Correlation Between Mammographic Breast Density, Breast Tissue Type in Ultrasonography, Fibroglandular Tissue, and Background Parenchymal Enhancement in Magnetic Resonance Imaging

Breast Cancer: Basic and Clinical Research
Volume 12: 1–8
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DOI: 10.1177/1178223418771971
SAGE

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ABSTRACT

OBJECTIVE: Breast cancer is the most common malignancy in the female population, and imaging studies play a critical role for its early detection. Mammographic breast density (MBD) is one of the markers used to predict the risk stratification of breast cancer in patients. We aimed to assess the correlations among MBD, ultrasound breast composition (USBC), fibroglandular tissue (FGT), and the amount of background parenchymal enhancement (BPE) in magnetic resonance imaging, after considering the subjects' menopausal status.

METHODS: In this retrospective cross-sectional study, the medical records' archives in a tertiary referral hospital were reviewed. Data including age, menopausal status, their mammograms, and ultrasound assessments were extracted from their records. All of their imaging studies were reviewed, and MBD, USBC, FGT, and BPE were determined, recorded, and entered into SPSS software for analysis.

RESULTS: A total of 121 women (mean age = 42.7 ± 11.0 years) were included, of which 35 out of 115 (30.4%) had reached menopause. Using the Jonckheere-Terpstra test for evaluating the trends among above mentioned 4 radiologic characteristics in the total sample population, a significant positive relation was found between each of these paired variables: (1) USBC-MBD ($P = .006$), (2) FGT-MBD ($P = .001$), (3) USBC-BPE ($P = .046$), (4) USBC-FGT ($P = .036$), and (5) BPE-FGT ($P < .001$). These trends were not found to be significant among premenopausal subjects.

CONCLUSIONS: Considering the trends between different measures of breast density in the 3 radiologic modalities, these factors can be used interchangeably in certain settings.

KEYWORDS: Breast density, ultrasonography, magnetic resonance imaging, background parenchymal enhancement, fibroglandular tissue

RECEIVED: December 17, 2017. **ACCEPTED:** March 18, 2018.

TYPE: Original Research

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Introduction

Breast cancer is the most common malignancy of the female population.[1] To decrease breast cancer's mortality rates, imaging studies still play a critical role in its early detection.[2]

Various tools have been proposed for assessing the risk of breast cancer. Accordingly, the search for other factors of breast cancer risk is still ongoing. One of these promising factors is mammographic breast density (MBD). Studies have reported the breast cancer risk in women with high MBDs to be 3 to 5 times greater than in women with lower MBDs.[3,4] Breast composition on ultrasound has also been found to provide valuable information regarding the risk of breast cancer.[5]

The proportion of fibroglandular tissue (FGT) on breast magnetic resonance imaging (MRI), which is a 3-dimensional method, may yield more accurate breast density assessments.[6] The background parenchymal enhancement (BPE) of the breast, visualized on MRI after administration of contrast material, is another characteristic which can possibly affect the accuracy of an MRI in detecting breast cancer.[7] This factor is greatly dependent on the age and subject's hormonal status[8] and so it has been suggested that breast MRI should be performed during the second week of menstrual cycle to minimize the BPE effects.[9] Some studies have shown that more dense breasts on a mammography show higher BPE on the MRI.[10] If this correlation is verified, MBD can be used to estimate BPE level on an MRI.[11] Moreover, because a positive correlation has been established between MBD and risk of breast cancer, such a relationship might also be true for BPE and breast cancer. Further studies are required.

In this study, we aimed to assess the associations among MBD, breast composition on ultrasound breast composition (USBC), FGT, and BPE.

Materials and Methods

Study design

In this retrospective cross-sectional study, the medical record archives in a tertiary referral hospital over a limited time in first semester of 2017 were reviewed, and 121 consecutive breast MRI cases were selected via simple random sampling. However, patients with a history of conservative breast surgery, chemotherapy, hormone replacement therapy, and patients who underwent mammography or sonography with more than 6 months since the last MRI examination were excluded. Eventually, 121 subjects were included, in which MRI was performed as additional evaluation of vague mammography or sonography findings, follow-up of previous Breast Imaging Reporting and Data System (BI-RADS) 3 lesions, discrepancies in lesion characteristics between ultrasound and mammography findings, or unexplained clinical findings.

Ethical considerations

The study protocol was evaluated and approved by the hospital institutional ethics committee. Considering the retrospective setting of the study, the requirement for obtaining informed written consent from the participants was waived. Gathered information was considered confidential and used anonymously and was only accessible to the authors of the survey.

This study was conducted according to the principles of the Declaration of Helsinki, and the participating researchers declare no conflicts of interests.

Magnetic resonance imaging

Using a dedicated surface breast coil and the same techniques according to the standard protocols in a 1.5-T MRI scanner, T1-weighted non–fat-suppressed sequences and T2-weighted fat-suppressed sequences were obtained followed by intravenous administration of 0.1 mmol/L gadopentetate dimeglumine (Magnevist; Bayer, Leverkusen, Germany). Six sequences with contrast series were subtracted pixel by pixel from the first acquired noncontrast images. Fibroglandular tissue proportion was visually assessed using precontrast T1-weighted images and was graded according to the BI-RADS criteria into 4 categories: (1) almost entirely fatty (<25% FGT), (2) scattered FGT (25%-50% FGT), (3) heterogeneously FGT (50%-75% FGT), and (4) extreme FGT (>76% FGT). The breast BPE was also visually assessed in postcontrast fat-suppressed T1-weighted and subtraction images. The BPE classification was made on the basis of the second edition of BI-RADS criteria as minimal, mild, moderate, and marked.[12]

Mammography

Among the 121 subjects, medical records from 56 patients were found to also include mammograms. A breast specialist radiologist who was blind to the study design and results visually interpreted craniocaudal and mediolateral oblique views of these available screening mammograms obtained within 6 months prior to MRI. According to the fifth edition of BI-RADS criteria, MBD was classified into 4 categories: almost entirely fatty, scattered areas of fibroglandular density, heterogeneously dense, and extremely dense.[13] All mammograms had been recorded by Selenia Dimensions Mammography System (Hologic Inc., Marlborough, MA, USA) (Figure 1).

Ultrasonography

Whole breast screening ultrasonography with a digital ultrasound scanner (Esaote MyLab Five) equipped with a 6- to 14-MHz probe was performed for 104 patients by another specialized radiologist in a handheld system who was also blind to the study data. Ultrasound breast composition was categorized into 3 groups, including homogeneous fatty and homogeneous and heterogeneous fibroglandular according to the American College of Radiology guidelines[14] (Figure 2).

Statistical analysis

All data were collected in MS Office Excel (Microsoft, Redmond, WA, USA) datasheets and all analyses were conducted using SPSS software for Windows, version 22 (IBM Corp, Armonk, NY, USA).[15] Descriptive statistics including frequency distribution and mean and standard deviation were used to report study findings. Age distribution was evaluated in the subgroups of MBD, USBC, BPE, and FGT, and considering the non-normal distribution observed, Kruskal-Wallis H test was used to determine the significance of age differences between these subgroups. This test was also used to evaluate the significance of differences between the subgroups of MBD, USBC, BPE, and FGT, regarding the time of MRI acquisition. The Mann-Whitney U test was used to assess the significance of differences in menopausal status between the subgroups of these ordinal variables. The trends between ordinal variables were assessed using the Jonckheere-Terpstra test and Spearman rank order correlation test. Eventually, similar analyses were performed on premenopausal and postmenopausal patient subgroups. A P value <.05 was considered as statistically significant in all analyses.

Results

Descriptive statistics

A total of 121 women were included in the study with an average age of 42.7 ± 11.0 years ranging from 18 to 74 years. Menstrual status was recorded for 115 patients, of which 35 (30.4%) had reached menopause. Among the remaining 80, time of MRI acquisition in their menstrual cycle was recorded for 63 subjects. Accordingly, MRI was acquired during the first week of menstrual cycle in 26 (41.3%), during the second week

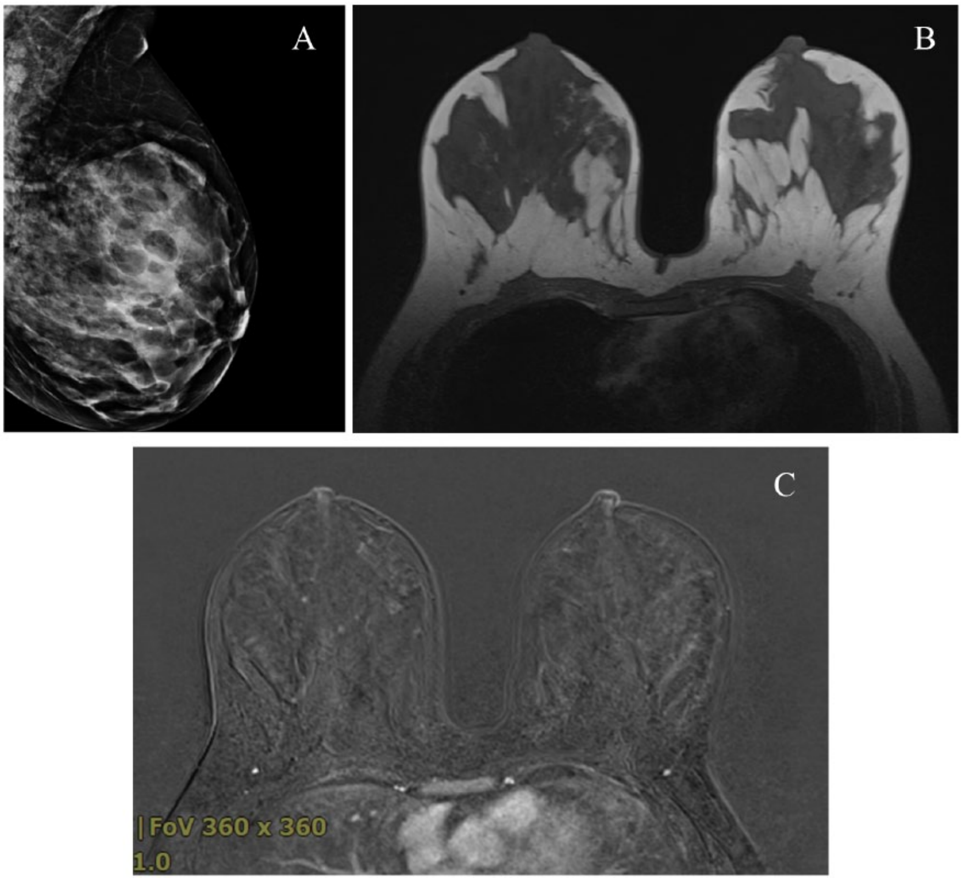

Figure 1. A 40-year-old patient's (A) MLO (mediolateral oblique) mammography with breast density type c; (B) T1-weighted MRI without fat suppression, heterogeneous density type fibroglandular tissue in same patient; and (C) mild background parenchymal enhancement in MRI with subtracted image after contrast injection. MRI indicates magnetic resonance imaging.

in 21 (33.3%), during the third week in 11 (17.5%), and during the last week of menstrual cycle in 5 patients (7.9%).

As mentioned, mammograms were available from the medical records of 56 subjects. According to these results, MBD was reported as fatty in 4 study subjects (7.1%) and as scattered, heterogeneous, and severely dense in 14 (25.0%), 26 (46.4%), and 12 (12.4%), respectively.

The reports of ultrasound assessments were available in the medical records from 104 subjects. According to the findings of this imaging modality, USBC was reported as homogeneous fatty in 7 (6.7%), homogeneous fibroglandular in 23 (22.1%), and heterogeneous fibroglandular in 74 patients (71.2%).

Based on the findings on breast MRI, BPE was minimal in 17 (14.0%), mild in 52 (43.0%), moderate in 39 (32.2%), and marked in 13 subjects (10.7%). Fibroglandular tissue was also reported as fatty in 5 patients (4.1%) and as scattered, heterogeneous, and severely dense in 33 (27.3%), 65 (53.7%), and 18 subjects (14.9%), respectively. Table 1 presents descriptive statistics of evaluated study variables.

Analytical statistics

In our first analysis, the differences in age, menopausal status, and time of MRI acquisition between subgroups of MBD, USBC, BPE, and FGT are presented in Table 2. As can be seen, the differences in age between subgroups of MBD were not statistically significant, with the lowest mean age observed among patients with severely dense breasts ($P = .225$). As for the USBC, the lowest mean age was observed among subjects with USBCs of homogeneous fibroglandular, but the differences for this variable were not statistically significant ($P = .160$). Similar findings were yielded for the BPE as well ($P = .076$). However, the differences in age between FGT subgroups of patients' MRIs were found to be statistically significant with the lowest average age observed among patients with severely dense FGT ($P < .001$).

Regarding the menopausal status of the participants, higher levels of all 4 radiologic characteristics were found to be more prevalent among premenopausal subjects, and the differences were found to be statistically significant, except for the USBC ($P = .062$). However, the time of MRI acquisition according to the menstrual cycle of the patients did not differ significantly between the subgroups of BPE ($P = .849$) and FGT ($P = .499$).

In the next step, the Jonckheere-Terpstra test was used to evaluate the trends between the 4 ordinal variables of MBD, USBC, BPE, and FGT. The results of these analyses on the total sample population along with the subgroup analyses based on participants' menopausal status are presented in

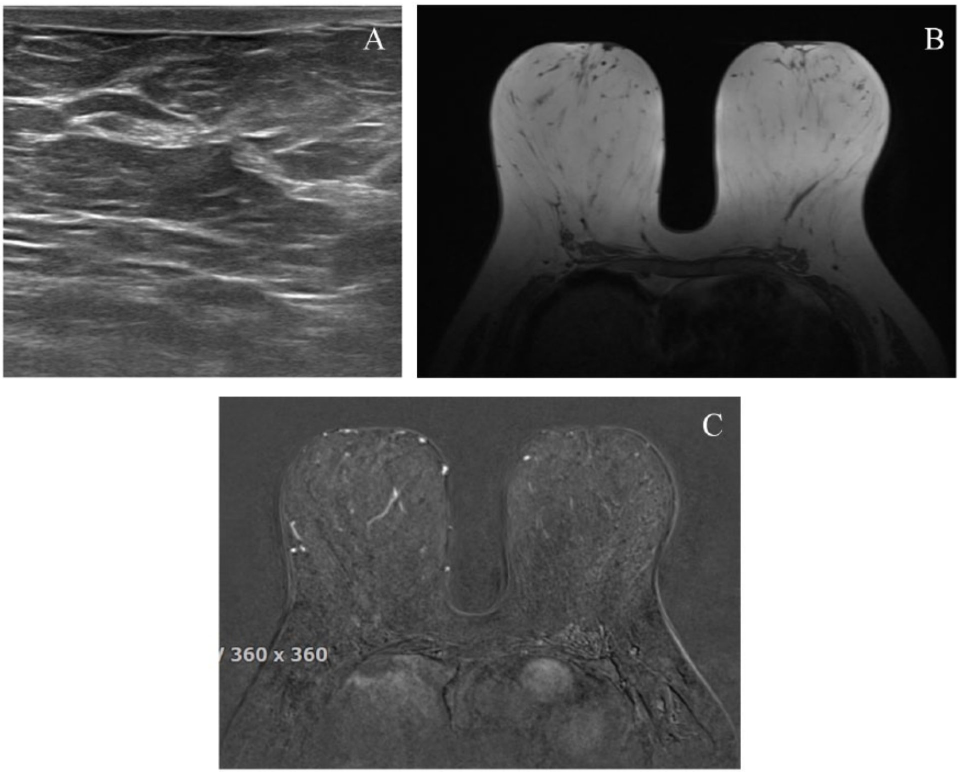

Figure 2. A 52-year-old patient's (A) sonography image with homogeneous fatty breast, (B) T1-weighted MRI without fat suppression in same patient with almost entirely fatty breast, and (C) minimal background parenchymal enhancement in MRI with subtracted image after contrast injection. MRI indicates magnetic resonance imaging.

Tables 3 and 4. As can be seen, there was a significant positive trend between the USBC and MBD in both the total sample population ($P = .006$) and postmenopausal participants ($P = .006$); however, the trend was not statistically significant among premenopausal subjects ($P = .895$).

No trend between BPE and MBD was found to be statistically significant in both the overall and subgroup analyses. However, a significant positive trend was observed between FGT and MBD both among the whole population ($P = .001$) and postmenopausal patients ($P = .009$).

Ultrasound breast composition was found to have a positive significant association with BPE in the whole sample population ($P = .046$), but neither of the subgroup analyses in pre- and postmenopausal subjects were found to be statistically significant. Ultrasound breast composition was also found to be positively associated with FGT both in the total population ($P = .036$) and among postmenopausal subjects ($P = .007$). However, the trend between them was not statistically significant in patients who had not yet reached menopause ($P = .716$).

Both FGT and BPE were also found to have a positive trend in the overall analysis ($P < .001$) and among postmenopausal patients ($P = .003$). Subgroup analysis in premenopausal subjects found an insignificant positive trend between the 2 ($P = .076$). The results of Spearman rank order correlation were also found to be congruent with the findings of the Jonckheere-Terpstra test in all analyses.

Discussion

This study found a negative association between age and MBD, BPE, and FGT of the patients, which was found to be significant only for the FGT on the breast MRI. As for the USBC, the lowest mean age was observed among subjects with USBCs of heterogeneous fibroglandular and the increase in breast density according to ultrasound did not show a linear association with subjects' ages. These findings were quite compatible with the results of previous studies indicating a decrease in breast density with increasing age in women.[16] Regarding the menopausal status of the participants, higher levels of all 4 radiologic characteristics were found to be more prevalent among premenopausal subjects with the trends being statistically significant, except for USBC. In these assessments, the age variable was analyzed as a dichotomous variable of pre- and postmenopausal status, and because the hormonal status of women goes through a significant change after menopause, it is reasonable to find greater differences between these 2 groups of patients. As mentioned in various studies following the hormonal changes after menopause, the proportion of FGT decreases and the overall density of the breasts declines,[17] to which the previously described results could be attributed. King et al[8] have also reported significant decreases in BPE and FGT on MRI in postmenopausal women.

Some previous studies have reported significant changes in BPE and FGT amounts in different phases of menstrual cycle,[9,18] and it has been proposed that the best time for breast MRI would be in the second week of the patient's menstrual

Table 1. Descriptive statistics of evaluated variables in the study.

VARIABLES	FREQUENCY (%)
Menopause	
No	80 (69.6)
Yes	35 (30.4)
Time of MRI acquisition (menstrual cycle)	
First week	26 (41.3)
Second week	21 (33.3)
Third week	11 (17.5)
Fourth week	5 (7.9)
Mammographic breast density	
Fatty	4 (7.1)
Scattered density	14 (25.0)
Heterogeneous density	26 (46.4)
Severe density	12 (21.4)
Ultrasound breast density	
Homogeneous fatty	7 (6.7)
Homogeneous fibroglandular	23 (22.1)
Heterogeneous fibroglandular	74 (71.2)
Background parenchymal enhancement	
Minimal	17 (14.0)
Mild	52 (43.0)
Moderate	39 (32.2)
Marked	13 (10.7)
Fibroglandular tissue in MRI	
Fatty	5 (4.1)
Scattered density	33 (27.3)
Heterogeneous density	65 (53.7)
Severe density	18 (14.9)

Abbreviation: MRI, magnetic resonance imaging.

cycle to minimize the effect of BPE; we did not find significant differences between BPE and FGT in patients whose MRIs were performed at different weeks of their menstrual cycles. However, this discrepancy could be attributed to several reasons: (1) interpersonal differences in the baseline BPE and FGT regardless of the MRI acquisition timing, (2) limited number of study subjects, and (3) it was routine in our hospital to propose the second week of the month for breast MRI; otherwise, patients or their referring doctors were not accepted or in emergency situations. It is possible that if the subjects' BPE levels had been followed through their menstrual cycles, and their changes had been evaluated in each person individually, similar results would have been obtained, and BPE might have been reported at its lowest level during the second week of the cycle.

This is the first study that used the Jonckheere-Terpstra test for evaluating trends between the 4 radiologic characteristics (MBD, USBC, BPE, and FGT), to also take their ordinal nature into account. As a result of these analyses in the total sample population, a significant positive trend was found between each of these paired variables: (1) USBC-MBD, (2) FGT-MBD, (3) USBC-BPE, (4) USBC-FGT, and (5) BPE-FGT. Among premenopausal subjects, none of the trends between pairwise comparisons were found to be statistically significant; however, analyses performed on postmenopausal subjects found significant positive trends between these pairs of variables: (1) USBC-MBD, (2) FGT-MBD, (3) USBC-FGT, and (4) BPE-FGT. These findings are indicative of a considerable association between different measures of breast density in the 3 radiologic modalities of mammography, ultrasound, and MRI. However, it should be noted that such trends were not present in the population of premenopausal women. It should be mentioned that the results of Jonckheere-Terpstra test were compatible with that of the Spearman rank order correlation in all the analyses.

In 2011, Ko et al assessed the relationship between MBD and BPE by reviewing mammograms and MRIs from 142 patients. To assess this relationship, they used the Fisher exact test, based on the results in which there were no significant association between MBD and BPE in either the total sample population or in each group of pre- and postmenopausal patients.[10] Their findings were compatible with the results of the study by Cubuk et al,[19] which was conducted on 26 patients. In another retrospective study from 2015, Kuwamura et al included 160 women and reviewed their mammograms and MRIs. They considered BPE and MBD as dichotomous variables and used the χ^2 test to assess their relationship. Based on their findings, there was no significant association between MBD and BPE; however, BPE was found to be significantly correlated with breast parenchymal echotexture on ultrasound images.[20] In agreement with the results of these studies, our results also demonstrated no significant trends between MBD and BPE, but USBC and BPE were found to have a significant trend in the total population but not in patient subgroups.

Lee et al[21] reported a significant association between MBD and FGT in a study conducted on 40 women aged 20 to 83 years. Our findings considered the relationship between MBD and FGT and were also compatible with the results from the study of Lee et al.

In a study published in 2015, Rijiravanich and Chayakulkheeree evaluated the relationship between BPE and FGT on the MRIs of 95 healthy Thai women, and using Spearman rank correlation test, they found no significant relationship between BPE and FGT in their subjects.[22] Hence, the results reported by King et al[8] were compatible with ours as opposed to the findings of Rijiravanich and Chayakulkheeree.[22] These discrepancies could be explained by different sample populations included in each study, the participants' nationali-

Table 2. Relationships between age, menopausal status and time of MRI acquisition with mammographic breast density, ultrasound breast composition, background parenchymal enhancement, and fibroglandular tissue.

VARIABLES	AGE MEAN (SD)	*P* VALUE[a]	MENOPAUSE FREQUENCY (%)		*P* VALUE[b]	TIME OF MRI ACQUISITION (MENSTRUAL CYCLE) FREQUENCY (%)				*P* VALUE[a]
			NO	YES		FIRST WEEK	SECOND WEEK	THIRD WEEK	FOURTH WEEK	
Mammographic breast density										
Fatty	59.8 (15.8)	.225	1 (3.3)	3 (13.0)	.044					
Scattered density	49.1 (1.8)		6 (20.0)	7 (30.4)						
Heterogeneous density	46.5 (8.5)		15 (50.0)	11 (47.8)						
Severe density	43.6 (6.6)		8 (26.7)	2 (8.7)						
Ultrasound breast composition										
Homogeneous fatty	52.3 (14.7)	.160	3 (4.2)	4 (13.8)	.062					
Homogeneous fibroglandular	41.5 (14.7)		14 (19.7)	8 (27.6)						
Heterogeneous fibroglandular	42.0 (9.1)		54 (76.1)	17 (58.6)						
Background parenchymal enhancement										
Minimal	46.1 (13.2)	.076	8 (10.0)	9 (25.7)	.007	2 (7.7)	2 (9.5)	1 (9.1)	1 (20.0)	.849
Mild	43.4 (11.6)		34 (42.5)	17 (48.6)		12 (46.2)	8 (38.1)	4 (36.4)	2 (40.0)	
Moderate	42.6 (9.1)		28 (35.0)	8 (22.9)		10 (35.8)	6 (28.6)	4 (36.4)	1 (20.0)	
Marked	36.2 (8.4)		10 (12.5)	1 (2.9)		2 (7.7)	5 (23.8)	2 (18.2)	1 (20.0)	
Fibroglandular tissue										
Fatty	52.0 (15.9)	<.001	2 (2.5)	3 (8.6)	<.001	1 (3.8)	0 (0.0)	1 (9.1)	0 (0.0)	.499
Scattered density	47.5 (11.8)		15 (18.8)	17 (48.6)		8 (30.8)	4 (19.0)	0 (0.0)	2 (40.0)	
Heterogeneous density	42.4 (8.8)		46 (57.5)	15 (42.9)		11 (42.3)	12 (57.1)	6 (54.5)	2 (40.0)	
Severe density	32.8 (8.0)		17 (21.3)	0 (0.0)		6 (23.1)	5 (23.8)	4 (36.4)	1 (20.0)	

Abbreviation: MRI, magnetic resonance imaging.
[a] Kruskal-Wallis *H* test.
[b] Mann-Whitney *U* test.

ties, and the fact that determination of the values of these variables was observer dependent.

One of the main limitations of this study was the limited sample population, which could have affected the results of our analyses when considering the multiple levels of each included variable. We also could not assess the variations in our radiologic characteristics during different phases of participants' menstrual cycles, and thus, the results yielded from the analyses on the relations between timing of MRI acquisition with other factors may be unreliable considering the limited number of patients assessed. Additional limitations that might be worth mentioning are the fact that retrospective data collection may include bias and we did not have data on interobserver variation. The observer-dependent and qualitative assessments of the radiologic characteristics could also be improved by application of various innovative quantitative factors as measured via different modalities.

This study showed considerable trends between different measures of breast density in the 3 radiologic modalities of mammography (MBD), ultrasound (USBC), and MRI (BPE and FGT), which were not confirmed in the subgroup of population of premenopausal women. Thus, using these factors interchangeably for different aims should be done cautiously with the intent of determining the best time for MRI acquisition according to the level of BPE, estimation of BPE based on the findings of mammography or ultrasound assessment, and/or the risk factors for breast cancer.

Table 3. Trends between ultrasound breast composition, background parenchymal enhancement, and fibroglandular tissue with mammographic breast density.

VARIABLES	MAMMOGRAPHIC BREAST DENSITY FREQUENCY (%)				JONCKHEERE-TERPSTRA TEST			SPEARMAN RANK ORDER CORRELATION
	FATTY	SCATTERED DENSITY	HETEROGENEOUS DENSITY	SEVERE DENSITY	TOTAL	PREMENOPAUSAL	POSTMENOPAUSAL	
Ultrasound breast composition								
Homogeneous fatty	1 (25.0)	2 (15.4)	1 (4.3)	0 (0.0)	$P=.006$ $T=585.0$ $z=2.7$	$P=.895$ $T=145.0$ $z=0.1$	$P=.006$ $T=95.0$ $z=2.7$	Coefficient = 0.383 $P=.005$
Homogeneous fibroglandular	2 (50.0)	2 (15.4)	5 (21.7)	0 (0.0)				
Heterogeneous fibroglandular	1 (25.0)	9 (69.2)	17 (73.9)	12 (100.0)				
Background parenchymal enhancement								
Minimal	2 (50.0)	5 (25.7)	2 (7.7)	2 (16.7)	$P=.070$ $T=639.0$ $z=1.8$	$P=.950$ $T=145.0$ $z=0.1$	$P=.167$ $T=109.0$ $z=1.4$	Coefficient = 0.239 $P=.076$
Mild	0 (0.0)	4 (28.6)	16 (61.5)	3 (25.0)				
Moderate	2 (50.0)	5 (35.7)	6 (23.1)	4 (33.3)				
Marked	0 (0.0)	0 (0.0)	2 (7.7)	3 (25.0)				
Fibroglandular tissue								
Fatty	2 (50.0)	2 (14.3)	0 (0.0)	0 (0.0)	$P=.001$ $T=731.0$ $z=3.5$	$P=.065$ $T=183.0$ $z=1.8$	$P=.009$ $T=127.0$ $z=2.6$	Coefficient = 0.0450 $P=.001$
Scattered density	1 (25.0)	7 (50.0)	8 (30.8)	3 (25.0)				
Heterogeneous density	1 (25.0)	5 (35.7)	18 (69.2)	6 (50.0)				
Severe density	0 (0.0)	0 (0.0)	0 (0.0)	3 (25.0)				

Table 4. Trends between background parenchymal enhancement and fibroglandular tissue with ultrasound breast composition.

VARIABLES	ULTRASOUND BREAST COMPOSITION FREQUENCY (%)			JONCKHEERE-TERPSTRA TEST			SPEARMAN RANK ORDER CORRELATION
	HOMOGENEOUS FATTY	HOMOGENEOUS FIBROGLANDULAR	HETEROGENEOUS FIBROGLANDULAR	TOTAL	PREMENOPAUSAL	POSTMENOPAUSAL	
Background parenchymal enhancement							
Minimal	3 (42.9)	2 (8.7)	10 (13.5)	$P = .046$ $T = 1455.0$ $z = 2.0$	$P = .758$ $T = 501.5$ $z = 0.3$	$P = .095$ $T = 154.5$ $z = 1.7$	Coefficient = 0.193 $P = .050$
Mild	3 (42.9)	14 (60.9)	25 (33.8)				
Moderate	0 (0.0)	5 (21.7)	32 (43.2)				
Marked	1 (14.3)	2 (8.7)	7 (9.5)				
Fibroglandular tissue							
Fatty	2 (28.6)	1 (4.3)	1 (1.4)	$P = .036$ $T = 1455.0$ $z = 2.1$	$P = .716$ $T = 456.5$ $z = -0.4$	$P = .007$ $T = 175.0$ $z = 2.7$	Coefficient = 0.206 $P = .036$
Scattered density	1 (14.3)	10 (43.5)	14 (18.9)				
Heterogeneous density	4 (57.1)	7 (30.4)	48 (64.9)				
Severe density	0 (0.0)	5 (21.7)	11 (14.9)				

Author Contributions

AA designed the concept. All authors collaborated in data acquisition. MB provided statistical advice on study design and data analyses. SNMY, SAK and HA interpreted the data. SNMY and MB drafted the manuscript. All authors reviewed the manuscript and approved the final draft. AA takes responsibility for the paper as a whole.

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