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CORRELATIONS BETWEEN BACKGROUND PARENCHYMAL ENHANCEMENT ON BREAST MRI AND MORPHOPHYSIOLOGICAL PARAMETERS OF BREAST AND BREAST LESIONS

MEME MR'DA ARKA PLAN KONTRASTLANMASININ MEME PARANKİMİ VE MEME LEZYONLARININ MORFOFİZYOLOJİK ÖZELLİKLERİ İLE İLİŞKİSİ

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SUMMARY

Introduction: *To assess possible relationships between background parenchymal enhancement (BPE) of the breast and breast parenchymal density (BPD), the benign and malignant nature of lesions, malignant lesion subtypes (according to hormone receptor status), benign lesions subtypes, patient age and breast volume.*

Material and Methods: *During the study period, a total of 1210 patients were evaluated with dynamic breast magnetic resonance imaging. Males and patients who had under gone neoadjuvant chemotherapy, hormonal therapy and breast surgery were excluded. Also, patients who were initially classified as BI-RADS 1 with MRI but presented any lesions with other modalities were also excluded from the study. Finally, this study was carried out on 899 patients.*

Results: *It was determined that all lesion types were mostly seen in the perimenopausal period. In the study group, 256 patients had histopathological results which showed the presence of malignancy in 140 patients, while 116 had benign lesions. The patients with benign lesions were found to have higher but the patients with malignant lesions have lower BPD and BPE levels. No statistically significant differences were found between the molecular subtypes of malignant lesions in terms of BPE, BPD, menopausal status and breast volume ($p = 0.739$, 0.426, 0.344, 0.933, respectively).A statistically significant difference was found between patients without any lesions (BIRADS-1) and patients with benign or malignant lesions according to their menopausal status ($p<0.001$).*

Conclusion: *Patients with benign lesions were found to have a higher BPD and BPE, but no correlation was found between the benign subgroups. In the same way, the BPD and BPE was lower in patients with malignant breast lesions. There were no correlation between high BPE and malign lesions or molecular subtypes. It can be concluded by this study that high BPE and high BPD are not risk factors for development of malignancy.*

ÖZ

Giriş: *Bu çalışmadaki amacımız; meme arka plan kontrastlanmasını (APK) tiplendirerek, meme parankimal doku yoğunluğu (PDY), malign ve benign lezyonların dağılımı, malign (hormon reseptörlerine göre) ve benign lezyonların subtipleri, hasta yaşı ve meme hacmi ile ilişkisinin olup olmadığını göstermektir.*

Gereç ve Yöntem: *Çalışmamızda 1210 hasta dinamik meme manyetik rezonans görüntüleme (MR) ile değerlendirildi. APK şiddetinin düzgün değerlendirilmesi için neoadjuvan kemoterapi, hormon terapi, mastektomili*

hastalar ve erkek hastalar ile meme MR bulgularına göre BIRADS 1 olarak raporlanan ancak diğer meme görüntülemelerinde her hangi lezyon tespit edilen hastalar çalışma dışı bırakıldı. Bu kriterlere uyan toplam 899 hasta çalışmaya dahil edildi.

Bulgular: *Tüm lezyonların en sık perimenapozal dönemde görüldüğü belirlendi. Toplam 256 hastanın patolojik sonucu olup bu hastaların 140'ı malign,116'ı benign grupta değerlendirildi. Benign lezyonu olan hastalarda APK ve PDY daha yüksek bulundu, fakat benign subgruplar arasında korelasyon saptanmadı. Öte yandan, malign lezyonu olan hastalarda APK ve PDY daha düşük bulundu. APK ve PDY açısından malign lezyonların moleküler subtipleri, menapoz durumu ve meme hacmi arasında istatistiksel anlamlı fark bulunmadı (p = 0.739, 0.426, 0.344, 0.933, sırasıyla). Memede BIRADS 1, benign ve malign lezyon görülen hastalarda menopoz durumları açısından gruplar arasında istatistiki açıdan anlamlı fark saptandı (p<0.001).*

Sonuç: *Benign lezyonu olan hastalarda APK ve PDY yüksektir, ancak benign subgruplar arasında ilişki gösterilememiştir. Aynı şekilde PDY ve APK malign hastalarda düşüktür. Yüksek APK ile malign lezyonlar ve subtipleri arasında ilişki saptanmamıştır. Çalışmamıza göre yüksek APK, dens meme parankim yoğunluğu meme malignitesi gelişimi için bir risk faktörü değildir.*

INTRODUCTION

Background parenchymal enhancement (BPE) in dynamic contrast breast magnetic resonance imaging (DC-MRI) is caused by the normal staining of fibroglandular tissue after contrast administration. BPE is increased in young women during lactation and in those receiving hormone replacement therapy (1-2). Fibrogenic tissue enhancement reduces imaging sensitivity in some situations, such as mammographic examination of parenchymal dense breasts, so the BPE grade in MRI results should be specified as a pattern (3). Normal background enhancement has been classified as minimal (Type 1, 0–25% enhancement of glandular tissue), mild (type 2; 26-50% enhancement of glandular tissue), moderate (type 3; 51-75% enhancement of glandular tissue), and marked enhancement (type 4; >75% enhancement of glandular tissue) (4-5). A typical BPE demonstrates bilateral, symmetric and diffuse scattering of high signal within the breast parenchyma. In these cases, there is usually no difficulty in reporting. However, in cases where BPE is focal and/or asymmetric, it may lead to confusions in terms of determining whether the enhancement is pathological or a type 3/4 BPE, making the imaging of lesions, especially smaller ones, difficult (6). As such, the evaluation of BPE and recognizing its inherent characteristics is vital for accurate image assessment in patients undergoing breast MRI. Therefore, quantifying BPE with regard to other characteristics of the breast and/or lesions may prove critical for diagnosis and treatment approach.

Our primary aim was to classify breast BPE and compare its levels with breast density, and to determine whether BPE was associated with benign and malignant lesions, the different subtypes of malignant and benign lesions, and other characteristics such as patient age and breast volume.

MATERIAL AND METHOD

This retrospective cohort study was carried out in the Department of Radiology of İzmir Bozyaka Training and Research Hospital between May 2015 and December 2016 among the patients who had undergone breast MRI examinations, after obtaining ethics committee approval.

During the study period, a total of 1210 patients were evaluated with dynamic breast MRI. In our hospital, breast MRI examinations are carried out between the 7th and 14th days of the menstrual cycling order to avoid adverse effects of the cycle on BPE values, especially in premenopausal women. Those undergoing neoadjuvant chemotherapy, hormone therapy and mastectomy, and male patients were excluded from the study in order to be able to evaluate BPE values in a homogenous group. Patients who were reported as BIRADS 1 according to breast MRI findings but were found to have any detectable lesions with other imaging modalities were also excluded from the study. A total of 899 patients who met these criteria were included in the study.

Patient selection and characterization

Patient demographics and clinical/imaging findings were obtained from patient files or imaging records. Patients were grouped with regard to BPE and BPD levels, pathological results (malignant vs. benign), hormone receptor

status and BIRADS classification. Patients with malignant or benign lesions were further placed into subgroups. Benign lesion subgroups and included conditions/lesion types are in subgroups: Group 1 (non-proliferative breast lesions):Ductal ecstasy, cyst, apocrin metaplasia, adenosis, non-complex fibroadenoma, lipoma, hamartoma, fat necrosis, intramammarial lymph node, mastitis; Group 2 (proliferative breast lesions): Simple ductal hyperplasia, intractable papilloma, sclerosis adenosis, benign type filloides tumor, periductal stromal tumor, radial scar; Group 3 (proliferative breast lesions with atypia):Atypical ductal hyperplasia, atypical lobular hyperplasia, lobular carcinoma insitu (4)

The histopathological results of patients who had undergone pathological evaluation were also recorded, and malignant lesions were categorized according to hormone receptor status (Estrogen receptor, ER; progesterone receptor, PR; and human epidermal growth factor receptor 2,HER2). ER or PR positivity of the lesions were determined according to a minimum 1% staining level (7). Lesions were categorized according to 4 histopathologic subtypes: Luminal A (ER + and / or PR +, HER2 -); Luminal B (ER + and / or PR +, HER2 +) or (ER + and / or PR +, HER2 -, Ki 67 ≥14); HER2 + (ER- and PR-, HER2+) and Triple negative (ER-, PR-, HER2-) (8). The pathological diagnosis of malignant lesions, histopathologic subtypes (luminal A, luminal B, HER2 +, Triple-), hormone receptor status (ER, PR) were noted and the relationship between these parameters and BPE, BPD, menopausal status and breast volume were evaluated.

Ethical issues

The ethical approval for this study was obtained from the Clinical Research Ethical Committee of Bozyaka Education and Research Hospital. All procedures were performed according to the principles of the Helsinki Declaration.

Breast MRI technique and interpretation of images

Breast MRI was performed using a 1.5 Tesla MR device (Achieva; Philips Healthcare, Best, the Netherlands). The MRI parameters were: TR:550 ms For T1-Weighted TSE, 1741 for Diffusion weighted images (DWI), TE: 8.0 ms for T1-Weighted TSE, 74 for DWI, Nex: 2 for T1-Weighted TSE, 8 for DWI. Slice thickness was 3 mm, FOV was 300 mm, matrix width 300x240 mm for both of the sequences. The images of the patients included in the study were evaluated separately and independently by two radiologists. In case of any differences in the interpretation of images, a single outcome was determined by the consensus of these two radiologists. While breast parenchymal density (BPD) was assessed on axial fat suppressed T1-weighted spin echo images, background enhancement was assessed on post-contrast fat suppressed T1-images. Images were graded according to BIRADS and the following characteristics were recorded: BPD, BPE, BIRADS categorization of lesions, patient age and breast volume (the largest antero-posterior and transverse diameters on the section passing from areola/nipple).

Patients were grouped into 4 categories according to BPD as follows: BIRADS type A lipomatous (parenchymal fat ratio≤25%), BIRADS type B-lipomatous weighted liposclerosis (parenchymal fat ratio=26–50%), BIRADS type C-liposclerosis heterogeneous (parenchymal fat ratio=51–75%), BIRADS type D-sclerosis (parenchymal fat ratio greater than 75%). According to breast BPE, patients were divided into 4 groups:minimal (type 1) (glandular tissue enhancement (less than 25%), mild (type 2) (26–50% glandular tissue enhancement), moderate (type 3) (51–75% glandular tissue enhancement) and severe (type 4) (greater than 75% glandular tissue enhancement) (Figure 1) (4-5). Breast MRI results were concluded as BIRADS 1 (negative-normal), 2 (benign), 3 (high likelihood of benign lesion), 4 (high risk for malignancy), and 5 (malignant).

Patients were divided into three groups according to their age: premenopausal (0-40 years), perimenopausal (41-55 years) and postmenopausal (>56 years). Breast volume (largest antero-posterior and transverse diameters on the section crossing on the nipple/areola) were measured and recorded. Cross-sectional volumes were calculated for each patient and mean right and left breast volumes were obtained.

Benign lesions were examined in 3 groups according to pathological diagnosis. The first group included benign and non-proliferative breast lesions, the second group included benign and proliferative lesions, while the third group

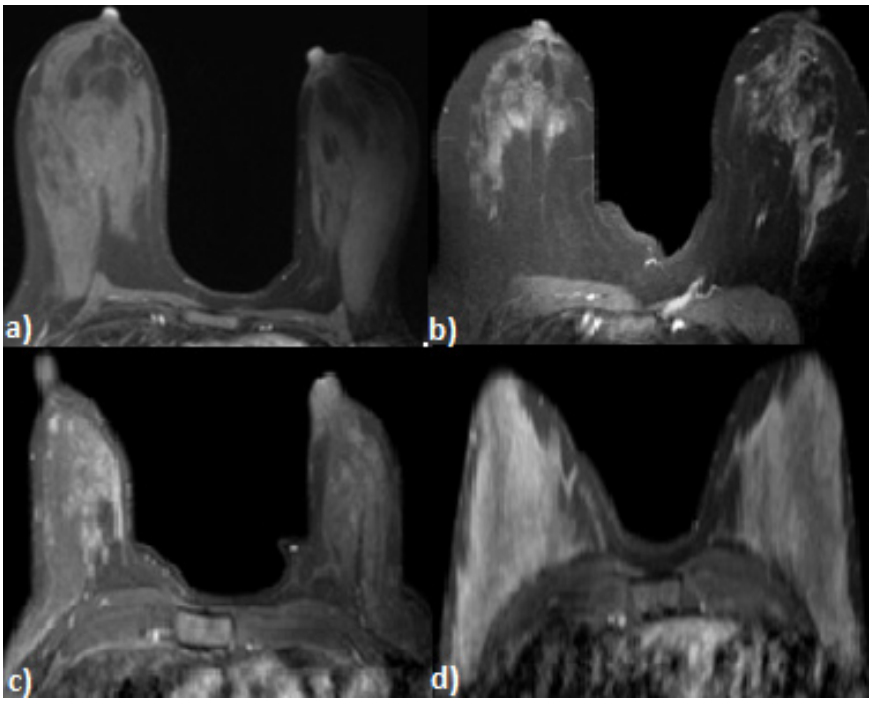

Figure 1. Breast BPE types.
a) Minimal (TYPE 1) BPE in 27 elderly patient b) Mild (TYPE 2) BPE in 39 elderly patient
c) Moderate (TYPE 3) BPE in 37 elderly patient d) Severe (TYPE 4) BPE in 21 elderly patient
(BPE: Background parankimal enhancement)

was comprised of atypical proliferative lesions. The relationship between BPE type, BPD type, menopausal status and breast volume were evaluated among these groups.

Additionally, patients with benign and malignant lesions were compared with patients with BIRADS 1 lesions. These patients were evaluated in terms of whether they had a significant difference in BPE, BPD, menopausal status and breast volume.

Statistical analysis

The suitability of the variables to normal distribution was examined by visual (histogram) and analytical methods (Kolmogorov Smirnov test). The numerical values collected in the study were expressed with mean, median, standard deviation and range values, while categorical data were expressed by descriptive values such as number (n) and percentage (%). Comparisons between the means of two independent groups were performed with the Student t-test or the Mann-Whitney U test, depending on normality of distribution. Whether or not there was a difference between categorical parameters (in cross-tables) was assessed using Chi-square or Fisher tests. One-way variance analysis method was used for the comparison of measured variables expressed in multiple groups and multiple variables in one group. The homogeneity of variances was assessed by the Levene test. Two-way post-hoc analysis was used to evaluate statistically significant differences between two specific groups after initial comparisons. We used the Tukey test for homogeneous variances and the Tamhane's T2 test for inhomogeneous variances. Hosmer-Lemeshow test was used for model adaptation. Cases in which the Type1 error level was below 5% were interpreted to demonstrate statistical significance. The SPSS version 22.0 statistical package program was used in all analyses.

RESULTS

Demographic and clinical characteristics of the study group are depicted in Table 1. The mean age of the 899 female patients included in our study was calculated as 47.10 ± 11.90 years. BPE was observed in 246 (27.4%) patients as

type 1, in 286 (31.8%) patients as type 2, in 237 (26.4%) patients as type 3 and in 130 (14.5%) patients as type 4. The level of BPE in fatty breasts were found to be significantly lower compared to dense breasts in overall comparisons and also in each menopausal subgroup (premenopausal, perimenopausal and postmenopausal) (p<0.001, p=0.013, p<0.001, p=0.001, respectively)

Table 1. Demographic and clinical data of the study group

Age (Mean ±SD)	47,10±11,90	
Menopausestatus	Number	%
Premenopausal(<40years)	243	27,0
Perimenopausal(41-55years)	462	51,4
Postmenopausal(>56years)	194	21,6
Total	899	100
Breastdensity on MRI	Number	%
BIRADS Type A	101	11,2
BIRADS Type B	314	34,9
BIRADS Type C	329	36,6
BIRADS Type D	155	17,2
Total	899	100
BPE	Number	%
Type 1(Minimal)	246	27,4
Type 2(Mild)	286	31,8
Type 3(Moderate)	237	26,4
Type 4(Severe)	130	14,5
Total	899	100
MRI results	Number	%
BIRADS 1	110	12.2
BIRADS 2	175	19.5
BIRADS 3	380	42.3
BIRADS 4	126	14
BIRADS 5	108	12
TOTAL	899	100
Pathologicalresults	Number	%
Benign	116	45.3
Malign	140	54,7
Summary	256	100
Breastsdimensions	Mean ±SD	
Right breastdimensions (mm^2)	9604± 4424	
Leftbreastdimensions (mm^2)	9664 ± 4691	
Meanbreastdimensions (mm^2)	9634 ± 4443	

BIRADS: Breast Imaging Reporting and Data system, BPD: Background parenchymal density, BPE: Background parenchymal enhancement,

SD: Standards deviation,

minimal (type 1) (glandular tissue enhancement (less than 25%), mild (type 2) (26–50% glandular tissue enhancement), moderate (type 3) (51–75% glandular tissue enhancement) and severe (type 4)

A total of 256 patients had pathological results and 140 of these samples were deemed to be malignant, while 116 were benign. One lesion that turned out to be malignant could not be distinguished in MR images and was reported as BIRADS 2; whereas pathologic microcalcifications of this lesion were detected on mammography. The pathology result of another patient who was reported to have a BIRADS 5 lesion on MRI was conclusive for atypical ductal hyperplasia, hence this patient was transferred to the benign group. In malignant cases, BPE was significantly lower compared to benign cases (p = 0.002). Also the prevalence of fatty breast was also more frequent in the malignant group compared to benign group (58.6% vs. 36.2%, p <0.001, Table 2). BPD, type of BPE, menopausal status and breast volume of 116 patients having benign pathological results were evaluated in also table 2.The prevalence of BIRADS 2 and 3 in benign cases was significantly higher compared to malignant cases (p <0.001). While 58.6% of benign cases were BIRADS 2 and 3; only 0.7% of malignant cases were BIRADS 2 and 3. There was no statistically significant difference between breast volumes of benign and malignant cases (p = 0.143).

There was statistically significant difference in BPE and BPD between groups according to the BIRADS classifications of benign lesions (Table 3). The difference in BPE was caused by the higher BPE in BIRADS 3 group compared to BIRADS 1 and BIRADS 2 (p <0.001). The difference in BPD was caused by higher incidence of dense breasts in BIRADS 3 group compared to BIRADS 1, BIRADS 4 and BIRADS 5 groups (p <0.001). The breast volumes of those with low BPE were significantly higher compared to those with high BPE (in overall comparisons and also in benign and malignant subgroups)(p <0.001; 0.002; <0.001, respectively).

There was a significant difference between menopausal groups in terms of the frequency of malignancy. In subgroup analyses, it was determined that this difference existed due to the higher prevalence of malignant cases in the perimenopausal period compared to premenopausal period (p = 0.007), and also due to the higher prevalence in the postmenopausal period compared to both premenopausal and perimenopausal periods (p<0.001; p<0.001, respectively). Moreover, all lesions were found to be seen most frequently in the perimenopausal period.

Table 2. Comparison of benign and malignant cases.

	Benign cases	Malignant cases	*Statistical Analysis*	
	n(%)	*n(%)*	X^2	*p*
Background parenchymal enhancement (BPE)				
Low	54(46.6)	92(65.7)	9.506	0.002
High	62(53.4)	48(34.3)		
Background parenchymal density (BPD)				
Fatty Breast	42(36.2)	82(58.6)	12.704	<0.001
Dense Breast	74(63.8)	58(41.4)		
Menopause Status				
Premenopausal	43(37.1)	20(14.3)	31.073	<0.001
Perimenopause	59(50.9)	65(46.4)		
Postmenopausal	14(12.1)	55(39.3)		
BIRADS				
2 and 3	68(58.6)	1(0.7)	108.041	<0.001
4 and higher	48(41.4)	139(99.3)		
Breast Volume: *Mean±SSMean± SS*	*p*			
	9593±4869	10464±4589	0.143	

FattyBreast: BIRADS type A lipomatous (parenchymal fat ratio≤25%), BIRADS type B-lipomatous weighted liposclerosis (parenchymal fat ratio=26–50%), Dense Breast: BIRADS type C-liposclerosis heterogeneous (parenchymal fat ratio=51–75%), BIRADS type D-sclerosis (parenchymal fat ratio greater than 75%). Low BPE: minimal (type 1) (glandular tissue enhancement (less than 25%) and mild (type 2) (26–50% glandular tissue enhancement), High BPE: moderate (type 3) (51–75% glandular tissue enhancement) and severe (type 4) (greater than 75% glandular tissue enhancement)

Table 3. Comparison of benign groups according to BIRADS classification in terms of BPE and BPD

	BPE				BPD			
Pathologic subtypes	Low	High	Statystical analysis		Fatty breast	Dense breast	Statystical analysis	
	n(%)	*n(%)*	X^2	*p*	*n(%)*	*n(%)*	X^2	*p*
Group 1	42 (50)	42(50)	1.742	0.418	30 (35.7)	54 (64.3)	0.341	0.843
Group 2	10 (40)	15 (60)			10 (40.0)	15 (60)		
Group 3	2 (28.6)	5 (71.4)			2 (28.6)	5 (71.4)		
Premenopousal 43								
Group 1	14 (45.2)	17(54.8)	0.043	0.836	3 (9.7)	28 (90.3)	*	0.325
Group 2	5 (41.7)	7 (58.3)			3 (25)	9 (75)		
Group 3	-	-			-	-		
Perimenopousal 59								
Group 1	19 (44.2)	24 (55.8)	1.881	0.390	19 (44.2)	24 (55.8)	1.126	0.570
Group 2	3 (27.3)	8 (72.7)			5 (45.5)	6 (54.5)		
Group 3	1 (20)	4 (80)			1 (20)	4 (80)		
Postmenopousal 14								
Group 1	9 (90)	1 (10)	2.567	0.277	8 (80)	2 (20)	1.527	0.446
Group 2	2 (100)	0 (0)			2 (100)	0 (0)		
Group 3	1 (50)	1(50)			1 (50)	1 (50)		

Group 1 (non-proliferative breast lesions): Ductal ecstasy, cyst, apocrin metaplasia, adenosis, non-complex fibroadenoma, lipoma, hamartoma, fat necrosis, intramammarial lymph node, mastitis; Group 2 (proliferative breast lesions): Simple ductal hyperplasia, intractable papilloma, sclerosis adenosis, benign type filloides tumor, periductal stromal tumor, radial scar; Group 3 (proliferative breast lesions with atypia): Atypical ductal hyperplasia, atypical lobular hyperplasia, lobular carcinoma insitu; Background parenchymal density (BPD), Background parenchymal enhancement (BPE)

A separate categorization was performed in 110 patients who had been reported as BIRADS 1 according to breast MRI. Breast BPE, BPD, and menopause status of patients were also evaluated and these parameters were assessed with regard to benignancy/malignancy (Table 4). There was a statistically significant difference found between groups of patients with BIRADS 1, benign and malignant lesions in terms of BPE (p <0.001). Again with further subgroup analysis, we found that malignant patients tended to have a significantly lower BPE level compared to benign lesions.

In two patients, pathologic diagnoses were isolated ductal carcinoma in situ, and hormone receptor status of these patients was not defined. In 138 malignant patients, no statistically significant differences were found between the molecular subtypes of malignant lesions (Luminal A, Luminal B, Triple- and HER2+ subgroups) in terms of BPE, BPD, menopausal status and breast volume. Patients with benign lesions also did not demonstrate any significant differences in regard to these parameters. Also there wasn't any statistically significant difference in BPE and BPD between estrogen and progesterone receptor status in malignant patients regardless of menopausal status.

Regression analysis revealed that each SD of increase in mean age caused an increase in the likelihood of malignancy by an OR of 1.08. Higher BPE was inversely associated with the likelihood of malignancy (OR: 0.454, 95% CI: (0.274-0.753). Dense BPD also provided a similar protective effect compared to lower BPD (OR: 0.401, 95% CI (0.242 to 0.666). However, BPE and BPD lost statistical significance in multivariate analysis; whereas the age variable maintained its significance (OR: 1.082; 95% CI: 1.050-1.115) (Table 5).

Table 4. Relationship of BPE and BPD according to malignancy status.

Background parenchymal density (BPD)	Background parenchymal enhancement (BPE)			
	Low BPE (%)	High BPE (%)	Statistical analysis	
Total Patients (899 patients)				
	n(%)	n(%)	X^2	*p*
Fatty Breast(A,B)	331(79.8)	84(20.2)	135.172	<0.001
Dense Breast(C,D)	201(41.5)	283(58.5)		
BIRADS 1 (110 patients)				
Fatty Breast(A,B)	56(86.2)	9(13.8)	14.441	<0.001
Dense Breast(C,D)	24(53.3)	21(46.7)		
BENIGN (116 patients)				
Fatty Breast(A,B)	31(73.8)	11(26.2)	19.660	<0.001
Dense Breast(C,D)	23(31.1)	51(68.9)		
MALIGN (140 patients)				
Fatty Breast(A,B)	67(81.7)	15(18.3)	22.479	<0.001
Dense Breast(C,D)	25(43.1)	33(68.8)		

Table 5. Odds ratios of the variables related to the malignancy in breast lesions.

Risk factor	Rough OR (%95 CI)	P value	Adjusted OR(%95 CI)	P value
Age	1,081 (1,054-1,109)	<0,001	1,082 (1,050-1,115)	<0,001
BPE (ref:Low)	1	0,002	1	0,224
High	0,454 (0,274-0,753)		0,690 (0,379-1,255)	
BPD (ref:fatty)	1	<0,001	1	0,511
Dense	0,401 (0,242-0,666)		1,254 (0,639-2,463)	

DISCUSSION

Breast tissue consists of fat and fibroglandular tissue. Radiologically, the proportion of fibroglandular tissue to fat tissue is always of interest in studies, due to possible relationships with breast cancer. In some of the studies, BPE has also been somewhat associated with breast cancer (5, 9, 10, and 11). In our study, prevalence of BPD was found to be highest in patients with benign histopathology followed by malignant and BIRADS 1 patients table 4). In the same manner, prevalence of BPE was found to be highest in the benign group followed by malignant and BIRADS 1 patients (Table 4). In a similar study to ours, Bennani-Baiti et al. also observed a lower BPE in malignant lesions (9). Contrarily, in a study by King et al. higher background enhancement was observed in malignant lesions. We think this outcome may have resulted from the difference in patient selection criteria, in the latter study patients receiving HRT treatment were also included (5).

Menopausal status is also another issue to be evaluated. Since risk of breast cancer increases with longer exposure to estrogen during lifetime; the incidence and prevalence is predominantly higher in post-menopausal period women(1).Our results show that the peri-menopausal period is the most common timeframe for diagnosis of each and all radiological/histopathological groups of lesions; either for BIRADS 1, benign or malignant (table 2, 4). In contrast to our results, Bennani-Baiti et al. and a few others reported a higher incidence of breast masses in the postmenopausal period 9). There are also studies showing a lack of difference in regard to menopausal status, such as Öztürk et al., who found similar frequencies in the premenopausal and postmenopausal periods (12).We concluded that this may have been related to the characteristics of our study population, institutional policies and ease of access to diagnostic services allowing earlier diagnosis – hence affecting the age of diagnosis. However, many other explanations, including ethnic and racial differences, patient and family history and the public's knowledge levels regarding breast cancers, could also be true.

The relationships between BPD and BPE (and other factors) may be seen as an issue of interest in breast cancer, especially in the absence of imaging methods that have very high accuracy in diagnosis. In our study, there was a significant relationship between breast BPE and BPD (Table 2, 4, 5). This relationship was demonstrated to be significant in all premenopausal, perimenopausal and postmenopausal groups; whereas this association was found to be significant only in premenopausal patients in the study by Talale and colleagues (2), and in postmenopausal patients in the study by Wei et al. (3).

We have found that the BPE of fatty (low BPD) breasts were significantly lower than that of dense (high BPD) breasts regardless of menopausal status (Table 4). Although BPE and BPD had differed among benign and malignant lesions, we could not find any difference among the Luminal A, Luminal B, Triple- andHER2+ subgroups of malignant lesions. Our results may also be influenced from statistically unequal distribution among molecular subgroups. In our study, we did not observe any change in BPE and BPD related to estrogen and progesterone receptor status in any group of patients regardless of menopausal status. Supportively, Bennani-Baiti et al. also found no significant relationships between hormone receptor and BPE values (10). However, Öztürk et al. reported that BPE was significantly higher in estrogen-positive patients (12).

The levels of BPE and BPD, menopausal status and breast volume didn't differ with regard to histopathological subgroups of benign patients (Table 3). In a study by Tice et al., a significant correlation between benign lesions and BPD was demonstrated; high BPD came out to be most prevalent in benign group 3 patients (atypical proliferative). Since the patients in these groups were at risk for malignancy, it was concluded that BPD was a risk for malignancy (13). Based on the low number of patients in this group, we could not estimate this outcome confidentially with our study. Tice et al, did not evaluate the other parameters that we have studied here. Our results conclude that BPE and BPD characteristics and their possible relationships are independent of the histopathological nature of lesions and menopausal status of patients.

Although histopathological subgroup analysis of benign lesions did not demonstrate any

differences, BIRADS subgroups of benign lesions significantly differed due to their BPE and BPD status (table 4). With our results, it may be feasible to suggest that low BPE may influence diagnoses in benign and malignant patients. Yet, how many of such patients are subject to possibly false diagnoses due to BPE effects on MRI results, has not been evaluated within the scope of our study.

Although we have demonstrated that BPD and BPE differ among BIRADS 1, benign and malignant groups, we could not establish an important linear correlation between BPE/BPD and malignancy. Even though multivariate analysis pointed out that age is the sole variable positively correlating with malignancy. Despite this, as a result of pair wise correlations, higher BPE and BPD values seem to be associated with lesser risk for developing breast cancer. Contrarily, in a study by Dontchos et al., it was reported that there was a significant positive relationship between malignant lesions and high breast parenchymal density. However, the authors of said study only included 23 histopathologically confirmed malignant cases (11). In our study, this number was 140, ensuring reliability.

There are also some limitations in our study. These limitations primarily consisted of retrospective nature of the study, low number of patients in the benign group, inability to follow BIRADS 3 lesions due to cross-sectional study design, lack of quantitative BPE measurements, and also the exclusion of BIRADS 1 patients who had been diagnosed to have lesions in other diagnostic modalities.

CONCLUSION

The evaluation of the relationships between lesion characteristics and imaging findings from MRI studies in our group of 899 patients demonstrated significant relationships between the degree of BPE or BPD and various parameters investigated. We found that BPE was often at a higher degree in patients with dense breasts, regardless of menopausal status. Interestingly, a higher proportion of malignant patients were found to have fatty breast tissue and low BPE. Despite these relationships in larger groups, no significant differences were found in subgroups –neither in the benign nor the malignant groups. Age was the only parameter that remained significantly associated with a higher likelihood of malignancy in multivariate analysis.

Although the results of our study suggest a relationship between BPE and BPD and the pathological diagnoses of patients, it is evident that these relationships are mostly marginal. Furthermore, multivariate analyses demonstrated that neither BPE nor BPD were associated with a statistically increased risk for malignancy. Any future studies on this topic should aim to include a wider group of patients from different centers while ensuring that each and every one of their patients have pathologically-proven diagnoses in order to provide a basis for the assessment of the relationships between BPE and diagnostic results.

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