Research Article

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Evaluation of *BRCA1/2* gene mutations in patients with high-risk breast and/or ovarian cancer in Turkey

Türkiye'de yüksek riskli meme ve/veya over kanserli hastalarda *BRCA1/2* gen mutasyonlarının değerlendirilmesi

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Abstract

Objectives: To find *BRCA1/2* test selection criteria unique to the Turkish population, as well as to provide the *BRCA1/2* gene mutation distributions of patient population to the literature.

Methods: Genetic counseling was given to 2,373 cases with a family history of high-risk breast and/or ovarian cancer who applied to Istanbul University, Oncology Institute, Department of Cancer Genetics between 1994 and 2021 and selected by NCCN Guidelines for the *BRCA1/2* test criteria. In our clinic, mutation screenings in *BRCA1/2* genes were performed by Sanger sequencing method in patients admitted between 1994 and 2014 and by NGS method in patients admitted between 2015 and 2021.

Results: The overall mutation rate in our patient group selected from high-risk patients was 16.5% (391/2,373) after *BRCA1/2* gene mutation screening performed in 2,373 cases who applied to the Cancer Genetics clinic. Of the patients with mutations, 57.5% (225/391) had *BRCA1* mutation, 41.9% (164/391) had *BRCA2* mutation, and 0.6% (2/391) had both *BRCA1* and *BRCA2* pathogenic mutations. People diagnosed before the age of 60 who have a history of triple-negative breast cancer had a 28.5% overall mutation rate.

Conclusions: *BRCA1/2* mutation in Turkish population were evaluated in accordance with NCCN *BRCA1/2* genetic test selection criteria; we discovered that all of our study results were statistically significant ($p<0.05$).

Keywords: *BRCA1/2* genes; breast cancer; gene mutation; national comprehensive cancer network; ovarian cancer.

Öz

Amaç: Türk popülasyonuna özgü *BRCA1/2* testi seçim kriterlerini bulmak ve hasta popülasyonunun *BRCA1/2* gen mutasyon dağılımlarını literatüre kazandırmak.

Yöntemler: 1994–2019 yılları arasında İstanbul Üniversitesi, Onkoloji Enstitüsü, Kanser Genetiği Bölümü'ne başvuran yüksek riskli meme ve/veya over kanser aile

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hikayesine sahip ve NCCN *BRCA1/2* test kriterini sağlayan 2,373 vakaya poliklinik kapsamında genetik danışmanlık hizmeti verilmiştir. 1994–2014 yılları arasında başvuran kişilerde *BRCA1/2* genlerindeki nokta mutasyonları, küçük delesyon ve insersiyonları belirlemek için Sanger dizileme metodu kullanılırken büyük delesyon ya da duplikasyonları belirlemek için ise Multiplex Ligation Probe Amplification (MLPA) metodu kullanılmıştır. 2015–2019 yılları arasında başvuran kişilerde ise *BRCA1/2* genlerindeki mutasyon taramaları Next-Generation Sequencing (NGS) metodu ile gerçekleşti. Bu metod ile uygulanan analizlerde büyük delesyon ve duplikasyon analizleri Copy Number Variation (CNV) ile belirlendi.

Bulgular: Kanser Genetiği polikliniğine başvuran 2,373 olguda yapılan *BRCA1/2* gen mutasyon taraması sonucunda yüksek riskli hastalardan seçilen hasta grubumuzda genel mutasyon oranı %16.5 (391/2,373) olarak bulunmuştur. Mutasyon saptanan hastaların %57,5'inde (225/391) *BRCA1* mutasyonu, %41.9'unda (164/391) *BRCA2* mutasyonu ve % 0,6'sında (2/391) hem *BRCA1* hem de *BRCA2* patojenik mutasyonları vardı. 60 yaşından önce teşhis konan ve triple negatif meme kanseri öyküsü olan kişilerde genel mutasyon oranı %28.5 idi.

Sonuç: Türk popülasyonunda *BRCA1/2* mutasyonu NCCN genetik test seçim kriterlerine göre değerlendirildi; tüm çalışma sonuçlarımızın istatistiksel olarak anlamlı olduğunu keşfettik ($p<0.05$).

Çıkar Çatışması: Yazarların herhangi bir çıkar çatışması yoktur.

Anahtar Kelimeler: *BRCA1/2* genleri; gen mutasyonu; meme kanseri; ulusal kapsamlı kanser ağı; yumurtalık kanseri.

Introduction

The incidence of cancer is increasing rapidly all over the world. Breast and ovarian cancers, which are particularly common in women, are among the leading causes of cancer morbidity and mortality around the world. Each year, 2.088.849 (11.6%) individuals are newly diagnosed with breast cancer, while 295.414 (1.6%) people are newly diagnosed with ovarian cancer, according to Globocan 2018 data. With a mortality rate of 6.6%, cases diagnosed with breast cancer had the fourth highest mortality rate [1].

According to Globocan 2018 Turkey data; In 2018, 22.375 (10.6%) people were newly diagnosed with breast cancer; 3,729 (1.8%) people were diagnosed with ovarian cancer [1]. In recent years, the incidence of breast and ovarian cancer has nearly doubled in Turkey [2]. The primary causes of this increase in occurrence are unknown. However, genetic factors have been implicated in the development of hereditary breast and ovarian cancer (HBOC) syndrome. Many genes have been linked to breast and ovarian cancers, however the majority of them have a medium or low penetrance [3]. Mutations in high penetrance susceptibility genes like *BRCA1/2* are linked to the majority of inherited breast and ovarian malignancies [4]. Although the *BRCA1/2* mutation rate in breast cancer cases in the general population is found to be 3–8%, approximately 10–15% of ovarian cancer patients and 5–10% of breast cancer patients have a *BRCA1/2* gene mutation characterized by hereditary breast and ovarian cancer syndrome [5]. Studies show that *BRCA1* accounts for 0.7–29% of mutations observed in HBOC and 1.5–25% of *BRCA2* [6]. Because the majority of breast and ovarian cancers are hereditary, it's critical to look into *BRCA1/2* gene variations in patients who have a family history of breast, ovarian, or other malignancies. As a result, identifying people at risk, offering genetic counseling, and choosing people who are candidates for *BRCA1/2* gene testing and directing them to the test is a critical and complex task. Individuals at high risk of breast or ovarian cancer are provided genetic counseling before *BRCA1/2* mutation testing in most developed nations. Genetic counseling is an important technique that should be used when asking and recording questions about people's medical histories, reviewing their family histories precisely and comprehensively, and selecting the right people for genetic test.

BRCA1/2 test criteria for BRCA-Related Breast and/or Ovarian Cancer Syndrome are frequently determined using National Comprehensive Cancer Network (NCCN) Guidelines around the world [7]. Even in high-risk families, the frequency of *BRCA1/2* gene mutations is only 3.4–15.5%, despite the fact that family history is common in HBOC syndrome [8]. The prevalence of *BRCA1/2* gene mutations, as well as variations in geographies and races, make it difficult to develop a valid model for *BRCA1/2* mutation estimations. Furthermore, due to the low reporting rate of *BRCA1/2* gene mutations, the frequency of *BRCA1/2* gene mutations is unknown. This is due to factors such as the inability to screen across a broad spectrum with excellent quality and the high cost of test pricing. According to the research, *BRCA1/2* gene mutation rates in high-risk families range from 2.9 to 38% depending on different geographical regions [9]. These significant mutational differences draw attention to the importance of genetic testing and create the necessity to determine whether the criteria used in the selection of risky people differ according to regional distributions. As a result, the primary goal of this study was to determine the *BRCA1/2* test selection criteria specific to the

Turkish population, to present the *BRCA1/2* gene mutation distributions in the Turkish population to the literature, to determine the patients' treatment options, and to provide an early diagnosis advantage in high-risk individuals. In this study, 2,373 high-risk individuals with breast and/or ovarian cancer in the Turkish community and 159 participants without a cancer diagnosis but with a known *BRCA1/2* pathogenic variation in their family received genetic counseling. Individuals who met the NCCN *BRCA1/2* test criteria underwent genetic testing, and mutation frequencies in the *BRCA1/2* genes were determined.

Materials and methods

Selection of study population

From 1994 to 2021, 2,373 people with a family history of high-risk breast and/or ovarian cancer who applied to Istanbul University, Oncology Institute, Department of Cancer Genetics and met the NCCN *BRCA1/2* test requirements received genetic counseling. Cancer patients diagnosed with high-risk breast and/or ovarian cancer and met the NCCN *BRCA1/2* test requirements received genetic counseling. Prior to genetic test patients were informed about the necessities of the genetic test and its results by a genetic counselor, who works in the Cancer Genetic departments of Istanbul University Oncology Institute. The recommendation of risk-reducing techniques through genetic counseling, was given to the cancer patients in order to reduced the incidence of cancer in the family for next generations. If the patients and the family members are in high risk group, the necessary examinations and scans were recommended to provide an early diagnostic advantage. All of the cases were evaluated clinically, demographically, and histopathologically. In addition, patient consent was obtained from all patients included in the study that they accepted the test, and this study was approved by the Istanbul University Ethics Committee (19.09.2011, and No 1455).

Mutation analysis

Mutation screenings in patients, applied to the Cancer Genetics clinic between 1994 and 2021 were performed using different technological methods, considering the innovations over the years.

First, lymphocytes were isolated from blood samples of participants who applied between 1994 and 2014 using the Ficoll (Sigma-Aldrich, Darmstadt, Germany)methods. The QIAamp DNA micro kit (Qiagen, 40724 Hilden, Germany) was used to isolate DNA from lymphocyte pellets according to the manufacturer's instructions. Nanodrop was used to measure the quantity of genomic DNAs. Sanger sequencing method was used to detect point mutations, small deletions and insertions in *BRCA1/2* genes in applicants between 1994 and 2014, while Multiplex Ligation Probe Amplification (MLPA) method was used to identify large deletions or duplications. In Sanger sequencing method, all encoded exons and adjacent intronic splicing and binding regions of *BRCA1/2* genes were divided into 96–110 different fragments with lengths ranging from 197 to 823 base pairs and scanned for mutation. Probemix P002 *BRCA1*, Probemix P087 *BRCA1* Confirmation probes from MRC Holland were used for the *BRCA1* gene, and Probemix P045 *BRCA2/CHEK2* and Probemix P077 *BRCA2* Confirmation probes from MRC Holland were used for the *BRCA2* gene.

QIAcube was used to isolate DNA in patients hospitalised between 2015 and 2021 (Qiagen, Germany). The genomic DNAs were measured using a Qubit fluorimeter (ThermoFisher Scientific, Paisley PA4 9RF, UK). The Next-Generation Sequencing (NGS) technology was used to screen for mutations in the *BRCA1/2* genes. In the analyzes performed with this method, large deletion and duplication analyzes were determined by Copy Number Variation (CNV).

Clinicopathological features evaluation

The pathology reports in the patients' clinical files were used to acquire information regarding the patients' diagnoses, age at diagnosis, estrogen (ER), progesterone (PR), and HER2 status. The term triple negative is used for cases where ER, PR and HER2 receptors are all negative.

Statistical analysis

The Chi-Square test was used to assess the connection between the NCCN *BRCA1/2* test criteria, the patients' age at diagnosis, and their *BRCA1/2* mutation carrier status. The SPSS (SPSS version 21; SPSS Science, Chicago, IL, USA) program was used for all statistical analyses, and those with a p value of 0.05 were considered statistically significant.

Results

Between 1994 and 2021, approximately 3,000 cases applied to the "Cancer Genetics" polyclinic of Istanbul University, Institute of Oncology. While 2,373 cases were found to be appropriate for *BRCA1/2* mutation screening and were included, the remaining cases were denied due to a lack of test parameters. When 2,373 cases were categorized in terms of cancer diagnosis, 61.6% (1,461/2,373) were diagnosed with unilateral breast cancer, 4.7% (111/2,373) with bilateral breast cancer, 1.9% (45/2,373) with male breast cancer, 15.8% (376/2,373) with ovarian cancer, 1.8% (43/2,373) with ovarian cancer combined with breast cancer, 14.2% (338/2,373) with cases diagnosed with ovarian cancer together with breast cancer. The overall mutation rate in our patient group selected from high-risk patients was 16.5% (391/2,373) as a consequence of *BRCA1/2* gene mutation testing performed in 2,373 cases who applied to the Cancer Genetics outpatient clinic. 57.5% (225/391) of the patients with mutations carry pathogenic mutations in *BRCA1*, 41.9% (164/391) *BRCA2*, 0.6% (2/391) both *BRCA1* and *BRCA2* genes. *BRCA1* mutation rate was 9.5% (225/2,373) and *BRCA2* mutation rate was 6.9% (164/2,373). 0.08% (2/2,373) of the patients had

Table 1: The frequency of *BRCA1* and *BRCA2* gene mutations in all patients according to diagnosis in high risk breast and/or ovarian cancer cases in Turkey.

Diagnosis of patients	BRCA negative, n (%)	*BRCA1* carriers, n (%)	*BRCA2* carriers, n (%)	*BRCA1* and *BRCA2* carriers, n (%)	Overall mutation rate, n (%)	Total number of patients, n
Unilateral breast cancer	1,259 (86.2%)	108 (7.4%)	94 (6.4%)	0 (0%)	202 (13.8%)	1,461
Bilateral breast cancer	81 (73%)	18 (16.2%)	12 (10.8%)	0 (0%)	30 (27%)	111
Male breast cancer	36 (81.8%)	2 (4.6%)	6 (13.6%)	0 (0%)	8 (18.2%)	44
Unilateral breast cancer and ovarian cancer	16 (39%)	18 (43.9%)	6 (14.7%)	1 (2.4%)	25 (60.9%)	41
Unilateral breast cancer and other type of cancer	292 (87.7%)	23 (6.9%)	18 (5.4%)	0 (0%)	41 (12.3%)	333
Male breast cancer and other type of cancer	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1
Bilateral breast cancer and other type of cancer	4 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	4
Bilateral breast cancer and ovarian cancer	2 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2
Ovarian cancer	291 (77.4%)	56 (14.9%)	28 (7.4%)	1 (0.3%)	85 (22.6%)	376
Total	1,982 (83.5%)	225 (9.5%)	164 (6.9%)	2 (0.08%)	391 (16.5%)	2,373

both *BRCA1* and *BRCA2* gene mutation. Table 1 shows the frequency of *BRCA1/2* gene mutations in high-risk breast and/or ovarian cancer patients according to diagnosis. The continent ascertainment of *BRCA1/2* mutation distribution in high risk breast and ovarian cancer families were shown in Table 2 [10].

The mean age at diagnosis of breast cancer patients was 41 ± 10.1 (20–87), while it was 48 ± 10.9 (17–84) in ovarian cancer patients. When patients' *BRCA1/2* gene mutation status was analyzed by age, it was discovered that 76.6% of breast cancer patients with *BRCA1/2* mutation carriers and 34.3% of ovarian cancer patients were diagnosed before the age of 45.

After statistical analyzes, it is noteworthy that *BRCA1/2* mutation carriers are diagnosed at an early age in both breast and ovarian cancers ($p<0.05$). The *BRCA1/2* status according to the age of diagnosis of the patients is shown in Supplementary Table 3.

Table 2: The worldwide *BRCA1/2* mutation distrubition in high risk breast and ovarian cancer families.

Continent of ascertainment	*BRCA1* mutation rate (%)	*BRCA2* mutation rate (%)	
North America	14%	19.5%	Rebbeck et al. [10]
Africa	43.5%	15.9%	Rebbeck et al. [10]
Asia	17%	19.2%	Rebbeck et al. [10]
South/Central America	27.8%	26.1%	Rebbeck et al. [10]
Europe	10.9%	12.9%	Rebbeck et al. [10]
Austria	29.8%	17.1%	Rebbeck et al. [10]

When the *BRCA1/2* status is evaluated according to the data specific to the Turkish population, the overall mutation rate was 23.9% (38/159) in individuals without a diagnosis of cancer but with a known *BRCA1/2* pathogenic variant in their family, according to the NCCN Guidelines Version 3.2019 *BRCA1/2* test criteria. The overall mutation rate in people diagnosed with breast cancer before age 45 was 16.3% (196/1,202); 15% (3/20) of people aged 46–50 years diagnosed with breast cancer and diagnosed with a second primary breast cancer at any age; Again, the overall mutation rate was 19.8% (27/136) in people aged 46–50 with breast cancer who had 1 or more than 1 close relative diagnosed with breast cancer at any age. In persons diagnosed before the age of 60 who have a history of triple-negative breast cancer, the overall mutation rate is 28.5% (87/305).

The overall mutation rate is 21.2% (233/1,101) in individuals diagnosed with breast cancer at any age and have 1 or more than 1 close relative with a history of breast cancer before the age of 50, 24.5% (136/555) of people with a history of breast cancer in two or more patients or near relatives, 38% (98/258) of people with a history of ovarian cancer in one or more close relatives.

BRCA1/2 mutations are found in 26.2% (110/419) of people diagnosed with ovarian cancer. This rate is 17.8% (8/45) among male breast cancer patients. All of our study results were found to be statistically significant when the *BRCA1/2* mutation data from the Turkish population was examined utilizing the NCCN *BRCA1/2* genetic test selection criteria ($p<0.05$). Between 1994 and 2021, only one patient of Ashkenazi Jewish origin applied to the Cancer

Table 3: The frequency of *BRCA1* and *BRCA2* gene mutations according to NCCN Guidelines Version 3.2019 *BRCA1/2* Testing Criteria in Turkish population.

BRCA1/2 testing criteria according to NCCN guidelines version 3.2019	BRCA negative, n (%)	*BRCA1* carriers, n (%)	*BRCA2* carriers, n (%)	*BRCA1* and *BRCA2* carriers, n (%)	Overall mutation rate, n (%)	Total number of patients, n	p-Value
A. Individual without a cancer diagnosis from a family with a known *BRCA1/2* pathogenic variant	121 (76.1%)	26 (16.4%)	12 (7.5%)	0 (0%)	38 (23.9%)	159	0.000*
B. Personal history of breast cancer + one or more of the following							
B.1. Diagnosed <=45 y	1,006 (83.7%)	111 (9.2%)	85 (7.1%)	0 (0%)	196 (16.3%)	1,202	0.000*
B.2. Diagnosed 46–50 y with:							
B.2.1. An additional breast cancer primary at any age	17 (85%)	2 (10%)	1 (5%)	0 (0%)	3 (15%)	20	0.000*
B.2.2. ≥1 close blood relative with breast cancer at any age	109 (80.1%)	14 (10.3%)	13 (9.6%)	0 (0%)	27 (19.8%)	136	0.000*
B.3. Diagnosed ≤60 years with:							
B.3.1. Triple-negative breast cancer	218 (71.5%)	67 (22%)	20 (6.5%)	0 (0%)	87 (28.5%)	305	0.000*
B.4. Diagnosed at any age with:							
B.4.1. ≥1 close blood relative with:							
B.4.1.1. Breast cancer diagnosed ≤50 years or	868 (78.8%)	144 (13.1%)	89 (8.1%)	0 (0%)	233 (21.2%)	1,101	0.000*
B.4.1.2. Ovarian carcinoma	160 (62%)	79 (30.6%)	19 (7.4%)	0 (0.0%)	98 (38%)	258	0.000*
B.4.2. >=2 additional diagnosis of breast cancer at any age in patient and/or in close blood relatives	419 (75.5%)	86 (15.5%)	50 (9%)	0 (0%)	136 (24.5%)	555	0.000*
B.5. Ashkenazi Jewish ancestry	1 (100%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1	0.914
C. Personal history of ovarian cancer	309 (73.7%)	74 (17.7%)	34 (8.1%)	2 (0.5%)	110 (26.2%)	419	0.000*
D. Personal history of male breast cancer	37 (82.2%)	2 (4.4%)	6 (13.3%)	0 (0%)	8 (17.8%)	45	0.000*

* indicates that p-value is significant.

Genetics Polyclinic. No pathogenic mutation was found in the *BRCA1/2* genes in this person either (p>0.05). Table 3 shows the *BRCA1/2* mutation status in the Turkish population based on the NCCN Guidelines Version 3.2019 *BRCA1/2* test criteria.

Discussion

Here in the study, a total of 2,373 cases with a family history of high-risk breast and/or ovarian cancer who applied to Istanbul University, Institute of Oncology, Department of Cancer Genetics between 1994 and 2021 and selected by NCCN Guidelines for the *BRCA1/2* test criteria. The mutation screenings in *BRCA1/2* genes were performed by Sanger sequencing method in patients admitted between 1994 and 2014 and by NGS method in patients admitted between 2015 and 2021. Sanger sequence was used as a gold standard over the years and it was the main sequencing method used in first human genome till 2000. Thanks to development in NGS technology since the begining of twenty first century NGS has overtaken Sanger sequencing. Unlike the conventional molecular techniques, highly productive new-generation sequencing technique can sequence millions of DNA fragments at ever-decreasing costs and in shorter time. In addition, different types of genomic changes can be detected with a single test.

Hereditary Breast/Ovarian Cancer (HBOC) syndrome is a cancer susceptibility syndrome associated with pathogenic variants in the *BRCA1/2* genes. It is estimated that the risk of developing breast and ovarian cancer due to this syndrome is approximately 70–80% and 20–50%, respectively [11]. Cancer risk management for *BRCA1/2* mutation carriers is a complex and difficult process. *BRCA1/2* mutation carriers, surveillance (breast self-exam, clinical breast examination, screening using mammography and breast magnetic resonance imaging), chemoprevention (estrogen receptor modulator (SERM) or an aromatase inhibitor) and prophylactic surgery (Prophylactic bilateral salpingo-oophorectomy (different risk reduction strategies are recommended, including PBSO) and bilateral prophylactic mastectomy (BPM) [12]. However, risk reduction methods vary in their effectiveness. Many studies have been

conducted on whether prophylactic surgery can reduce the risk of cancer and mortality in *BRCA1/2* mutation carriers, and in people with a pathogenic variant in *BRCA1/2*, risk-reducing surgical intervention has been shown to reduce overall mortality [13, 14]. As a result, early detection of people with a *BRCA1/2* pathogenic variation has the potential to minimize cancer morbidity and mortality in people who are at high risk of developing cancer. 38 people who were determined to be mutation carriers among 159 healthy adults with a known *BRCA1/2* pathogenic mutation in their family were provided risk-reducing procedures, and 25 of them were over 40 years old. Bilateral salpingo-oophorectomy and bilateral prophylactic mastectomy were performed as preventative procedures. As a result, these people's chances of developing cancer are reduced. In 13 individuals who are mutation carriers and under the age of 40, risk-reducing surveillance measures such as breast self-examination, clinical breast examination, mammography screening, and breast magnetic resonance imaging have been advised to provide the advantage of early detection. When our study results are evaluated in this respect; it has been revealed how important genetic counseling and *BRCA1/2* gene testing are, especially in the selection of high-risk individuals. Many people benefit from genetic counseling in terms of cancer prevention now and in the future, as well as identifying treatment alternatives for patients. With the selection of genetically high-risk individuals and the recommendation of risk-reducing techniques through genetic counseling, it is envisaged that the incidence of cancer in the population will decrease with each new generation.

Male breast cancer is a very uncommon cancer in men. Men's breast cancers account for less than 1% of all cases. Despite the fact that *BRCA2* mutations are more common, *BRCA1/2* mutations account for 10% of all *BRCA1/2* mutations [15]. Within the scope of the study, it was seen that 45 of the 1997 breast cancer patients who applied to our Cancer Genetics outpatient clinic between 1994 and 2019 were male breast cancer patients, that is, the frequency of male breast cancer patients in our population is approximately 2.2%. In the Turkish population, the total *BRCA1/2* mutation rate in male breast cancer patients is 17.8% (8/45). Both the incidence of male breast cancer patients and the rate of *BRCA1/2* mutations are much higher than the global norm. Furthermore, when the mutation distribution in *BRCA1/2* genes was analyzed, 75% (6/8) of male breast cancer patients had mutations in the *BRCA2* gene, which is consistent with the literature.

Triple Negative Breast Cancer (TNBC) is a kind of breast cancer that lacks Estrogen receptor (ER), Progesterone receptor (PR), and little or no HER2 protein expression. It accounts for 10–15% of all breast cancers diagnosed each year [16]. TNBC represents an aggressive form of disease diagnosed at an advanced stage, usually characterized by a high tumor grade, larger size, poorly differentiated histology, frequent lymph node metastases, and younger age at diagnosis [17]. The NCCN changed the *BRCA1/2* test criteria in 2011 to cover patients with Triple-negative breast cancer because of the link between germline *BRCA1* mutations and TNBC [18]. Current guidelines allow testing for patients with a diagnosis of TNBC aged ≤60 years, with or without a significant family history of breast cancer [19]. According to the findings of our study, people over 60 years old with TNBC account for 15.3% (305/1997) of all breast cancer patients. Overall, 28.5% (87/305) of people tested positive for *BRCA1/2* mutations. When looking at the literature, it's clear that only 15.4% of TNBC patients have *BRCA1/2* mutations. It's worth noting that TNBC patients in the Turkish community had a two-fold increase in *BRCA1/2* gene mutations.

The prevalence and breadth of *BRCA1/2* gene mutations in hereditary breast and ovarian cancer syndrome fluctuate significantly depending on geography and ethnicity [20]. As a result, it's critical to comprehend the role of *BRCA1/2* mutations in the development of disease in any community. The distribution of *BRCA1/2* gene mutations in patients with breast and/or ovarian cancer in the Turkish population was examined in this study. Pathogenic mutations in the *BRCA1/2* genes are found in around 10% of all breast cancer cases and 10–15% of ovarian cancer patients over the world. In the Turkish population, large deletion and duplication rates of *BRCA1/2* genes were found to be around 2% [21]. *BRCA1/2* mutation rates in the Turkish population were found to be 15.3% for breast and/or ovarian malignancies and 22.6% for ovarian cancer, according to the study. In comparison to mutation rates in the overall population, Turkey has a high mutation frequency.

The general mutation rate in our patient group selected from high-risk individuals is greater than the rest of the globe as a consequence of *BRCA1/2* gene mutation testing performed in 2,373 breast and/or ovarian cancer cases. Furthermore, patients with TNBC and male breast cancer patients had greater frequencies of *BRCA1/2* mutations than the general population. All of our analysis results were found to be statistically significant ($p<0.05$) when our *BRCA1/2* mutation data from the Turkish population was assessed in accordance with the NCCN *BRCA1/2* genetic test selection criteria. When the relevance of genetic counseling and *BRCA1/2* genetic testing is widely recognized around the world, and data from bigger populations is collected, it is projected that overall mutation rates would rise dramatically. Furthermore, providing genetic counseling services to

patients with a known *BRCA1/2* mutation in their family and providing risk-reduction techniques to those with genetic testing who were at high risk of illness formation lowered the chance of disease formation. All of these findings demonstrate the need of genetic counseling and *BRCA1/2* gene testing in cancer treatment. Genetic counseling is an advantageous stage in cancer prevention for many people, both now and in future generations, as well as determining treatment options for the patient. With the selection of genetically high-risk individuals and the recommendation of risk-reducing techniques through genetic counseling, it is envisaged that the incidence of cancer in the community will be reduced in each new generation. As part of this endeavor, we at Istanbul University, Oncology Institute, Department of Cancer Genetics will continue to raise awareness of genetic counseling in cancer and reach out to a wider audience.

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