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Germline mutations of *BRCA1* and *BRCA2* genes in Turkish breast, ovarian, and prostate cancer patients

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Abstract Distribution and prevalence of germline mutations in *BRCA1* and *BRCA2* differ among different populations. For the Turkish population, several studies have addressed high-risk breast cancer and ovarian cancer (BC–OC) patients. In most studies, both genes were analyzed in part, and a quite heterogeneous mutation spectrum was observed. For high-risk Turkish prostate cancer (PCa) patients, however, there are no data available about mutations of germline *BRCA* genes. To accurately determine the contribution of germline mutations in *BRCA1* and *BRCA2* in Turkish BC, OC, and PCa high-risk patients, 106 high-risk BC–OC patients, 50 high-risk PCa patients, and 50 control subjects were recruited. The study represents the only full screening, to date, of a large series of Turkish high-risk BC–OC patients and the only study in Turkish high-risk PCa patients. Mutation screenings were performed on coding exons of both genes with either denaturing gradient gel electrophoresis or denaturing high performance liquid chromatography, or with both techniques. Three deleterious mutations in *BRCA1* and three deleterious mutations in *BRCA2* were detected in different BC–OC patients, and one truncating mutation was detected in a high-risk PCa patient. In addition, 28 different unclassified and mostly novel variants were detected in both genes, as well as several silent polymorphisms. These findings reflect the genetic heterogeneity of the Turkish population and are relevant to genetic counseling and clinical management.

1. Introduction

The *BRCA1* and *BRCA2* genes have been of great interest for cancer predisposition since their discovery in the early 1990s [1,2]. The *BRCA1* locus at chromosome 17q21 was first identified as an early-onset BC susceptibility gene [1]. Later, the germline mutations in the gene were confirmed to be linked with both BC and OC in families [3]. Furthermore, observations and haplotype analysis early led to the proposal that BC genes might predispose to prostate cancer (PCa) in male carriers and an increased risk for PCa and colon cancer were determined in *BRCA1* mutation carriers in addition to increased BC and OCs [4,5]. In *BRCA1* mutation carriers, by age 70, female BC risk, OC risk, and second primary BC risk were identified as 72.8%, 40.7%, and 40.5%, respectively [6]. In a recent study in which 1,188 female *BRCA1* mutation carriers were recruited, the cumulative incidence by age 70 was 71.4% for BC and 58.9% for OC. In a study of *BRCA2* mutation carriers, cumulative incidence by age 70 was 87.5% for BC and 34.5% for OC [7]. *BRCA2* mutations have been associated with an increased risk of PCa, and some pathological features are linked to *BRCA*-associated PCa [8]. Threefold risk increase for PCa was reported for *BRCA2* mutation carriers, and tumors were less differentiated; moreover, *BRCA1* and *BRCA2* mutation carriers were found to have higher risk of recurrence and death due to PCa [8].

Germline mutations have been extensively studied for high-risk individuals, and large numbers of mutations are described in both genes. According to the Breast Cancer

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Information Core (BIC) database (http://research.nhgri.nih.gov/bic/), there are >1,600 clinically important distinct mutation entry for the *BRCA1* and *BRCA2* genes [9]. Different techniques are applied to detect mutations. Most of the mutations detected techniques based on polymerase chain reaction (PCR) encompass only one or a few nucleotides; however, at least 81 *BRCA1* and 17 *BRCA2* large genomic rearrangements have been reported (for a review, see ref. [10].) Although there are many founder mutations associated with certain populations, the vast majority of mutations are reported only once and are family specific [9].

In previous studies, at least 385 Turkish high-risk BC–OC patients have been reported to be screened for germline *BRCA1* and *BRCA2* mutations. Different patient selection criteria and different mutation screening strategies were applied, and no predominant mutation was detected in this group (Table l) [11–17].

In a study of Turkish high-risk BC–OC families that included mutation screening in 15 families, three germline mutations were identified by using screening conformation-sensitive gel electrophoresis and protein truncation test techniques [11]. From a study of 50 high-risk BC–OC patients, using heteroduplex analyses to screen for mutations, Özdağ et al. [12] identified three frameshift mutations and four missense mutations, in addition to silent polymorphisms. In two consecutive studies notable for the number of cases included, Yazici et al. [13,14] reported on 105 BC, OC, or BC+OC patients; of the 102 OC patients screened using protein truncation test and heteroduplex analyses, 27 were found to have frameshift mutation and 1 patient was found to have a missense mutation. Our own research group had earlier identified three truncating mutations and three missense mutations as a result of screening 53 high-risk BC–OC patients using protein truncation test and denaturing gradient gel electrophoresis [15]. In another study, one truncating mutation was found in 1 family out of 22 high-risk BC–OC families studied by polyacrylamide gel electrophoresis (PAGE) [16]. In a study of 87 women from 38 BC, OC, or BC+OC families, using heteroduplex analyses, four families were found to carry frameshift mutations; in addition, two missense mutations and an intronic substitution were also reported in several families [17].

Although high-risk BC–OC patients have been extensively studied, to our knowledge no previous report has addressed the contribution of *BRCA* genes to PCa in a Turkish population. Here, we present our data on germline mutation screening for the *BRCA1* and *BRCA2* genes in Turkish high-risk BC, OC, and PCa patients.

2. Patients and methods

The BC–OC families were recruited from Akdeniz University Hospital (Surgery and Obstetrics and Gynecology) and from Gazi University Hospital (Internal Medicine). The PCa cases and healthy controls were recruited from Akdeniz University Hospital (Urology) and from Gulhane Military Medical Academy (Medical Biology).

This study was approved by the Akdeniz University Ethics committee; information was given to all patients, and all patients signed informed consent.

2.1. Patient selection

A total of 206 individuals were included in the study, divided into seven patient groups, with one control group, as follows.

(1) The familial BC–OC patients group comprised 27 BC and 5 OC patients; 21 patients had one first- or second-degree relative diagnosed with BC or OC cancer, 5 patients had two first- or second-degree relatives affected, and only 6 patients had four or more first- or second-degree relatives affected. Age at diagnosis ranged from 23 to 59 years (mean, 47.0 years).
(2) The bilateral BC group comprised 10 patients, of whom 4 had family history of BC or OC; the remaining 6 patients had no relevant family history. Age at diagnosis ranged from 29 to 75 years (mean, 54.0 years).
(3) The BC+OC group comprised three patients, none of whom had any family history of cancer among first- or second-degree relatives. Age at diagnosis ranged from 44 to 58 years (mean, 51.5 years).
(4) The male BC group comprised three men, diagnosed at age 51, 65, and 75 years. One of the men had two second-degree female relatives diagnosed with BC; the other two had no family history of cancer.
(5) The early-onset BC–OC group comprised 53 BC and 5 OC patients who were diagnosed with the disease at or before the age of 40. The earliest diagnosis in this group was at age 20 years (mean, 35.3 years).
(6) The early-onset PCa group comprised 32 PCa patients. Age at diagnosis ranged from 42 to 55 years (mean, 51.9 years).
(7) The group of PCa patients with relevant family history comprised 18 patients. Three patients had three additional cases of BC, OC, or PCa among first- or second-degree relatives, and three patients had two additional cases among close relatives; the remaining 12 patients had only one first- or second-degree relative affected with BC, OC, or PCa. Age at diagnosis ranged from 47 to 75 years (mean, 50.1 years).

The healthy control group comprised 50 healthy individuals, age 34 –58 years (mean, 46.4 years).

2.2. DNA isolation, mutation screening, and characterization

DNA isolation from peripheral leukocytes was performed by a standard salting-out method [18]. All coding regions and exon–intron boundaries of both *BRCA1* and