Correlation of Background Parenchymal Enhancement on Breast Magnetic Resonance Imaging with Quantitative Mammographic Parameters Derived using fully Automated Volumetric Software

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Research Article

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Abstract

Background: Background parenchymal enhancement (BPE) and mammographic breast density are risk factors for breast cancer. However, existing evidence regarding the association between these risk factors is inconclusive. This study aimed to evaluate the relationship between BPE and quantitative and subdivided mammographic density parameters, such as fibroglandular tissue (FGT) volume, entire breast volume, and volumetric density (%), measured using a fully automated volumetric software.

Methods: From July 2017 to August 2018, patients with newly diagnosed breast cancer who had undergone preoperative mammography and magnetic resonance imaging (MRI) at our hospital were identified. Mammographic density analysis was performed using a fully automated volumetric software. Two breast radiologists consensually rated BPE and the amount of FGT in each contralateral normal breast MRI based on four categories of the Breast Imaging-Reporting and Data System. The Pearson correlation coefficient was used to analyze the relationship between mammographic density and the FGT and BPE observed on breast MRI.

Results: A total of 364 women were included, of whom 153 (42%) were premenopausal (mean age, 44.22±6.29 years) and 211 (58%) were postmenopausal (mean age, 57.91±9.59 years).The premenopause group had significantly higher levels of BPE and FGT on MRI and FGT volume and volumetric density (%) on mammography. FGT and BPE observed on breast MRI were correlated in the overall sample and postmenopause group(r=0.352and 0.265, respectively). The FGT volume on mammography was significantly correlated with BPE in the overall sample and in the pre- and postmenopause groups (r=0.290, 0.166, and 0.294, respectively). Volumetric density (%) on mammography and BPE were correlated in the total sample and postmenopause group(r=0.369 and 0.281, respectively).

Conclusion: Mammographic breast density and BPE on MRI are significantly correlated in patients with breast cancer. The mammographic FGT volume is particularly correlated with BPE on MRI, regardless of the patient's menopausal state.

Background

Background parenchymal enhancement(BPE) is the enhancement of normal fibroglandular tissue on dynamic contrast-enhanced breast magnetic resonance imaging (MRI).It is usually observed as a bilateral and symmetrical enhancement during early dynamically enhanced phases[1–5].BPE is a dynamic phenomenon and varies among individuals and over time in the same individual. It can be influenced by various factors, such as hormonal levels, menopausal status, menstrual cycle, and age [6, 7].BPE on MRI may negatively influence the evaluation of breast cancer because it may obscure underlying malignancy and over- or underestimate the extent of malignancy determined through mammographic breast density [1, 8].Several studies have shown that moderate and marked BPEs are significantly associated with an increased risk of breast cancer [9–11].

Mammographic breast density is also a moderate independent risk factor for breast cancer[12].High mammographic breast density decreases the sensitivity of detecting breast cancer on mammography[13].The evaluation of mammographic breast density using four Breast Imaging-Reporting and Data System(BI-RADS) categories is somewhat subjective, with only a moderate inter-reader agreement[14–17]. Thus, a fully automated volumetric software has been developed for objective evaluation and control of inter-reader variability in measuring mammographic breast density. The software also assesses the breast as a three-dimensional structure and automatically quantifies the fibroglandular tissue (FGT) volume, entire breast volume, and volumetric density (%, proportion of FGT to the entire breast) [18].

Some studies explore the relationship between BPE on MRI and mammographic density, but the outcomes are conflicting [2–6]. However, existing studies used a subjective four-category classification of mammographic density to analyze the relationship with BPE. Other studies showed that BPE was positively associated with the amount of FGT on MRI [5, 19, 20].FGT reflects the connective and epithelial tissue components of the breast and is comparable to the mammographic FGT volume determined using a fully automated volumetric software [21]. Therefore, we can assume that the FGT volume analyzed using a fully automated volumetric software may also be associated with BPE.

To the best of our knowledge, there are no reports regarding the relationship between BPE and the quantitative parameters of mammographic density measured using a fully automated volumetric software. Therefore, we aimed to examine the relationship between BPE and quantitative and subdivided mammographic density parameters, such as the FGT volume, entire breast volume and volumetric density, determined using a fully automated volumetric software.

Methods

Patient characteristics

This study adhered to the ethical tenets of the Declaration of Helsinki and was approved by the institutional review board (No. 2020-04-032). The requirement for patients' informed consent was waived owing to the retrospective nature of the study.

Using the breast imaging data of our facility from July 2017 to August 2018, we identified patients with newly diagnosed breast cancer who had undergone preoperative mammography and MRI at our hospital. All women who had a prior history of breast cancer (n = 11), had undergone excision biopsy within one month before the study (n = 2), or had undergone mammoplasty (n = 5) were excluded. Postmenopausal women who received hormonal therapy within the last six months before the imaging studies (n = 3) were also excluded.

Mammography

Throughout the study period, mammography was performed in two standard imaging planes (craniocaudal and mediolateral oblique views) using a full-field digital mammography machine (Selenia Dimensions, Hologic, Bedford, MA).

Mammography analysis using a fully automated volumetric software

We used the Quantra version 2.1.1 (Hologic, Bedford, MA, USA) on each raw full-field digital mammography, for fully automated volumetric analysis. The software separates the breast area from the background and estimate tissue composition by computing X-ray attenuation [22]. This process is achieved separately for each breast; the final outcome includes a separate estimate per breast and an average of bilateral breasts. When Quantra analysis is over, processing data can be displayed as DICOM (Digital Imaging and COmmunications in Medicine) capture images (Fig. 1).

Breast MRI

All MRI examinations were performed using either of two 3-T scanners (Magnetom Vida, Siemens Healthcare, Erlangen, Germany; Magnetom Skyra, Siemens Healthcare, Erlangen, Germany). All patients underwent MRI in prone position with dedicated 16-channel breast coils. The standard imaging protocol for breast MRI included fat-saturated T2-weighted images, pre-contrast and contrast-enhanced fat saturated T1-weighted images and delayed contrast-enhanced fat saturated T1-weighted images for lymph node staging. Dynamic contrast enhanced sequences were performed, over a period of 6 min, following intravenous injection of the contrast material (0.1 mmol/ kg per body weight, gadoteratedimeglumine [Dotarem, Guerbet, Villepinte, France]). The post processing protocol for analysis were standard subtraction, reverse subtraction, maximum intensity projection images and multiplanar reconstruction images.

Assessment of BPE and FGT observed on breast MRI

The examination findings of each patient were interpreted by two breast radiologists (B.M.S. and B.K.K.) who were blinded to the mammographic and clinical findings. BPE on contralateral normal breast MRI was rated as one of the following four categories based on one- or two-minute subtraction images: minimal, mild, moderate, and marked according to the BI-RADS category [17]. A consensus interpretation was reached in cases of disagreement. We also rated the FGT amount on contralateral normal breast MRI as one of the following BI-RADS categories based on pre-contrast T1-weighted images: almost entirely fatty(< 25% FGT), scattered (25–50%), heterogeneous (50–75%), and extreme (> 76%; Fig. 2)[17].

Statistical analysis

T-tests were used to evaluate whether there were differences in the distribution of mammographic breast density and the BPE and FGT observed on breast MRI between premenopausal and postmenopausal women. The Pearson correlation coefficient was used to analyze the relationship between BPE observed on breast MRI, mammographic breast density, and FGT. Statistical analyses were performed using SPSS software(version 21.0; IBM Corp, Armonk, NY).Statistical significance was assigned if the P-value was < 0.05.

Results

A total of 364 female patients were included in the study, of whom 153 (42%) were premenopausal and 211 (58%) were postmenopausal. BPE and FGT observed on MRI were significantly higher in the premenopause group than in the postmenopause group. On mammography, the FGT volume and volumetric density (%) were significantly higher in the premenopause group than in the postmenopause group, whereas the entire breast volume was significantly lower among premenopausal women than among postmenopausal ones(Table 1).

Table 1
Distribution of magnetic resonance imaging and mammographic findings according to menopausal status

	Menopausal status		**p-value**
	Premenopause	**Postmenopause**	
	Mean ± SD	**Mean ± SD**	
Age (years)	44.22 ± 6.29	57.91 ± 9.59	0.000
MRI			
BPE	2.27 ± 0.99	1.39 ± 0.70	0.000
FGT	2.97 ± 0.77	2.14 ± 0.84	0.000
Mammography			
Volume of fibroglandular tissue (cm^3)	108.35 ± 54.39	86.51 ± 50.41	0.000
Volume of entire breast (cm^3)	470.96 ± 22.65	594.01 ± 277.29	0.000
Volumetric breast density (%)	23.95 ± 6.89	15.78 ± 8.38	0.000
BPE, background parenchymal enhancement; FGT, fibroglandular tissue; MRI, magnetic resonance imaging; SD, standard deviation			

Relationship between BPE and FGT according to menopausal status

FGT was correlated with BPE in the overall sample(r = 0.352, p = 0.000) and the postmenopause group(r = 0.265, p = 0.000); however, this was not true in the premenopause group(r = 0.095, p = 0.241).

Relationship between BPE and mammography according to menopausal status

The FGT volume on mammography was significantly correlated with BPE observed on MRI in the overall sample (r = 0.290, p = 0.000) and in both groups (premenopause: r = 0.166, p = 0.040; and postmenopause: r = 0.295, p = 0.000). The entire breast volume was not significantly correlated with BPE in the overall sample (r=-0.047, p = 0.369) or either group (premenopause: r = 0.143, p = 0.078; and postmenopause: r = 0.015, p = 0.831). However, the volumetric breast density (%) was significantly correlated with BPE in the overall sample (r = 0.369, p = 0.000) and the postmenopause group(r = 0.281, p = 0.000) but not in the premenopause group(r = 0.116, p = 0.152; Table 2).

Table 2
Correlation between background parenchymal enhancement and mammographic breast density

	Background parenchymal enhancement		
	Total	**Menopause status**	
		Premenopause (n=153)	**Postmenopause (n=211)**
	***r* (p-value)**	***r* (p-value)**	***r* (p-value)**
Volume of fibroglandular tissue	0.290 (0.000)	0.166 (0.040)	0.295 (0.000)
Volume of entire breast	-0.047 (0.369)	0.143 (0.078)	0.015 (0.831)
Volumetric breast density	0.369 (0.000)	0.116 (0.152)	0.281 (0.000)

Discussion

Evaluations according to the four categories of BI-RADS are based on visual estimation of the proportion of FGT to that of the total breast area on mammography [17]. Thus, these evaluations are subjective and dependent on the reader’s accuracy. Previous studies examined the relationship between BPE and mammographic breast density using the four subjective categories of BI-RADS. In contrast, we analyzed mammographic findings using a fully automated volumetric software and derived them as objective quantitative data in this study. Although the correlation between BPE and the quantitative data of mammographic density is weak, we found that the volume of mammographic FGT is associated with BPE observed on MRI in pre- and postmenopausal women and that the volumetric breast density is significantly correlated with BPE in postmenopausal women.

Some studies have previously explored the relationship between BPE and mammography density. Ko et al reported that there was no significant association between mammographic density and BPE in either the total sample or in either the pre-or postmenopause group [3]. Their findings were compatible with the results of previous studies [2, 3, 5] but contrary to another study. In 2012, Uematsu et al. assessed the relationship between MBD and BPE by reviewing mammograms and MRIs from 146 patients. They reported a significant correlation between MBD and BPE without adjusting for the phase in the patients’ menstrual cycle [4].However, these studies used a subjective four-category classification of mammographic density to analyze its relationship with BPE [3, 5, 13, 23].

Prior to study initiation, we assumed that the relationship between BPE and mammographic FGT volume would corroborate the findings of the relationship between BPE and FGT observed on MRI in previous studies [5, 9]. MRI provides the possibility of a more quantitative determination of breast FGT volume because of its cross-sectional, three-dimensional coverage of breast tissue [24]. Our findings are comparable to those of previous studies; a significant correlation was found between FGT and BPE in the overall sample and the postmenopause group in one study [5] and in the pre- and postmenopause groups of healthy women in another study [20].

Although a significant association is observed between FGT volume and BPE, the degree of this association is weak. BPE is specifically associated with the glandular component of fibroglandular tissue. Because BPE is considered to reflect the vascularity of fibroglandular issue, and microvessels are more closely associated with glandular tissue [25, 26]. This could potentially explain the weak but significant association between FGT and BPE. In the study by Sung et al., strong correlations of BPE with microvessel density (MVD), cluster of differentiation (CD) 34, glandular concentration, and vascular endothelial growth factor (VEGF) level in premenopausal patients were noted. MVD, CD34, and VEGF are markers of angiogenesis or vascularization and were associated with glandular concentration [27].

The correlation of quantitative parameters of mammographic density and BPE was lower in the premenopausal group than in the postmenopause group. This could be because these factors do not reflect the hormonal differences among and with individuals. There may be inter- and intra-individual differences in hormone levels or hormone activity [23]. Within an individual, these variables may change depending on the menstrual cycle[28].This intra-individual difference of BPE can be explained by the histamine-like effect of estrogen that includes an increase in microvascular permeability and vasodilation, and the mitogenic effect of progesterone, which may promote metabolic activity and result in increased perfusion [25, 29]. However, the present study did not consider the menstrual cycle in BPE assessment. Further research that adjusts for the menstrual cycle is warranted to obtain more precise results in premenopausal women.

This study had a few limitations. First, we only included patients with breast cancer, and the study was conducted retrospectively in a single center. In addition, the data were obtained from Korean patients with relatively dense breasts. These factors could limit the generalization of our results. Second, the effect of the patient’s menstrual cycle could not be considered. Although we recommended the patients to undergo breast MRI in the second week of their menstrual cycle, some women required urgent treatment and had to undergo breast MRI regardless of the menstrual cycle phase. Third, the assessment of BPE and FGT on breast MRI was somewhat subjective as it was performed via visual assessments by radiologists. To overcome this shortcoming, the consensus of two experienced radiologists was taken for the assessment of BPE.

Conclusion

We demonstrated that there is a significant correlation between the quantitative parameters of mammographic density and BPE observed on MRIs. Compared to other quantitative parameters of mammographic density measured using a fully automated breast volumetric software, the mammographic FGT volume was particularly correlated with BPE observed on MRIs of both pre- and postmenopausal women. Quantitative parameters of mammographic density, measured using fully automated volumetric software, can be a good predictor of BPE prior to breast MRI in women with breast cancer.

List Of Abbreviations

BPE Background parenchymal enhancement

BI-RADS Breast Imaging-Reporting and Data System

CD34 Cluster of differentiation 34

FGT Fibroglandular tissue

MBD Mammographic breast density

MRI Magnetic resonance imaging

MVD Microvessel density

VEGF Vascular endothelial growth factor

Declarations

Ethics approval and consent to participate

This study was approved by the institutional review board of Ulsan University Hospital (No. 2020–04-013), and the need for informed consent was waived due to the retrospective design of the study

Consent for publication

Not applicable

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests

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Authors' contributions

L.G.Y is a major contributor in writing the manuscript. B.K.K and B.M.S analyzed and interpreted the images of patients. B.M.S made a concept of this study. P.G.M and L.S.Y analyzed patient’s data. All authors read and approved the final manuscript.

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Figures

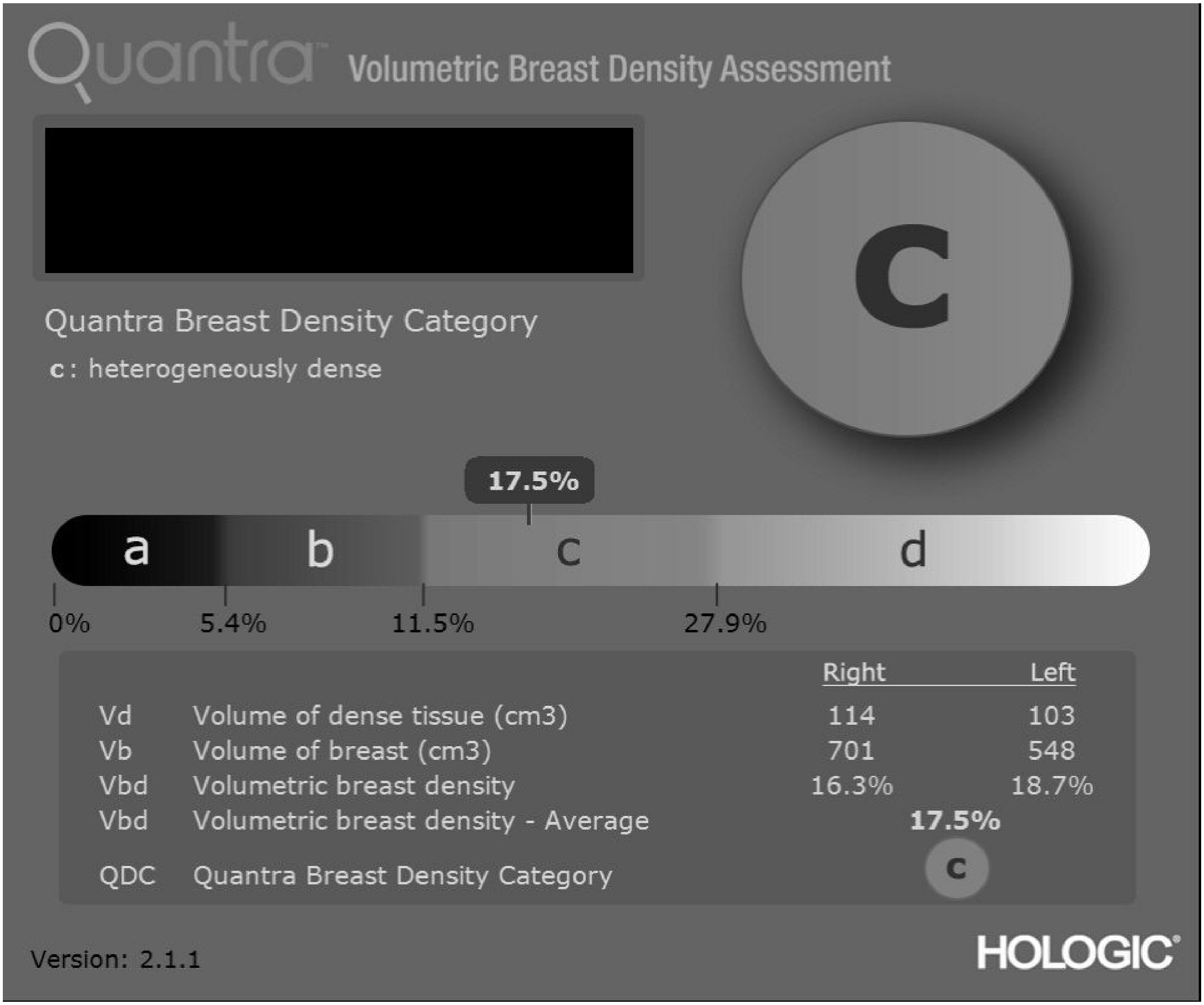

Figure 1

Result of mammographic density measured using Quantra 2.1.1

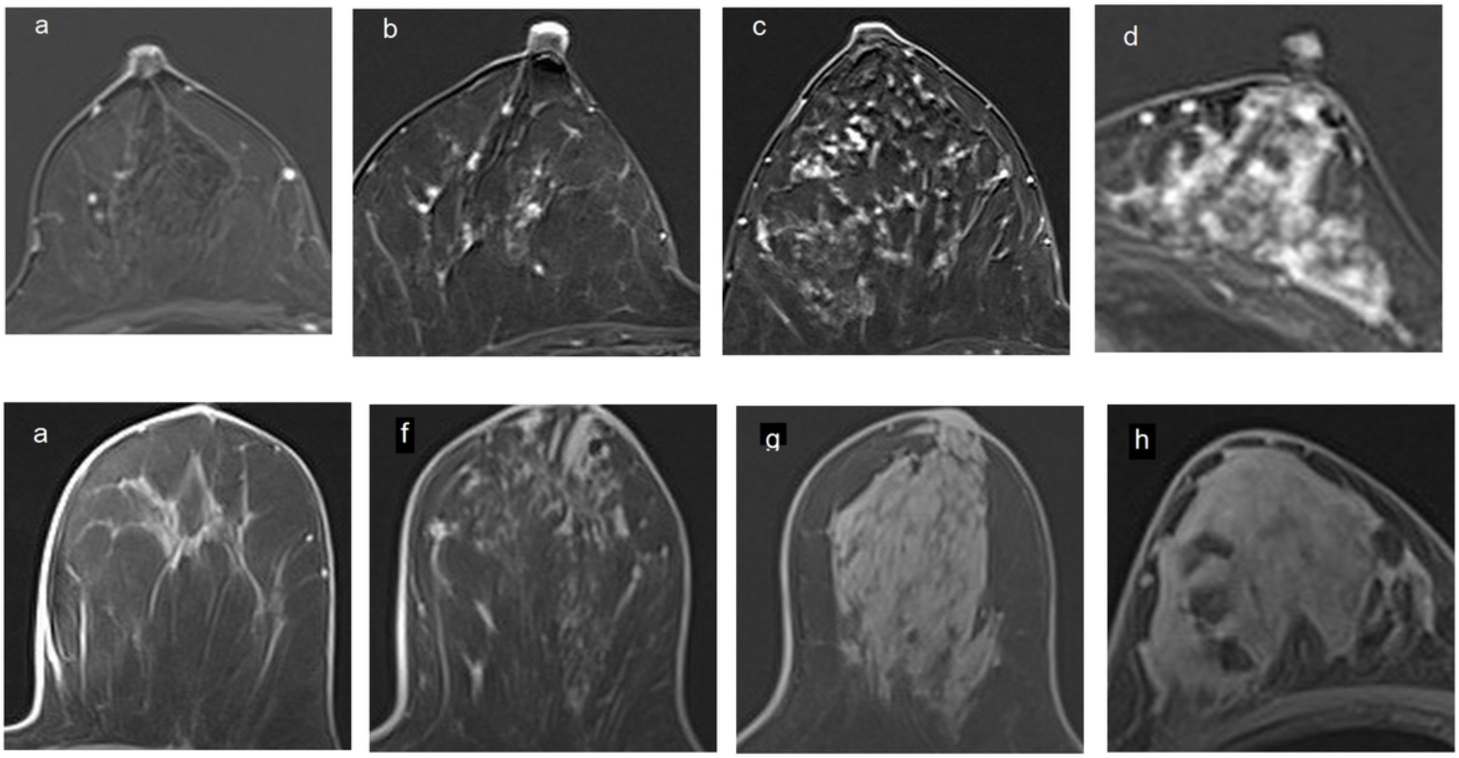

Figure 2

Representative image of breast tissue composition of breast MRI according to BI-RADS (a) BPE-Minimal (b) BPE-Mild (c) BPE-Moderate (d) BPE-Marked (e) FTG-Almost entirely fat (f) FTG-Scattered fibroglandular tissue (g) FTG-Heterogeneous fibroglandular tissue (h) FTG-Extreme fibroglandular tissue BI-RADS: Breast Imaging-Reporting and Data System; MRI: magnetic resonance imaging; BPE: background parenchymal enhancement; FTG: fibroglandular tissue