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ORIGINAL ARTICLE

# *BRCA 1/BRCA 2* PATHOGENIC/LIKELY PATHOGENIC VARIANT PATIENTS WITH BREAST, OVARIAN, AND OTHER CANCERS

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## ABSTRACT

The demographic and clinical characteristics of patients who have *BRCA 1/BRCA 2* pathogenic/likely pathogenic variants may differ from their relatives who had *BRCA*-related cancer. In this study, we aimed to demonstrate the clinical and demographic findings of patients who had *BRCA*-related cancer and to assess the differences comparing their relatives who had *BRCA*-related cancer with breast, genital tract, prostate, and pancreas cancers as well. The results of sequencing analysis of 200 cancer patients (190 women, 10 men) who have been directed to genetic counseling with an indication of *BRCA1/BRCA2* testing from different regions across 9 medical oncology centers were retrospectively analyzed. A total of 200 consecutive cancer patients who harbored the *BRCA1/BRCA2* pathogenic/likely pathogenic variant (130 (65%) patients harbored *BRCA 1* pathogenic/likely pathogenic variant, and 70 harbored *BRCA 2* pathogenic/likely pathogenic variant) were included. Of these, 64.0% had breast cancer (43.8% of them had the triple-negative disease, and about 2.3% had only the HER-2 mutant), 31.5% had genital cancers (92.1% of them had ovarian cancer, 3.2% had endometrium, and 1.6% had peritoneum cancer as the primary site and mostly serous adenocarcinoma was the most common histopathology and 14.3% of the patients had endometrioid adenocarcinoma), 3.5% had prostate (median time from metastasis to castration-resistant status was 28 months) and 1.0% had pancreas cancer. Newly diagnosed cancer (breast and ovary) patients who had *BRCA 1/BRCA* 2 pathogenic/likely pathogenic variant were younger than their previous cancer diagnosed (breast, ovary, and pancreas) parents who harbored *BRCA* pathogenic/likely pathogenic variant. We suggest that the genetic screening of *BRCA 1/BRCA 2* pathogenic/likely pathogenic variant is needed as a routine screening for those with a personal or family history of breast, ovarian, tubal, or peritoneal cancer. In addition, once *BRCA 1* or *BRCA 2* germline pathogenic variant has been identified in a family, testing of at-risk next-generation relatives earlier can identify those family members who also have the familial pathogenic variant, and thus need increased surveillance.

**Keywords:** *BRCA 1, BRCA 2*, breast, pancreas, genital cancers, prostate, pancreas

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## INTRODUCTION

Every cell has DNA damage response mechanisms that protect the genome against the harmful effects of mutations. DNA double-strand breaks are a very dangerous form of DNA damage and can be repaired by homologous recombination repair which includes the breast cancer susceptibility genes *BRCA1* and *BRCA2.* These genes act as a tumor suppressor to promote homologous recombination repair mechanism and their inherited mutations result in homologous recombination repair deficiency and leading to confer significant lifetime risks of breast, ovarian, and other cancers [1].

*BRCA*-related hereditary breast, ovarian and other cancers have inherited an autosomal dominant condition, for which early identification and intervention have meaningful potential for clinical actionability and a positive impact on public health. In routine practice, genetic testing for these conditions is based on family history and other demographic characteristics [2, 3]. Genetic counseling should be given to the patients with *BRCA 1/BRCA 2* carriers and other family members. Due to the fact that *BRCA*-related cancers are diagnosed at an earlier age than non-*BRCA 1/ BRCA 2* carriers, earlier screening program protocols are recommended. On the other hand, there is not enough data on whether the diagnosis age of *BRCA 1/BRCA 2* pathogenic/likely pathogenic variant patients is different than their parents who had *BRCA 1/BRCA 2* carriers with cancer.

In this study, we aimed to demonstrate the clinical and demographic findings of the patients who harbor *BRCA 1/BRCA 2* pathogenic/likely pathogenic variants with breast, genital tract, prostate, and pancreas cancer in Turkish patients.

## MATERIAL AND METHODS

**Study subjects.** This retrospective multicenter study includes the results of sequencing analysis of 200 patients (190 women, 10 men) who have been directed to genetic counseling with an indication *BRCA1*/ *BRCA2* test from different regions of Turkey. This study was approved by the local ethics committee.

**DNA isolation.** Genomic DNA was isolated from peripheral blood samples by using the EasyOne DNA isolation system (Qiagen, Hilden, Germany) and isolated DNA samples were assessed spectrophotometrically with NanoDrop (Thermo Fisher Scientific). Samples whose A260/280 values were between 1.8-2.0 were used for Next-Generation Sequencing. Low quality DNA samples were re-extracted from stored blood samples.

**Next Generation Sequencing (NGS).** For NGS, a QIAseq Targeted Amplicon Panel (Qiagen, Hilden, Germany), covering the coding regions of *BRCA1* and *BRCA2* genes with 20bp intron padding primers was used. Amplicon libraries were prepared according to the instructions of the manufacturer (Qiagen, Hilden, Germany). Pooled libraries were sequenced on the MiSeq System (Illumina, San Diego, CA, USA) following the target enrichment process. Fastq generation was performed on MiseqReporter Software (Illumina, San Diego, CA). Quality control of sequenced amplicons and variant call format (vcf) file generation were performed using QCI analysis (Qiagen, Hilden, Germany) software. Variant analysis was performed using Ingenuity and Clinical Insight Softwares (Qiagen, Hilden, Germany), and all rare and novel variants were visually controlled by using IGV 2.4.8 (www.broadinstitute.com). Segregation analysis of family members were performed using Sanger Sequencing with in-house designed primer sets covering the mutation regions.

**Data Analysis and Variant Classification.** The latest versions of gnomAD [4], dbSNP [5], and ClinVar [6] databases were considered for comparing known variant frequencies. HGMD [7] and literature accessions were also considered. ACMG 2015 [8] guidelines were used for final classification of the variants .

All statistical analyses were performed using IBM SPSS ver. 22 (SPSS Inc., Chicago, IL). Data were presented as median (25th-75th interquartile range). Categorical variables were reported as frequencies and group percentages. Progression-free survival was defined as the time from the date of initial diagnosis to disease progression or death due to any cause. The Pearson chi-square test was used to compare the categorical variables of the two groups, and the independent sample t-test or Mann–Whitney U-test was used to compare the continuous variables of the two groups. The Kaplan–Meier method was used for the survival analysis. $P < 0.05$ was considered statistically significant.

## RESULTS

**Study patients**

A total of 200 *BRCA* pathogenic/likely pathogenic variant patients were analyzed across 9 medical oncology centers. Table 1 shows the clinical and demographic characteristics of the study subjects. Of these, 130 (65%) patients harbored the *BRCA 1* pathogenic/likely pathogenic variant, and 70 of them harbored the *BRCA 2* pathogenic/ likely pathogenic variant. Only 1 patient had a synchronous disease and 11 patients had metachronous (breast and ovary) multiple primary disease. The median age at diagnosis was 45 (IQR: 38-54) years. About 45.5% of the patients had a family history. The presence of malignancy was 33.5% in first-degree relatives and 11.0% in second-degree relatives. Of these, the parent *BRCA 1 or 2*

pathogenic/likely pathogenic variant was 14% (n=28) and the diagnosis age of parent was higher than the diagnosis age of the study subjects (Figure 1). The diagnosis ages of siblings or cousins and second-degree relatives were 44.5 and 40 years, respectively.

**Table 1.** Clinical and demographic findings of the study subjects

| | |
|---|---|
| **Age, years** | |
| Median (Interquartile range) | 45 (38-54) |
| **Gender, n (%)** | |
| Female | 190 (95.0) |
| Male | 10 (5.0) |
| **ECOG-PS, n (%)** | |
| 0 | 162 (81.0) |
| 1 | 38 (19.0) |
| **Primary tumor, n (%)** | |
| Breast | 128 (64.0) |
| Genital | 63 (31.5) |
| Prostate | 7 (3.5) |
| Pancreas | 2 (1.0) |
| **Family history, n (%)** | 91 (45.5) |
| **Degree of relatives, n (%)** | |
| First-degree | 67 (33.5) |
| Second degree | 22 (11.0) |
| Third degree | 2 (1.0) |
| **Diagnosis age of relatives**, median (IQR) | |
| Parent diagnosis | 57 (50-66) |
| Sibling diagnosis | 44.5 (35-49) |
| Second relatives | 40 (35.5-48.5) |
| **Multiple primary tumor, n (%)** | 12 (6.0) |
| Synchronous | 1 (0.5) |
| Metachronous | 11 (5.5) |
| **Multiple primary tumor site, n (%)** | |
| Breast-ovary | 11 (5.5) |
| **BRCA, n (%)** | |
| BRCA-1 | 130 (65.0) |
| BRCA-2 | 70 (35.0) |

ECOG-PS: Eastern Cooperative Oncology Group- performance score, IQR: Interquartile range

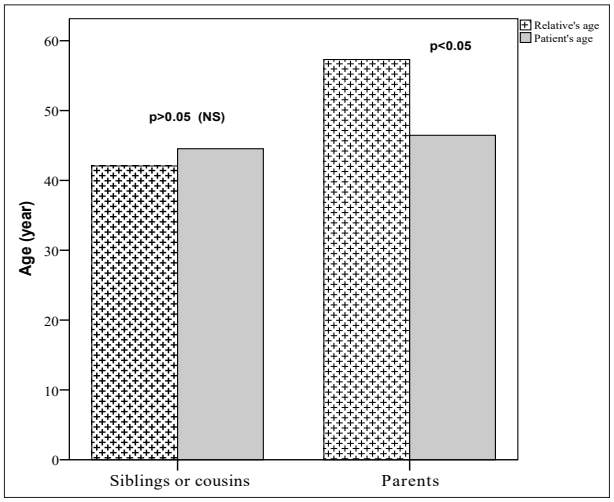


**Figure 1.** Diagnosis age of all patients and their relatives

### Breast cancer

Table 2 shows demographic and clinical characteristics of breast cancer patients who harbored *BRCA* pathogenic/likely pathogenic variant. Breast cancer prevalence was 67% (95% CI 60.2 to 73.8 percent) in all patients, and the median

**Table 2.** Clinical and demographic data of breast cancer patients

| | |
|---|---|
| **Age, years** | |
| Median (Interquartile range) | 41.5 (34-50) |
| **Gender, n (%)** | |
| Female | 126 (98.4) |
| Male | 2 (1.6) |
| **ECOG-PS, n (%)** | |
| 0 | 114 (89.1) |
| 1 | 14 (10.9) |
| **BRCA, n (%)** | |
| BRCA1 | 79 (61.7) |
| BRCA2 | 49 (38.3) |
| **Primary tumor size (T), n (%)** | |
| 0-2 cm –T1 | 79 (79.0) |
| 2-5 cm- T2 | 15 (15.0) |
| 5 cm and above-T3 | 4 (4.0) |
| **Lymph node metastasis, n (%)** | 61 (47.7) |
| **Stage, n (%)** | |
| Stage I | 30 (23.4) |
| Stage II | 53 (41.4) |
| Stage III | 29 (22.7) |
| Stage IV | 14 (10.9) |
| **Histopathology** | |
| ER, %, median (IQR) | 45 (0-90) |
| PgR, %, median (IQR) | 0 (0-65) |
| **CerbB2, IHC, n (%)** | |
| 1+ | 17 (13.3) |
| 2+ | 22 (17.2) |
| 3+ | 8 (6.3) |
| cerbB2, FISH | 12 (9.4) |
| Ki-67, %, median (IQR) | 30 (15-50) |
| **Subtypes, n(%)** | |
| Triple negative | 56 (43.8) |
| Luminal Her2- | 57 (44.5) |
| Luminal Her2+ | 9 (7.0) |
| cerbB2+ | 3 (2.3) |
| **Tumor location, n (%)** | |
| Right | 65 (50.8) |
| Left | 58 (45.3) |
| Bilateral | 5 (3.9) |
| **De novo metastasis, n (%)** | 14 (10.9) |
| **Metastasis site, n (%)** | |
| Lung | 10 (7.8) |
| Bone | 18 (14.1) |
| Liver | 8 (6.3) |
| Lymph node | 4 (3.1) |
| **Family history, n (%)** | 64 (50.0) |
| **Diagnosis age of relatives**, median (IQR) | |
| Parent diagnosis (n=15) | 51 (46-57.5) |
| Sibling diagnosis (n=7) | 44 (35-49) |

cerbB2-IHC: C-erbB-2- immunohistochemistry, ECOG-PS: Eastern Cooperative Oncology Group-performance score, ER: Estrogen receptor, PFS: progression-free-survival, PR: Progresterone receptor

age of those was 41.5 (34-50) years, and patients who diagnosed with breast cancer under 45 years was much more in *BRCA1* pathogenic/likely pathogenic variant than *BRCA2* pathogenic/likely pathogenic variant (73.4% vs 55.1%, p=0.03, respectively). Luminal (A or B) disease (without Her-2 positivity 44.5%, with Her-2 positivity 7.0%), triple-negative disease (43.8%), and only HER-2 mutant (2.3%) diseases were common subtypes. Triple negative breast cancer (TNBC) was the most common (60.5%) histopathology of *BRCA1* pathogenic/likely pathogenic variant patients and hormone receptor-positive disease was the most common (79.6%) type of *BRCA2* pathogenic/likely pathogenic variant patients (p<0.001). About 10.9% of the patients were diagnosed at the metastatic stage, there was no difference between *BRCA1 vs BRCA2* pathogenic/likely pathogenic variant patients. Half of the patients had a positive family history regarding breast and ovarian cancers. The diagnosis age of parents who had *BRCA* related cancer was 51 (46-57.5) years, and it was 44 (35-49) years in siblings or cousins who had *BRCA* related cancer (Figure 2). About 58.3% of the relatives who had malignancy were diagnosed before 50 years and their cancers were mostly breast and ovarian cancers.

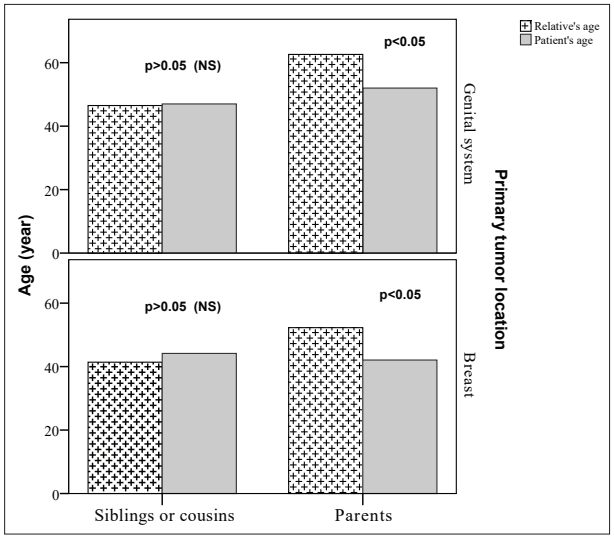


**Figure 2.** Diagnosis age of breast and genital cancer pat

**Table 3.** Clinical charactersitics of the genital site tumors

| | |
|---|---|
| **Age, years** | |
| Median (Interquartile range) | 50 (44-59) |
| **ECOG-PS, n (%)** | |
| 0 | 43 (68.3) |
| 1 | 20 (31.7) |
| **Tumor Location, n (%)** | |
| Ovary | 58 (92.1) |
| Endometrium | 2 (3.2) |
| Peritoneum | 1 (1.6) |
| **FIGO stage, n (%)** | |
| Stage I | 12 (19.0) |
| Stage II | 9 (14.3) |
| Stage III | 26 (41.3) |
| Stage IV | 12 (19.0) |
| **De novo metastasis, n (%)** | 20 (31.7) |
| **Histopathology, n (%)** | |
| Serous | 48 (76.2) |
| Endometrioid | 9 (14.3) |
| Serous+Endometrioid | 4 (6.3) |
| **Postop residual disease, n (%)** | 13 (20.6) |
| **Ca125 at diagnosis** | |
| Median (Interquartile range) | 155 (41-560) |
| **BRCA, n (%)** | |
| BRCA1 | 49 (77.8) |
| BRCA2 | 14 (22.2) |
| **Platinum-based therapy cycles** | |
| Median (Interquartile range) | 6 (6-6) |
| **Platinum-therapy response, n (%)** | |
| CR | 43 (68.3) |
| PR | 12 (19.2) |
| **PFS of platinum based regimen (first-line)** | |
| <6 months | 0 |
| 6-12 months | 14 (22.2) |
| >12 months | 28 (44.4) |
| **Platinum based line number** | |
| Median (minimum-maximum) | 1 (1-6) |
| **Family history, n (%)** | 24 (38.1) |
| **Diagnosis age of relatives**, median (IQR) | |
| Parent diagnosis | 63 (58-68) |

Ca 125: Cancer antigen 125, ECOG-PS: Eastern Cooperative Oncology Group- performance score, PFS: progression-free-survival

### Genital cancer

Table 3 shows the clinical and demographic characteristics of patients with the *BRCA* pathogenic/likely pathogenic variant who had genital site tumors. The median age was significantly lower than parent's diagnosis age of *BRCA* related cancer (50 (44-59) vs 63 (58-68) years, respectively, p<0.05, Figure 2). On the other hand, the diagnosis age of patients was similar to their sibling or cousins who had *BRCA* related cancers (p>0.05, Figure 2). Ovarian cancer was the most common (92.1%) primary site, endometrium (3.2%), and peritoneum (1.6%) were detected as well. Serous adenocarcinoma was the most common histopathology and 14.3% of the patients had endometrioid adenocarcinoma. About 77.8% of them had the *BRCA 1* pathogenic/likely pathogenic variant and 22.2% had the *BRCA 2* pathogenic/likely pathogenic variant. About 38.1% of them had a positive family history. In additon, patients who had first-line progression-free survival time above 12 months were significantly more frequent in *BRCA2* (100%) carriers compared with those in *BRCA1* (56.3%) carriers (p=0.01).

### Other

Table 4 shows data regarding the *BRCA* related prostate cancer patients. The median age was 57 (57-60) years.

**Table 4.** Clinical and demographic findings of patients with prostate cancer

| | |
|---|---|
| **Age, years**<br>Median (Interquartile range) | <br>57 (57-60) |
| **De novo metastasis, n (%)** | 3 (42.9) |
| **PSA** | 47 (14-74) |
| **mCRPC, n (%)** | 7 (100) |
| **Time from metastasis to CRPC status (months)** | 28 (14-58) |
| **Treatment line settings**<br>Docetaxel at 1 line<br>Enzalutamid at 2 line<br>Abiraterone at 2 line<br>Lutesyum at 3 line<br>Olaparib at 3 line | <br>7 (100)<br>5 (71.4)<br>1 (14.2)<br>3 (42.9)<br>5 (71.4) |
| **Docetaxel PFS (months)** | 13 (12-14) |
| **Postdocetaxel treatment options**<br>Enzalutamide<br>Abiraterone<br>Cabazitaxel | <br>5 (71.4)<br>1 (14.2)<br>1 (14.2) |

mCRPC metastatic castration resistant prostate cancer,
PFS: progression-free-survival, PSA prostate specific antigen,

All of the patients were diagnosed at the castration-resistant time. The median time from metastasis to castration-resistant status was 28 (14-58) months. On the other hand, only 2 male patients had *BRCA* related pancreas cancer. The primary tumor was located at the corpus site of the pancreas.

## DISCUSSION

This multicenter study, in which we assessed the clinical and demographic characteristics of 200 patients who harbored the *BRCA 1 or 2* pathogenic/likely pathogenic variant, demonstrated comparable findings with literature. In addition, the diagnosis age of patients who harbored the *BRCA 1/BRCA 2* pathogenic/likely pathogenic variant was younger than the diagnosed age of their parents who harbored the *BRCA 1/BRCA 2* pathogenic/likely pathogenic variant with cancer. We suggest that the family members of the patients who harbored the *BRCA* pathogenic/likely pathogenic variant should be alerted to be aware of this issue, and genetic counseling should be provided earlier.

Breast cancer is the most frequently diagnosed cancer in women. Although most of the newly diagnosed cases are sporadic, germline variants account for a small percentage of breast cancer [9]. The breast cancer types 1 or 2 pathogenic/likely pathogenic variant (*BRCA 1 and BRCA 2*) constitute the majority of hereditary ovarian and breast cancer and their identified pathogenic alterations are characterized by an autosomal dominant pattern of highly penetrant germline inheritance. A prospective cohort study showed that cumulative breast cancer risk was 72% (95% CI 65 to 79 percent) in *BRCA1* pathogenic/likely pathogenic variant and 69% (95% CI 61 to 77 percent) in *BRCA2* pathogenic/likely pathogenic variant carriers, respectively [10]. Early-onset breast cancer is more prominent in patients who had *BRCA* related BC disease [11]. Additionally, breast cancer incidence was noted to rise in early adulthood, namely until 30 to 40 years for *BRCA 1* carriers and until 40 to 50 years for *BRCA2* carriers [10, 12]. In our study, the median age at initial diagnosis was 41.5 (34-50) years, and breast cancer patients under 45 years were significantly much more in *BRCA 1* pathogenic/likely pathogenic variant group than those with the *BRCA 2* pathogenic/likely pathogenic variant. Family history is a risk factor for breast cancer and its incidence varies between *BRCA* related cancer patients [9, 13]. O'Shaughnessy et al. showed that family history was present in 45.5% of *BRCA* pathogenic/likely pathogenic variant breast cancer patients [9]. In our study, family history was present in 50% patients. Moreover, we found that patients with the *BRCA* pathogenic/likely pathogenic variant breast cancer were diagnosed at an earlier age compared to their *BRCA* pathogenic/likely pathogenic variant parent's diagnosis age. Breast cancer screening programs and prior knowledge of their hereditary risk factors from parents might be the reason for this difference. In addition, average-risk screening protocols for breast cancer screening, such as mammography at age 50 in women, do not adequately detect disease early enough for *BRCA* pathogenic/likely pathogenic variant individuals [3, 14]. Assessment of newly diagnosed breast cancer patients for hereditary cancer conditions and genetic counseling for high-risk patients should be kept in mind with every newly diagnosed patient**.** On the other hand, triple-negative breast cancer histopathology was more frequent in the *BRCA* pathogenic/likely pathogenic variant patients, especially in *BRCA1* pathogenic/likely pathogenic variant patients [15-17]. In addition, it was shown that hormone-receptor-positive disease is more frequently associated with *BRCA 2* mutant breast cancer [18]. Similarly, we showed that TNBC was the most common histopathology of *BRCA 1* pathogenic/likely pathogenic variant patients and hormone receptor-positive disease was the most common type of *BRCA 2* pathogenic/likely pathogenic variant patients. Additionally, female breast cancer patients ≤45 years old were significantly more numerous in the *BRCA 1* pathogenic/likely pathogenic variant group, and the most common histopathology was triple-negative disease. Patients above 45 years old, triple-negative histology in *BRCA1* pathogenic/likely pathogenic variant patients were comparable to those in *BRCA2* pathogenic/likely pathogenic variant breast cancer patients. On the other hand, the presence of germline pathogenic variations is influenced by the

regional distribution of the population and ethnic-specific factors regarding adaptation and effects of genetic drift. *BRCA* variation information may provide identification the pathogenic variation causing cancer risk in the population. In our study, we identified the median diagnosis age and tumor histopathological findings were similar, compared to the Greek population [19]. Moreover, it was demonstrated that the median age at diagnosis of breast cancer in Mediterranean countries is younger compared with Western European countries [20]. These differences may be attributed to the regional distribution of the population and/or ethnic-specific factors.

Female genital tract cancers and their relationship with the *BRCA 1/BRCA 2* pathogenic/likely pathogenic variant are most frequently observed with ovarian cancers. Apart from epithelial ovarian cancer, peritoneum, fallopian tube, peritoneum and endometrium are also less frequently affected. One study from the Japanese HBOC consortium showed that the fallopian tube and peritoneum as a primary tumor site was less than 10% of *BRCA1* pathogenic/likely pathogenic variant patients and was significantly higher in *BRCA2* compared with *BRCA2* pathogenic/likely pathogenic variant patients [21]. In our study, 4.8% of *BRCA 1/BRCA 2* pathogenic/likely pathogenic variant patients had primary endometrium and peritoneal cancer sites, and all of them were diagnosed with the *BRCA1* mutant variant. Germline *BRCA 1/BRCA 2* pathogenic/likely pathogenic variant related to epithelial ovarian cancer are consist with at least 10% of the newly diagnosed cases and its cumulative risk by 80 years of age was 44% for *BRCA1* pathogenic/likely pathogenic variant carriers and 17% for *BRCA2* pathogenic/likely pathogenic variant carriers [10]. The histopathology of *BRCA 1/BRCA 2* pathogenic/likely pathogenic variant ovarian cancer is mainly serous adenocarcinoma [22]. On the other hand, a European study from Lakhani et al. showed that endometrioid histology was the second common histology of ovarian cancers in *BRCA1 and BRCA2* carriers [23]. Similarly, we showed that serous carcinoma and endometrioid carcinoma histologies were the main histology types of *BRCA 1/BRCA 2* carriers. *BRCA 1/BRCA 2* pathogenic/likely pathogenic variant status affects both progression-free survival and overall survival [24]. Firstly, it was shown that ovarian cancers in *BRCA 1/BRCA 2* pathogenic/likely pathogenic variant carriers had favorable survival outcomes, compared with non-carrier patients [25-27]. Platinium sensitivity, repeatedly responded to platin-based regimens and longer duration of response, might play important role in favorable survival advantage in BRCA 1/BRCA 2 carriers with ovarian cancer patients. By the emergence of new treatment options, such as poly (ADP-ribose) polymerase (PARP) inhibitors, it is thought that *BRCA 1/BRCA 2* carriers with ovarian cancer will benefit from these options. Additionally, *BRCA2* carriers with ovarian cancer had favorable survival outcomes [24, 28]. Similarly, we revealed that progression-free survival longer than 12 months was significantly more frequent in *BRCA2* carriers compared with those in *BRCA1* carriers. Age at diagnosis was also found to be an independent risk factor associated with survival [28]. It is not clear whether age at diagnosis in ovarian cancer patients who harbor *BRCA 1/BRCA 2* pathogenic/likely pathogenic variants differs from non-carriers. It was shown that *BRCA1* pathogenic/likely pathogenic variant ovarian cancer patients were younger compared with non-carriers, but it was not observed for *BRCA2* carriers [25]. Another study showed that age at diagnosis in ovarian cancer patients who harbor the *BRCA 1/BRCA 2* pathogenic/likely pathogenic variant was comparable to non-carriers [27]. In our study, we revealed that the age of diagnosis of ovarian cancer patients who harbor the *BRCA* pathogenic/likely pathogenic variant was younger than their parents' age of diagnosis of *BRCA*-associated cancer. Due to fact that there is no evidence-based effective screening program for ovarian cancer, genetic counseling of all ovarian cancer patients who diagnosed<70 years may help the early diagnosis of *BRCA 1/BRCA 2* carriers and may enhance the prevention of disease occurrence.

The frequency of germline HRR deficiency-related mutations in metastatic prostate cancer was found to be around 12 percent according to one study, and *BRCA2* was the most common of these mutations, with 5.3%. The *BRCA 1* pathogenic/likely pathogenic variant frequency was found to be 1 percent [29]. Prostate cancers with these mutations may have a worse prognosis and overall survival compared to those without such mutations, however, with appropriate genomic targeted therapies (such as PARP inhibitors, platinum-based therapies) they may have a better response [30-32]. The median age of our patients is 57 and they are 10 years younger than the patients in Phase 1/2/3 studies [33-35] in which the efficacy of Olaparib in patients with the *BRCA* pathogenic/likely pathogenic variant was evaluated. As expected, approximately half of our patients had metastatic disease at the time of diagnosis, consistent with the course of more aggressive disease in patients with the *BRCA* pathogenic/likely pathogenic variant, and the time to progression to the CRPC period was short (approximately 28 months). Both the de novo metastatic disease rate and the time until CRPC were found to be consistent with the literature. If we examine 7 castration-resistant prostate cancer patients who constitute our cohort, all of these patients received docetaxel and, interestingly, the use of docetaxel in these patients had much better results than docetaxel's own castration-resistant prostate cancer 1st line treatment phase 3 PFS results (13 months vs. 9

months, respectively) [36]. We know that in cancers with the *BRCA* pathogenic/likely pathogenic variant, very good treatment responses are obtained with platinum treatments. It is unknown whether there is such a treatment response situation between docetaxel and the *BRCA* pathogenic/likely pathogenic variant. This situation requires more detailed research. In our study, the disease is more aggressive in *BRCA* pathogenic/likely pathogenic variant patients (young age, high de novo metastasis rate). Therefore, in terms of prostate cancer screening in carriers with this mutation, especially those with the *BRCA* 2 pathogenic/likely pathogenic variant, the use of multiparametric MRI should also be considered, unless monitoring with PSA alone.

The incidence of pancreatic cancer is increasing in developed and developing countries. Some syndromes cause a genetic predisposition for this cancer. There is a higher level of evidence that *BRCA* 2 is associated with an increased risk for this cancer than for *BRCA 1.* In *BRCA 2* pathogenic/likely pathogenic variant carriers, the risk of pancreatic cancer is 3.5-10 (1.87-6.58) times higher [37, 38]. No relationship could be demonstrated between pancreatic cancer and germline pathological variant (e.g., *BRCA 1/BRCA 2*) carriage in terms of age, family history, or disease stage. It was also not found that there was an independent relationship between overall survival in those with pathological mutations. It has been shown that there is a favorable trend in overall survival with platinum-based therapies in patients with HRR. This appears to be a predictive factor for PARP inhibitor maintenance therapies.

There are several limitations in our study. First, retrospective clinical data of *BRCA 1/BRCA 2* pathogenic/likely pathogenic variant patients from medical records has disadvantages to control for all potential confounding biases. These confounding factors may include selection and institutional biases due to actively conducted genetic testing by medical genetics specialists at different medical centers. Despite these limitations, a noteworthy strength of our study is that the diagnosis age of patients who harbored the *BRCA 1/BRCA 2* pathogenic/likely pathogenic variant was younger than the diagnosed age of their parents who harbored the *BRCA* 1/*BRCA* 2 pathogenic/likely pathogenic variant with cancer. Our study findings were consistent with the literature.

In conclusion, newly diagnosed *BRCA 1/BRCA 2* carriers with cancers were younger than their parents who harbored the *BRCA* pathogenic/likely pathogenic variant with cancer. We suggest that genetic screening of the *BRCA 1/BRCA 2* pathogenic/likely pathogenic variant is needed as a routine screening for those with a personal or family history of breast, ovarian, tubal, or peritoneal cancer. In addition, once *BRCA1 or BRCA2* germline pathogenic variant has been identified in a family, testing of at-risk next-generation relatives earlier can identify those family members who also have the familial pathogenic variant, and thus need increased surveillance.

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