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Original Article

The clinical association between breast cancer molecular subtype and clinical stage with breast density

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Abstract

Aim: Breast cancer is the most common malignancy in women, and dense breast tissue is a risk factor for breast cancer. However, it remains unclear whether there is an association between the breast density and molecular subtypes and clinical stage of breast cancer patients diagnosed with invasive breast cancer. We performed a retrospective cohort study to determine the association between molecular subtype and TNM clinical stage with breast density

Materials and Methods: The data of female breast cancer patients who underwent treatment in our general surgery clinic between January 2019–April 2021 participated in the study. Patients' gender, mammographic density, mammographic BI-RADS category, tumor location, TNM clinical stage, and breast cancer molecular subtypes were noted. Descriptive statistics and inferential statistics as cross-tabulations and chi-square tests were used, where applicable.

Results: 230 female patients participated in the study. The mean age of the patients was 56.8 (29–88) years old. The most frequent mammographic breast density was category C (39.4%), followed by category B (33.3%). Furthermore, the most frequent mammographic BI-RADS category was category 4 (38.1%), followed by category 5 (37.2%). There was no statistically significant relationship between mammographic density and the TNM clinical stage of the patients (p=0.247). There was no statistically significant relationship between the mammographic density and molecular subtype (p=0.397).

Conclusion: Mammographic breast density was not linked with the subtype or clinical stage of breast cancer. The focus of breast cancer clinical trials should be early detection, particularly in cases with dense breast tissue, regardless of molecular subtype.

Keywords: Mammography, breast density, breast cancer, breast imaging, BI-RADS

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer worldwide, including in low- and middle-income countries. The incidence rates are highest in North America, Australia/New Zealand, and Western and Northern Europe (1). Breast cancer is thought to belong to a group of heterogeneous diseases resulting from biological and molecular properties originating in the breast tissue. Genetic predispositions and originating areas of the ducts, lobules, and other areas of the breast differ in distinct types of cancer. Breast development is controlled by stem cells regulated by estrogen receptors (ERs), Human epidermal growth factor 2 (HER2), Wnt/β-catenin signaling pathways, epigenetic regulations, and non-coding RNAs (2). Importantly, breast cancer is classified into four molecular subtypes by Perou and Sorlie, i.e., Luminal A and Luminal B (expressing the estrogen receptor), basal-like (triple-negative), and HER2 enriched (without ER expression). The molecular study of the disease is primarily focused on therapy taking a biology-centered approach (3). Due to the difference in prognosis between molecular subtypes, treatment approaches have also been diversified (4). Nevertheless, the importance of the early diagnosis of breast cancer remains paramount (5).

Worldwide, screening mammography is the main imaging modality for providing an early diagnosis. Mammographically detectable dense breast structure is recognized as a factor that increases the risk of breast cancer by one-to-six times (6).

In this study, we analyze the potential relationship between the mammographic breast density, breast cancer molecular subtype, and clinical stage of the disease.

MATERIALS AND METHODS

Following approval of the local ethical committee (Kutahya University Local Ethical Committee Approval Number: 2021/12–02), the data of female breast cancer patients who underwent treatment in our general surgery clinic between January 2019–April 2021 participated in the study. The patients were diagnosed based on symptoms, personal and family history information, physical examination findings, and imaging-guided biopsies performed mostly after mammography and ultrasonography. Patients' gender, mammographic density, mammographic ACR (American College of Radiology), BI-RADS (Breast Imaging-Reporting and Data System) category, tumor location, AJCC (The American Joint Committee on Cancer), TNM clinical stage, according to the 8th edition (7), and breast cancer molecular subtypes were noted.

According to the mammographic BI-RADS reporting system, breast density is classified as; A: almost entirely fatty, B: scattered areas of fibroglandular density, C: heterogeneously dense; D: extremely dense (8).

Breast cancer molecular subtypes were categorized as 'Luminal A,' 'Luminal B,' 'HER2-enriched' and 'basal-like' (triple-negative) (9).

Patients diagnosed with infiltrating ductal carcinoma participated in the study.

Patients who had differing cancers, breast cancer rather than infiltrating ductal carcinoma, chronic liver disease, or missing information were excluded from the study.

Statistical Analysis

Statistical results were obtained with the IBM SPSS 20 (Statistical Package for Social Sciences) program. Descriptive statistics were used for numerical variables. Frequency tables were used for categorical variables. Cross tabulations and chi-square test statistics were used to examine the status of two categorical variables relative to each other. The Gamma relationship coefficient was calculated from the relationship coefficients. The bar graph shows the distribution of TNM stage categories and subtype categories in mammographic density categories.

RESULTS

A total of 230 female patients participated in the study. The mean age of the patients was 56.8 (29–88) years old; 126 patients had breast cancer in their left breast and 104 in their right breast cancer. Patients' mammographic breast density categories and mammographic BI-RADS categories are shown in Table 1.

The TNM stages of the patients were as follows: clinical stage 1: 30.3% (n:70); stage 2: 38.5% (n:89); stage 3: 14.7% (n:34); stage 4: 16.5% (n:38). The patients' molecular subtype is displayed in Table 2.

Table 1. Mammographic BRADS and breast density categories of the patients

		Frequency (n)	Percentage (%)
Mammographic BI-RADS Category	0	24	10.4
	1	5	2.2
	2	5	2.2
	3	22	9.5
	4	88	38.1
	5	86	37.2
	6	1	.4
	Total	231	100.0
		Frequency (n)	**Percentage (%)**
Mammographic Density	A	39	16.9
	B	77	33.3
	C	91	39.4
	D	24	10.4
	Total	231	100.0

Table 2. Molecular subtypes of the breast cancer patients

		Number (n)	Percentage (%)
Subtype	HER2-Positive	22	9.5
	Luminal A	110	47.6
	Luminal B	85	36.8
	Triple Negative	14	6.1
	Total	231	100.0

There was no statistically significant relationship between mammographic density and the TNM clinical stage of the patients (p=0.247). Based on the TNM stage category in each of the mammographic density categories, the rate of those in the second clinical stage was higher. This was followed by stages 1, 4, and 3, respectively (Table 3, Figure 1).

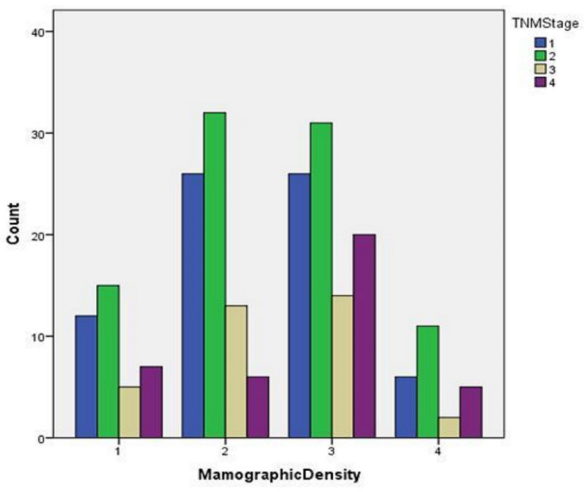

Figure 1. Statistical relationship between the mammographic density and TNM clinical stage of the breast cancer patients

Table 3. Statistical relationship between the mammographic density and TNM clinical stage of the breast cancer patients

Mammographic Density and TNM Stage

		TNM Stage				Total
		1	2	3	4	
Mammographic Density	A	12	15	5	7	39
		30.8%	38.5%	12.8%	17.9%	100.0%
	B	26	32	13	6	77
		33.8%	41.6%	16.9%	7.8%	100.0%
	C	26	31	14	20	91
		28.6%	34.1%	15.4%	22.0%	100.0%
	D	6	11	2	5	24
		25.0%	45.8%	8.3%	20.8%	100.0%
Total		70	89	34	38	231
		30.3%	38.5%	14.7%	16.5%	100.0%

Chi-Square 8.172; Gamma: 0.093; p-value:0.247

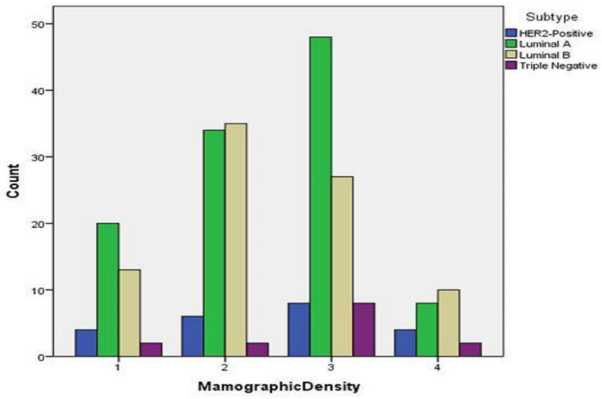

Figure 2. Statistical relationship between the mammographic density and molecular subtype of the breast cancer patients

Table 4. Statistical relationship between the mammographic density and molecular subtype of the breast cancer patients

Mammographic Density * Subtype

		Subtype				Total
		1	2	3	4	
Mammographic Density	A	4	20	13	2	39
		10.3%	51.3%	33.3%	5.1%	100.0%
	B	6	34	35	2	77
		7,8%	44.2%	45.5%	2.6%	100.0%
	C	8	48	27	8	91
		8.8%	52.7%	29.7%	8.8%	100.0%
	D	4	8	10	2	24
		16.7%	33.3%	41.7%	8.3%	100.0%
Total		22	110	85	14	231
		9.5%	47.6%	36.8%	6.1%	100.0%

Chi-Square: 9.447; Gamma: 0.117; p-value:0.397

There was no statistically significant relationship between the mammographic density and molecular subtype (p=0.397). According to the subtype category in each of the mammographic density categories, the rate of those in Luminal A and Luminal B were higher, while HER2-positive and triple-negative rates were lower (Table 4, Figure 2).

DISCUSSION

In this study, we investigated the relationship between mammographic breast density, molecular subtype, and the clinical stage of breast cancer patients. Accordingly, there was no statistical correlation between these entities.

As the grade of breast density increases, it becomes more difficult to diagnose breast cancer; as such, it is expected that, consequently, the clinical stage of breast cancer could be affected (10).

Breast cancer therapy has evolved during the past decade after progress was made concerning the understanding of the molecular properties of the disease (11). However, early diagnosis is the most important step for all breast cancer subtypes in terms of survival rates (12).

Digital mammography has been used to detect the disease at an earlier stage. This approach has a sensitivity of 97%, a specificity of 64.5%, a positive predictive value of 89%, and a negative predictive value of 90.9%, with a diagnostic accuracy of 89.3% (13). Nevertheless, screening mammography must be supported by clinical examination, breast ultrasonography, and MRI because less than 1% of breast cancers appear occult or present with distant metastasis (14, 15).

Our study group consisted mostly of postmenopausal women. Women older than 55 years have an increased risk for breast cancer, based on the literature (16). In this study, the distribution of patients' breast density was almost equal, when the most frequent mammographic breast density category was category C. Due to a lack of enough data, we could not separate patients who underwent screening or diagnostic mammography. So, it is possible that, regarding such heterogeneity, there is no statistical correlation between mammographic breast density and the BI-RADS category.

In the literature, 43% of US women had breast density category types C and D (17). The most frequent clinical stage of breast cancer in patients was stage 2. Treatment modalities differ as the clinical stage of the disease progresses. For early breast cancer, surgery is the mainstay of treatment and comprises breast-conserving surgery accompanied by oncoplastic techniques (18). Neoadjuvant therapy is an option for axillary-positive patients or those with locally advanced diseases. This can enable breast-conserving therapy or prevent axillary dissection, particularly for patients with high-risk HER2-positive or triple-negative breast cancer (TNBC). However, in the metastatic clinical stage of the disease, the benefits from surgery are debatable and the mainstay of therapy comprises chemotherapy (19). So, early diagnosis is

thus crucial for the prevention of morbidity and mortality.

Mammograms are an essential part of the early diagnosis of the disease. In Turkey, women older than 40 years are recommended to have mammograms, with the target population indicated as being women between 40–69 years old (20). It has been shown that screening mammography may contribute to a shift in the stage of breast cancer at diagnosis (21). Several institutions worldwide have established guidelines for breast cancer screening for average-risk women, with differences reflected by age for the target population. Most guidelines recommend frequent screening (annually or biennially) for women 40–74 years old, for which mammography is an accepted primary screening modality. For high-grade breast density, ACR recommends breast MRI; however, the Chinese NCCN prefers ultrasonography and mammography annually. Ultrasonography is accepted as an adjunctive tool, particularly for situations when MRI is not suitable (22).

In this study, there was no statistical correlation between the mammographic density and the clinical stage of patients, but clinical stage 2 was the most common clinical stage in all density categories. This may have been related to the volume of clinical stage 2 cancer patients in this study.

In our study group, the most common molecular subtype of breast cancer patients was Luminal A, consistent with the literature, where it represents 50–60% of all breast cancers (9). In line with the volume of the patients with the Luminal A or Luminal B subtype, for all breast density categories, these subtypes were commonly observed. Several studies have analyzed the potential relationship between breast density and the molecular subtype of breast cancer. As our study has shown, there is no evidence in the literature to conclusively demonstrate this relationship. Increased mammographic density, a proven risk factor for breast cancer, was not significantly different between breast cancer molecular subtypes (23). Contrastingly, only in Asian women, an association has been found between HER2-enriched and Luminal B types with an increased mammographic density. However, this mechanism is unknown (24). In molecular subtypes with poor prognosis, like triple-negative breast cancer, it usually appears as a mass with a relatively circumscribed margin and without calcifications (25). A stellar-shaped mammogram with an echogenic halo in Luminal A and architectural distortion in Luminal B-type tumors are common features (26).

It appeared that tumor phenotype and breast density may independently contribute to the progression of breast cancer, as with interval cancers, when triple-negative tumors were observed more often in fatty breasts (27). Therefore, not only molecular subtypes of breast cancer but also their phenotypic appearance should be examined with radiologic imaging, along with breast density.

In addition, the study revealed that breast cancer patients had higher-than-anticipated BRADS 1, 2, and 3 mammograms. This is significant because it demonstrates the significance of other imaging modalities, especially physical examination, and ultrasound, in breast cancer diagnosis.

Study Limitations

A retrospective observational study with a limited number of breast cancer patients may not show the association between breast density, molecular subtype, and clinical stage of breast cancer. The demographic data of the patients, such as chronic diseases, obesity, and family history of cancer, were missing. In addition, histological characteristics of the cancer were not part of the study.,

CONCLUSION

There was no association between dense breast structure and breast cancer molecular subtypes or stages. As early detection increases the chances of curative treatment for all types of breast cancer, studies focusing on early detection in patients with dense breast tissue are of greater importance.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
Kutahya University Local Ethical Committee Approval Number: 2021/12–02.

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