the age and BPE, the Shapiro-Wilk test was used for both groups to check the normal distribution model. Then, analysis of variance using Welch's method was performed. We also used a post-hoc test (Games-Howell multiple comparison procedure) to evaluate the association between the age and BPE of MRI in both groups.

To assess the influence of menopausal status on BPE, Fisher's exact test was used for both groups separately. To assess the influence of lactation experience on BPE, we also used Fisher's exact test.

In addition, we separated the 2 mammographic density groups into 4 subgroups based on the combination of the menopausal status (menopause or pre-menopause) and lactation experience (lactation and non-lactation): (A: menopause and lactation; B: menopause and non-lactation; C: pre-menopause and lactation; D: pre-menopause and non-lactation). Then, Fisher's exact test was used to analyze whether these 4 subgroups showed differences in BPE in the mammographically dense and fatty groups. Four combinations were compared (A and B, A and C, B and D, C and D) with Fisher's exact test; then, Bonferroni correction for multiple comparisons, which defined a significant difference between the groups if the test showed a p-value less than 0.0125 (= 0.05/4).

All statistical analyses were performed using R (version 3.1. 0, The R Foundation of Statistical Computing, Vienna, Austria).

Results

Inter-rater agreement

The calculated results of the kappa and weighted kappa statistics of inter-rater agreement between the two radiologists for the classification of tissue density on mammograms were 0.93 and 0.99, respectively, and those of BPE on MRI were 0.85 and 0.98, respectively.

The rate of BPE on MRI classified by mammographical density

The ratios of BPE on MRI classified by the mammographical density are summarized in Table 1, 2 and Fig. 2. The majority of the mammographically

Table 1 Numbers and mean age of women with mammographically dense fibroglandular breast tissue classified by the degree of background parenchymal enhancement (BPE) on MRI (n=103).

BPE	Rates (%) (n)	Mean age (years)
Minimal	38.8 (40)	52.7
Mild	35.0 (36)	43.3
Moderate	12.6 (13)	43.6
Marked	13.6 (14)	42.6

Table 2 Numbers and mean age of women with mammographically fatty fibroglandular breast tissue classified by BPE on MRI (n=41).

BPE	Rates (%) (n)	Mean age (years)
Minimal	43.9 (18)	60.3
Mild	43.9 (18)	51.9
Moderate	12.2 (5)	45.4
Marked	0 (0)	0

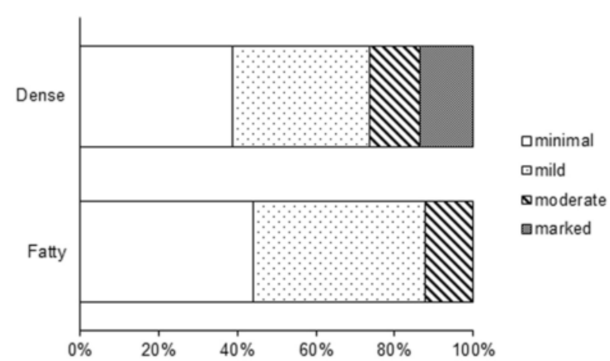

Fig. 2 Rates of each category of BPE on MRI in mammographically dense and fatty groups.

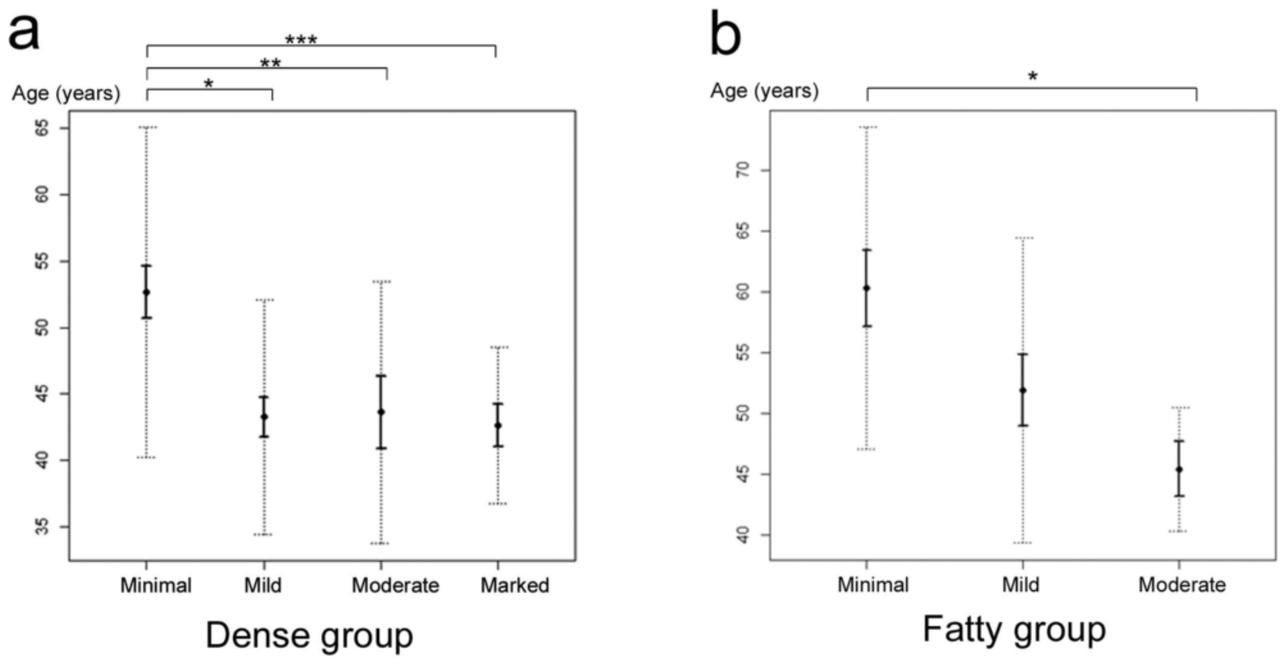

Fig. 3 Mean age (dots), standard deviations (solid lines) and age ranges (dotted lines) of the mammographically dense (a) and fatty (b) group classified by BPE. In the dense group, subjects with minimal BPE had a significantly older age than those with mild ($p = 0.0015$, *) or marked ($p=0.0013$, ***) BPE. Also, subjects with minimal BPE were older than those with moderate BPE, although the difference was not significant ($p=0.0573$, **). In the fatty group, Subjects with minimal BPE were significantly older than those with moderate BPE ($p=0.0031$).

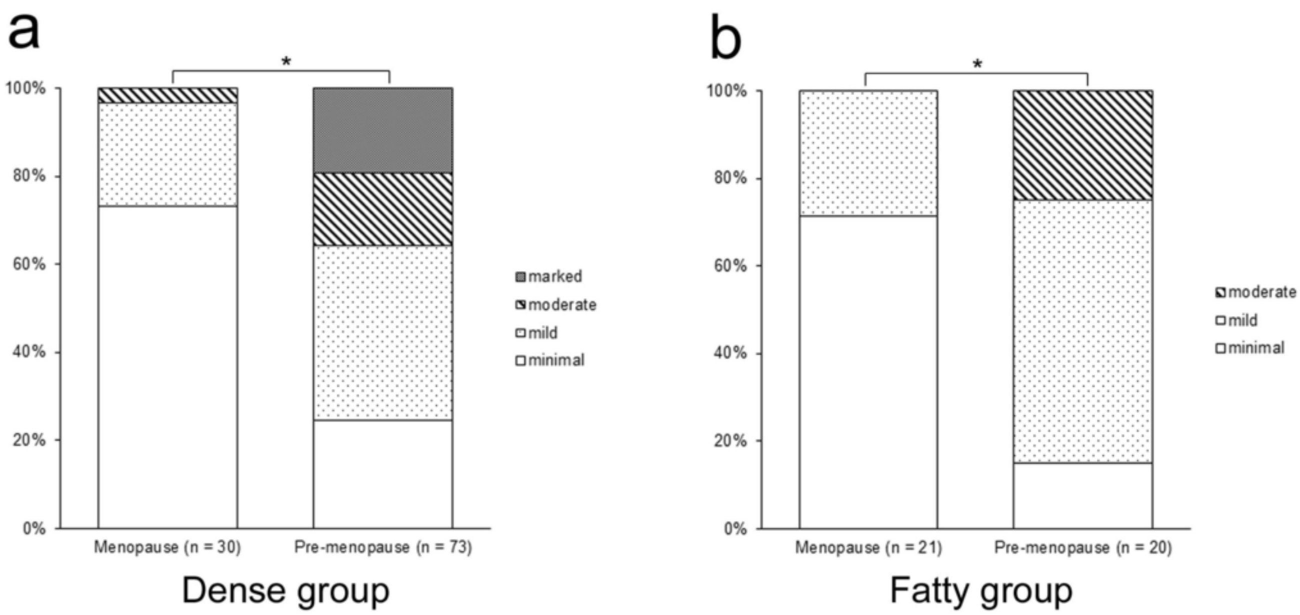

Fig. 4 Influence of the menopausal status upon BPE in the mammographically dense (a) and fatty (b) groups. There were statistically significant differences (*: $p<0.0001$ in the figure 4a, *: $p=0.0004$ in the figure 4b) between the premenopausal and menopausal groups using Fisher's exact test.

dense group showed minimal (38.8%) or mild (35.0%) BPE on MRI, and 12.6% of the group showed moderate and 13.6% showed marked BPE. This result indicates that the enhanced breast MRI may be useful for 73.8% of patients who showed heterogeneously dense breasts on mammograms, considering the possibility of the detection of masses which are likely to be obscured by dense normal fibroglandular tissue on mammograms.

Age factor

The mean ages, number and percentage of subjects in each BPE classification by the mammographic density group are shown in Tables 1 and 2. The mean age (dots), standard errors (solid lines), and standard deviations (dotted lines) of each BPE classification in the mammographically dense group are plotted in Figure 3a. Subjects with minimal BPE in the mammographically dense group had a significantly older age

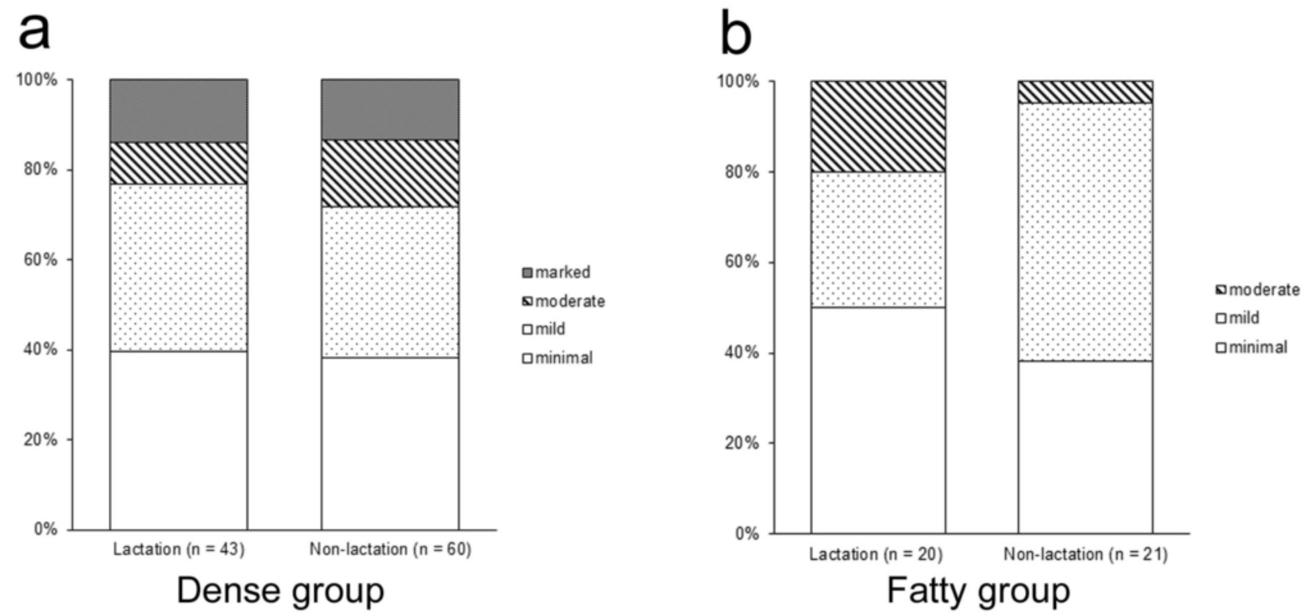

Fig. 5 Influence of lactation experience on the degree of BPE in the mammographically dense (a) and fatty (b) groups. Lactation experience did not influence the BPE in either group (p=0.8838 for the mammographically dense group and p=0.1653 for the mammographically fatty group) using Fisher's exact test.

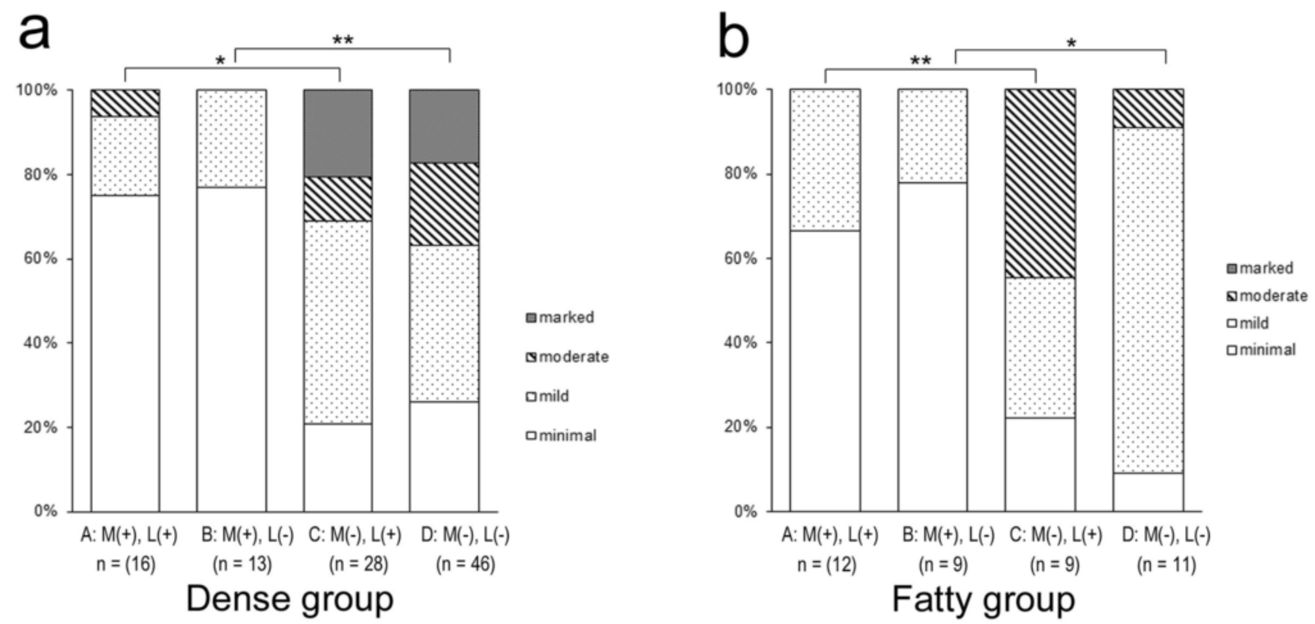

Fig. 6 Mammographically dense and fatty groups were further classified into 4 subgroups (A: post-menopause, lactation; B: post-menopause, non-lactation; C: pre-menopause, lactation; D: pre-menopause, non-lactation). The 4 subgroups were compared regarding the degree of BPE on MRI. The status of menopause significantly affected the degree of BPE in both dense and fatty groups (dense group: differences between A and C: *p=0.0029; B and D: **p=0.0075 in the figure 6a) (fatty group: difference between B and D: *p=0.0045 in the figure 6b). In subjects with lactation experience in the fatty group, the menopausal status mildly affected the degree of BPE (difference between A and C: **p=0.031 in the figure 6b).

(mean age = 52.7) than those with mild BPE (mean age = 43.3 years, p = 0.0015), or marked BPE (mean age = 42.6 years, p = 0.0013). The statistically significant difference was not seen between the minimal BPE and moderate BPE subjects, though a similar tendency was seen for the moderate BPE subjects (mean age = 43.6 years, p = 0.0573) (Fig. 3a).

In the mammographically fatty group, subjects with minimal BPE showed a significantly older age (mean age = 60.3 years) than those with moderate BPE (mean age = 45.4 years, p = 0.0031) (Fig. 3b).

Menopausal status

The rates of each BPE classification were significantly different between menopausal and premenopausal subjects in both mammographically dense and fatty groups (Fig. 4a and 4b) based on Fisher's exact test (2 × 4) (dense group; $p<0.0001$, fatty group; $p = 0.0004$). The menopausal group showed a tendency toward a lower BPE regardless of the mammographical density.

Experience of lactation

Fig. 5a and 5b represent the influence of lactation experience on BPE in the mammographically dense (Fig. 5a) and fatty (Fig. 5b) groups. Experience of lactation did not show a significant influence on the degree of BPE in either group (dense group: $p = 0.8838$; fatty group: $p = 0.1653$).

Comparison of 4 subgroups by combination of menopausal status and lactation experience

We subcategorized the mammographically dense and fatty groups into 4 types: (A: menopause and lactation; B: menopause and non-lactation; C: premenopause and lactation; D: premenopause and non-lactation) (Fig. 6a and 6b). The numbers of subjects in groups A to D were 16, 13, 28, and 46 in the dense group (Fig. 6a) and 12, 9, 9, and 11 in the fatty group (Fig. 6b), respectively. The results showed that only the menopausal status significantly affected the degree of BPE in both groups (dense group: difference between subgroups A and C: $p = 0.0029$; B and D: $p = 0.0075$, fatty group: difference between B and D: $p = 0.0045$). In the subgroups with lactation experience in the fatty group, the menopausal status mildly affected the degree of BPE (difference between A and C: $p = 0.031$) (Fig. 6b).

Discussion

We investigated the associations among BPE on MRI, age, menopausal status, and lactation experience by the mammographic breast density in Japanese women. Our results showed that the subjects with minimal BPE in the mammographically dense group were significantly older than those with mild, moderate, or marked BPE. Also, subjects with minimal BPE in the mammographical fatty group were significantly older than those with moderate BPE.

Although the majority of the mammographically dense group showed minimal (38.8%) or mild (35.0%) BPE on MRI, 12.6% of the dense group showed moderate and 13.6% showed marked BPE. This indicates that contrast-enhanced breast MRI diagnosis will be useful for 73.8% of women who show dense or heterogeneously dense breasts on mammography for the detection of a lesion likely to be obscured by fibroglandular tissue on mammography, because enhanced MRI can differentiate tumor from fibroglandular tissue.

Mean ages of minimal, mild, moderate, and marked BPE women who showed dense or heterogeneously dense breasts on mammography were 52.7, 43.3, 43.6 and 42.6 years old, respectively, with a significantly older age in the minimal BPE subjects compared with the others. Namely, younger women show a tendency to have more strongly-enhanced fibroglandular tissues of the breasts, as reported previously.[13,16,19–22] The menopausal status has been reported to markedly contribute to the contrast enhancement of normal breast parenchyma. King V et al. reported that BPE and fibroglandular tissue shown on MRI decreased after menopause in significant numbers of women, and that the decrease of BPE was greater than that of fibroglandular tissue.[22] Our results basically agree with theirs.

Post-menopausal women who show dense or heterogeneously dense breasts on mammography have a tendency toward exhibiting lower BPE than younger women. Therefore, considering the detectability of a mammographically obscured lesion, it is reasonable to recommend additional MRI for women with equivocal mammographic findings, especially for post-menopausal women who show dense breasts on mammography.

In the mammographically fatty breast group, subjects with minimal, mild, moderate, and marked enhancement comprised 43.9, 43.9, 12.2, and 0%, respectively. For the 87.8% of subjects showing scattered fibroglandular densities in mammography (fatty breast group), enhanced breast MRI is also thought to be useful, in the same manner as those with mammographically dense or heterogeneous dense breast (dense breast group). The mean ages of women with minimal, mild, and moderate enhancement in the mammographically fatty group were 60.3, 51.9, and 45.4 years old, respectively, with a significant difference between the mean ages of those with minimal and mild enhancement. This indicates that older women who show scattered fibroglandular densities or fatty breasts on mammograms also show a tendency toward lower-level enhancement on breast MRI, so breast MRI is considered useful.

Breast tissues consist of fibroglandular tissue and fat. The appearance of the breast on mammograms is directly related to its fat content.[23] The rate of the density associated with fibroglandular tissue in the whole breast is referred to as the "mammographic density". The fibroglandular tissue is a mixture of fibrous connective tissue (the stroma) and functional (or glandular) epithelial cells that line the ducts of the breast (the parenchyma). Fat has a lower X-ray attenuation coefficient than fibroglandular tissue; therefore, it is more transparent to X-rays. Thus, we can recognize the differences in the densities of fibroglandular tissue and fat on mammograms.[15] The pattern of brightness on mammographic images are relative on the amount or ratio of fibroglandular tissue and fat.[15]

In this study, we used the classification of the mammographic density based on the breast composition illustrations from "BI-RADS 2013" as fatty (the breasts are almost entirely fatty), scattered fibroglandular tissue (there are scattered areas of fibroglandular density), heterogeneously dense (the breasts are heterogeneously dense, which may obscure small masses), and extremely dense (the breasts are extremely dense, which lowers the sensitivity of mammography).[12]

Examinations of Japan Central Organization of Quality Assurance of Breast Cancer Screening are also conducted according to this classification.

Similar to the breast density on mammograms, for normal breast tissues, the amount of fibroglandular tissues can be evaluated on breast MRI and the degree of BPE is observed after contrast material administration. BI-RADS stated that the four categories of breast composition (almost entirely fat, scattered fibroglandular tissue, heterogeneous fibroglandular tissue, and extreme fibroglandular tissue) are defined by the visually estimated content of fibroglandular tissue within the breasts in both mammography and breast MRI. Fibroglandular tissue can be distinguished from fat based on differences in the signal intensity on MRI. It would also be a challenge to identify differences in the kinetics of vascular flow in tissue with MRI after injection of contrast media to identify a malignant lesion. However, increased enhancement of normal fibroglandular tissue may mask the breast lesion.

We investigated the degree of BPE on MRI in two mammographic density groups: fatty or dense breasts. This analysis method is believed to be reasonable because mammography is generally the first-choice exam for diagnosis of the breast. Our results suggest that it is worthwhile to perform breast MRI for patients showing dense breasts on mammograms due to the suspicion of a masked breast lesion, especially for women after menopause, because their BPE on MRI is likely to be low.

Uematsu et al. reported that the degree of BPE affected the accuracy of the extent of breast cancer on MRI[11] and staging of breast cancer using MRI.[24] They reported that the accuracy with moderate/marked BPE was significantly lower than that with minimal/mild BPE. Therefore, it should be reasonable to analyze factors influencing BPE on MRI.[13,16,22]

Cubuk et al. reported that BPE did not correlate with the mammographic breast density in either pre- or postmenopausal women, and normal fibroglandular tissue on breast MRI cannot be predicted on the basis of the mammographic breast density.[25] We also found that normal fibroglandular tissue may not always be enhanced moderately or markedly on MRI.

Hambly et al. reported that among their subjects undergoing breast MRI, 24.8% showed minimal; 34%, mild; 24%, moderate; and 17.2%, marked enhancement.[14] In our study, 40.3% showed minimal (n = 58); 37.5%, mild (n = 54); 12.5% (n = 18), moderate; and 10.0% (n = 14), marked enhancement. Our subjects showed a tendency toward a lower BPE than Hambly's study subjects. These may be due to racial differences or the age range of subjects.

De Martini et al. reported that moderate or marked BPE was more frequently seen in women younger than 50 years (39.7%) than in those 50 years old or older (18.9%) ($p<0.0001$).[16] Our correlation-based findings between BPE and the subjects' age were similar to those of their study. In our mammographically dense breast group, the mean age of subjects with minimal BPE was significantly older (52.7 years old) than those with mild (43.3 y.o.), moderate (43.6 y.o.), or marked (42.6 y.o.) BPE. Whereas, in the mammographically fatty group, the mean age of subjects with minimal BPE was significantly older (60.3 y.o.) than those with moderate BPE (45.4 y.o.). This suggests that breast MRI is useful to detect a breast mass in relatively old patients.

There still remain controversies on the relation between BPE on MR images and mannmographic density. Uematsu et. al. reported that younger patients with dense breasts more likely demonstrated moderate/marked background enhancement. They also found significant correlation between mammographic breast density and BPE.[26] At this point, however, our results suggest that considerable cases with mammographic dense breast may demonstrate lower BPE. Furthermore, our results suggest that BPE may not be influenced by the status of lactation experience. To the best of our knowledge, there has been no similar report in the literature.

Another report by Hansen et al. concluded that the mammographic breast density did not correlate with the degree of background enhancement in MRI and that scores for BPE on MRI may be lower than the respective mammographic density scores.[27] Their report supports our results, although they enrolled European subjects while we enrolled Japanese subjects. Our results suggest that considerable number of women with mammographic dense breast may demonstrate lower BPE on MRI regardless of race.

Our study has a few limitations. First, the patient distribution might be biased; there was only one patient with mammographically identified extremely dense breasts, and only one with almost entirely fatty breasts. Second, the subjects' menstrual cycles were not available in premenopausal patients in this retrospective study, though menstrual cycle has been known to influence fibroglandular tissue.[13,28–30] European society of breast imaging guideline recommends that contrast-enhanced breast MRI is preferentially performed between days 7 and 14 of the menstrual cycle, when the BPE of the normal fibroglandular breast tissue is low, and hence abnormalities are better detected and false positives less frequent in premenopausal women.[31] Some researchers, however, reported that the influence of menstrual cycles on the enhancement of breast parenchyma differs according to the breast composition.[13,28] Further improvement may be encouraged to detect abnormalities better with less frequent false positives. Third, we did not assess the amount of fibroglandular tissue on breast MRI, though BI-RADS MRI 2013 recommends to classify breast findings into four categories in the breast MRI reporting system based on the visually estimated breast compositions. Because one of the aims of this study was to clarify when to recommend breast MRI for patients with mammogramphic dense breast, the estimation of breast compositions would be not essential. Finally, this was a study with a small sample size, and the number of cases were not balanced between the dense breast and the fatty breast groups, which may lead to a bias.

In conclusion, 73.8% of the mammographically dense breast group showed mild or minimal BPE on breast MRI. BPE is considered to be affected by the age and menopausal status, but not by breast-feeding experience, regardless of the mammographical density. Our results suggest that contrast-enhanced breast MRI may be effective in postmenopausal women who demonstrate dense breast on mammograms, because mild or minimal BPE can be reasonably expected on MRI in them.

Conflict of interest

None

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