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The Association Between Mammographic Breast Density and Breast Cancer Biology among Breast Cancer Women in Jordan

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ABSTRACT

Background: A mammogram is considered the gold standard modality for breast cancer screening. The sensitivity of breast mammograms is highly linked to mammographic breast density (MBD) which is strongly linked to women's age, ethnicity, and other factors. Higher breast density is considered one of the risk factors for breast cancer development and may be associated with different pathological and biological features of breast cancer. Our study aimed to explore the association between MBD and breast cancer biology among women in Jordan diagnosed with breast cancer.

Methods: This cross-sectional, retrospective review included 97 women diagnosed with breast cancer at a tertiary hospital in Jordan between 2018 and 2020. Mammographic breast density (MBD) and breast cancer biological characteristics were assessed, including the expression of estrogen receptors (ER+), progesterone receptors (PR+), and HER2 overexpression. The correlation between these biological characteristics and MBD was investigated.

Results: The analysis included 97 patients, of whom, 87.6% had either a PR^+ or an ER^+, and 38.1% of whom were positive for HER2/neu protein. The mean age was 56.4 and most patients were obese (56.7%). The MBD of our cohort was 30.9% (30/97) fatty, 29.9% (29/97) scattered, 23.7% (23/97) heterogeneously dense, and 15.5% (15/97) dense. The ER^+/PR^+ group was more common in fatty (35.3% vs 0.0%) and scattered (31.8% vs 25.0%) MBD types than in the ER^-/PR^- group, and less common in dense breasts (9.4% vs 58.3%), with the association being statistically significant ($P < 0.001$). However, no statistically significant association was found between MBD and the HER2/neu protein status.

Conclusion: Among Jordanian women with breast cancer, patients in the ER+/PR+ group showed fatty and scattered mammographic breast density (MBD) types more frequently than those in the ER-/PR- group. No association between MBD and HER2 status was identified. Larger randomized cohorts are needed to further investigate the association between breast cancer biological subtypes and MBD.

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INTRODUCTION

Breast cancer is considered one of the most common causes of cancer-related deaths in women worldwide.[1] Over the last few decades, much research has been conducted to understand breast cancer pathology, clinical behavior, biological features, early detection, and treatment outcomes. Shifting the focus from treatment to the detection of breast cancer has significantly advanced

the field of breast pathology. This progress has necessitated improvements in three key areas: women's awareness programs, screening protocols, and breast cancer screening tools.[2]

In 1966, Shapiro *et al*. described the possibility of detecting early breast cancer by understanding the process of breast cancer, risk factors, and different patterns of presentation. Since then, the mammogram has been used as the tool of choice for screening and evaluating breast masses among women.[3]

In 1976, Wolfe *et al*. published a study about mammographic breast density and breast cancer.[4] Since then, breast parenchymal characteristics, such as breast density, have become a major focus of research, where associations between breast density and other variables such as age, gender, and tumor hormonal receptors have been investigated.[5]

Mammographic breast density (MBD) is defined as the relative amount of radiologically dense stromal and epithelial tissue in relation to radiolucent adipose tissue and it has been accepted as an independent risk factor for breast cancer.[6]

Studies of primarily Western populations have suggested that elevated MBD is considered a general marker of breast cancer risk, irrespective of breast cancer molecular subtypes.[7]

MBD is adversely related to breast tumor clinical characteristics including larger tumor size, nodal involvement, and advanced stage at diagnosis.[5,6,8] According to the American College of Radiology (ACR), mammographic breast density is classified into four categories: A (fatty), B (scattered), C (heterogeneously dense), and D (dense).[9]

Patients with higher breast density are at higher risk of missing small cancers as mammogram has lower sensitivity in those groups.[10] Among the western population, mammographic breast density (MBD) has been extensively investigated. While MBD is considered a high-risk factor for breast cancer[6,8,11,12], its reporting based on the Breast Imaging Reporting and Data System (BI-RADS) is considered subjective and prone to suboptimal reproducibility.[13-15]

In contrast to the western population, MBD has not been seriously investigated among Arab women except for a few reports from Jordan and Lebanon which linked MBD to women's age and breast cancer risk, respectively.[16,17]

In this study, we aimed to assess MBD in women with a recent diagnosis of breast cancer with respect to their breast cancer biology, specifically with progesterone (PR), estrogen receptors (ER), and the human epidermal growth factor receptor 2 (HER2/neu). To the best of our knowledge, this is the first paper discussing the correlation between breast biology and MBD in Jordan.

METHODS

Study design and Participants

This is a cross-sectional retrospective review of 97 women with a diagnosis of breast cancer who were primarily diagnosed at our breast surgery clinic in a tertiary hospital in Amman, Jordan during the period between 2018 and 2020. Patients' demographics and tumor characteristics were retrieved from the electronic health records. Mammographic breast density was reported in concordance with the Breast Imaging Reporting and Data System (BI-RADS) classification system. Breast density was evaluated by two radiologists independently and blindly. Any discrepancy between the radiologists' evaluations was solved blindly by a 3rd opinion from an expert breast surgeon. Breast density was classified into 4 categories; fatty, scattered, heterogeneous dense, and dense breast. This study was approved by the institutional review board (IRB) at our institute, and it was performed according to the principles of the Declaration of Helsinki. Informed consent was waived by the IRB committee due to the retrospective nature of the study. Patients' data were anonymized and maintained with complete confidentiality.

Pathological evaluation

Two senior pathologists evaluated the cases, each with more than 20 years' experience in the field of pathology. HER2/neu gene expression and the status of the estrogen and progesterone hormone receptors were routinely assessed immunohistochemically in all cases using the immunoperoxidase method. The local pathologists evaluated immunohistochemistry (IHC) staining in accordance with international guidelines. The results for hormone receptors were expressed as positive or negative, whereas the results for HER2 expression were reported in accordance with the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guideline, updated in 2018. Breast tumors were considered positive if they expressed ER and PR in >1% of neoplastic cells. Tumors for Her2/neu were given a score of 0 or 1+ if the membrane staining was negative or weak and incomplete in less than or equal to 10% of tumor cells, whereas cases with strong complete membrane staining in >10% of cells were given a value of 3+ if it was positive. All cases with weak to moderate complete membrane screening found in >10% of tumor cells were classified as equivocal (score 2+) and either negative or positive according to the results of the Fluorescence in situ hybridization (FISH) analysis.

Statistical analysis

Descriptive measures included means ± standard deviations, medians, and minimum-maximum values

for continuous data. Categorical data were presented by frequencies and percentages (%). For univariate analyses, patients were grouped based on receptors status into PR^+ or ER^+ groups and PR^-/ER^- group and based on HER2/neu protein status into $HER2^+$ and $HER2^-$ groups. Continuous data were compared using the student's t-test in normally distributed variables, and the Mann-Whitney U test if not normally distributed according to the Shapiro-Wilk test of normality. Categorical data were compared using the Chi-square test, or Fisher's exact test if one cell had an expected count of less than five. The pairwise deletion method was used when dealing with missing data, considering that it was missing completely at random. Statistical significance was considered at a two-sided P-value of ≤ 0.05. All data analyses were performed using the IBM Statistical Package for the Social Sciences (SPSS) software for Windows, version 26.0 (18).

RESULTS

Patients' and tumor characteristics

A total of 97 patients were included from our institute, of whom 87.6% (85/97) had positive receptors for either Progesterone (PR) or Estrogen (ER) hormones, and 81.4% (79/97) were positive for both. In addition, the HER2/neu protein status was positive in 38.1% (37/97) of patients. Overall, the patients had a mean (SD) age of 56.4 (13.6) years and most of them were obese (55/97, 56.7%). The tumor was mostly left-sided (58/97, 59.8%) with Invasive Ductal Carcinoma (IDC) being the most common histopathological type (69/97, 71.9%). The Ki-76 percentages mean (SD) was 32.1 (24.2) for patients with available data, with most falling between 14% and 50% (36/78, 46.2%). Lastly, mammographic densities of our cohort were 30.9% (30/97) fatty, 29.9% (29/97) scattered, 23.7% (23/97) heterogeneously dense, and 15.5% (15/97) dense. Patients' characteristics are summarized in Table 1.

PR/ER receptors and HER2/neu protein status

As presented in Table 1, upon comparing the PR^+ or ER^+ group and the PR^-/ER^- group, the PR^+ or ER+ group had a higher mean (SD) age of 57.4 (13.8) years compared to 49.3 (9.8) years in the PR^-/ER^- group, although not statistically significant (P = 0.073). The two groups' cancer-sidedness and histopathological subtypes were similar (P = 0.370 and P = 0.260, respectively).

Table 1. Baseline and tumor characteristics in patients with breast cancer compared in PR/EP and HER2/neu status groups.

Patient characteristics	PR/ER receptors			HER2/neu status			
	Negative (N=12)	Positive (N=85)	P-value	Negative (N=60)	Positive (N=37)	P-value	Overall (N=97)
Age							
Mean (SD)	49.3 (9.8)	57.4 (13.8)	0.073*	58.2 (14.2)	53.4 (12.3)	0.096	56.4 (13.6)
Median (Min, Max)	49.5 (33-65)	56.0 (32-89)		56.5 (32-89)	52.0 (32-79)		55.0 (32, 89)
Side							
Right	3 (25.0%)	32 (37.6%)	0.370	16 (26.7%)	19 (51.4%)	0.023	35 (36.1%)
Left	8 (66.7%)	50 (58.8%)		42 (70.0%)	16 (43.2%)		58 (59.8%)
Bilateral	1 (8.3%)	3 (3.5%)		2 (3.3%)	2 (5.4%)		4 (4.1%)
Histopathology							
IDC	7 (58.3%)	62 (73.8%)	0.260	37 (62.7%)	32 (86.5%)	0.298	69 (71.9%)
ILC	1 (8.3%)	7 (8.3%)		6 (10.2%)	2 (5.4%)		8 (8.3%)
DCIS	0 (0.0%)	2 (2.4%)		2 (3.4%)	0 (0.0%)		2 (2.1%)
IDC + DCIS	3 (25.0%)	11 (13.1%)		11 (18.6%)	3 (8.1%)		14 (14.6%)
IDC + LCIS	0 (0.0%)	1 (1.2%)		1 (1.7%)	0 (0.0%)		1 (1.0%)
IDC + Small Cell Carcinoma	1 (8.3%)	0 (0.0%)		1 (1.7%)	0 (0.0%)		1 (1.0%)
DCIS microinvasion	0 (0.0%)	1 (1.2%)		1 (1.7%)	0 (0.0%)		1 (1.0%)
Ki-76 index							
Percentages mean (SD)	51.67 (9.31)	30.51 (24.39)	0.015*	27.15 (21.08)	41.54 (27.33)	0.026*	32.06 (24.22)
<14%	0 (0.0%)	27 (37.0%)	0.042	20 (39.2%)	7 (25.9%)	0.197	27 (34.6%)
14%-50%	2 (40.0%)	34 (46.6%)		24 (47.1%)	12 (44.4%)		36 (46.2%)
>50%	3 (60.0%)	12 (16.4%)		7 (13.7%)	8 (29.6%)		15 (19.2%)
Obesity							
Normal BMI	5 (41.7%)	37 (43.5%)	0.903	25 (41.7%)	17 (45.9%)	0.679	42 (43.3%)
Overweight/Obese	7 (58.3%)	45 (56.5%)		35 (58.3%)	20 (54.1%)		55 (56.7%)

Abbreviations: PR, progesterone receptor. ER, estrogen receptor. IDC, Invasive ductal carcinoma. ILC, Invasive lobular carcinoma. DCIS, Ductal carcinoma in situ. LCIS, Lobular carcinoma in situ.
* The P-value was calculated using the Mann-Whitney U test.

The PR^+ or ER^+ group had a statistically significant lower Ki-76 percentage mean compared to the PR^-/ER^- group (30.5 vs. 51.7, P = 0.015), with most of the patients in the PR^+ or ER^+ group having percentages of 14% to 50% (46.6% vs 40.0%), followed by <14% (37.0% vs 0.0%) (P = 0.042). The two groups had similar BMI scores with mostly obese patients in both (P = 0.903).

For the HER2/neu protein status, the $HER2^+$ group had a lower mean (SD) age of 53.4 (12.3) years compared to 58.2 (14.2) years in the $HER2^-$ group, but with no statistical significance (P = 0.096). The tumor

was most commonly in the right breast for the HER2$^+$ group (51.4% vs 26.7%) and in the left breast for the HER2$^-$ group (70.0% vs 43.2%, P = 0.023), while the histopathological subtypes were similarly distributed (P = 0.298). The HER2$^+$ group had a significantly higher Ki-76 percentage mean compared to of the HER2$^-$ group (41.5 vs 27.2, P = 0.026), with most of the patients in both groups having percentages of 14% to 50% (44.4% in the HER2$^+$ group vs 47.1% in the HER2$^-$ group) followed by <14% (25.9% vs 39.2%, respectively) (P = 0.197). The BMI was also similar in the two groups, and most patients were obese (P = 0.679).

Associations between mammographic density findings and PR/ER receptors and HER2/neu protein status

When analyzing the association between the PR/ER receptor status and the mammographic density findings, compared to the PR-/ER- group, the PR+ or ER+ group was more associated with the fatty type (35.3% vs 0.0%) and the scattered type (31.8% vs 16.7%), and less associated with the dense type (9.4% vs 58.3%) (P < 0.001). The HER2/neu status did not impact the mammographic findings significantly (P = 0.695), although the HER2+ group was less associated with the fatty type (24.3% vs 35.0%), and more associated with all the other types, compared to the HER2- group. The results of this analysis are summarized in Table 2 and visualized in

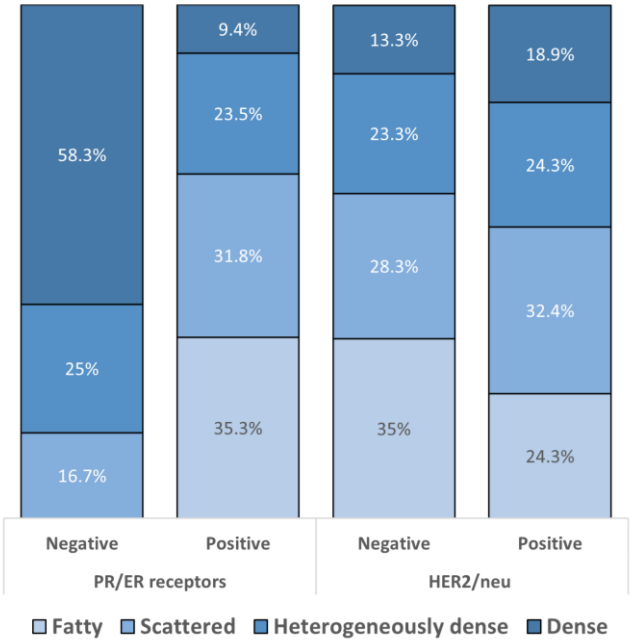

Figure 1.
Figure 1. Distribution of densities based on Hormonal Receptors Status and HER2/neu Status

Table 2. Associations between the mammographic density findings and the PR/ER receptors and HER2/neu protein status.

Variables	PR/ER receptors			HER2/neu status			
	Negative (N=12)	Positive (N=85)	P-value	Negative (N=60)	Positive (N=37)	P-value	Overall (N=97)
Mammographic density							
Fatty	0 (0.0%)	30 (35.3%)	<0.001	21 (35.0%)	9 (24.3%)	0.695	30 (30.9%)
Scattered	2 (16.7%)	27 (31.8%)		17 (28.3%)	12 (32.4%)		29 (29.9%)
Heterogeneously dense	3 (25.0%)	20 (23.5%)		14 (23.3%)	9 (24.3%)		23 (23.7%)
Dense	7 (58.3%)	8 (9.4%)		8 (13.3%)	7 (18.9%)		15 (15.5%)

Abbreviations: PR, progesterone. ER, estrogen.

DISCUSSION

Mammographic breast density is considered an important topic in the medical literature because of its association with the risk of breast carcinoma as well as its impact on screening strategies.[15] It has been reported that women with extremely dense breasts are at 3-fold higher risk to develop breast cancer in comparison to those with fatty breasts, and this is considered a general risk that is not limited to the breast side.[15,19] In addition, the literature shows lower sensitivity of 2D mammography in women with dense breasts in comparison to those with non-dense breasts (67.9% vs. 89.2%) (20), which could result in higher rates of interval cancers that limit the efficacy of breast screening programs.[20,21]

Previous studies describing the association between MBD and molecular/biological subtype or receptor status have reported conflicting results.[22-25] Regarding the association between MBD and ER/PR expression, our results have shown a significant inverse relationship (i.e., higher MBD in ER/PR negative tumors), which was similar to results reported by Yaghjyan *et al*., and Sartor *et al.*[26,27] On the contrary, Ding *et al*. and Conroy *et al.* described a positive correlation between MBD and ER expression[28,29], while other studies failed to demonstrate an association between them, which is against our findings.[19,30-33] A meta-analysis in 2012 has found conflicting results in this association. Antoni *et al.* have explained the heterogeneity in previous studies by proposing that this association is

underestimated by the effect of masking bias at screening.[7] Similar to hormone receptor expression, results regarding the association between MBD and HER2 expression are also conflicting. Multiple studies have showed no association between MBD and the expression of HER in breast cancer cells, which is consistent with our findings.[26,32] An association between increased MBD and HER2 expression was reported by Edwards *et al.*[34] and Park *et al.* in Korean postmenopausal women only.[35]

As a result, legislative changes in 39 states and the District of Columbia now require some level of breast density notification following a mammogram. Radiologists must inform their patients about their breast density based on the mammogram results and may also recommend additional screening methods, such as digital breast tomosynthesis, whole-breast ultrasonography, and gadolinium-enhanced magnetic resonance imaging for women with dense breasts.[15,40] To date, much of the literature investigating MBD has focused on Western populations with few reports from other regions. This study is the first among breast cancer women in Jordan aiming to investigate the association between mammographic breast density and breast cancer biology.

Results from twin studies indicate that breast density appears to be mainly determined genetically; however, breast density may also vary as a result of endogenous or external variables.[36] Reproductive hormones decline with normal aging, which is linked to terminal duct unit involution. Likewise, natural aging tends to reduce women's breast density.[37,38]

In this study, approximately 60.7% of breast cancer patients had low MBD on their diagnostic mammogram (ACR BI-RADS A or B). This figure is higher than what was previously reported from a study among Jordanian women who had their mammogram for screening (29.9%).[16] Also, we demonstrated a significant inverse relationship between MBD and patient age (i.e., higher MBD in younger women), which is consistent with previously reported data from Jordan and Western countries.[16,39]

This study is the first study to describe MBD in breast cancer patients in the context of biological subtypes in Jordan. The assessment of MBD was performed blindly by two expert radiologists in reporting breast mammograms.

Similar to many previously published studies in this field, we relied on the BI-RADS density category classification, which is known to be subjective with only moderate inter- and intra-reader agreement. The occurrence of inter-reader variability was reported in approximately 15% of the cases, which was solved blindly by a 3rd opinion from an expert breast surgeon.

There is a need to establish a national database for breast cancer patients to perform a comprehensive assessment of MBD among breast cancer patients and to evaluate its association with tumor biological features as well as other demographics including patients' weight, menopausal status, hormonal treatment, and parity.

CONCLUSION

Mammographic breast density is recognized as an independent risk factor for breast cancer and a strong predictor of mammographic screening failure, although its association with breast cancer biology remains unclear. Our study found that women with low breast density were more likely to have positive expression of estrogen and progesterone receptors, with no correlation observed with HER2 status. Further research is needed to validate these findings.

ETHICAL CONSIDERATIONS

The statement of ethical approval was obtained from the Institutional Review Board (IRB) committee at the Hashemite University and Prince Hamza Hospital. Informed consent was waived by the IRB committee due to the retrospective nature of the study. Patients' data were anonymized and maintained with complete confidentiality.

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CONFLICT OF INTEREST

The authors declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this research.

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DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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