ORIGINAL RESEARCH

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Comparison of Clinicopathological Characteristics of BRCA1 and BRCA2 Carriers with Breast Cancer: The Role of Ki-67 Index

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ABSTRACT Objective: To elucidate the clinicopathological differences between breast cancer 1 (BRCA1) and BRCA2 carriers among patients with breast carcinoma. **Material and Methods:** The present retrospective study explored the demographic and clinicopathological features of 57 BRCA carriers with breast cancer. The age, family history, tumor Ki-67 index, tumor grade, hormone receptor status (estrogen and progesterone), human epidermal growth factor receptor 2 status, tumor T and N Stage, tumor multifocality, and tumor treatment modalities (surgical or adjuvant/neoadjuvant chemotherapy) were recorded for each patient from the hospital automation system. **Results:** The patients with a median age of 39 (range: 23-68 years) years comprised 35% BRCA1 and 65% BRCA2 carriers. Higher median Ki-67 index was revealed for the BRCA1 group than for the BRCA2 group (40% vs. 80%, p=0.006). The proportions of patients with estrogen receptor (+) and progesterone receptor (+) tumors were 35.0% and 35.0%, respectively, in the BRCA1 group, whereas 75.7% and 73.0%, respectively, in the BRCA2 group (p value 0.003 and 0.005, respectively). The BRCA1 group demonstrated significantly higher proportion of triple-negative patient rate as compared to the BRCA2 group (21.6% vs. 55.0%, p=0.011). Multivariate logistic regression analysis conducted with the Ki-67 index, estrogen receptor status, progesterone receptor status, and triple-negative disease status identified the Ki-67 index as the only independent predictive factor that could distinguish the BRCA1 from the BRCA2 mutation. A high Ki-67 index (>45%) was correlated with the BRCA1 mutation (odds ratio: 0.970, 95% confidence interval: 0.943-0.999, p=0.044). **Conclusion:** A high Ki-67 index is more frequently prevalent in BRCA1 carriers than in BRCA2 mutation carriers among patients with breast cancer.

Keywords: BRCA1 protein; BRCA2 protein; breast; breast neoplasm

One in 8 women in the community are predisposed to develop breast cancer, and this risk significantly escalates in women with a family history of breast carcinoma.[1,2] Approximately, 10% of breast cancers are hereditary, and mutation in the breast cancer (BRCA) gene is one of the best-known mutations associated with breast cancer.[2-5] The factors that increase the chances of a BRCA mutation in breast cancer include young age (<40 years), triple-negative tumors, male gender, family history, ovarian cancer, and bilateral breast cancer.[6] Currently, BRCA mutations are evaluated in 2 subgroups, BRCA1 and BRCA2, and patients with BRCA mutations can develop secondary malignancies.

Studies conducted on patients with BRCA mutations have reported Grade 2 and 3 tumors in most patients, while patients with Grade 1 tumors are rare.[7] The tumor grade is closely related to disease prognosis.[8] However, conflicting results are obtained regarding the prognostic significance of BRCA mutations in breast cancer.[9] Studies comparing the clinicopathological characteristics and survival of pa-

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tients with breast cancer with BRCA1 and BRCA2 mutations confirmed higher rates of hormone-positive tumor in carriers of BRCA2 mutations than in carriers of BRCA1 mutations.[6,7] Association of triple-negative breast cancer with BRCA1 mutations has also been documented.[7] The Prospective Outcomes in Sporadic Versus Hereditary Breast Cancer (POSH) study revealed higher numbers of patients with Grade 3 tumors in the BRCA1 group than the BRCA2 group.[7] Another study that investigated the relationship between tumor multifocality and BRCA mutation in breast cancer patients indicated greater multifocality in patients with BRCA2 mutations.[10]

The clinicopathological characteristics of patients with breast cancer differ in some crucial areas depending on whether the patients are carriers of BRCA1 or BRCA2 mutations. Our aim in the present study was to retrospectively evaluate the clinicopathological features of BRCA1 or BRCA2 carriers with breast cancer to highlight the key differences between these carriers.

MATERIAL AND METHODS

This retrospective study was conducted with BRCA carriers suffering from breast cancer treated between 2018 and 2020. University of Health Sciences Dr. Abdurrahman Yurtaslan Oncology Health Practice And Research Center Clinical Research Ethics Committee approval was obtained for the study on 13/01/2021 (number 01/962). The study was approved by the local ethics board according to good clinical practice and applicable laws, and the Declaration of Helsinki.

PATIENTS

Inclusion criteria included a histopathologically confirmed breast cancer diagnosis, age 18 years and older, and being a BRCA1 or BRCA2 carrier. This study excluded patients with unknown clinicopathological features and missing data. The retrospective file scanning confirmed metastasis only in 3 patients. These patients were not included in the study due to missing data. In total, 57 female BRCA-positive patients satisfying the study criteria were included in the study. BRCA mutations are more prevalent, especially in young people, those with triple-negative disease, and those with a family history of breast and ovarian cancer. In our clinic, BRCA mutation analysis was generally done for patients with these features. The time of breast cancer diagnosis of the patients included in the study was between 2001 and 2020. BRCA mutation analysis of the patients was conducted between 2017 and 2021.

STUDY DESIGN AND VARIABLES

Patient age, family history, body mass index, histopathological tumor type, tumor Ki-67 index, tumor grade, hormone receptor status (estrogen and progesterone), human epidermal growth factor receptor 2 (HER2) status, tumor T and N Stage, tumor multifocality, tumor treatment modalities (surgical, adjuvant/neoadjuvant chemotherapy) were recorded from the hospital automation system. The study categorized the patients into 2 groups as BRCA1 and BRCA2 carriers. The group differences were determined by comparing the demographic and clinicopathological characteristics of the patients.

BRCA MUTATION ANALYSIS

DNA Extraction

Collecting the blood samples EDTA tubes, DNA of the patients were extracted by QIAcube® automated DNA isolation system (Qiagen Inc. Mississauga, ON, Canada). Isolated DNA samples were stored at -20 °C. Before sequencing, the DNA concentration and quality were measured by NanoDrop (ND-1000) spectrophotometer (Nano-Drop Technologies, Wilmington, DE, USA) for OD260/OD280, 1.8-2.0. Genetic testing was calculated between 1.75 and 2.15. The Coffalyser software (MRC-Holland®) was adopted for analyzing the MLPA data.

Variant Classification

The recent American College of Medical Genetics and Genomics/Association for Molecular Pathology guideline for standardized variant interpretation in Mendelian disorders was employed for classification. Pathogenic variants are well-established disease-causing DNA changes in in-house database and/or literature. Strong clinical findings and family history, independent confirmatory observations, and support-

ing pathogenicity functional studies represented the main evaluation criteria. Likely pathogenic variants are considered the probable cause of the disease or the effect on the protein function is predicted to be likely deleterious (>90% probability of causing the disease).

All of the BRCA mutations mentioned in the study consisted of pathogenic variants. Variant of uncertain significance and unclassified variants were excluded from the study. All of the BRCA mutations were germline.

STATISTICAL ANALYSIS

SPSS (Statistical Package for Social Sciences, IBM SPSS Statistics for Windows, Version 25.0) was exploited for the statistical analysis. Continuous variables were expressed as median (range or interquartile range) and categorical data as frequency (percentage). The Mann-Whitney test was applied to compare the non-parametric data of the 2 independent groups. Categorical groups were compared using Pearson's chi-square test. Variables with statistically significant differences, according to univariate analysis, were evaluated by multivariate logistic regression analysis, and independent predictive factors were determined. A p value <0.05 was considered statistically significant.

RESULTS

The median age of the patients was 39 (range: 23-68 years) years. The study population comprised 35% BRCA1 and 65% BRCA2 carriers. Overall, 80.7% of the patients manifested invasive ductal carcinoma. The median Ki-67 index was 40% (interquartile range: 30-70). In most patients, the hormone receptor status was positive (estrogen receptor 61.4%, progesterone receptor 59.6%), with a HER2 positivity of 8.8%. None of the patients exhibited metastatic breast cancer (Table 1). The median follow-up time was 19 (range: 4-174 months) months. During the follow-up period, recurrence was diagnosed in 4 (3 patients with BRCA1, 1 patient with BRCA2) patients.

No significant difference was obtained between the BRCA1 and BRCA2 groups in terms of age, body mass index, family history, tumor histology, tumor grade, T and N Stage, lymphovascular invasion, or chemotheraphy. A higher median Ki-67 index was noted for the BRCA1 carriers than for the BRCA2 carriers (40% vs. 80%, p=0.006). The proportion of patients with estrogen receptor (+) and progesterone receptor (+) tumors was 35.0% and 35%, respectively, in the BRCA1 group and 75.7% and 73.0%, respectively, in the BRCA2 group (p value 0.003 and 0.005, respectively). As compared to the BRCA2 group, the triple-negative rate was significantly elevated in the BRCA1 group (21.6% vs. 55.0%, p=0.011). The rates of multifocal tumors were 15.0% and 13.5% in the BRCA1 and BRCA2 groups, respectively (p=0.140). Prophylactic oophorectomy rates were 30.0% in the BRCA1 group and 10.8% in the BRCA1 group (p=0.141) (Table 1).

Multivariate logistic regression analysis was conducted with the Ki-67 index, estrogen receptor status, progesterone receptor status, and triple-negative disease status. These results prominently suggested the Ki-67 index as an independent predictive factor that could distinguish between BRCA1 and BRCA2 mutations. The BRCA1 mutation was associated with a higher Ki-67 index (odds ratio: 0.970, 95% confidence interval: 0.943-0.999, p=0.044) (Table 2).

A receiver operating characteristic (ROC) analysis confirmed that the optimum cut-off value of the Ki-67 index for distinguishing BRCA1 and BRCA2 was 45% (area under the ROC curve 0.742, sensitivity 69%, specificity 61%; p=0.006) (Figure 1).

DISCUSSION

This study compared the clinicopathological characteristics of patients with BRCA1 and BRCA2 mutant non-metastatic breast cancer. The study results claimed a higher Ki-67 index in BRCA1 mutants than in BRCA2 mutants and that a high Ki-67 index could predict a BRCA1 mutation.

A cell proliferation marker, Ki-67, is a specific nuclear antigen expressed in all phases of the cell cycle except G0.[11,12] Generally, earlier research has substantiated the association of a high Ki-67 index

TABLE 1: Comparison of the BRCA1 and BRCA2 carriers' clinicopathological features.

	All patients n=57	BRCA1 n=20	BRCA2 n=37	p value
Age, year, median (range)	39 (23-68)	37 (23-68)	40 (24-66)	0.860
Family history				
Yes	34 (59.6)	13 (65.0)	21 (56.8)	0.545
No	23 (40.4)	7 (35.0)	16 (43.2)	
BMI, n (%)				
<25	12 (21.1)	6 (30.0)	6 (16.2)	0.273
≥25-<30	19 (33.3)	4 (20.0)	15 (40.5)	
≥30	16 (28.1)	5 (25.0)	11 (29.7)	
Unknown	10 (17.5)	5 (25.0)	5 (13.5)	
Histology, n (%)				
IDC	46 (80.7)	16 (80.0)	30 (81.1)	0.987
ILC	3 (5.3)	1 (5.0)	2 (5.4)	
Other	8 (14.0)	3 (15.0)	5 (13.5)	
Ki-67 index, median (Q1-Q3)*	40 (30-70)	80 (27-90)	40 (30-50)	0.006
Tumor grade				
2	14 (24.6)	2 (10.0)	12 (32.4)	0.107
3	34 (59.6)	13 (65.0)	21 (56.8)	
Unknown	9 (15.8)	5 (25.0)	4 (10.8)	
Estrogen-receptor status, n (%)				
Negative	22 (38.6)	13 (65.0)	9 (24.3)	0.003
Positive	35 (61.4)	7 (35.0)	28 (75.7)	
Progesterone-receptor status, n (%)				
Negative	23 (40.4)	13 (65.0)	10 (27.0)	0.005
Positive	34 (59.6)	7 (35.0)	27 (73.0)	
HER2 status, n (%)				
Negative	52 (91.2)	19 (95.0)	33 (89.2)	0.647
Positive	5 (8.8)	1 (5.0)	4 (10.8)	
Triple-negative breast cancer status, n (%)				
No	38 (66.7)	9 (45.0)	29 (78.4)	0.011
Yes	19 (33.3)	11 (55.0)	8 (21.6)	
T Stage, n (%)				
T1	10 (17.5)	2 (10.0)	8 (21.6)	NA
T2	29 (50.9)	14 (75.0)	15 (40.5)	
T3	11 (19.3)	1 (5.0)	10 (27.0)	
T4	3 (5.3)	2 (10.0)	1 (2.7)	
Unknown	4 (7.0)	1 (5.0)	3 (8.1)	
Pathological N Stage, n (%)				
N0	20 (35.1)	10 (50.0)	10 (27.0)	0.251
N1	30 (52.6)	9 (45.0)	21 (56.8)	
N2	3 (5.3)	0 (0)	3 (8.1)	
Unknown	4 (7.0)	1 (5.0)	3 (8.1)	
Lymphovascular invasion, n (%)				
No	33 (57.9)	14 (70.0)	19 (51.4)	0.167
Yes	5 (8.8)	0 (0)	5 (13.5)	
Unknown	19 (33.3)	6 (30.0)	13 (35.1)	
Tumor multifocality, n (%)				
No	47 (82.5)	15 (75.0)	32 (86.5)	0.140
Yes	8 (14.0)	3 (15.0)	5 (13.5)	
Unknown	2 (3.5)	2 (10.0)	0 (0)	

continue...→

TABLE 1: Comparison of the BRCA1 and BRCA2 carriers' clinicopathological features (*continued*).

	All patients n=57	BRCA1 n=20	BRCA2 n=37	p value
CT, n (%)				
None	5 (8.8)	0 (0)	5 (13.5)	0.096
Adjuvant	34 (59.6)	16 (80.0)	18 (48.6)	
Neoadjuvant	15 (26.3)	3 (15.0)	12 (32.4)	
Palliative	3 (5.3)	1 (5.0)	2 (5.5)	
CT regimen, n (%)				
None	5 (8.8)	0 (0)	5 (13.5)	NA
Anthracyclines	8 (14.0)	5 (25.0)	3 (8.1)	
Taxanes	4 (7.0)	3 (15.0)	1 (2.7)	
Antracylines and taxanes	36 (63.2)	10 (50.0)	26 (70.3)	
Other	4 (7.0)	2 (10.0)	2 (5.4)	
Neoadjuvant CT complete response n=15 (%)				
Yes	14 (93.3)	3 (100.0)	11 (91.7)	1.000
No	1 (6.7)	0 (0)	1 (8.3)	
Prophylactic oophorectomy				
No	47 (82.5)	14 (70.0)	33 (89.2)	0.141
Yes	10 (17.5)	6 (30.0)	4 (10.8)	

*The Ki-67 index of eight patients was unknown and was not included in the analysis; BRCA: Breast cancer gene; BMI: Body mass index; IDC: Invasive ductal carcinoma; ILC: Invasive lobular carcinoma; HER: Human epidermal growth factor receptor; CT: Chemotherapy.

TABLE 2: A multivariate logistic regression model to determine independent predictive factors distinguishing BRCA1 and BRCA2.

	OR, (95% CI)	p value
ER		
Negative	1.000	0.060
Positive	4.186 (0.943-18.579)	
PR		
Negative	1.000	0.824
Positive	1.380 (0.080-23.768)	
Triple-negative tumor		
No	1.000	0.899
Yes	5.786 (0.999-21.156)	
Ki 67 index*		
Low (<45)	1.000	0.044
High (≥45)	0.970 (0.943-0.999)	

*The Ki-67 index of eight patients was unknown and was not included in the analysis; BRCA: Breast cancer gene; ER: Estrogen receptor; PR: Progesterone receptor.

level with aggressive tumors.[12] Apart from being one of the breast cancer luminal classification criteria, the Ki-67 index is also used as a marker that can predict a complete pathological response.[12] One limitation of the Ki-67 index is that it is subjective and does not have a universal cut-off value.[13] Our study proposed the significance of the Ki-67 index in distinguishing the subgroups of BRCA mutations. In accordance with our findings, Sønderstrup et al. also evaluated the relationship between BRCA mutations and prognosis in breast cancer and confirmed a high Ki-67 index (≥20%) evident in patients with BRCA1 mutations when compared with BRCA2 mutant patients.[14]

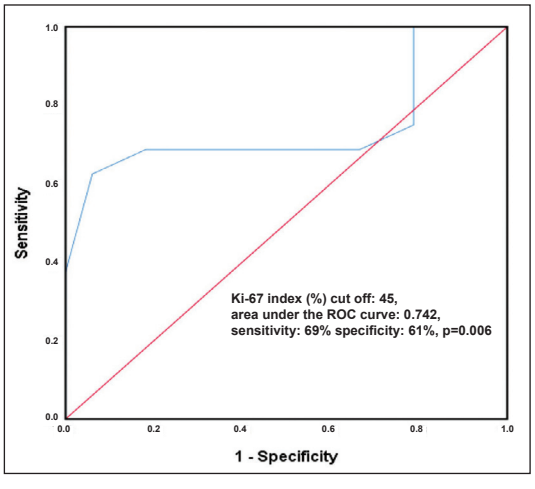

FIGURE 1: ROC analysis of Ki-67 index.
ROC: Receiver operating characteristic.

Several studies have addressed the relationship between hormone receptor status and BRCA mutation subgroups.[6] Patients with BRCA2 mutations highlight a higher estrogen receptor and progesterone receptor positivity than in BRCA1 mutants, but triple negativity is less common.[7] The POSH study reported a statistically significant difference in estrogen receptor positivity, with 85% in patients with BRCA2 mutations and 25% in patients with BRCA1 mutations.[7]

The same study documented higher numbers of triple-negative breast cancer patients with BRCA1 mutations than with BRCA2 mutations (61% vs. 10%).[7] Comparing the clinicopathological characteristics of patients diagnosed with BRCA1 and BRCA2 mutant breast cancer, another study reported estrogen receptor (+) rates were found to be 23.6% and 78.4% in BRCA1 and BRCA2 carriers, respectively.[6] In line with these findings, the estrogen receptor positivity rates in our study were 35.0% and 75.7%, respectively, in the BRCA1 and BRCA2 groups.

In the POSH study, 35 and 37 years were the median ages of BRCA1 and BRCA2 carriers, respectively, and the difference was statistically significant.[7] Another study revealed that 68% of BRCA1 carriers were younger than 45 years of age, whereas only 48% of BRCA2 carriers were part of that group.[6] The median ages of BRCA1 and BRCA 2 carriers in our study were found to be 37 and 40 years, respectively, which was in agreement with the POSH study indicating that the median age of BRCA1 carriers tended to be lower. However, it may be due to the small sample size that this difference was statistically insignificant.

Variations in the tumor characteristics of the BRCA1 and BRCA2 carrier breast cancer patients are also evident in different studies.[10,15] A study suggested a relationship between BRCA and tumor multifocality in patients with breast carcinoma.[10] Comparing the clinicopathological features and BRCA mutation subtypes of multifocal and unifocal breast cancer patients, McCorie et al. reported a higher rate of multifocal tumors in BRCA2 carriers relative to BRCA1 carriers (33% vs. 13%), but no justification was provided regarding the increase in multifocal in BRCA2 carriers.[10] In the current study, multifocality was 15.0% in the BRCA1 carriers and 13.5% in the BRCA2 carriers, and no meaningful difference was noted between the groups, suggesting further evaluation of the relationship between multifocality and BRCA subgroups with larger studies.

There are limited studies investigating BRCA mutations in Turkey, and the BRCA carriage rates in patients with breast cancer are not known.[16-18] BRCA1 carriage was observed more frequently in some studies, while BRCA2 carriage in others, as in our study. On the other hand, the presented BRCA1 and BRCA2 frequencies fail to reflect the general population rates, since the study we presented was not conducted to elucidate the BRCA carrier frequency of the population.

The study had some limitations. The short duration of the patient follow-up periods restricted the assessment of the relationship between BRCA mutation types and prognosis. The small number of study subjects is another limitation, but the significant differences in terms of pathological features between the BRCA groups make the study valuable. The neoadjuvant treatment rate was low in the present study. Owing to the history of a breast cancer diagnosis in the early 2000s, some of the patients did not receive neoadjuvant treatments. Moreover, without evaluating some patients as multidisciplinary, they were directly operated and then referred to us. This may contribute to the low rate of neoadjuvant treatment. Furthermore, the complete response rate to neoadjuvant therapy was high (100%). This response rate might not represent the general population due to the very small number of patients. In our study, the rates of prophylactic oophorectomy appear to be very low, but the dearth of data about the reason for this situation has prevented us from offering a solution.

CONCLUSION

Patients carrying BRCA1 and BRCA2 mutations exhibit significant differences in some of their clinical features, and the Ki-67 index is one of them. Patients carrying BRCA1 mutations more frequently demonstrate a higher Ki-67 index than

those carrying BRCA-2 mutations. However, conflicting data are obtained regarding the relationship between BRCA and prognosis in breast cancer. "Since Ki-67 is higher in BRCA 1 mutant tumors, can it be inferred that BRCA1 mutant tumors are more aggressive?" our study suggests that the answer to this question necessitates further investigations.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Ömür Berna Öksüzoğlu, Cengiz Karaçin, Recep Ak;* ***Design:*** *Cengiz Karaçin, Recep Ak;* ***Control/Supervision:*** *Ömür Berna Öksüzoğlu;* ***Data Collection and/or Processing:*** *Taha Bahsi, Recep Ak;* ***Analysis and/or Interpretation:*** *Cengiz Karaçin;* ***Literature Review:*** *Cengiz Karaçin, Recep Ak;* ***Writing the Article:*** *Recep Ak, Cengiz Karaçin;* ***Critical Review:*** *Ömür Berna Öksüzoğlu;* ***References and Fundings:*** *Recep Ak, Cengiz Karaçin;* ***Materials:*** *Taha Bahsi.*

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