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Correlation of Mammographic Breast Density (MD) And Background Parenchymal Enhancement (BPE) With Various Factors Especially Receptor Status In Pakistani Population

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IMPORTANCE Breast is one of the most common cause of malignancy related mortality all over the world accounting for more than 5 million deaths per year. Mammographic dense breast tissue is one of the most common problem in diagnosing breast CA in females. It increases the risk of breast CA up to five times and is also associated with larger tumor size, axillary lymph node involvement, higher stage of tumor owing to delay in the diagnosis.

Background parenchymal enhancement is seen on MRI breast after administration of contrast. The level of BPE is variable among different age groups being higher in young women. It is affected by several factors including age, hormone levels, and menstrual cycle phase.

OBJECTIVE This study was done to investigate the correlation between mammographic breast density (MGD) and background parenchymal enhancement (BPE) at breast MRI with receptor status in our population.

MATERIALS AND METHODS It is a retrospective study conducted at women imaging department of Shaukat Khanum Memorial Cancer Hospital from January 2013 till January 2019. All the newly diagnosed breast cancer patients aged 20 to 70 years, with dense mammogram who underwent MR imaging prior to treatment will be included. The MR imaging detection rate of additional malignant cancers occult to mammography and ultrasound will be calculated. Data will be analyzed according to the following parameters: histopathological features of the index tumor and mammographic density. The histopathological examination will be taken as gold standard. The data will be compiled and analyzed using SPSS

CONCLUSIONS High mammographic density and increased BPE are independent risk factors for the development of breast cancer. Exposure to hormones influence the BPE grade and thus is associated with increased risk of breast CA with a positive correlation between increased MGD and high BPE with both estrogen and progesterone receptors.

KEYWORDS Background parenchymal enhancement (BPE) mammographic density (MD), MRI, Breast cancer (CA)

KEYWORDS Breast Cancer, Radiology, Mammographic Breast Density, Background Parenchymal Enhancement.

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Breast carcinoma (CA) is one of the most common cause of malignancy related mortality all over the world accounting for more than 5 million deaths per year.[1] Better diagnostic modalities have been devised leading to early detection of the tumor, in which mammogram and ultrasound (USG) play initial role. The mammographic dense breast tissue, however is one of the most common problem in diagnosing breast CA in females. Almost half of the women above 50 years have high mammographic density breast tissue making the diagnosis difficult.[2] High breast density is because of increased amount of fibroglandular tissue including fibroblast, connective tissue and epithelial cells. It appears as an opaque region on mammogram.[3] In dense breasts the lesions can be masked which can lead to increases the risk of breast CA up to 5 times and is also associated with larger tumor size, axillary lymph node involvement and higher stage of tumor owing to delay in detection.[4] BIRADS guidelines are followed to describe mammographic density (MD) as four categories on mammogram ranging from extremely fatty to extremely dense.[5]

In contrary to MD, the background parenchymal enhancement (BPE) is seen on magnetic resonance imaging (MRI) of breast after administration of contrast. [6] Following the new BIRADS MRI Lexicon, this is qualitatively classified as minimal, mild, moderate and marked on the basis of degree of enhancement.[7] The level of BPE is variable among

different age groups being higher in young women. It is affected by several factors including age, hormone levels and menstrual cycle phase.[8] It has been established by recent studies that increase in BPE is associated with increased risk of cancer.[9]

Our study was done to see correlation between mammographic breast density (MD) and background parenchymal enhancement (BPE) seen on breast MRI in patients with breast CA as well as to establish their relationship with other factors like receptor status, type of tumor and stage of tumor at the time of presentation in our population.

MATERIAL AND METHODS:

It is a retrospective cross-sectional study conducted at the Women Imaging Radiology Department, Shaukat Khanum Cancer and Memorial Hospital Lahore. Our study included a total 336 patients in a study duration of 3 years, from 01-January 2015 to 31-December 2019. A total 152 patients of breast CA diagnosed on histopathology of all stages for whom preoperative mammography, ultrasound and MRI breast had been acquired were included in our study. Patient who received any treatment like chemotherapy, radiotherapy or hormonal treatment in between the imaging were excluded. Also, the patients with history of previously treated breast CA and those with incomplete or missing report or any investigation were also excluded.

Breast MRI were performed on Philips 1.5 T MRI system with a dedicated 7 channel breast coil. Bilateral Breast examination performed while patient lying in prone position. After obtaining a three plane localizer, axial fat-suppressed T2-weighted fast spin-echo sequence and T1 weighted Fast Spin Echo sequence acquired consecutively. Gadovist (Gadobutrol) contrast was injected through an automated injector by following the access of ante-cubital vein at the dose of 0.1mmol/kg of body weight with flow rate of 3ml/sec followed by 20ml saline flush. Dynamic contrast-enhanced MRI examination including one pre-contrast and five post-contrast series. Sagittal Images of Right and left breast acquired by using Fat-suppressed T1 weighted Fast Spin echo sequence consecutively. The MRI images used for analysis in this study were maximum intensity projections (MIP) of the subtracted images of the first and last post-contrast image from the stack of dynamic series.

The interpretation on MRI was done by two experienced radiologists with a minimum of 5 years expertise in breast imaging. All the patients were reviewed in detail regarding radiological imaging including USG, mammography followed by MRI and histopathological analysis. The MD were divided into 4 grades from fatty to dense according to American College of Radiology.[10] Histopathological features of the index tumor including histological grade and size of tumor and nodal metastasis status were registered. The hormone receptors status was determined by Allered score. Three receptors including estrogen receptor ER, progesterone receptor (PR) and Human epidermal growth factor receptors were identified using immunohistochemistry. The findings obtained on MRI were correlated with the conventional imaging results. Lesion description was noted and on MRI, each lesion was classified according to Breast Imaging Reporting and Data System (BI-RADS) classification system. The enhancement of normal breast parenchymal tissue on immediate post contrast acquisition was regarded as BPE and it was categorized into four grades from minimal to mark. MRI of contralateral breast was also assessed in detail for BPE. Results were formulated using SPSS. Descriptive and inferential statistical tests were applied for data analysis.

RESULTS

Out of total 152 patients, 122 (80.3%) were premenopausal and 30(19.7%) were postmenopausal. The low number of postmenopausal patients is attributed to the institutional policy in which age criteria is prioritized. The age range was 20 to 70 years with a mean age of 40.8 years SD 10.8. The histological analysis revealed 110 (72.4%) patients with ductal CA, 28 (18.4%) with lobular CA and rest 14 (9.2%) patients had both ductal and lobular histological types. Similarly infiltrating CA was present in 104 (68.4%) patients, in situ was seen in 8 (5.3%) patients and both infiltrating and insitu types were seen in 40 (26.3%) patients. The results are explained in table 1.

			Menopausal Status			
			Postmenopausal		premenopausal	
			Count	Column N %	Count	Colum n N %
Type of Breast Cancer	Infiltrating	Ductal	8	33.3%	72	90.0%
		Lobular	12	50.0%	8	10.0%
		Ductal+ Lobular	4	16.7%	0	0.0%
	In situ	Ductal	0	0.0%	6	75.0%
		Lobular	0	0.0%	2	25.0%
		Ductal+ Lobular	0	0.0%	0	0.0%
	Infiltrating + In situ	Ductal	2	33.3%	22	64.7%
		Lobular	0	0.0%	6	17.6%
		Ductal+ Lobular	4	66.7%	6	17.6%

Table 1 : Type of Breast Carcinomas in relation to menopausal status.

Among all the premenopausal and postmenopausal patients, the moderately dense category C mammographic density was observed in 70 (46.1%) patients, followed by high density category D mammographic density in 60 patients (39.5%). Similarly, minimal BPE was seen in 70 (46.1%) patients as depicted in Table 2. The categories of MD were divided in low (category A and category B) and high (category C and D). The BPE categories were also divided into high (moderate and marked) and low grade (minimal and mild).

		Count	Column N %
MD	Entirely fatty cat A	0	0.0%
	Mild fibro glandular cat B	22	14.5%
	Moderately dense cat C	70	46.1%
	Highly dense cat D	60	39.5%
BPE	Minimal	70	46.1%
	Mild	48	31.6%
	Moderate	20	13.2%
	Marked	14	9.2%

Table 2: Count and percentage of MD and BPE in study.

		MD GRADE				BPE GRADE			
		High		Low		High		Low	
		Count	Row N %	Count	Row N %	Count	Row N %	Count	Row N %
Menopausal status	Postmenopausal	18	60.0%	12	40.0%	16	53.3%	14	46.7%
	Premenopausal	112	91.8%	10	8.2%	18	14.8%	104	85.2%

Table 3: Relationship of MD and BPE with menopausal status.

MGD and BPE grading results were observed in premenopausal and post-menopausal patients as shown in Table 3. It was seen that high MGD was seen in 60 % (18/30) patients and 91.8 % (112/122) premenopausal patients. A significant correlation was observed with a p value < 0.001 in premenopausal patients and they were more likely to have high Mammographic density. For BPE, 104/120 (85.2%) premenopausal patients have low BPE showing a significant correlation p<0.05.

Variables		MD GRADE					BPE GRADE				
		High		Low		P-Value	High		Low		P-Value
		Count	N %	Count	N %		Count	N %	Count	N %	
Size Of The Index Lesion On U/S And Mammogram	Less Than 2cm	40	26.3%	6	3.9%	0.122	10	6.6%	36	23.7%	0.405
	More Than 2 Cm Less Than 5cm	88	57.9%	14	9.2%		22	14.5%	80	52.6%	
	More Than 5 Cm	2	1.3%	2	1.3%		2	1.3%	2	1.3%	
	Occult Lesion	0	0.0%	0	0.0%		0	0.0%	0	0.0%	
Lesion Location And Laterality On Mammogram And U/S	Unifocal	84	55.3%	12	7.9%	0.002	18	11.8%	78	51.3%	0.07
	Multifocal Unilateral	8	5.3%	4	2.6%		4	2.6%	8	5.3%	
	Multicentric Unilateral	30	19.7%	2	1.3%		8	5.3%	24	15.8%	
	Bilateral	8	5.3%	2	1.3%		2	1.3%	8	5.3%	
	Occult Lesion Nodes Positive	0	0.0%	2	1.3%		2	1.3%	0	0.0%	
Malignant Nodes On U/S Or Mammogram	No Nodes	58	38.2%	8	5.3%	0.619	10	6.6%	56	36.8%	0.11
	Ipsilateral Nodes	70	46.1%	14	9.2%		24	15.8%	60	39.5%	
	Contralateral Nodes	2	1.3%	0	0.0%		0	0.0%	2	1.3%	
	Ipsilateral + Contralateral	0	0.0%	0	0.0%		0	0.0%	0	0.0%	

Table 4: Correlation of MD and BPE with different variables

The correlation among variables with BPE and MGD was established (table 4)

A significant correlation was seen among location of breast CA lesion and mammographic density (p=0.002). Rest of the variables were not affected by MD. The type of CA, size of tumor, location and laterality, present of malignant nodes show no correlation with high BPE.

Table 5 explains the relationship of MD and BPE with receptor status. Among receptor status, both ER and PR

showed a significant relation with high BPE and MGD whereas HER2 (p=0.12) status was not affected by grade of BPE. The patients with high MD were most likely to have ER and PR positivity (p=<0.05).

Parameters		MD GRADE					BPE GRADE				
		High		Low		P-Value	High		Low		P-Value
		Count	N %	Count	N %		Count	N %	Count	N %	
Estrogen Receptor	Negative	90	59.2%	4	2.6%	<0.0001	2	1.3%	92	60.5%	<0.001
	Positive	38	25.0%	18	11.8%		32	21.1%	24	15.8%	
	Not Done	2	1.3%	0	0.0%		0	0.0%	2	1.3%	
Progesterone Receptor	Negative	88	57.9%	8	5.3%	0.005	4	2.6%	92	60.5%	<0.001
	Positive	42	27.6%	14	9.2%		30	19.7%	26	17.1%	
	Not Done	0	0.0%	0	0.0%		0	0.0%	0	0.0%	
Human Epidermal Growth Factor Receptor Type 2	Negative	72	47.4%	14	9.2%	0.589	16	10.5%	70	46.1%	0.083
	Positive	48	31.6%	8	5.3%		18	11.8%	38	25.0%	
	Equivocal	6	3.9%	0	0.0%		0	0.0%	6	3.9%	
	Not Done	4	2.6%	0	0.0%		0	0.0%	4	2.6%	

Table 5: Relationship of MD and BPE with Receptor status

Variables		MD GRADE					BPE GRADE				
		High		Low		P-Value	High		Low		P-Value
		Count	N %	Count	N %		Count	N %	Count	N %	
Name Of CA Ductal / Lobular	Ductal	98	64.5%	12	7.9%	0.06	16	10.5 %	94	61.8%	0.00026
	Lobular	20	13.2%	8	5.3%		14	9.2%	14	9.2%	
	Ductal+Lobular	12	7.9%	2	1.3%		4	2.6%	10	6.6%	
Type Of CA	Infiltrating	86	56.6%	18	11.8%	0.117	26	17.1 %	78	51.3%	0.241
	In Situ	6	3.9%	2	1.3%		0	0.0%	8	5.3%	
	Infilterating + In Situ	38	25.0%	2	1.3%		8	5.3%	32	21.1%	

Table 6: Correlation of MD and BPE with Breast cancer type.

POSTMENOPAUSAL PATIENTS		BPEGRADE				
		High		Low		P value
		N	Column N %	N	Column N %	
MDGRADE	High	4	25.0%	14	100.0%	<0.001
	Low	12	75.0%	0	0.0%	

PREMENOPAUSAL PATIENTS		BPEGRADE				
		High		Low		P value
		Count	Column N %	Count	Column N %	
MDGRADE	High	12	66.7%	100	96.2%	<0.001
	Low	6	33.3%	4	3.8%	

Table 7: Correlation of BPE and MD grade with Menopausal status

In Table 7 the BPE grade was compared with MD grade in pre-menopausal and post-menopausal patients, and it showed a significant correlation.

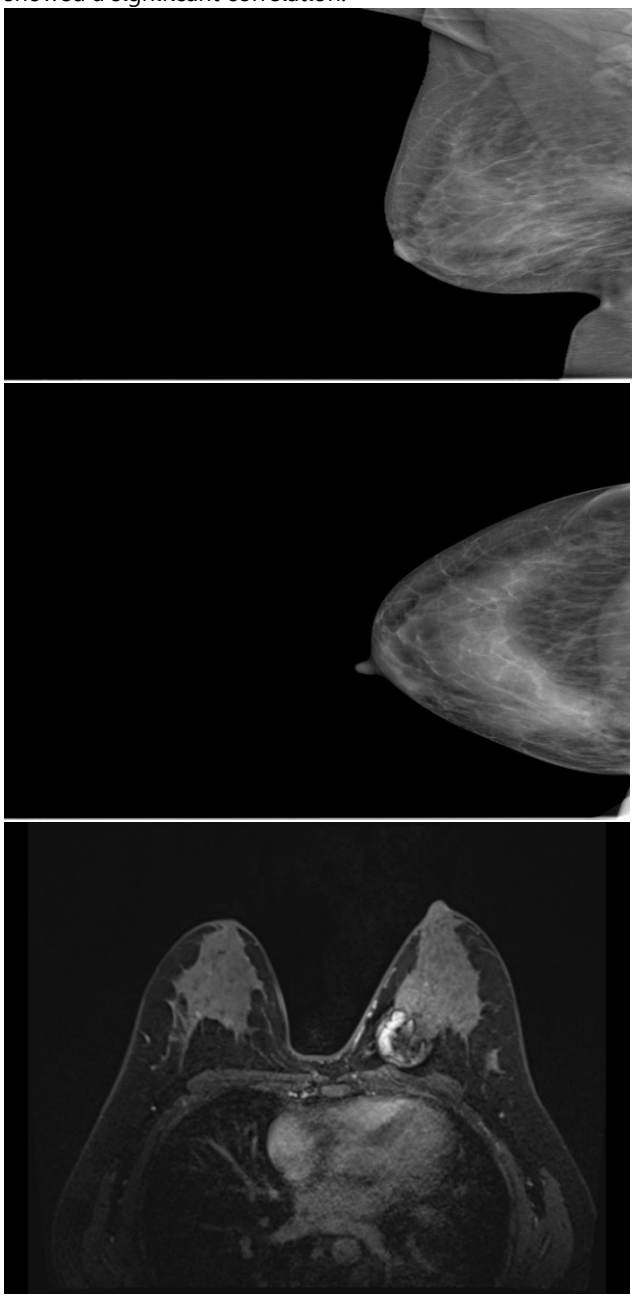

Figure 1: Image (a) and (b) Left breast mammogram CC and MLO views of a 40 year old premenopausal woman show markedly dense breast parendenchyma which leads to partial obscuration of the lesion. The lesion is difficult to visualize yet can be noticed at upper inner quadrant more appreciated on MLO view. Image (c) Show immediate post contrast T1 fat-sate axial image to look for BPE, we can appreciate that only minimal BPE is noted in this particular case.

DISCUSSION:

High Mammographic density is a major risk factor for the development of breast cancer. Also, it has a strong masking effect when it comes to the detection of small sized breast tumors.[11, 12] MRI is used to measure breast tissue density accurately. Normally BPE is increased in patients undergoing hormone replacement therapy or in lactating mothers due to increased fibroglandular tissue. However increased BPE is considered an independent risk factor for breast cancer[13] In our study we have correlated various factors with MD and BPE to determine significant difference among these. Our study revealed that menopausal status can play a significant role in developing Breast CA as it has significant association with high grade mammographic density and BPE as well. In a study done by Arsalan G, causes of raised BPE were evaluated that depicted a positive correlation with increased age hence needs to be observed closely. In premenopausal women, BPE was associates with hormonal status mainly.[14] Estrogen is considered to increase the vascularity and permeability of the blood vessels and results in BPE enhancement.[15, 16]

The type of breast CA, either ductal or lobular, has no significant correlation on mammographic density according to our study. However, the majority of patients with ductal CA have low BPE grade depicting a significant correlation. A study done by Suzaan Vreeman et al concluded that in the patients with unliteral breast CA, lower BPE in contralateral breast has direct association with high grade tumor.[17]

However, a study done by Valden V. et al investigated patients with invasive unilateral breast CA, and suggested that parenchymal enhancement in contralateral breast has significant association with the long-term outcome of the disease and has a predictive role especially when combined with receptor status.[18]

Other tumor characters including in situ or infiltrating nature of tumor and size of the lesion seems to have no direct correlation with parenchymal enhancement according to our results. Similarly, we assessed nodal status in all the patients and stratified them as patients ipsilateral, contralateral or no nodal involvement. The nodal involvement has no effect on BPE according to our study. A study done by Kim J Y et al also suggested that tumor size less than 2 cm has no correlation with BPE, however the tumors with more than 2 cm in size were associated with high BPE and may affect the size estimation of lesion.[19]

Hormonal status of receptors in the breast tissue has always been under discussion. Higher BPE and MD are associated with increased proliferative activity of the tumor. It has been postulated that exposure to hormones influence the BPE grade and thus is associated with increased risk of breast CA. Our study has depicted a positive correlation between increased MGD and high BPE with both estrogen and progesterone receptors. It explains that high estrogen and progesterone receptors are associated with increased BPE hence leading to increased risk of breast cancer. However, the Her 2 receptor has shown no significant association. Previous studies have shown variable results in this regard. Few studies have shown no association between estrogen receptor and BPE grading.[20, 21]

Interestingly one of the studies, done by Aiello EJ et al has shown that the relationship between high grade BPE and ER can be reverted by correcting the BMI.[22] This association between low grade tumor and receptor positivity has been shown in various studies. This explains the positive correlation between BPE and estrogen, progesterone receptor.[23] Contrarily, the increased expression of hormone receptor associated with increase BPE is related to increased risk of breast cancer.[24] This might explain that the pathogenesis of low grade and high-grade breast tumor is different. Positive correlation between progesterone receptor and high BPE has also been established in previous studies.[25] The expression of HER 2 in breast cancers has shown no significant correlation with BPE and MGD grade in our study. Previously many studies have shown the relation of HER-2 expression and decreased expression of BPE, however there is a need to further evaluate the relation between these entitites.[26]

In our study, there is a significant association between BPE and MD grade ($p<0.001$) regardless of the menopausal status. It implies that the patients with high MD grade should be subjected to MRI for accurate assessment. However previous studies have shown controversies in this regard. A study by Ko Es et al (2011) [13] found no significant correlation between BPE and MD. Contrarily, few studies have shown direct association between both entities.[27] Lately it has been described that high grade BPE is associated with high risk of breast cancer and can be used as an independent risk predictor of the disease.[28]

CONCLUSION:

BPE has been proved as a useful predictor of increasing risk of breast cancer. It can be used as an independent predictor of breast CA and can be combined with several other factors to enhance its predictive value. Particularly if used with hormonal expression and imagining characteristic of the tumor, it can be used as a novel entity for screening of breast cancer. This will help to choose a better treatment strategy for affected females and can also lead to adopt preventive measures before proceeding to invasive prophylactic methods.

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