Original Article

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Clinical and Pathological Characteristics of Patients with High-Risk Breast Cancer Based on BRCA Mutation Profiles: A Retrospective Study

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ABSTRACT

Objective: This study aimed to determine the differences in clinicopathological features of Turkish patients with high-risk breast cancer based on the mutation status of two breast cancer susceptibility genes (BRCA1/2) .

Materials and Methods: This study enrolled patients with invasive breast cancer who have been evaluated for BRCA1/2 mutations due to the presence of high-risk factors admitted to two tertiary referral centers in Turkey. Clinical and histopathological features were analyzed in BRCA1 mutation carriers, BRCA2 mutation carriers, and non-carriers.

Results: A total of 302 patients with a mean age of 44.2±9.9 (22–82) years were included. BRCA1/2 mutation was found in 75 (24%) patients, of whom 41 (13.6%) were BRCA1 mutation carriers and 37 (12.3%) were BRCA2 mutation carriers. Moreover, 104 (34.4%) and 4 (1.3%) patients had family history of breast and ovarian carcinoma, respectively. The rates of triple negativity (56.1%), histologic grade 3 (65.9%), and lymphovascular invasion (78%) were significantly higher in BRCA1 mutation carriers than in non-carriers and BRCA2 mutation carriers. Furthermore, 87% of triple-negative BRCA1 mutation carriers had histologic grade 3 tumors compared with 38.9% in non-triple-negative BRCA1 mutation carriers, and the difference was significant.

Conclusion: Findings of this study showed that BRCA1-related breast cancers represent a distinct group with unique pathological features, which are usually associated with a poor prognosis.

Keywords: BRCA, breast cancer, Triple-negative, lymphovascular invasion, grade

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Key Points

- The rates of triple negativity, histologic grade 3, and lymphovascular invasion were significantly higher in BRCA1 mutation carriers.
- While most of the triple-negative BRCA1 mutation carriers had histologic grade 3 tumor, it was not common in non-triple-negative BRCA1 mutation carriers.
- These findings showed that BRCA1-related breast cancers have pathological features related with poor prognosis.

Introduction

Evaluation of two breast cancer susceptibility genes, namely, *BRCA1* and *BRCA2*, is essential in patients with a predisposition to carry these mutations. Number of family members with breast cancer, young age at diagnosis, bilateral disease, and family history of ovarian cancer have been proposed as predictors of BRCA 1/2 mutations in patients with breast cancer (1). The frequency of BRCA1 and BRCA2 mutations may vary between ethnic groups (2). However, only a few studies have investigated the frequency of BRCA1/2 mutations in Turkish patients with breast cancer (3,4). Additionally, it is crucial to determine the clinical characteristics and pathological features in BRCA1/2 mutation carriers, which is also essential to define the differences between them and BRCA mutation non-carriers (5). In this study, we aimed to elucidate the frequency of BRCA1/2 mutations in a large series of patients with high-risk breast cancer and its relationship with personal/family history

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profiles and to perform clinicopathological analysis of patients with BRCA1/2-associated breast carcinoma from two tertiary referral centers in Turkey.

Materials and Methods

Among patients diagnosed with invasive breast cancer between 2015 and 2020 in two tertiary referral centers in İstanbul, patients with breast cancer who have been evaluated for BRCA1/2 mutations due to the presence of high-risk factors including younger age at diagnosis (<40 years old), male sex, bilateral localization of the tumor, and personal/family history of breast and ovarian cancer were enrolled in this study. BRCA1/2 mutations were investigated using next-generation sequencing. Patients' data including demographic information and frequency of BRCA mutation according to personal/family history risk factors were retrospectively analyzed. In addition, BRCA1 mutation carriers, BRCA2 mutation carriers, and non-carriers were analyzed in terms of the clinical and histopathological features including hormonal status, histologic grade, lymphovascular invasion, and perineural invasion.

The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Review Committee of İstanbul Professor Doctor Cemil Taşçıoğlu City Hospital (approval no. 48670771-514.10/210).

Statistical analysis

Data were analyzed using SPSS 22.0 software program. All continuous values were presented as median (range) and mean ± standard deviation. Categorical data were expressed as a percentage and number. Associations between patients' BRCA mutation status and demographical, clinical, and histopathological characteristics were assessed using the chi-square test. The p-value of <0.05 was considered significant.

Results

A total of 302 patients with a mean age of 44.2±9.9 (22–82) years, of whom five were male, were included in this study. Moreover, 203 (68.4%) and 94 (31.6%) female patients had premenopausal and postmenopausal states, respectively. Breast carcinoma was localized bilaterally in 21 (7%) patients, and only 6% of our patients had metastatic disease. A total of 75 (24%) patients were BRCA1/2 mutation carriers. Forty-one (13.6%) patients were BRCA1 mutation carriers, 37 (12.3%) were BRCA2 mutation carriers, and three (1%) were both BRCA1 and BRCA2 mutation carriers. First-/second-degree relatives of 104 (34.4%) and 4 (1.3 %) patients had history of breast and ovarian carcinoma, respectively. Additionally, the frequency of BRCA mutation was the highest in patients with breast carcinoma with a family history of ovarian carcinoma (75%), followed by patients with breast carcinoma with a personal history of ovarian carcinoma (62.5%), and male patients with breast cancer (60%).

Comparison of demographic, clinical, and pathological data of patients according to the BRCA mutation profile are shown in Table 1. Most of the BRCA1 mutation carriers (75.6%) were >40 years old (p<0.05). Among BRCA1 mutation carriers, 19.5%, 43.9%, and 31.7% were 30–39, 40–49, and 50–59 years of age, respectively. Among BRCA2 mutation carriers, 43.2%, 31.7%, and 5.4% were 30–39, 40–49, and 50–59 years of age, respectively. No significant difference was found among BRCA1 mutation carriers, BRCA2 mutation carriers, and BRCA non-carriers in terms of menopausal status and body mass index (Table 1).

Characteristics of patients' tumors were evaluated according to their BRCA mutation profiles (Table 1). As regards the histological type of tumors, invasive ductal carcinomas were found in 260 (86%), invasive lobular in 20 (6.6%), and other types in 22 (7.3%) patients. Disease stage, tumor histology, mean tumor size, axillary nodal status, perineural invasion, and Ki-67 proliferation index were comparable among BRCA1 mutation carriers, BRCA2 mutation carriers, and non-carriers (Table 1). However, the rate of lymphovascular invasion was significantly higher in BRCA1 mutation carriers (78%) than in BRCA2 mutation carriers (54.1%) and non-carriers (55.3%) (Table 1).

The interrelationship between the estrogen receptor (ER) status, progesterone receptor (PR) status, Her2-neu status, histologic grade, and BRCA mutation profiles of our patients was also evaluated. BRCA1 mutation carriers were more likely to be diagnosed with triple-negative breast cancer (56.1%) than non-carriers (32.2%) and BRCA2 mutation carriers (29.7%) (p = 0.01) (Table 1). ER, PR, and HER-2/neu states were comparable between BRCA1/2 mutation carriers and non-carriers. Moreover, 65.9% of BRCA1 mutation carriers had histologic grade 3 tumor, compared with 32.2% and 37.8% in BRCA non-carriers and BRCA2 mutation carriers, respectively (Table 1). The distribution of BRCA1 carriers was also evaluated according to the triple-/non-triple-negative status and histologic grade of the tumor (Table 2). Moreover, 87% of the triple-negative BRCA1 mutation carriers had histologic grade 3 tumor, compared with 38.9% of non-triple-negative BRCA1 mutation carriers, and the difference was significant (Table 2).

Discussion and Conclusion

In this study, we identified the clinical and pathological characteristics of patients based on their BRCA mutation profiles from a cohort of Turkish patients with high-risk breast cancer. We found that more cases of BRCA1-related breast cancers were triple-negative with a higher ratio of histologic grade 3 tumor and lymphovascular invasion than were BRCA-negative and BRCA2-related breast cancers, which are usually associated with a poor prognosis.

BRCA mutation carriers have a very high-risk of breast cancer by age 70, with incidence of 47%–66% (1). Overall, mutations in these genes are implicated in approximately 15% of women with familial breast cancer and a similar proportion of all women with incidental ovarian cancers (6). Because women with BRCA mutation-associated breast cancer also have an elevated risk of other malignancies, identifying these mutations is essential for genetic counseling, testing, screening, and prevention strategies (1). However, the prevalence of BRCA1/2 mutation varies based on several factors, including ethnicity, age at diagnosis, sex, tumor histology, and family history (1, 2). A few studies from Turkey have reported that the mutation prevalence in patients with high-risk breast carcinoma ranged from 14% to 19% (3, 4). In our study, the total prevalence rates of BRCA, BRCA1, and BRCA2 mutations were 24%, 13.6%, and 12.3%, respectively, among patients with high-risk breast cancer. In a study conducted in Malaysia, patients were grouped according to their personal/family history, and the likelihood of having these mutations was reported highest (60%) in patients with breast and ovarian cancer, followed by patients with

Table 1. Clinical and pathological characteristics of patients with breast cancer according to BRCA mutation status.

Characteristics		BRCA1 carriers	BRCA2 carriers	BRCA non-carriers	p-value
		n = 41 (%)	n = 37 (%)	n = 227 (%)	
Age (years)	**≤40**	10 (24.4)	19 (51.4)	105 (46.3)	0.021
	>40	31 (75.6)	18 (48.6)	122 (53.7)	
BMI (kg/m²)		28.4±5.5	28.7±6.8	27.6±5.0	0.583
Menapousal status	**Premenopausal**	28 (68.3)	26 (74.3)	151 (67.4)	0.718
	Postmenopausal	13 (31.7)	9 (25.7)	73 (32.6)	
Mean tumor size (mm)		32.9±21.3	31.9±22.1	29.2±17.2	0.618
Axillary nodal status	**Positive**	16 (42.1)	11 (39.3)	95 (49.7)	0.453
Lymphovascular invasion	**Positive**	32 (78.0)	20 (54.1)	125 (55.3)	0.022
Perineural invasion	**Positive**	28 (68.3)	18 (48.6)	114 (50.7)	0.099
Tumor histology	**IDC**	35 (85.4)	34 (91.9)	194 (85.5)	0.451
	ILC	1 (2.4)	1 (2.7)	18 (7.9)	
	Others	5 (12.2)	2 (5.4)	15 (6.6)	
Ki-67(%)	**≤5%**	1 (2.4)	2 (5.4)	20 (8.8)	0.585
	5%–20%	12 (29.3)	14 (37.8)	77 (33.9)	
	>20	28 (68.3)	21 (56.8)	130 (57.3)	
Triple-negative		23 (56.1)	11 (29.7)	73 (32.2)	***0.010***
ER	**Positive**	17 (41.5)	23 (62.2)	139 (61.2)	0.055
PR	**Positive**	15 (36.6)	19 (51.4)	113 (49.8)	0.274
Her2/neu	**Positive**	3 (7.3)	6 (16.2)	44 (19.4)	0.169
Histologic grade	**1**	2 (4.9)	0 (0.0)	11 (4.8)	***<0.001***
	2	12 (29.3)	23 (62.2)	143 (63)	
	3	27 (65.9)	14 (37.8)	73 (32.2)	
Stage	**1**	7 (17.1)	8 (21.6)	39 (17.2)	0.280
	2	22 (53.7)	14 (37.8)	115 (50.7)	
	3	7 (17.1)	12 (32.4)	63 (27.8)	
	4	5 (12.2)	3 (8.1)	10 (4.4)	

Significant p-values are shown in bold and italic.
IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; BMI: Body mass index; ER: Estrogen receptor; PR: Progesterone receptor; n: Number

Table 2. Distribution of BRCA1 mutation carriers according to the receptor status and histologic grade of the tumor

	BRCA1 mutation carriers				p-value
	Triple-negative		Non-triple-negative		
	n	%	n	%	
Grade 1	1	4.3	1	5.6	***0.001***
Grade 2	2	8.7	10	55.6	
Grade 3	20	87.0	7	38.9	

Significant p-values are shown in bold and italic.
n: Number

breast carcinoma with a family history of ovarian cancer (50%), similar to our results (7).

In the present study, no significant difference was found between BRCA mutation profile and stage, tumor histology, mean tumor size, axillary nodal status, perineural invasion, and Ki-67 proliferation index. Numerous studies have also reported that tumor size, tumor type, and axillary nodal status were not significantly different between patients according to the BRCA mutation profile, similar to our results (8-11). However, in our study, lymphovascular invasion was more often noted in BRCA1 mutation carriers (78%) than in BRCA2 mutation carriers (54.1%) and non-carriers (55.3%). A study conducted in Turkey, which evaluated the axillary nodal involvement in patients with breast cancer regardless of BRCA mutation status, reported that lymphovascular invasion occurred in 59.2% of their patients, which was lower than that in BRCA1 mutation carriers in our study (12). Additionally, a few studies have evaluated the incidence of lymphovascular invasion in patients with BRCA-related breast cancer, but did not find a significantly higher incidence of lymphovascular invasion in BRCA1 mutation carriers (8-10, 13-16). In one of these previous studies, which is a hospital-based cohort study analyzing whether tumors of patients with BRCA1-associated breast carcinomas are different from those of patients with breast cancer without BRCA mutation, the lymphovascular invasion was more common (50%) in BRCA1 mutation carriers than in non-carriers (21%), but the difference did not reach significance (8). In another study, lymphatic invasion was noted in a higher proportion (52.5% and 52.4%) of BRCA1 mutation carriers than of BRCA1 non-carriers (26.2% and 35.7%) with familial and sporadic breast cancer, respectively (16). Interestingly, in a previous study, lymphovascular invasion was more often reported (53%) in BRCA2 mutation carriers than in BRCA1 mutation carriers (39%) and non-carriers (48%) (17).

In some studies that have analyzed the distribution of hormonal status in BRCA mutation carriers, BRCA1 and BRCA2 mutation carriers were grouped together instead of being examined as two different groups, culminating with the inconsistent results (14, 18). However, in subsequent studies, when BRCA1 and BRCA2 mutation carriers were grouped separately, BRCA1 mutation carriers were more likely to be diagnosed with triple-negative breast cancer than non-carriers, and pathological characteristics were comparable between BRCA2 mutation carriers and non-carriers, similar to our results (5, 17, 19). In studies that have analyzed the relationship between BRCA mutation profile and triple-negative tumor pathology, 50%–88% of BRCA1 mutation carriers were diagnosed with triple-negative breast cancer against 14.6%–34% in BRCA mutation non-carriers (17, 20-22). Additionally, in a study of a large group of patients with breast cancer, triple-negative breast cancer was diagnosed in 57.1%, 23.3%, and 13.8% of BRCA1 mutation carriers, BRCA2 mutation carriers, and non-carriers, respectively (5). In our study, the ratio of patients with triple-negative cancer based on the BRCA mutation profiles was consistent with those reported in above-mentioned previous studies (5, 17, 20-22). In some studies including different ethnic groups, a hormone receptor status was evaluated in BRCA1 mutation carriers, and these patients were more likely to have ER-negative breast cancer (5, 8, 9, 17, 19). In our study, the number of ER-negative BRCA1 mutation carriers was higher than those of BRCA2 mutation carriers and non-carriers, but the difference did not reach significance.

Tumors in BRCA1 carriers had a higher histologic and nuclear grades than those in BRCA non-carriers (5, 8, 9, 17). In our study, 65.9% of BRCA1 mutation carriers had histologic grade 3 tumors compared with 32.3% and 37.8% of non-carriers and BRCA2 mutation carriers, respectively. In another study, BRCA1 mutation carriers with triple-negative disease were reported as having higher nuclear grade (grade 3, 93.5%) than non-triple-negative BRCA1 mutation carriers (grade 3, 75%) (5). In our study, BRCA1 mutation carriers with triple-negative disease had a higher histologic grade (grade 3, 87%) than non-triple-negative BRCA1 mutation carriers (grade 3, 38.9%). The ratio of non-triple-negative BRCA1 mutation carriers with a higher histologic grade was lower (38.9%) in our study than in the aforementioned study that evaluated the nuclear grade status (75%) in these patients (5).

This study has some limitations. First, this had a retrospective design, which may have restricted the retrieval of the data from patient archives. Second, it was conducted in two tertiary care centers in İstanbul. However, no studies have investigated Turkish patients with breast cancer and focused on the clinical and pathological characteristics of these patients based on their BRCA mutation profiles. Therefore, to the best of our knowledge, this study is the first to report this issue that represents the Turkish population in a large series of patients with high-risk breast cancer.

In conclusion, in this study, more patients with BRCA1-related breast cancers had triple-negative disease, poorly differentiated with a high histologic grade, and a higher ratio of lymphovascular invasion than patients with BRCA-negative and BRCA2-related breast cancers. In our clinical practice, all these findings, which are usually associated with a poor prognosis, support that BRCA1-related breast cancers represent a distinct group of patients with unique clinical and pathological features from other patients with breast cancer.

Ethics Committee Approval: The study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of İstanbul Professor Doctor Cemil Taşçıoğlu City Hospital (approval no: 48670771-514.10/210).

Informed Consent: Retrospective study.

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Authorship Contributions

Conception: M.M.A., Ç.G., Ş.S., N.Y., A.S., Se.A., M.G.; Design: M.M.A., Ç.G., Ş.S., S.A., R.Ç., O.C., Ş.C., A.S., Se.A., M.G.; Supervision: Ç.G., S.A., R.Ç., N.Y., O.C., Ş.C., A.S., Se.A., M.G.; Materials: B.E., N.Y., O.C., Se.A., M.G.; Data Collection or Processing: M.M.A., B.E., Ş.C., S.A., R.Ç., N.Y., O.C., Ş.C., Se.A., M.G.; Analysis or Interpretation: M.M.A., Ç.G., B.E., S.A., R.Ç., N.Y., O.C., Ş.C., A.S., Se.A., M.G.; Literature Search: M.M.A., S.A., R.Ç., A.S; Writing: M.M.A., Ç.G., Ş.S., N.Y., O.C., Ş.C., A.S; Critical Review: M.M.A., Ç.G., Ş.S., S.A., R.Ç., N.Y., O.C., Ş.C., A.S., Se.A., M.G.

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