Original Article

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Comparison of Clinical, Pathological, and Prognostic Features in *BRCA* Mutant and Wild-Type Male Breast Cancer Patients

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ABSTRACT

Objective: Published studies on male breast cancer (MBC) and *BRCA* mutations are scarce and usually include, a small number of patients. The clinicopathological characteristics of *BRCA* mutant and wild-type MBC patients were compared in more than forty patients in this study.

Materials and Methods: A retrospective review of MBC patients' clinical and histopathological data was conducted. To compare the patients' characteristics, chi-square test and Fisher's Exact test were utilized. Kaplan–Meier analysis was used to examine the survival analysis.

Results: In total 43 cases were reviewed. The average duration of follow-up was 35.8 months. *BRCA* mutations were found in 11 (25.6%) of the patients. *BRCA1* mutations were found in four patients (9.3%), *BRCA2* mutations in six patients (14%), and *BRCA1* and *BRCA2* mutations in one patient (2.3%). The median age at diagnosis was 58 years old, and there was no statistically significant difference between groups (p = 0.7). Tumor location (p = 0.3), human epidermal growth factor receptor 2 overexpression (p = 0.5), estrogen receptor status (p = 0.05), progesterone receptor status (p = 0.6), tumor stage (p = 0.9), lymph node positivity (p = 0.5), tumor histology (p = 0.06), and recurrence status (p = 0.6) were similar between *BRCA*-wild type and -mutated patients. Overall survival averaged 115.6 months (range: 76.0–155.3), with no statistically significant differences between groups (p = 0.6).

Conclusion: This study investigated clinical and pathological characteristics and prognoses of *BRCA* wild and mutant-type MBC and these were similar in all groups studied.

Keywords: *BRCA* mutations; male breast cancer; pathology features; prognosis

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Key Points

- Patients with *BRCA* mutant or wild-type male breast cancer (MBC) had similar clinical features.
- Patients with *BRCA* mutant or wild-type MBC had similar pathological features.
- Patients with *BRCA* mutant or wild-type MBC had similar survival outcomes.

Introduction

Breast cancer is rarely diagnosed in men and accounts for less than 1% of cancers in men (1). Many risk factors have been identified in the development of male breast cancer (MBC), such as age, obesity, orchitis, and radiation exposure (2). About 5% of patients present with *de novo* metastatic disease (3). In terms of tumor subtypes, more than 80% are hormone-positive and less than 5% are triple-negative (4). In general, the treatment approach in MBC patients is similar to that in female breast cancer (FBC) patients. However, the prognosis in patients with MBC was found to be worse than in patients with FBC (5).

BRCA1 and *BRCA2* mutations are risk factors for the development of many cancers, including breast, ovarian, prostate, and pancreatic cancer. The *BRCA1* gene is located at position 21 of the q arm of chromosome 17, while the *BRCA2* gene is located at positions 12 and 13 of the q arm of chromosome 13 (6). *BRCA1* and *BRCA2* genes maintain the genomic stability of DNA by repairing double-strand breaks (7). The

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presence of *BRCA* mutation may lead to the development of cancer due to the disruption of DNA repair mechanisms. *BRCA1* and *BRCA2* mutations have been defined as risk factors for the development of MBC. The cumulative risk of developing breast cancer in men with a *BRCA1* mutation is around 1%, while it is around 7% in those with a *BRCA2* mutation (8). Also, in patients with MBC, *BRCA1* mutation is detected in approximately 0–5%, and *BRCA2* mutation in approximately 5–15% (9). In the literature, there are limited data on the clinicopathological features and prognosis of MBC patients based on the *BRCA* mutation status. The aim of this study was to compare the disease characteristics according to the *BRCA* mutation status in a cohort of patients with MBC.

Materials and Methods

Patients and Data Collection

The study was designed retrospectively. Ethics committee and academic board approval were obtained before the study. The local ethics committee approved this study at the Istanbul University Faculty of Medicine (approval no: 1398, date: 28.11.2019). The study was conducted according to good clinical practice guidelines. The patients were identified from the hospital data processing system and cancer genetic center database, Patients that were diagnosed and treated in the outpatient clinic of a single oncology center between 2005 and 2020 were evaluated. Patients with MBC whose *BRCA* mutation was analyzed were included in the study. Patients with insufficient statistical data were excluded from the study. Genetic, pathological, clinical, and radiological features of the patients were recorded. All treatments (surgery, chemotherapy, radiotherapy, and hormone therapy) administered to the patients during the entire follow-up period were recorded.

Estrogen receptor (ER) and progesterone receptor (PR) were examined by the immunohistochemistry (IHC) method. Patients with a score of 3+ by IHC or positive by fluorescence in situ hybridization were considered human epidermal growth factor 2 (HER2)/neu positive. *BRCA* mutation analysis was performed with next-generation sequencing and multiplex ligation-dependent probe amplification methods. The smoking histories of the patients were recorded as never, current and former. Alcohol use more than three times a week was defined as regular alcohol intake. Body Mass Index was calculated as kilograms/height in metres^2. Tumor staging was performed according to the 8th TNM Classification of malignant tumors, and molecular subtyping was performed according to the St Gallen consensus. Histopathological type, ER, PR, HER2, tumor grade, tumor stage, smoking history, and alcohol use history were compared between groups stratified by *BRCA* mutation status of the patients.

The time from diagnosis to death from all causes was defined as overall survival (OS). The living conditions of the patients were evaluated through the death notification system of the Ministry of Health. The factors affecting the survival of the patients were analyzed, and the effect of *BRCA* mutation status on OS was evaluated.

Statistical Analysis

Statistical analysis was performed with SPSS, version 25 (IBM Inc., Armonk, NY, USA). Continuous variables are shown as median value (with minimum–maximum value), and categorical variables are shown as numbers and percentages. The Kaplan–Meier method was used for survival analysis and curve. Multivariate analysis was performed with Cox regression analysis. Clinical and pathological differences between groups were evaluated using chi-square and Fisher's Exact test. Independent sample t–test was used for comparison to mean values. A p-value of <0.05 was assumed to indicate significance.

Results

Patient Characteristic

The data of 43 MBC patients were evaluated. Thirty-two (74.4%) patients had no *BRCA* mutations, and 11 (25.6%) patients had *BRCA* mutations. There were six (14%) patients with *BRCA2* mutations and four (9.3%) patients with *BRCA1* mutations. One (2.3%) patient had both *BRCA1* and *BRCA2* mutations. All patients with *BRCA* mutations had pathogenic variants. The median age was 62 in *BRCA* wild-type patients and 57 in *BRCA* mutant patients. The mean value of age between the two groups was similar (p = 0.7). *BRCA* mutant or wild-type MBC patients had similar clinical features (Table 1). Although a multifocal tumor was detected more frequently in *BRCA* mutant patients, no statistically significant difference was found (p = 0.07). When the two groups were compared in terms of pathological features, ER positivity and invasive ductal adenocarcinoma histology were found more frequently in *BRCA* wild-type patients (Table 2). The patients showed similar characteristics in terms of surgery, chemotherapy, radiotherapy, and endocrine therapy (Table 3).

Survival Outcomes and Prognosis

The patients were followed up for a median of 35 months (2.2–225). Ten (23.2%) patients had died by the time of analysis. Median OS was 115.6 (95% confidence interval, 76–155) in all patients (Figure 1). When parameters affecting OS were evaluated in univariate analysis, *BRCA* mutation status was not found to be statistically significant (p = 0.6) for OS (Figure 2). Also, age (p = 0.6), tumor stage at diagnosis (p = 0.7), tumor focality (p = 0.1), histopathological type (p = 0.1), ER status (p = 0.2), PR status (p = 0.09), and HER2 status (p = 0.5) were not statistically significant for OS. Multivariate analysis could not be performed due to the limited number of events.

Discussion and Conclusion

In this study, we compared the clinical and pathological features of MBC patients according to the presence of *BRCA* mutations. In one of the rare studies in the literature published by Ottini et al. (10) it was reported that family history of breast cancer, contralateral breast cancer, grade 3 tumor, PR negativity, and HER2 positivity was more common in patients with MBC with *BRCA2* mutation compared to *BRCA* wild type patients. Although the number of patients is limited due to being a rare tumor, we found that *BRCA* mutant and wild-type patients showed similar characteristics in our study. However, although it was not statistically significant in terms of tumor focality, histopathological subtype and ER positivity, we detected proportional differences between patient groups. MBC is a tumor that shows biological differences from FBC, and hormone receptor positivity and *BRCA2* mutation are detected more frequently (11). In addition, in a multicenter study comparing *BRCA* mutant MBC and FBC in terms of pathological features, it was found that *BRCA2* mutant MBC patients showed more aggressive features than FBC patients in terms of stage and tumor grade at the time of diagnosis, and hormone positivity was more frequent (12). Studies evaluating breast cancer characteristics according to *BRCA* mutation status were mostly conducted in patients with FBC. In a study conducted by Atchley et al. (13), when evaluated according to the *BRCA* mutation status, triple-negative and high-grade

Table 1. Clinical characteristics of the patients according to *BRCA* status

	Patients with *BRCA* wild type		Patients with *BRCA* mutant type		p
	Number	%	Number	%	
Age at diagnosis, years					
Mean age at diagnosis	58.2		59.7		0.7
Family history of breast cancer (n = 37)					
Yes	8	29.6	5	50	0.2
No	19	70.4	5	50	
Body Mass Index (n = 32)					
Obese	4	17.3	3	33.3	0.3
Non-obese	19	82.7	6	66.7	
Smoking status (n = 39)					
Current	17	58.6	5	50	0.7
Never	12	41.4	5	50	
Regular alcohol consumption (n = 37)					
Yes	7	25.9	2	20	0.5
No	20	74.1	8	80	
Tumor locations (n = 41)					
Right side	16	51.6	4	40	0.3
Left side	15	48.4	6	60	
Tumor focality (n = 39)					
Unifocal	28	100	9	81.8	0.07
Multifocal	0	0	2	12.2	
The stage at diagnosis (n = 41)					
Stage 1	8	26.7	3	27.3	0.9
Stage 2	11	36.7	5	45.4	
Stage 3	10	33.3	3	27.3	
Stage 4	1	3	0	0	

tumors were significantly more common in patients with *BRCA1* mutation in FBC. In another study, the relationship between triple-negative disease and *BRCA* mutation in FBC was evaluated with a meta-analysis, and it was found that *BRCA1* mutation was associated with triple-negative disease, larger tumor burden, and higher-grade tumor (14).

In the literature, there are very limited studies evaluating survival according to *BRCA* mutation status in MBC. In a study published by Gargiulo et al. (15), which included 17 patients with MBC with known *BRCA* mutation status, OS was found to be better in patients with *BRCA* wild type in the survival analysis performed according to *BRCA* mutation status. Seven of the patients included in this study were *BRCA* mutant, ten were *BRCA* wild type, and the *p*-value was borderline significant ($p = 0.044$). In our study, patients with *BRCA* wild type showed a better trend in terms of OS compared to *BRCA* mutant patients, but this trend was not significant. This inconsistency can be explained by the limited number of patients in both studies, and patient heterogeneity. In a meta-analysis conducted on patients with FBC according to *BRCA* mutation status, it was found that patients with a *BRCA1* mutation had a worse prognosis in terms of OS than those with *BRCA* wild type. Also, patients with *BRCA2* mutation were shown to have a worse prognosis in terms of breast cancer-specific mortality than those with *BRCA* wild type (16). In another meta-analysis, it was reported that patients with FBC with *BRCA1* mutation had a significantly worse prognosis in terms of OS but similar characteristics in terms of progression-free survival (PFS). Also, the presence of *BRCA2* mutation did not make a difference in terms of OS and PFS (17). There seems to be a need for better-designed studies showing the impact of *BRCA* mutations on the prognosis in MBC and FBC.

Study Limitations

Our study had some limitations. Due to the rarity of MBC, the number of patients in our study was limited. The patient group in the study was heterogeneous, and some data were missing.

In our study, we showed the real-life outcomes of MBC patients, and compared the clinicopathological features in *BRCA* mutant or wild-type patients. We found that patients with *BRCA* mutations or wild-type MBC had similar clinical and pathological features.

Table 2. Pathological features of the patients according to *BRCA* status

	Patients with *BRCA* wild type		Patients with *BRCA* mutant type		p
	Number	%	Number	%	
pT status (n = 39)					
pT1-pT2	33	86.8	8	61.5	0.4
pT3-pT4	5	13.2	5	38.5	
pN status (n = 38)					
Node negative	16	57.1	4	40	0.5
Node positive	12	42.9	6	60	
Histological type (n = 41)					
Invasive ductal carcinoma	27	90	7	63.6	0.06
Other types	3	10	4	36.4	
Molecular subtype (n = 41)					
Luminal A	6	19.3	3	30	0.07
Luminal B	20	64.5	4	40	
HER2 positive	5	16.2	1	10	
Bazal-like	0	0	2	20	
ER receptor (n = 41)					
Positive	31	100	8	80	0.055
Negative	0	0	2	20	
PR receptor (n = 41)					
Positive	22	71	6	60	0.6
Negative	9	29	4	40	
HER2 receptor (n = 41)					
Positive	5	16.1	1	10	0.5
Negative	26	83.9	9	90	
Grade (n = 32)					
1-2	12	46.1	3	50	0.8
3	14	53.9	3	50	

ER: estrogen receptor; PR: progesterone receptor; HER2: human epidermal growth factor 2

Table 3. Treatment approaches in the patients according to *BRCA* status

	Patients with *BRCA* wild type		Patients with *BRCA* mutant type		p
	Number	%	Number	%	
Breast surgery (n = 41)					
Simple mastectomy +SNB	11	36.6	5	50	0.2
Modified radical mastectomy	19	63.4	5	50	
Radiotherapy (n = 41)					
Adjuvant-neoadjuvant	19	63.4	8	72.7	0.3
No radiotherapy	11	36.6	3	27.3	
Chemotherapy (n = 42)					
Adjuvant-neoadjuvant	21	67.7	9	81.8	0.4
No chemotherapy	10	32.3	2	18.2	
Endocrine therapy (n = 41)					
Adjuvant	26	86.6	9	81.8	0.9
No endocrine therapy	4	13.4	2	18.2	

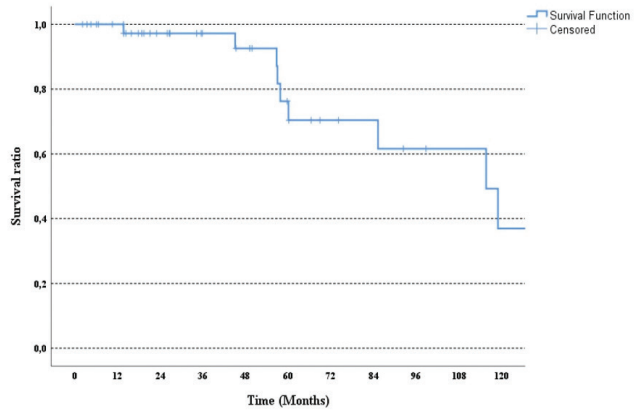


Figure 1. Kaplan–Meier curve for OS in the patients with MBC

OS: overall survival; MBC: male breast cancer

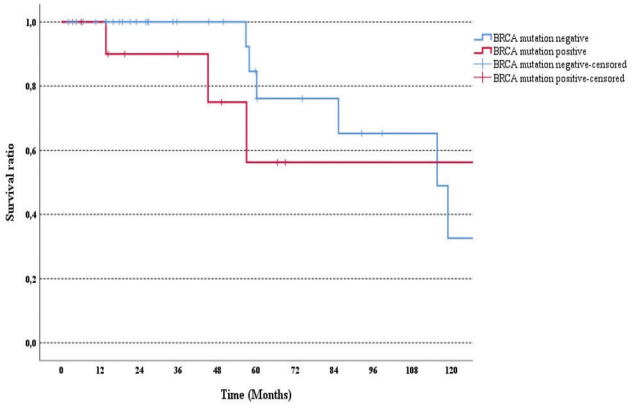


Figure 2. Kaplan–Meier curve for OS by *BRCA* mutation status in the patients with MBC

OS: overall survival; MBC: male breast cancer

This study is one of the few published studies examining the differences in MBC according to *BRCA* mutation status. In our study, some clinical and pathological factors remained at the limit in terms of statistical significance. Multicenter studies with larger patient groups are needed for verification of our findings. Furthermore, cancer development and treatment processes will be better understood with translational studies examining the relationship between *BRCA* mutation and the development of MBC.

Presentation at a meeting: This study was presented as a poster at 2020 San Antonio Breast Cancer symposium.

Ethics Committee Approval: The local ethics committee approved this study at the Istanbul University Faculty of Medicine (approval no: 1398, date: 28.11.2019).

Informed Consent: For this type of research, informed consent is not required.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: İ.D., E.A., H.Y., P.S.; Concept: İ.D., E.A., H.Y., P.S.; Design: İ.D., E.A., H.Y., P.S.; Data Collection and/or Processing: İ.D., E.A., H.Y., P.S.; Analysis and/or Interpretation: İ.D., E.A., H.Y., P.S.; Literature Search: İ.D., E.A., H.Y., P.S.; Writing: İ.D., E.A., H.Y., P.S.

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