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Correlation of mammographic density and breast cancer characteristics

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Abstract

Background and objective: Mammographic density is regarded as one of the most prevalent risk factors for developing breast cancer. However, there is limited data on its relationship with tumor characteristics. Therefore, this study has been conducted to evaluate the association between mammographic density and breast cancer subtypes as well as tumor characteristics.

Methods: This retrospective cross-sectional study was performed on 105 women with pathologically proved breast cancer. Mammographic breast density was scored according to Breast Imaging Reporting and Data System classification before receiving treatment, followed by correlation with some risk factors and tumor characteristics.

Results: From the 105 enrolled cases, about 70% had low mammographic density, and 30% had high mammographic density. Mammographic breast density was significantly associated with age and menopausal status, where high density was more prevalent among age group <45 years (58%) and among premenopausal women (71%). No significant association was found between density and Body Mass Index. Overall, estrogen positive, progesterone positive and luminal B were more prevalent in both low and high breast density cases; however, these findings were not significant. No significant relationship between mammography density and tumor grade, stage, size or lymph node involvement was observed.

Conclusion: Mammographic breast density is positively associated with age and menopausal status but not associated with Body Mass Index or tumor characteristics.

Keywords: Mammographic density, Breast cancer, Tumor subtype and BI-RADS.

Introduction

The difference in the breast tissue composition like fat, stromal and epithelial tissues and the way they appear on the radiological images have been found to be associated with the risk of breast cancer.[1, 2] Mammographic density (MD) indicates the relative amounts of radiodense (fibroglandular tissue) with radiolucent adipose tissue.[2,3] Accordingly, the larger amount of epithelial/ stromal tissue indicates high MD and vice versa.[3] Mammographic density can be scored using the American College of Radiology Breast Imaging Reporting and Data System classification (BIRAD). This classification categorizes MD into four categories (A= almost entirely fat < 25% glandular, B= scattered fibroglandular density 25 -50 % glandular, C= heterogenous dense 51 – 75% glandular, D =extreme dense > 75 %).[4] Elevated MD is the most prevalent risk factor for breast cancer.[5] It has been studied that females with a high classification of MD (extremely dense) have a 4-6-fold increase in the risk of breast cancer compared with those having the lowest classification (fatty tissue).[2] There is a difference in MD among women and even in the same woman throughout different stages of her

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life, being affected by several risk factors of breast cancer, including body mass index (BMI), age, and menopausal state.[6] Mammographic density is radio-dense, as are tumors; consequently, density can hide tumours. Accordingly, density decreases mammographic sensitivity, and is associated with higher risk of interval cancer[1]. Furthermore, higher MD might be associated with aggressive breast tumour characteristics including nodal involvement,[2] large tumour size.[7] advanced stage at diagnosis,[1] higher grade and possibly more aggressive molecular subtype.[8] Breast cancer is regarded as a highly heterogeneous disease. This might be due to specific clinicopathologic characteristics and prognoses of each breast cancer subtypes (luminal A, luminal B, HER2-positive and triple-negative).[9] A meta-analysis study revealed the association of similar magnitude between MD and tumour subtypes. However, significant heterogeneity was found in that study.[10] consequently leading to an inconsistent result. Furthermore; the majority of the studies were performed in western countries, where there is regular screening. Therefore the aim of this study is to evaluate the association between MD and breast cancer subtypes in our region. In addition, we are assessing the commonality and heterogeneity of breast cancer risk factors among breast cancer subtypes.

Materials and methods

The study was approved by the ethical committee of Kurdistan Higher Council of Medical Specialties; this study employed a retrospective cross-sectional design to include the pathologically confirmed breast cancer cases during three years period (Jan 2017- Oct 2019) in a teaching hospital for Cancer & blood disease. The study population included 105 confirmed breast cancer cases. Inclusion criteria included cases with a confirmed breast cancer diagnosis, confirmed estrogen receptor (ER) status by immunohistochemical staining, complete information about the included risk factors, and available report of diagnostic mammograms. About 400 cases were excluded due to missing data such as missing or unclear pathological examination, lack of mammographic report, and lack of information about risk factors (age, body mass index (BMI), and menopausal status). Information about age, BMI, menopausal state, ER/PR/HER-2 status, molecular subtype, tumour size, tumour stage, tumour grade, mammographic reports and lymph node involvement were obtained from the hospital's medical records. The sample's age was categorized into three groups (<45, 45-55, >55). BMI was measured (weight in kilogram divided by the squared length in meters) and was divided into three groups (<25, 25-30, >=30). Tumour grade was also categorized into two categories (I+ II, III). Tumour size was measured in cm and divided into two groups (<2 cm, >=2 cm). Other data were dichotomized such as menopausal status (Premenopausal/ postmenopausal), ER status (positive/ negative), progesterone receptor (PR) status (positive/ negative), HER-2 status (positive/ negative), and lymph node involvement (Yes/ No). Tumour stage was divided into four groups. Mammographic density was taken from report preceding treatment. Mammographic density was categorized using (BI-RADS) classification. Data were analyzed using the Statistical Package of Social Sciences SPSS V.20. Chi-square test was used to analyze the relation between MD with risk factors (age, BMI, menopausal status) and with clinical characteristics of breast cancer (molecular subtype, hormonal status, tumor grade/ stage/ size, and lymph node involvement. A p-value ≤ 0.05 was considered as statistically significant.

Results

The final study population was 105 cases, with a mean age of 49 years and age range (22-72), Table (1) and (2).

Table (1): Frequency and percentage of some risk factors of breast cancer.

Variables	Frequency	Percentage
Age		
<45	41	39
45-55	35	33.4
>55	29	27.6
BMI		
<25	12	11.4
25-30	25	23.8
>30	68	64.8
Menopausal status		
Premenapousal	58	55.2
Postmenopausal	47	44.8

Table (2): Frequency and percentage of tumour characteristics of breast cancer.

Variables	Frequency	Percentage
Molecular subtype		
Luminal A	22	21
Luminal B	39	37.1
HER2-enriched	33	31.4
Basal-like	4	3.8
Unknown	7	6.7
Grade		
Grade I/II	68	64.8
Grade III	37	35.2
Tumor size		
<2cm	24	22.9
>2cm	81	77.1
ER		
Negative	18	17.1
Positive	87	82.9
PR		
Negative	21	20
Positive	84	80
HER2		
Negative	66	62.9
Positive	39	37.1
Lymph nod metastasis		
No	32	30.5
Yes	73	69.5
Tumor stage		
I	11	10.5
II	50	47.6
III	38	36.2
IV	6	5.7

Among the collected samples, the high-density cases constitute about 30 % while the low-density cases were about 70%; the most recorded density was scattered fibro glandular density (56.2%). In comparison, only (2.9%) were extreme density, Table (3).

Table (3): Frequency and percentage of MD types.

Mammographic density	Frequency	Percentage
Low density		
• Almost fatty	15	14.3
• Fibro glandular density	59	56.2
High density		
• Heterogeneous density	15	26.7
• Extreme density	3	2.9

In the present study, a statistically significant association between MD to both age & menopausal state was observed, as high mammographic density was more common (58%) among the younger age group (less than 45 years) than older age group (>55 years) (9.7%), and more among premenopausal women (71%), while the low density was more prevalent among postmenopausal women (51.4%), (p-value < 0.05), as shown in Table (4). Concerning breast density and BMI, we observed that most of the cases with high MD (61.3%) belonged to the high BMI group (≥ 30), but this was not statistically significant. (p >0.05),Table (4).

Table (4): Relationship between MD and some risk factors.

	Mammographic density		p-vale
	Low density	High density	
Age (years)			
< 45	23 (31 %)	18 (58%)	<0.05
45-55	25 (33.8%)	10 (32.3%)	
>55	26 (35.2%)	3 (9.7%)	
Total	74 (100%)	31 (100%)	
Menopausal status			
pre	36 (48.6%)	22 (71%)	<0.05
Post	38 (51.4%)	9 (29%)	
Total	74 (100%)	31 (100%)	
BMI (kg/m^2)			
< 25	7 (9.5%)	5 (16.1%)	>0.05
25 - 29.9	18 (24.3%)	7 (22.6%)	
> =30	49 (66.2%)	19 (61.3%)	
Total	74 (100%)	31 (100%)	

We found that luminal B and HER-2 new were the most common molecular subtypes as a whole (37.1%, 31.4%, respectively) and luminal B was the most prevalent subtype among women with high breast density (48.4%); however, this was not statistically significant (p-value > 0.05), Table (5).

Table (5): Relationship between MD and molecular subtype

Molecular subtypes	Mammographic density		Total	*p*-value
	Low density	High density		
Luminal A	19 (25.7%)	3 (9.7%)	22 (21%)	>0.05
Luminal B	24 (32.4%)	15 (48.4%)	39 (37.1%)	
Basal like	3 (4%)	1 (3.2%)	4 (3.8%)	
Her-2 new	21 (28.4%)	12 (38.7%)	33 (31.4%)	
Unknown	7 (9.5%)	0 (0%)	7 (6.7%)	

No significant difference was identified among breast cancer density and ER or PR status; however, most cases were found to have positive ER and PR for high and low-density cases. HER-2 was more often negative in the whole population, but statistically, no significant association found (*p*-value > 0.05), Table (6). Tumours with grade I and II tended to be more common in both low-density (69 %) and high-density cases (54.9%) compared with grade III tumours, and this statistically was not significant (*p*-value > 0.05), Table (6). In cases diagnosed with high-density breast cancers, 71 % of them had lymph node involvement. This was not statistically significant (*p*-value > 0.05), Table (6). Stage II was the predominant stage in high density (58%) and low-density breast cancer cases (43.2%). This was not statistically significant (*p*-value > 0.05), Table (6). Tumours equal to or larger than 2 cm were recorded to be more common in high-density (87%) and low-density cases (73%). This was not statistically significant (*p*-value > 0.05), Table (6).

Table (6): Relationship between MD and characteristic of breast cancer.

	Mammographic density		*p*-value
	Low density	High density	
ER status			
Negative	11 (14.9%)	7 (22.6%)	>0.05
Positive	63 (85.1%)	24(77.4%)	
PR status			
Negative	13(17.6%)	8(25.8%)	>0.05
Positive	61(82.4%)	23(74.2%)	
HER-2 Status			
Negative	47(63.5%)	19(61.3%)	>0.05
Positive	27(36.5%)	12(38.7%)	
Tumour grade			
Grade I &II	51(69%)	17(54.9%)	>0.05
Grade III	23 (31%)	14(45.1%)	
LN involvement			
No	23(31%)	9 (29%)	>0.05
Yes	51 (69%)	22 (71%)	
Tumour stage			
Stage I	10 (13.5%)	1 (3.2%)	>0.05
Stage II	32 (43.2%)	18 (58%)	
Stage III	29 (39.1%)	9 (29%)	
Stage IV	3 (4.1%)	3 (9.7%)	
Tumor size(cm)			
< 2	20 (27%)	4 (13%)	>0.05
> =2	54 (73%)	27 (78%)	

Discussion

It is about more than 30 years of research; the evidence was supporting the association between breast cancer and MD.[11] Breast density might be a biomarker risk; however, the idea remains controversial.[12] Furthermore, its impact on breast cancer risk results in a reduction in a screening mammogram's accuracy. This is a case, especially among young females who are more likely to have denser breast .[13] As a result of the reduced screening accuracy, MD might be associated with an elevated risk of interval cancer and adverse prognosis of breast cancer.[13] In our study, the correlation between MD (low and high MD) with some breast cancer risks and tumour characteristics was investigated. We found a statistically significant interaction between age and MD. This is consistent with a large study conducted by Eriksson.[3] Li.[11] and Shaikh.[14] with higher MD was observed in younger than older women. Similarly, we found a significant association between MD and menopausal status with higher breast density observed among premenopausal women while less breast density observed among postmenopausal women. This is supported by Eriksson study which revealed postmenopausal women had lower MD than premenopausal women.[3] We found that most cases of high mammographic density were belonged to high BMI group (61.3%). However, we did not find any association between MD and BMI. This finding is supported by a study done by Shaikh, which found no statistically significant relationship between MD and BMI. However, they reported that high-dense and non-dense areas were observed more commonly in obese women than overweight women.[14] In contrast, an additional study found an association between MD and BMI and reported that women with lower BMI had higher breast density.[13] Regarding the correlation of MD with molecular subtypes, we noted that luminal B was the predominant type among low and high-density breast cancer cases. However, we couldn't find any association between MD and molecular subtypes. This is supported by Shin that used the quantitative method for MD measurement and didn't find an association between MD and molecular subtypes.[15] This was also supported by other studies that didn't find a statistically significant difference in MD among all molecular subtypes.[3,16] On the other hand, Ji found the association between HER-2 enriched subtype and high MD, which was observed only when MD was measured by BIRADS and not by software analysis of density.[17] In addition, high MD was associated with HER-2 enriched subtype in North American study; however, the association was significant while volumetric breast density was used and not BIRADS density.[16] Another large study conducted in China also demonstrated an association of MD and HER2 subtype using BIRADS for MD classification; this might explain the high rate of HER-2 enriched subtype among Asian women.[11] About the correlation of MD with receptor status, we found that high MD had more ER+ve and PR+ve compared with ER –ve and PR-ve status, but it was not significant statistically. This is supported by other studies that observed no difference between PR or ER hormone receptor status within different breast densities.[18-20] In contrast, Ding and colleagues and Conroy and colleagues' studies revealed the association between ER+ve tumours and MD.[21,22] Shaikh revealed that ER+ve patients had higher breast density than ER-ve patients.[14] In comparison, the study by Yaghjyan and colleagues reported an association between ER-ve tumours and MD.[23] A statistically stronger association between ER-ve and MD was reported in another study however, the association was examined by age group. They reported that women younger than 55 years had a stronger association of MD with ER-ve

breast cancer cases compared to women aged 55-65 and >= 65.[16] Besides, there was a significant association between MD on postmenopausal women and ER-ve compared to ER+ve. However, the number of ER-ve was smaller than ER+ve receptor status.[23] Furthermore, Sartor and colleagues supported the later association; however, only clinically detected cancers were included.[24] Most of the included cases were >= 2 cm, stage II, nodal involvement, and grade I and II. However, no significant association was noted. Supported by other studies which did not find an association between MD and tumor size, MD and lymph node metastasis[14, 25] and between MD and tumor grade.[7] In contrast, a study found a strong association between MD and large tumors compared to small tumors,[7] this is consistent with the findings of previous studies.[23] Additionally, a strong association was found between MD and lymph node involvement.[7] This finding is supported by a study which found a positive association between MD and aggressive tumor characteristics, including lymph node involvement and advanced stage.[26] Our study had several limitations which might have an impact on our findings. We used BIRADS classification for MD measurement instead of software analysis of density. However, the former is subjective, resulting in potential bias between radiologists' interpretation of MD measurement and the possibility of misclassification. Also, our study had a small number of higher breast density cases, limited number of included risk factor and was not designed as case control study.

Conclusion

We did not find a significant association between MD and breast cancer subtypes. However, Luminal B was the most common molecular subtype observed in this study. There was a significant association between MD and age. In addition, we noted a significant association between MD and menopausal status.

Conflicts of interest

The author reports no conflicts of interest.

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