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Original Research

The Relationship Between Mammographic Density and Factors Affecting Breast Cancer Risk

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Abstract

Objectives: Although the relationship between breast cancer (BC) risk factors and mammographic density (MD) patterns is not clear, high MD is well known as an independent risk factor for BC. Thus, the aim of this study was to examine the association between MD and BC risk factors in BC patients and find a correlation between MD and tumor characteristics in BC patients.

Methods: Our data included 242 patients with BC. Furthermore, the MD (type I - <25%; type II - 25–50%; type III - 51–75%; and type IV - >75%) was categorized according to percentile density, and the various types of MD were compared using risk factors for BC and tumor characteristics of patients.

Results: The results of this study indicated that younger age, pre-menopausal status, younger menarche age, nulliparity, low body mass index, and smoking significantly increase the percentage of MD ($p<0.001$, $p<0.001$, $p=0.04$, $p<0.001$, $p=0.003$, and $p=0.01$, respectively). Moreover, the distribution of MD patterns showed significant differences according to tumor subtypes. Type 4 mammographic pattern was higher in patients with human epidermal growth factor receptor 2 (Her2) type of tumor ($p=0.01$).

Conclusion: Higher MD is related to reproductive risk factors and tumor subtypes, especially Her2 type, in BC patients. Further studies are needed to identify the factors related to breast density.

Keywords: Breast cancer risk; breast cancer; human epidermal growth factor receptor 2-neu receptor; mammographic density; tumor characteristics.

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All over the world, breast cancer (BC) is the most frequently diagnosed life-threatening cancer and leading cause of cancer death among women.[1] If breast density and risk factors for BC, such as older age, reproductive factors, overweight, hormonotherapy, family history, and smoking, interact together, they may increase the chance of BC. On the other hand, current literature mentions the prognostic importance of various mammographic density (MD) patterns in patients with BC.[2-4]

In this study, we aim to examine the association between MD, BC risk factors, and tumor characteristics in Turkish women with BC.

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Methods

Study Design

For the purpose of this study, the records of BC patients treated at the Department of General Surgery, Ankara Numune Training and Research Hospital in Turkey were reviewed retrospectively. Local ethics board approval was obtained for this study, through registration number E.11609 (Date: December 21, 2020). Both computerized and documentary archives of participants were used in this study. During admission, participants were handed out questionnaires containing information about up dated breast health risk factors by health-care professionals. Furthermore, the participants were divided into four groups based on types of percent MD. Each group was compared on the basis of demographic features and risk factors for BC. In addition, the patients were categorized based on MD and compared in terms of the pathological and tumor characteristics they exhibited.

Exclusion Criteria

Cases with inoperable BC, breast surgery before mammographic shooting, and patients receiving neoadjuvant therapy were excluded from the analysis.

Variables

The available documentation of medical history associated with breast health, radiological, and pathological findings of the participants was documented for this study. This led to the collection of the following historical data: Age during mammographic shooting, body mass index (BMI) (kg/m^2) during mammographic shooting, age during menarche (<12, ≥12 years), parity (whether nulliparity), age during first labor (<20, ≥20 years), and menopausal status, whether the patient received hormonotherapy and oral contraceptives (OC), smoking status, and family history. Women who received OC for at least a period of 1 year were considered positive for OC intake. The family history of BC patients was defined as having first-degree relatives with BC. In addition, pathological features, such as age, pathological TNM stage (pTNM), nuclear grade, estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (Her2)-neu receptor, were collected from the patients' pathological records, and tumor subtypes were categorized as luminal A (ER+ and PR+, Her2-neu -), luminal B (ER+ and/or PR+, Her2-neu +), triple negative (ER-, PR-, Her2-neu -), and Her 2 type (ER-, PR-, Her2-neu +).

Evaluation of MD

The craniocaudal and mediolateral views of breasts that were achieved during conventional mammograms were collected into a database. The appearance of radiologically dense and lucent areas in the mammography was presented as the percentage of MD that was consistent with the existing literature.[5] Furthermore, the density of breast tissues was visually assessed prospectively by two experienced radiologists. The average percentage of MD of both breasts was used in this analysis. In the mammogram, the percentage of the area filled by radiologically dense breast tissues was analyzed and then divided into six different percentile categories according to the Boyd cutoff value (<5%, 5–10%, 10–25%, 25–50%, 5–75% or >75%).[6] This categorization, which was defined by Boyd et al. to categorize the various percentages of MD,[6] was further condensed into four categories (type I - <25%; type II - 25–50%; type III - 51–75%; and type IV - >75%) for this study for the convenience of interpreting the results.

Statistical Analysis

Statistical analyses were performed using SPSS ver. 17.0 (SPSS Inc., Chicago, IL, U.S.A.). The data were expressed as a mean±standard deviation for metric variables and as frequency (percentage) for categorical variables. To compare the groups in terms of metric variables, the Kruskal–Wallis variance analysis method was used. However, for categorical variables, the Chi-square test was used. For a non-randomized comparison of demographic features, we implemented the comparative-effectiveness propensity score methodology with weighted Cox modeling. A value of $p<0.05$ was accepted as statistically significant.

Results

A total of 242 cases were included in this study. The rates of patients based on type I, type II, type III, and type IV of percent MD were 46.3% (n=112), 28.5% (n=69), 19.8% (n=48), and 5.4% (n=13), respectively. All patients were female, and the mean age of the patients was 51.15±12.02 years. The demographic characteristics of these BC patients are listed in Table 1. The operative procedures conducted on these patients mainly included mastectomy for78% of

Table 1. Demographic features of BC patients

Patients (n=242)	(Mean±SD)
Age	51.15±12.02
Menarge age	13.49±1.27
Menopause age	47.59±4.95
Number of children	3.02±2.20
First birth age	21.88±4.71
BMI*	27.86±4.31

*BMI: Body mass index; BC: Breast cancer.

them (n=189/242) and breast-conserving surgery for the remaining 22% (n=53/242). The most diagnosed type of BC was invasive ductal carcinoma, with 92.6% of the patients (n=224/242) being diagnosed with it. The incidence of BC in patients <50 years of age and in postmenopausal and nulliparous patients was 47.5% (n=115/242), 49.8% (n=120/241), and 12% (n=29/242), respectively. Other risk factors, such as BMI ≥25, family history, history of hormone replacement therapy and OC usage, smoking, first labor after 19 years of age, the incidence of BC was 75.6% (n=183/242), 18.2% (n=44/242), 10.3% (n=25/242), 14.5% (n=35/242), 18.6% (n=45/242), and 65.7% (n=140/213), respectively.

Type III and type IV percent MD were higher in BC patients of <50 years, premenopausal patients, patients with a menarche age of ≥12, and patients with a child (p<0.001, p<0.001, p=0.04, and p<0.001, respectively). In addition, type III and type IV percent MD were statistically significantly higher in patients who had a BMI of <30 and exhibited smoking behavior (p=0.003 and p=0.01, respectively). Other risk factors, such as use of hormone replacement therapy and OC usage, did not show a statistically significant difference in patients in terms of types of percent MD (Table 2).

Types of percent MD were also compared with pathological features and tumor characteristics in BC patients. The distribution of percent MD types was statistically different

Table 2. The factors affecting mammographic density in patients with breast carcinoma

Risk factors	Percent mammographic density				p
	I n (%)	II n (%)	III n (%)	IV n (%)	
Age (n=242)					
<50 y	32 (25.2)	44 (34.6)	38 (29.9)	13 (10.2)	<0.001
≥50 y	80 (69.6)	25 (21.7)	10 (8.7)	0 (0)	
Menarge age (n=193)					
<12 y	14 (29.8)	15 (31.9)	15 (31.9)	3 (6.4)	0.04
≥12 y	98 (50.3)	54 (27.7)	33 (16.9)	10 (5.1)	
Menopause (n=241)					
Premenopause	31 (25.6)	43 (35.5)	35 (28.9)	12 (9.9)	<0.001
Postmenopause	80 (66.7)	26(21.7)	13 (10.8)	1 (0.8)	
Having Child (n=242)					
Absent	7 (24.1)	8 (27.6)	8 (27.6)	6 (20.7)	<0.001
Present	105 (49.5)	61 (28.6)	40 (18.8)	7 (3.3)	
Age of 1. Labor (n=213)					
<20 y	42 (57.5)	20 (27.4)	10 (13.7)	1 (1.4)	0.225
≥20 y	63 (45.0)	41 (29.3)	30 (21.4)	6 (4.3)	
Hormonotherapy (n=241)					
Absent	101 (46.5)	65 (30.0)	40 (18.4)	11 (5.1)	0.26
Present	11 (44.0)	4 (16.0)	8 (32.0)	2 (8.0)	
OC*usage (n=242)					
Absent	92 (44.4)	64 (30.9)	39 (18.8)	12 (5.8)	0.16
Present	20 (57.1)	5 (14.3)	9 (25.7)	1 (2.9)	
Smoking (n=242)					
Absent	99 (50.3)	56 (28.4)	32 (16.2)	10 (5.1)	0.01
Present	13 (28.9)	13 (28.9)	16 (35.6)	3 (6.7)	
Family History (n=242)					
Absent	96 (48.5)	53 (26.8)	37 (18.7)	12 (6.1)	0.26
Present	16 (36.4)	16 (36.4)	11 (25.0)	1 (2.3)	
BMI** (n=242)					
<25	17 (28.8)	18 (30.5)	18 (30.5)	6 (10.2)	0.003
25–30	47 (42.7)	34 (30.9)	24 (21.8)	5 (4.5)	
30–34	34 (61.8)	14 (25.5)	5 (9.1)	2 (3.6)	
≥35	14 (77.8)	3 (16.7)	1 (5.6)	0 (0)	

*OC: Oral contraceptive; **BMI: Body mass index.

based on pathological subtypes (p=0.01). Type IV percent MD was higher in patients with Her2 type (19.2%) than other subtypes (luminal A, luminal B, and triple negative; 1.3%, 4.3%, and 3.0%, respectively). The percentage of Her2-neu (+) patients with type IV MD was 7.7, whereas only 1.8% of Her2-neu (-) patients had type IV MD. However, there was no statistical difference with the borderline P-value (0.06). The distribution of percent MD types was not statistically different for other pathological parameters in BC patients (Table 3).

Discussion

variations in the composition of breast tissue and different X-ray attenuation characteristics of these tissues.[7] High MD not only reduces the sensitivity of the screening and diagnostic procedure, but it is also one of the strongest risk factors for BC.[5]

Nulliparity, younger age during menarche, and older age during 1st time giving birth have been identified as reproductive modifiable risk factors for BC.[8] In addition to this, some studies have found parity, age during first labor, and menarche age to influence MD.[2,9] Our results revealed that younger menarche age, premenopausal status, and nulliparity are associated with higher MD in BC patients. Moreover, MD was found to be higher in patients with Her2 subtype tumor.

van Gils et al. studied the relationship between parity and MD, and patients with nulliparity with >25% density were found to be 6.6 times more likely to develop BC.[10] Tesic et al., in their study, demonstrated a significant association between high MD and almost all reproductive risk factors.[2] However, patients with these risk factors will not develop BC, as the pattern of MD may help in the individual risk assessment of patients with risk factors before they develop BC. Thus, higher MD might be important for more accurately predicting BC in women with these reproductive risk factors. Physicians should keep this warning in mind that these risk factors along with higher MD maybe detected in BC patients. On the other hand, the lower MD is directly related to postmenopausal status.[3] Our results were consistent with the literature on BC patients. Cur-

Table 3. The correlation of breast density to clinic-pathologic parameters in patients with breast carcinoma

Tumor characteristics	Mammographic Density (Percent)				p
	I n (%)	II n (%)	III n (%)	IV n (%)	
TNM stage (n=236)					
I	29 (53.7)	13 (24.1)	9 (16.7)	3 (5.6)	0.26
II	50 (42.0)	38 (31.9)	24 (20.2)	7 (5.9)	
III	30 (50.8)	14 (23.7)	12 (20.3)	3 (5.1)	
IV	0 (0)	1 (25.0)	3 (75.0)	0 (0)	
Grade (n=198)					
I	25 (55.6)	12 (26.7)	6 (13.3)	2 (4.4)	0.19
II	50 (45.9)	37 (33.9)	18 (16.5)	4 (3.7)	
III	15 (34.1)	12 (27.3)	14 (31.8)	3 (6.8)	
ER* (n=229)					
Negative	39 (41.1)	26 (27.4)	22 (23.2)	8 (8.4)	0.11
Positive	66 (49.3)	40 (29.9)	25 (18.7)	2 (2.2)	
PR**(n=229)					
Negative	32 (47.1)	20 (29.4)	10 (14.7)	6 (8.8)	0.18
Positive	73 (45.3)	46 (28.6)	37 (23.0)	5 (3.1)	
Her2-neu (n=229)					
Negative	55 (49.1)	28 (25.0)	27 (24.1)	2 (1.8)	0.06
Positive	50 (42.7)	38 (32.5)	20 (17.1)	9 (7.7)	
Subtype (n=229)					
Luminal A†	38 (48.7)	17 (21.8)	22 (28.2)	1 (1.3)	0.01
Luminal B††	42 (45.7)	31 (33.7)	15 (16.3)	4 (4.3)	
Triple (–)‡	17 (51.5)	10 (30.3)	5 (15.2)	1 (3.0)	
Her 2 type	8 (30.8)	8 (30.8)	5 (15.2)	5 (19.2)	

*ER: Estrogen receptor; **PR: Progesterone receptor; †luminal A: ER+ and/or PR+, Her2-neu -, ††luminal B: ER+ and/or PR+, Her2-neu +, ‡triple (-): ER-, PR-, Her2-neu - , Her2 type: ER-, PR-, Her2-neu +.

rent literature mentions that older age during first labor is associated with increased breast density,[2,9] but our results were not compatible with this theory. Moreover, the usage of OC and hormone replacement therapy did not alter the rate of MD, which was again not consistent with the results of other some studies.[2,11-13] Hormone replacement therapy causes an increase in MD in 17–73% of women.[11,12] Greendale et al. showed that using conjugated estrogens with medroxyprogesterone acetate and estrogen alone increases MD in the 1st year of using, even if using the combined preparation increases more than just estrogen.[13] On the other hand, Palan et al. find that no significant difference in the MD before and after the medication in the transdermal gel, intranasal spray containing östrodiol and control groups.[14] This reason for these some conflicting results of our study may be that there were a limited number of participants and the time of the use of these agents was unknown.

It has been well reported that MD is inversely related to age and BMI.[2,9,15] Our study also observed an inverse relationship between age or BMI and MD. On the other hand, BMI and age were found to be independent risk factors for BC like MD, but this relationship is opposite to the relation between MD and BC.[2,15] These findings prove the hypothesis that MD and age or BMI affects BC through independent pathways.

Furthermore, we showed that family history does not affect the MD pattern in BC patients. Assi et al. found that the percentage of MD in BC patients with family history was not a significant risk factor for BC despite the significance of absolute MD for BC risk in these patient groups.[16] The reason for this discordance maybe associated with more complicated ways of patients with family history developing BC.

Although data on the effect of smoking are limited, some studies report an inverse relationship between smoking and breast density[17,18] while some others show a null association between the two in women with or without BC.[19,20] In addition, we determined that women smokers have a higher MD. Further studies need to be conducted to determine the long-term effects of heavy smoking on breast density.

Most studies that can help in understanding the prognostic value of MD focuses on the relationship between MD and tumor characteristics, but the effect of tumor characteristics on MD varies in the literature. Some studies noted that BC patients exhibit different MD patterns for different tumor characteristics, but other studies did not observe any significant interaction between these factors, even if a part of these studies showed a relationship between high MD and BC for some tumor characteristics.[15,21-25] Yaghjyan et al. found that high MD has a stronger association with ER-negative tumors than ER-positive ones.[22] Furthermore, Kim et al. found a relationship between ER and PR positivity and high MD, and they also detected different MD patterns based on tumor subtypes. They showed that MD was statistically significantly lower in patients with triple-negative tumors than other subtypes (p=0.02).[4] Bertrand et al. found that all tumor subtypes in BC patients, as opposed to healthy people, were significantly associated with high MD, but the MD patterns did not show any differences among type of grades, ER, PR, and Her 2-neu status.[21] They also found a relationship between high MD and ER (-) in BC patients aged <55 years.[21] However, Razzaghi et al., in their study, did not observe any differences between MDs of BC subtypes, such as luminal A, basal-like, and triple negative patients.[23] Domingo et al. obtained the same results for luminal A, luminal B, triple negative, and Her2 subtypes in patients diagnosed for the 1st time.[24] However, they found that the MD pattern was significantly higher for Her2-neu (+) subtypes and significantly lower for triple negative in interval patients. In our study, we showed significant differences in MD patterns for various tumor subtypes (p=0.013).

In our results, high-density breasts (density 3–4) showed lower estrogen positivity than low-density breasts (density 1–2), which is consistent with the findings of Yaghjyan et al.[22] The mammography of ourHer2 type patients (34.4% for MD ≥50%) exhibited a denser pattern than other subtypes (luminal A, 29.5%; luminal B, 20.6%; and triple negative, 18.2%; for MD ≥50%). On the other hand; a lower MD pattern was much more common in patients with triple negative and luminal B (81.8%, 79.4%, and for MD <50%, respectively) than others (luminal A, 70.5%; Her2 type, 61.4%; and for MD <50%, respectively).

Our study focused on the restricted factor that can besides one categorized method for MD patterns, but higher MD is an independent risk factor from MD classification methods for BC.[2] On the other hand, recent studies generally research the effect of MD as a risk factor for BC in women who exhibit other known risk factors. We want to look at this issue from another perspective to investigate the effect of percent MD patterns other risk factors. According to our study, women with an early menarche age no child have a high MD, which needs to be taken care of more than other risk factors for BC. Moreover, this relationship can clearly contribute to individual risk assessment in women with reproductive risk factors. On the other hand, high MD is not only associated with the risk of BC but also has prognostic significance. High MD was found to be associated with advanced stage, larger tumor size, and positive lymph nodes.[26] Consistent with this argument, we found that high MD has a stronger association with Her2 positive subtype than other tumor subtypes. The relationship between MD and the prognosis of BC as well as the risk of BC is not clear. Investigation of the relationship between tumor subtypes and MD may facilitate the understanding of the unclear mechanisms of the role of MD as risk and prognostic factor of BC.

Conclusion

This study suggests that status of menarche age, parity, and tumor subtypes exhibit different patterns of percent MD while age and BMI have an inverse interaction with percent MD in BC patients. Further studies are needed to identify the factors responsible for MD.

Disclosures

Ethics Committee Approval: Sakarya University Faculty of Medicine Ethics Committee, E.11609, date: December 28, 2020.

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