ORIGINAL ARTICLE

Association of mammographic and sonographic findings with prognostic molecular factors and hormone receptor expression in malignant breast lesions

Mahshid Bahrami[1], Fatemeh Karami[2], Ali Hekmatnia[1], Sepideh Soltani[3], Pedram Fadavi[3], Farzaneh Hekmatnia[4], Andrew Parviz Zarei[5], Hengameh Nazari[6]

[1]Department of Radiology, Isfahan University of Medical Sciences, Isfahan, Iran, [2]Department of Radiology, Shafa Imaging Center, Isfahan, Iran, [3]Department of Radiation Oncology, Iran University of Medical Sciences, Tehran, Iran, [4]Department of Radiology, Lister Hospital, London, UK, [5]Department of Medicine, The Princess Alexandra Hospital, London, UK, [6]Department of Radiology, Mazandaran University of Medical Sciences, Iran

Background: The aim of this study was to determine whether mammographic and sonographic features of malignant breast lesions are correlated with tumor histologic grade, hormonal receptor, human epidermal growth factor receptor 2 (HER2), and Ki-67 status. **Materials and Methods:** In this retrospective study, imaging and histopathological findings of 187 biopsy-proven breast cancer cases from November 2019 to February 2021 were reviewed. The Chi-square test was used to examine the potential correlation between mammographic and sonographic characteristics with histopathological features such as hormonal receptor, HER2 status, Ki-67 labeling index, and histological grade. **Results:** We observed that microlobulated margin as well as oval/round morphology in mammograms correlate with triple-negative intrinsic subtype ($P = 0.006$ and $P = 0.004$). The presence of calcification in sonography was significantly higher in the luminal-B subtype ($P = 0.002$). Furthermore, ill-defined margins in mammography were significantly higher in amplified HER2 expression ($P = 0.004$) in the same manner as an oval/round shape in higher levels of Ki-67 ($P = 0.030$). **Conclusion:** Mammography and sonography features may reflect the biological behavior of various subtypes of breast cancer and can detect more aggressive breast cancers that can mimic benign or less malignant appearing lesions. These findings may be an excellent predictor for some subtypes like triple-negative breast cancer. Studying the range of these imaging characteristics may help in better understanding the prognosis, choosing a treatment strategy, and predicting response to treatment.

Key words: Human epidermal growth factor receptor 2, intrinsic subtype, Ki-67, mammography, sonography

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INTRODUCTION

Breast cancer is the most common malignancy among women worldwide and has different characteristics. The incidence of breast cancer is growing, as well as its associated mortality. Therefore, this condition is a significant health issue.[1]

Breast cancer in Iran has a lower than international average incidence, similar to other Asian countries. However, it manifests in Iranian women at least one decade earlier than women in developed countries and is diagnosed at more advanced stages.[2]

The presence of specific molecular markers such as estrogen receptor (ER), progesterone receptor (PR), and HER2 may have prognostic value and enable targeted therapy.[3]

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Address for correspondence: Dr. Hengameh Nazari, Department of Radiology, Mazandaran University of Medical Sciences, Mazandaran, Iran.
E-mail: hengamehnazari1372@gmail.com

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Breast cancer is of heterogeneous pathology and molecular subtypes.[4] The St. Gallen International Expert Consensus defined a new biologic classification system based on ER, PR, human epidermal growth factor receptor 2 (HER2)–neu, and more recently, Ki-67 which are evaluated routinely due to their importance in guiding clinical care and determined a surrogate to differentiate luminal-A-like breast cancer from luminal-B like, HER2/neu, and triple-negative disease.[5]

Imaging findings can gather valuable histopathological information and predict biological behavior to treatment, regarding the importance of breast cancer and the high rate of mortality. This study was performed to correlate imaging findings and intrinsic subtypes in a population of Iranian breast cancer patients.

MATERIALS AND METHODS

The study was conducted on malignant breast cancer patients after surgically proven diagnosis following histopathological data collection between November 2019 and February 2021. This study was approved by our Institutional Review Board which granted a waiver of consent (Ethics code: IR.MUI.MED.REC.1400.036).

The inclusion criteria were female patients with the biopsy-proven disease who had at least one screening/diagnostic sonography or mammography within 2 years before diagnosis.

A total of 187 cases were enrolled in the study. The histopathological results and sonographic and mammographic reports were retrospectively analyzed. The imaging features were evaluated according to the Breast Imaging Reporting and Data System of the American College of Radiology.[6]

All bilateral standard view mammograms were obtained using a unit (Selenia Dimensions, 2010 Hologic, United States). We evaluated mammographic features, such as mass density (equivalent density or high density), shape (oval/round or irregular), presence of microcalcifications, breast density, and margins.

Breast density was classified into four groups (almost fatty, scattered fibroglandular, heterogeneous dense, and extremely dense), and mammographic margins were divided into five categories (microlobulated, spiculated, circumscribed, obscured, and ill-defined). Figure 1 represents some mammographic findings.

Breast sonography was performed with 10–16 MHz transducers on a Logiq (9xd clear 2015 R5) ultrasound unit. Followed by mass descriptors evaluated and categorized in sonographic imaging: echogenicity (hypoechoic or nonhypoechoic), shape (oval-to-round or irregular), margins (microlobulated, spiculated, circumscribed, and indistinct), size in ultrasound, and presence of calcification and vascularity.

Imaging findings were retrospectively evaluated by two experienced radiologists independently.

Pathology

Samples were stained using H and E. Histochemical and immunohistochemical analyses for ER, PR, HER2, and Ki-67 were performed.

The presence of ER was determined by nuclear staining, and semiquantitative analysis was performed. ER and PR expression was considered positive when >10% positive cells were present in an evaluated area. Pathological evaluations were performed according to the World Health Organization classification standard.[7]

HER2 status was evaluated according to the American Society of Clinical Oncology/College of American Pathologists guidelines,[8] and staining was graded as 0, 1+, 2+, and 3+.

Grade 0 and 1+ were considered negative HER2 status, 2+ was considered equivocal, and grade 3+ was considered positive. The equivocal specimens were subjected to FISH. A FISH ratio (HER2/neu gene signals to chromosome 17 signals) of >2.2 is also considered HER2-positive status.

Ki-67 protein is a cellular marker for proliferation and is a nuclear protein expressed in mitotic cells. Quantitative ki67 was evaluated by the number of cells, which is the hot spot in 1000 tumor cells, by immunohistochemistry (IHC) in high-power fields.

Tumor's intrinsic subtypes were categorized by IHC according to St. Gallen subtypes as follows: luminal-A (ER + and/or PR+, HER2– and Ki67<14%), luminal-B HER2– (ER + and/or PR+, HER2– and Ki67≥14%), luminal-B HER2+ (ER + and/or PR + and HER2+), HER2-neu nonluminal (ER/PR – and HER2+), and triple negative (ER/PR– and HER2–).[5]

Histological grades were categorized according to Elston and Ellis.[9]

Statistical analysis

The imaging and histopathological data were collected and entered into SPSS version 26 for Windows, manufactured by IBM Corporation, headquartered in Armonk, New York, United States. Descriptive analysis was performed to provide a comprehensive overview of the collected data. Continuous variables with a normal distribution were reported using the mean and standard deviation (SD) and compared using a Student's *t*-test. Using the Mann–Whitney

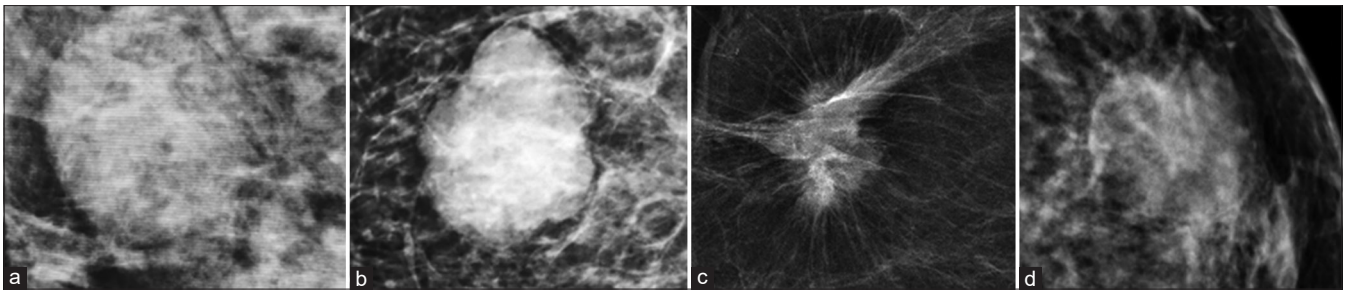

Figure 1: Mammographic findings in breast carcinoma cases. (a) Oval mass shape, circumscribed margin, and equivalent density (b) irregular mass shape, microlobulated margin, and high density (c) irregular mass shape, spiculated margin, and high density (d) oval mass shape, obscured margin, and equivalent density

U-test, nonnormally distributed variables represented as the median were compared between the two aforementioned groups. As applicable, the Chi-squared or Fisher's exact test was used to compare categorical variables with absolute frequencies and percentages. P <0.05 was considered statistically significant.

RESULTS

A total of 187 patients were evaluated. The mean age of patients was 51.6 years with an SD of 10.9. The initial data for intrinsic subtype, biological factor, histological grade, and subtype are summarized in Table 1.

Cancer grade

A significant association between intrinsic subtype and histologic grade was observed. The luminal-A subtype was significantly associated with grades 1 and 2 (mainly grade 2), whereas luminal-B, HER2, and triple-negative subtypes were associated with grade 3 ($P < 0.001$) [Table 2].

Figure 2 summarizes the results for the ratio of histological grade according to the different intrinsic subtypes.

Masses with a sonographic margin other than spiculated had a significant association with grade 3 tumors ($P = 0.003$).

Mammographic findings

Tables 3 and 4 summarize the mammographic findings and association with ER/PR and HER2 status. Mass morphology on mammograms differs significantly according to hormonal and molecular status. Mass irregularity was higher in PR-positive status and Ki-67 negative labeling index (P = 0.024 and P = 0.030, respectively). However, there was no significant correlation between HER2 level and morphology (P = 0.437).

ER-positive masses were more likely to have a spiculated margin in contrast to ER-negative ones, which tended to have a microlobulated margin ($P = 0.002$ for both). Although there was a positive association between PR-positive status and spiculated margin, the difference did not reach statistical significance.

Table 1: Characteristics of breast cancer patients (*n*=187)

Data characteristics	Frequency (%)
Histological grade	
1	27 (15)
2	82 (46)
3	69 (39)
Histologic tumor type	
Invasive ductal carcinoma	170 (91)
Invasive lobular carcinoma	11 (6)
Mucinous carcinoma	4 (2)
Adenoid cystic carcinoma	1 (0.5)
Sarcomatoid carcinoma	1 (0.5)
Biological factor	
ER positive	117 (78.5)
PR positive	104 (69.8)
HER2 positive	29 (19.5)
Ki-67 positive	59 (39.6)
Intrinsic subtype	
Luminal-A	85 (57)
Luminal-B	33 (22)
HER2 type	12 (8)
Triple negative	19 (13)

Data are *n* (%) of lesions. ER=Estrogen receptor; PR=Progesterone receptor; HER2=Human epidermal growth factor receptor 2

Table 2: Intrinsic subtypes and grade

Grade	Subtype				
	Luminal A	Luminal B	HER2	Triple negative	*P*
1	20 (95.2)	0	0	1 (4.8)	<0.001
2	59 (88.1)	7 (10.4)	0	1 (1.5)	
3	3 (5.3)	26 (45.6)	11 (19.3)	17 (29.8)	

Data are *n* (%) of lesions. HER2=Human epidermal growth factor receptor 2

The ill-defined margin was significantly higher in the HER2 positive group ($P = 0.004$). Microcalcifications were more likely to be seen on Ki-67 positive tumors' mammograms and tumors with a size of more than 15 mm on ultrasound ($P = 0.030$ for both). Oval shape and microlobulated/lobulated margin were significantly higher in the triple-negative intrinsic subtype ($P = 0.004$ and $P = 0.006$). Figure 3 summarizes results for the ratio of some mammographic findings according to different intrinsic subtypes.

Table 3: Mammographic features of estrogen receptor and progesterone receptor groups

Mammographic features	ER negative	ER positive	*P*	PR negative	PR positive	*P*
Mass margin						
Microlobulated	7 (35.0)	7 (8.4)	0.002	8 (26.7)	6 (8.2)	0.008
Spiculated	5 (25.0)	52 (62.7)		11 (36.7)	46 (63.0)	
Circumscribed	1 (5.0)	0		1 (3.3)	0	
Obscured	1 (5.0)	2 (2.4)		2 (6.7)	1 (1.4)	
Ill-defined	6 (30.0)	22 (26.5)		8 (26.7)	20 (27.4)	
Mass shape						
Oval/round	2 (10.5)	1 (1.3)	0.095	3 (10.3)	0	0.024
Irregular	17 (89.5)	78 (98.7)		26 (89.7)	69 (100.0)	
Calcification						
Absent	12 (63.2)	53 (67.1)	0.790	20 (69.0)	45 (65.2)	0.817
Present	7 (36.8)	26 (32.9)		9 (31.0)	24 (34.8)	
Mass density						
Equivalent density	5 (26.3)	29 (34.9)	0.594	9 (31.0)	25 (34.2)	0.819
High density	14 (73.7)	54 (65.1)		20 (69.0)	48 (65.8)	
Breast density						
Almost fatty	0	4 (4.3)	0.661	0	4 (4.9)	0.620
Scattered fibroglandular	9 (40.9)	34 (36.6)		12 (36.4)	31 (37.8)	
Heterogeneous dense	6 (27.3)	32 (34.4)		11 (33.3)	27 (32.9)	
Extremely dense	7 (31.8)	23 (24.7)		10 (30.3)	20 (24.4)	

Data are *n* (%) of lesions. ER=Estrogen receptor; PR=Progesterone receptor

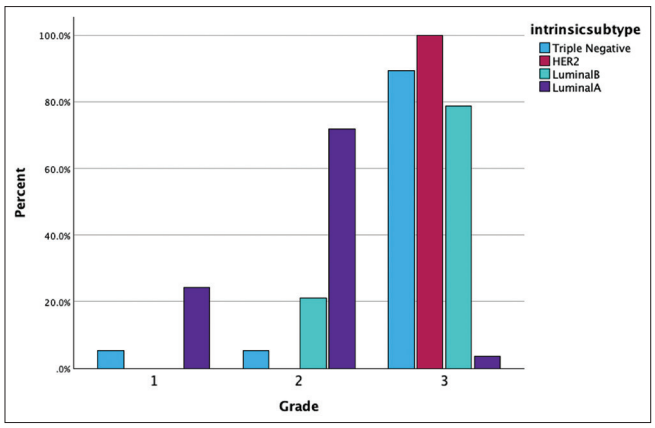

Figure 2: Histological grade according to the different intrinsic subtypes

Sonographic findings

Tables 4 and 5 summarize the sonographic findings and association with HER2 and ER/PR status. ER-positive and PR-positive status tumors were more likely to have a spiculated margin on ultrasound ($P < 0.05$ for both). There was a significant association between the presence of calcification on ultrasound and positive Ki-67 level just as overexpressed HER2 status ($P = 0.036$ for both). Among different intrinsic subtypes, luminal-B showed a significant correlation with the presence of sonographic calcification ($P = 0.002$). Figure 4 summarizes results for the ratio of some sonographic findings according to different intrinsic subtypes.

DISCUSSION

Various types of breast cancer present with different features on mammography and sonography. Better knowledge of these features and their histopathological correlations would help predict tumor biological behavior and response under treatment.

Hormone receptor-negative subtypes (HER2 and triple-negative) correlated with poorer prognosis.[10] In our study, luminal-B, HER2, and triple-negative subtypes were more likely to have a higher grade. Furthermore, the luminal-A subtype correlated with lower histological grades.

Several studies have shown that triple-negative subtypes have more oval or round shapes and more of circumscribed margins; however, microlobulated and obscured margins were also frequent.[11,12] In the current study, triple-negative subtypes were more likely to have microlobulated margins and oval shapes on mammography.

Spiculated margins have a significant association with positive hormone receptor status. Spiculated masses also tend to have HER2 negativity and a lower Ki-67 label index in comparison to nonspiculated masses.[13] In our study, ER-positive masses had a significant correlation with spiculated margin on mammograms, whereas ER-negative status correlated with microlobulated margin. There was no statistically significant association between PR-positive status and margin in mammography.

Park *et al*. demonstrated that there is a significant association between HER2-positive tumors and higher breast density.[14]

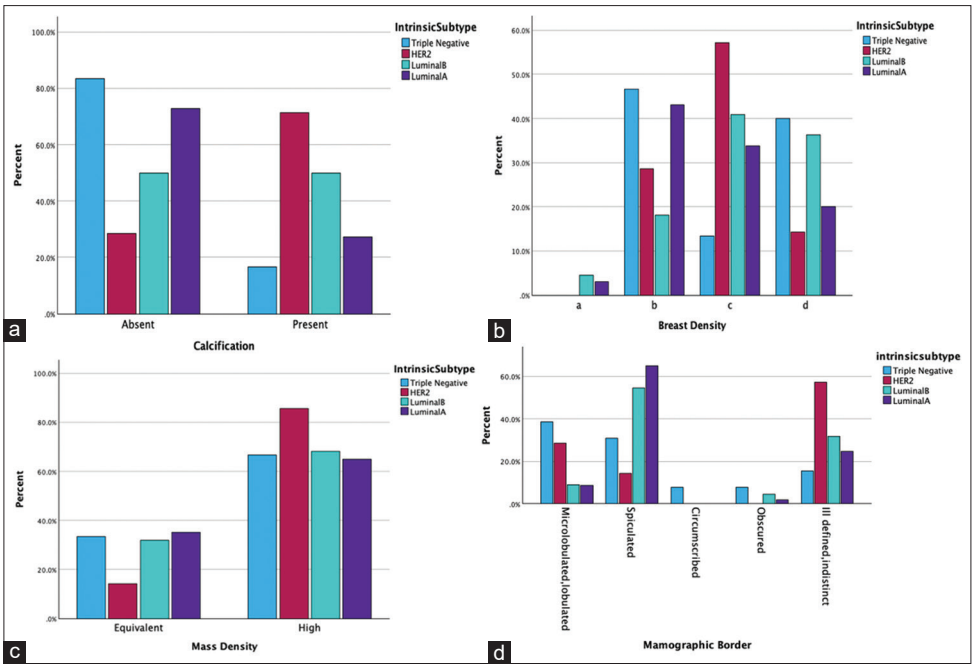

Figure 3: Mammographic findings according to intrinsic subtypes. (a) Calcification (b) breast density (c) mass density (d) mass border

Table 4: Mammographic and sonographic features of human epidermal growth factor receptor groups

Mammographic features	HER negative	HER positive	*P*	Sonographic features	HER negative	HER positive	*P*
Tumor margin				Tumor margin			
Microlobulated	11 (12.6)	3 (18.8)	0.031	Microlobulated	14 (15.6)	5 (25.0)	0.317
Spiculated	53 (60.9)	4 (25.0)		Spiculated	64 (71.1)	10 (50.0)	
Circumscribed	1 (1.1)	0		Circumscribed	1 (1.1)	0	
Obscured	3 (3.4)	0		Ill-defined	11 (12.2)	5 (25.0)	
Ill-defined	19 (21.8)	9 (56.3)		Tumor shape			
Tumor shape				Oval	1 (1.3)	0	0.634
Oval	3 (3.7)	0	0.437	Irregular	75 (98.7)	17 (100.0)	
Irregular	79 (96.3)	16 (100)		Calcification			
Calcification				Absent	51 (56.0)	6 (30.0)	0.035
Absent	58 (69.9)	7 (46.7)	0.080	Present	40 (44.0)	14 (70.0)	
Present	25 (30.1)	8 (53.3)		Vascularity			
Mass density				Absent	68 (73.9)	17 (89.5)	0.233
Equivalent density	29 (33.7)	5 (31.3)	0.847	Present	24 (26.1)	2 (10.5)	
High density	57 (66.3)	11 (68.8)		Tumor size			
Breast density				0–15 mm	25 (30.9)	4 (22.2)	0.575
Almost fatty	4 (4.1)	0	0.073	15 mm<	56 (69.1)	14 (77.8)	
Scattered fibroglandular	40 (40.8)	3 (17.6)		Echogenicity			
Heterogenous dense	28 (28.6)	10 (58.8)		Hypoechoic	91 (98.9)	20 (100)	0.640
Extremely dense	26 (26.5)	4 (23.5)		Other	1 (1.1)	0	

Data are *n* (%) of lesions. HER=Human epidermal growth factor receptor

Other literature has observed that women with the expression of hormonal receptors and any ki-67 staining had a minimally higher breast density percentage, but these findings were not statistically significant.[15]

In this study, we also observed a positive relationship between heterogeneous dense breasts and HER2-positive status. However, it did not demonstrate statistical significance.

Blaichman *et al*. reported that malignancy grade could be predicted by sonographic margin and grade 3 invasive ductal breast carcinoma was more likely to exhibit microlobulated margin and abrupt interfaces.[16] Costantini *et al*. found that high-grade tumors correlated with nonspiculated margins in sonography.[17] Conversely, Rotstein and Neerhut showed that grade 3 invasive ductal carcinoma exhibited spiculated, microlobulated, and angular margins.[18] However, Rotstein and Neerhut evaluated grade 3 invasive ductal breast carcinoma cases

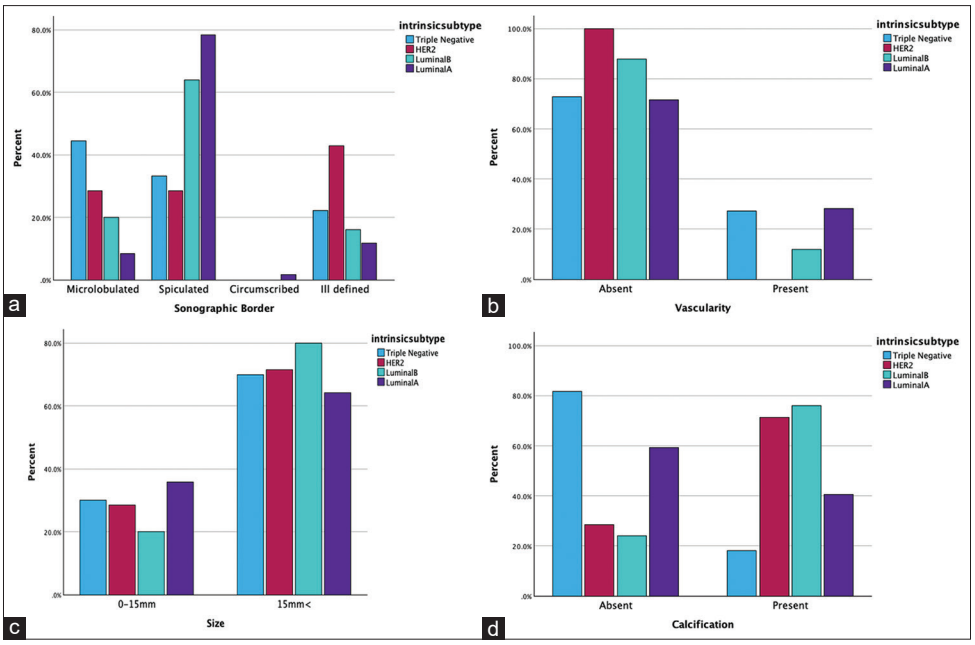

Figure 4: Percentage of sonographic findings according to intrinsic subtype. (a) Mass border (b) vascularity (c) tumor size (d) calcification

Table 5: Sonographic features of estrogen receptor and progesterone receptor groups

Sonographic features	ER negative	ER positive	*P*	PR negative	PR positive	*P*
Tumor margin						
Microlobulated	6 (37.5)	13 (13.8)	0.010	7 (31.8)	12 (13.8)	0.003
Spiculated	5 (31.3)	69 (73.4)		8 (36.4)	65 (74.7)	
Circumscribed	0	1 (1.1)		0	1 (1.1)	
Ill-defined	5 (31.3)	11 (11.7)		7 (31.8)	9 (10.3)	
Tumor shape						
Oval	0	1 (1.3)	0.659	0	1 (1.4)	0.596
Irregular	15 (100)	77 (98.7)		20 (100)	71 (98.6)	
Calcification						
Absent	11 (61.1)	46 (49.5)	0.585	15 (62.5)	42 (48.8)	0.489
Present	7 (38.9)	47 (50.5)		9 (37.5)	44 (51.2)	
Vascularity						
Absent	14 (82.4)	71 (75.5)	0.758	18 (78.3)	66 (75.9)	0.810
Present	3 (17.6)	23 (24.5)		5 (21.7)	21 (24.1)	
Tumor size						
0–15 mm	5 (29.4)	24 (29.3)	0.991	6 (27.3)	23 (30.3)	0.801
15 mm<	12 (70.6)	58 (70.7)		16 (72.7)	53 (69.7)	
Echogenicity						
Hypoechoic	17 (100)	94 (98.9)	0.671	23 (100)	87 (98.9)	0.608
Other	0	1 (1.1)		0	1 (1.1)	

Data are *n* (%) of lesions. ER=Estrogen receptor; PR=Progesterone receptor

only. In our study, grade 3 correlated with nonspiculated sonographic margin.

Masses with ER-positive/PR-positive status were associated with spiculated sonographic margins.[17] We reached the same conclusion in the present study.

HER2-positive cancers correlated with exhibiting calcifications on sonography,[19] In our study, there was a significant correlation between HER2 overexpression/higher Ki-67 levels and calcification on sonography. Among various intrinsic subtypes, luminal-B showed a strong association with the presence of calcification. Therefore, the presence of calcification can potentially predict the prognosis of breast malignancies.

Previous studies indicated that ki-67 high tumors were more likely to have a poor outcome, ER-negative receptors, and high HER2 levels.[20] The results of the current study demonstrated that Ki-67-positive masses are of higher histological grade and HER2 levels and lower hormonal receptors. Furthermore,

masses with microcalcifications on mammography were more often described as having a positive Ki-67 level.

Several studies found the presence of mammographic calcification associated with poor prognostic factors such as higher histological grade, HER2 positive, ER negative, or PR negative.[21,22]

Our results revealed that tumoral grade, hormonal receptor, HER2 status, and Ki-67 levels correlated with the imaging findings. These biological markers have prognostic and therapeutic values in breast cancer.

Radiologists should consider that some malignant breast lesions could have benign imaging features such as round-to-oval shapes and well-defined margins. Triple-negative phenotype is often associated with benign-appearing masses and lacks classical suspicious imaging findings.

The limitations of this study included conducting the survey in a single imaging center. However, we enrolled a large number of patients; further studies and a larger sample size are warranted to confirm our results and to be able to apply the conclusions to the general population. The fact of being retrospective was another limitation of our study.

CONCLUSION

We believe that mammography and sonography features may reflect the biological behavior of various subtypes of breast cancer. These findings may be an excellent predictor for some subtypes like triple-negative breast cancer. ER, PR, HER2, and Ki-67 expression have prognostic and therapeutic values in breast cancer. Studying the range of these imaging characteristics may help in better understanding the prognosis, choosing a treatment strategy, and predicting response to treatment.

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Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Tao Z, Shi A, Lu C, Song T, Zhang Z, Zhao J. Breast cancer: Epidemiology and etiology. Cell Biochem Biophys 2015;72:333-8.
2. Harirchi I, Karbakhsh M, Kashefi A, Momtahen AJ. Breast cancer in Iran: Results of a multi-center study. Asian Pac J Cancer Prev 2004;5:24-7.
3. Rakha EA, Ellis IO. An overview of assessment of prognostic and predictive factors in breast cancer needle core biopsy specimens. J Clin Pathol 2007;60:1300-6.
4. Stingl J, Caldas C. Molecular heterogeneity of breast carcinomas and the cancer stem cell hypothesis. Nat Rev Cancer 2007;7:791-9.
5. Vasconcelos I, Hussainzada A, Berger S, Fietze E, Linke J, Siedentopf F, *et al*. The St. Gallen surrogate classification for breast cancer subtypes successfully predicts tumor presenting features, nodal involvement, recurrence patterns and disease free survival. Breast 2016;29:181-5.
6. Burnside ES, Sickles EA, Bassett LW, Rubin DL, Lee CH, Ikeda DM, *et al*. The ACR BI-RADS experience: Learning from history. J Am Coll Radiol 2009;6:851-60.
7. Azzopardi J, Chepick O, Hartmann W, Jafarey N, Llombart Bosch A, Ozzello L, *et al*. The World Health Organization histological typing of breast tumors-second edition. Am J Clin Pathol 1982;78:806-16.
8. Wolff AC, Hammond ME, Hicks DG, Dowsett M, McShane LM, Allison KH, *et al*. Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline update. Arch Pathol Lab Med 2014;138:241-56.
9. Elston EW, Ellis IO. Method for grading breast cancer. J Clin Pathol 1993;46:189-90.
10. Shibuta K, Ueo H, Furusawa H, Komaki K, Rai Y, Sagara Y, *et al*. The relevance of intrinsic subtype to clinicopathological features and prognosis in 4,266 Japanese women with breast cancer. Breast Cancer 2011;18:292-8.
11. Gao B, Zhang H, Zhang SD, Cheng XY, Zheng SM, Sun YH, *et al*. Mammographic and clinicopathological features of triple-negative breast cancer. Br J Radiol 2014;87:20130496.
12. Çelebi F, Pilancı KN, Ordu Ç, Ağacayak F, Alço G, İlgün S, *et al*. The role of ultrasonographic findings to predict molecular subtype, histologic grade, and hormone receptor status of breast cancer. Diagn Interv Radiol 2015;21:448-53.
13. Jiang L, Ma T, Moran MS, Kong X, Li X, Haffty BG, *et al*. Mammographic features are associated with clinicopathological characteristics in invasive breast cancer. Anticancer Res 2011;31:2327-34.
14. Park IH, Ko K, Joo J, Park B, Jung SY, Lee S, *et al.* High volumetric breast density predicts risk for breast cancer in postmenopausal, but not premenopausal, Korean women. Ann Surg Oncol 2014;21:4124-32.
15. Verheus M, Maskarinec G, Erber E, Steude JS, Killeen J, Hernandez BY, *et al*. Mammographic density and epithelial histopathologic markers. BMC Cancer 2009;9:182.
16. Blaichman J, Marcus JC, Alsaadi T, El-Khoury M, Meterissian S, Mesurolle B. Sonographic appearance of invasive ductal carcinoma of the breast according to histologic grade. AJR Am J Roentgenol 2012;199:W402-8.
17. Costantini M, Belli P, Bufi E, Asunis AM, Ferra E, Bitti GT. Association between sonographic appearances of breast cancers and their histopathologic features and biomarkers. J Clin Ultrasound 2016;44:26-33.
18. Rotstein AH, Neerhut PK. Ultrasound characteristics of histologically proven grade 3 invasive ductal breast carcinoma. Australas Radiol 2005;49:476-9.
19. Kim SH, Seo BK, Lee J, Kim SJ, Cho KR, Lee KY, *et al*. Correlation of ultrasound findings with histology, tumor grade, and biological markers in breast cancer. Acta Oncol 2008;47:1531-8.
20. Kilickap S, Kaya Y, Yucel B, Tuncer E, Babacan NA, Elagoz S. Higher Ki67 expression is associates with unfavorable prognostic factors and shorter survival in breast cancer. Asian Pac J Cancer Prev 2014;15:1381-5.
21. Pálka I, Ormándi K, Gaál S, Boda K, Kahán Z. Casting-type calcifications on the mammogram suggest a higher probability of early relapse and death among high-risk breast cancer patients. Acta Oncol 2007;46:1178-83.
22. Shin HJ, Kim HH, Huh MO, Kim MJ, Yi A, Kim H, *et al*. Correlation between mammographic and sonographic findings and prognostic factors in patients with node-negative invasive breast cancer. Br J Radiol 2011;84:19-30.