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**Mini Review**

## Genetic Counseling in BRCA1 And BRCA2 Genes Mutation Carriers

**Neslihan Duzkale\****Department of Medical Genetic, Diskapi Yildirim Beyazit Training and Research Hospital, Turkey***Keywords:** BRCA1; BRCA2; Heredity; Breast cancer; Genetic counseling**Introduction****Breast cancer overview**

Breast cancer is the most common malignancy in female sex worldwide and is alone responsible for approximately 20% of all female cancers [1]. According to the World Health Organization report, this cancer affects 2.1 million women every year, ranks first among women in deaths caused by cancer, and breast cancer rates are rising all over the world [2]. Several risk factors have been identified that play a role in the development of this cancer round. The best known of these; that the incidence of breast cancer increases with age and doubles every decade in the period up to menopause. Risk of breast cancer increases in such cases that early age in menarche, late age in menopause, nulliparity or late age at birth. Oral contraceptive use and hormone replacement therapy may cause a slight increase in the relative risk of developing breast cancer. Also, women with benign breast disease, such as atypical epithelial hyperplasia, have a nine-fold increase in risk. Factors affecting breast cancer risk include ionizing radiation and geographic variations. Diet, weight, alcohol intake and smoking are factors that play an important role in this round of cancer [1].

**Breast cancer genetic**

The most important factor that increases the risk of developing breast cancer is the undisputed family history and approximately 20-25% of these patients have this. Not all patients with a family history may have a gene mutation that explains this condition. Because; the majority of all breast cancers are sporadic and only 5-10% of patients have a gene variant that is inherited and related to the disease [3]. To date, many genes have been identified that are known to play a role in the development of breast cancer. In breast cancer, one group of these genes is high-penetrance (BRCA1, BRCA2, PTEN, TP53, CDH1, STK11), while another group of genes is moderate-penetrance (CHEK2, BRIP1, ATM, PALB2). These genes can lead to a malignant and non-malignant typical clinical picture [4].

**BRCA1 and BRCA2 genes**

BRCA1 and BRCA2 genes responsible for approximately 15-40% of hereditary breast cancers. BRCA1 and BRCA2 are tumor suppressor genes located in 17q21.31 and 13q13.1 chromosomal regions, respectively. These genes play an important role in maintaining genomic integrity in the cell. While homologous recombination takes place during the cell cycle, proteins that this genes product are functions in the repair of damage occurring in double chain DNA. These genes are inherited in an autosomal dominant manner to subsequent generations and are responsible

**Table 1:** The ratio of increased risk of malignancy in individuals with BRCA1 and BRCA2 genes in HBOC

CANCER TYPE		BREAST	SECOND PRIMARY BREAST	OVARIAN	MALE BREAST	PROSTATE	PANCREATIC	MELANOMA
GENERAL POPULATION RISK		12%	2% within % 5 years	1%-2%	0,1%	6% through age 69	0,5%	1,6%
RISK FOR MALIGNANCY	BRCA1	46%-87%	21% within 10 years	39%-63%	1,2%	8,6% by age 65	1%-3%	-
	BRCA2	38%-84%	10% within 10 years, 62% by age 70	16%-27%	Up to 8,9%	15% by age 65, 20% lifetime	2%-7%	Elevated Risk

for hereditary breast and ovarian cancer syndrome associated with BRCA1 and BRCA2 (HBOC) [5]. The overall population prevalence of disease-causing variants of the BRCA1 / 2 genes is estimated to be approximately 1:500, while this ratio increases to 1:40 in the Ashkenazi Jewish population [6]. The rates of pathogenic variants of these two genes in HBOC; while it is 66% for BRCA1, it is 34% for BRCA2 [7].

### BRCA1 and BRCA2 associated with HBOC syndrome

HBOC; It is a syndrome characterized by an increased risk that breast and ovarian cancer in women (including primary peritoneal and fallopian tube malignancies) and breast and prostate cancer in the male gender. Also, there is an increased risk of pancreas cancer and malignant melanoma in both genders in this syndrome. Although the risk of cancers developing especially in the breast and ovarian organs is high; the risk of prostate, pancreas, and melanoma increased slightly compared to the risk of society. The organs where each of the BRCA1 and BRCA2 genes responsible for this syndrome increases the risk of malignancy and the comparison of risk increase rates with general population risks are presented in Table 1 [7].

### Genetic diagnosis in HBOC

To establish the diagnosis of HBOC, the germline disease-causing variants of the BRCA1 and BRCA2 genes in the carrier individual should be identified by molecular genetic tests. Some criteria defined in the NCCN guide are used in the selection of individuals to whom these tests will be performed [8]:

- All cases with ovarian cancer independent of diagnosis age
- Women diagnosed with breast cancer before 50 years of age
- Histopathologically triple-negative (estrogen, progesterone receptor and HER2 / neu parameters negative) women diagnosed with breast cancer especially before 60 years of age
- Multiple primary breast cancer foci in the same and/or contralateral breast
- Diagnosis of breast cancer in the male gender
- All breast cancer cases of the Ashkenazi Jewish race

- Observing some cancers with increased risk in HBOC in the same individual
- Having two or more relative with breast cancer (one of them must be under 50)
- Having 3 or more relatives with breast cancer independent of the age of diagnosis
- In the presence of disease-causing variants of BRCA1 and BRCA2 previously detected in relatives

In individuals who meet these criteria, the investigation of BRCA1 / 2 genes by molecular genetic methods and detection of possible pathogenic gene variants enables the diagnosis of HBOC. These molecular genetic tests are BRCA sequence analysis and BRCA-targeted deletion/duplication analysis, and the detection rate of BRCA gene mutations with these two techniques > 80% and ~ 10% respectively.

### Genetic counseling in HBOC

Appropriate genetic counseling should be given to those who receive this diagnosis. This counseling will be effective in informing individuals with increasing malignancy risks in HBOC, making important decisions regarding the management of the disease. These people should be informed about the option of 'bilateral mastectomy and oophorectomy' prophylactically due to an increased risk of developing cancer. Some patients do not prefer prophylactic surgery. In this case, it is recommended that the individual be included in regular and strict screening and follow-up programs. Women diagnosed with this syndrome are required to learn their own breast examination and do it regularly every month. It is recommended that these persons, from the age of 25, every year or every 6 months, undergo breast examinations by the clinician and also to be checked with annual mammography and breast MRI imaging methods.

In the literature, it has been claimed that the use of tamoxifen in healthy women with BRCA2 germline variant carriers may decrease the risk of breast cancer [9]. However, the use of tamoxifen therapy in healthy individuals is still controversial, as it prepares the ground for thromboembolism and causes an increased risk of endometrial cancer.

For ovarian cancer screening; although it is not very effective in detecting early-stage ovarian cancer, annual transvaginal ultrasonography scanning and monitoring of CA-125 levels starting from 35 years of age are required.

There is also an increased risk of breast cancer risk in male carriers, and these people should be given the necessary training every month to conduct breast examinations on their own, and the annual breast examinations by a clinician should be initiated from the age of 35. Men with the BRCA mutation carrier should be enrolled in the prostate cancer screening program from 45 years of age.

Due to family history, some individuals may need to be included in the melanoma screening program. It is recommended to carry out a screening analysis to determine the carrying status of these patients' relatives. In order to perform these predictive tests, the applicant must be over 18 years of age and give consent to the test. BRCA1 and BRCA2 genes are inherited as autosomal dominant, and the carriers have a 50% risk of transmitting these gene variants to subsequent generations. These gene mutations are known to be transferred from a parent to a large portion of carriers. malignancy may not be observed in carrier parents. This situation is explained by reasons such as; incomplete penetration, variable age in cancer development, preference for prophylactic surgery before the individual's cancer development, and a history of premature death.

## Results

Genetic counseling of individuals diagnosed with BRCA1/2 associated HBOC; it is important not only for the determination of the treatment approaches to be received and for the notification of the measures to be taken, but also the determination of other relatives who are the carrier.

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