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Article

The Relationship *BRCA1/2* Genes and Family History in Ovarian Cancers

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Abstract: *BRCA1/2* genes are responsible for the hereditary breast and ovarian cancer syndrome. In this study, Turkish women with ovarian cancer were investigated in terms of demographic, clinicopathologic and family cancer stories according to their condition of the *BRCA1/2* genes mutation carrier. During 2011 to 2017 in Turkey, *BRCA1* and *BRCA2* genes were analyzed in 38 women, who were diagnosed with cancer using Next Generation Sequencing technique. Pathogenic mutations were detected in 9 (23.7%) of patients. The diagnosis age for Ovarian cancer patients for *BRCA1/2* mutation carriers was found higher. It was seen that mutations mostly occurred in the *BRCA2* gene and frameshift mechanism and they were located in exon10 in the *BRCA1* gene and especially in exon11 in the *BRCA2* gene. According to the applied logistic regression model, it was found that patients with more than two relatives having cancer would have a 12.844 fold and high risk of being a *BRCA1/2* mutation carrier. In women with ovarian cancer, *BRCA1/2* gene mutations are observed more frequently in certain exons of these genes. *BRCA1* mutation carriers are diagnosed with ovarian cancer earlier than *BRCA2* mutation carriers. In hereditary ovarian cancers, besides *BRCA1/2*, many identified genes and many modifier candidate genes that are waiting to be discovered can cause this condition. In the family history, the numerical increase of cancerous relatives significantly increases the risk of *BRCA1/2* carrying mutation.

Keywords: *BRCA1/2*; gene; mutation; ovarian cancer; family history

1 Introduction

Ovarian cancer is the most frequent type of cancer observed in gynecological cancers among cervical and uterine cancers. Ovarian cancer is the fifth in renk and most prominent cause of gynecological death in women [1]. Until now, many factors associated with the risk of ovarian cancer have been described. Among these factors that can increase the risk of cancer are patient age, menstrual factors, endometriosis, previously diagnosed breast cancer, family history of cancer, gene mutations, low socioeconomic level. However, there are some factors causing to a decrease in ovarian cancer risk, such as parity, elderly age childbirth, contraceptive methods, breastfeeding. Besides this, there are still some factors that have been discussed about the increasing risk of ovarian cancer. Those factors are menarche and menopause age, pregnancy characteristics, pelvic inflammatory disease, hormone replacement therapy, infertility treatments, nutrition and diet, obesity and physical activity, alcohol, caffeine, and smoking [2]. This disease is generally asymptomatic so the cancer continues to grow insidiously. This disease is diagnosed up to 68% of patients at advanced stage. For these reasons, this type cancer has a poor prognosis and a high mortality rate [3]. The majority of the diagnosed ovarian cancers patient are epithelial type and approximately 70% of this group has high-grade serous ovarian cancer with histopathological type [4].

Although ovarian cancers are mostly sporadic; studies have shown that the germline mutations of *BRCA1/2* genes are responsible for (13–18%) of all ovarian cancer cases [5]. *BRCA1/2* genes are involved in

the formation of proteins included in tumor suppressor activation, which provides control in cell division and growth. These proteins provided for the repair of DNA fractures that may occur during physiological processes of the cells and the genomic integrity of the cell. There are variants of these genes, which are responsible for autosomal dominant disease characterized (HBOC) [6]. HBOC is an autosomal dominant disease characterized seen in individuals affected by this syndrome have an increased level of risk in the development of certain cancer types. Hereditary cancer syndromes patients mostly HOBC is observed. The risk of ovarian cancer in women has increased significantly compared to the general population risk in this syndrome. The patitents carry *BRCA1* mutation genes, the cumulative risk for ovarian cancer is up to 80 years old and 49%, while this rate is around 21% in *BRCA2* mutation carriers genes [2].

In this study, we investigated the demographic and clinical characteristics and the pathological details of their ovarian cancer (tumors) and family histories in association with *BRCA1/2* of 38 ovarian cancer women in Turkey.

2 Subjects and Methods

2.1 Data of Patients

Ovarian cancer in 38 female patients were investigated with *BRCA1/2* genes between 2011 and 2017 from Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital, Department of Medical Genetic in order to elucidate the genetic etiology for their diseases. All patients who participated in the study were in accordance with the National Comprehensive Cancer Network (NCCN) guidelines for *BRCA1/2* test standards [7]. Details about the demographic and clinical characteristics of the patients, their family history, and tumor characteristics were obtained from the patients themselves, medical records and hospital electronic data system. The family history was evaluated by examining the pedigree analyzes of at least 3 generations of patients. All patients agreed for performing genetic testing and use of their own information in this study. The present study involved human participants so, it was conducted considering ethical responsibilities according to the World Medical Association and the Declaration of Helsinki. The independent Ethics Committee of the Dr. Abdurrahman Yurtaslan Ankara Oncology Training and Research Hospital approved this descriptive case series study (Document No. 2020-02/536).

2.2 Detection Method

DNA obtained from the peripheral venous blood samples of the patients was analyzed with the next-generation sequencing method to examine the *BRCA1/2* genes. This analysis was carried out on the "Ion S5 ™ System (Ion Torrent ™)" platform using the "Oncomine ™ *BRCA* Research Assay" kit. In the analysis, all the coding regions of these genes and the part containing the 25 base pairs of exon-intron junctions were investigated. The sequence data obtained as a result of the study were compared to the "human genome of hg19" using the "Ion Reporter Software Version 5.4 (Thermo Fisher Scientific)" bioinformatics analysis program. The sequence variants obtained were classified using algorithms in the "American College of Medical Genetics and Genomics" guidelines [8]. For *BRCA1/2* genes analysis, the accession numbers of these genes were accepted as NM_007294.3(*BRCA1*) and NM_000059.3 (*BRCA2*), respectively.

2.3 Statistical Analysis

SPSS (IBM SPSS Statistics 24) program was used in the statistical evaluation of all results obtained. Sample Independent Sample-*t*" test (*t-table* value) and Mann-Whitney U" test (*Z-table* value) statistics were used to compare the measurement values of two independent variables. "χ^2-cross tables" were used in the study of the relations of the two qualitative variables. Also a binary logistic regression was performed. When the *p*-value used for the level of statistical significance was "0.05 or less", which was accepted as a meaningful result.

3 Results

The demographic and clinicopathological characteristics of 38 patients are given in Tab. 1.

Table 1: Demographic and clinicopathologic characteristics of OC patients

Characteristic (N = 38)	n	%
Age		
≤40	5	13,2
>40	33	86,8
Age at diagnosis		
≤40	9	23,7
>40	29	76,3
BRCA1/2 Carrier Status		
Non carrier	29	76,3
Carrier	9	23,7
Other Primer Cancer		
No	31	81,6
Yes	7	18,4
Age of Other Primer Cancer (years)		
≥40	7	100,0
The first symptome of OC		
Abdominal pain	7	18,3
Abdominal swelling	15	39,5
Bloody vaginal secretion	3	7,9
Painful mass in the abdomen	1	2,6
Irregular menstrual period	2	5,3
Routine control	8	21,1
Inguinal pain	2	5,3
Level of education		
Primary and secondary school	26	68,4
High school	5	13,2
University	7	18,4
Working Status		
Yes	8	21,1
No	30	78,9
Smoking		
No	30	78,9
Yes	8	21,1
Oral contraceptive use		
No	31	81,6
Yes	7	18,4
Allergy		
No	33	86,8
Yes	5	13,2
Chronic Disease		
No	21	55,3
Yes	17	44,7
Surgery History		
No	20	52,6
Yes	18	47,4
Menarche Age (years)		
<12	10	26,3
12–14	26	68,4
≥14 yaş	2	5,3

Characteristic (N = 38)	n	%
At diagnosis laterality of OC		
Right	13	34,2
Left	13	34,2
Bilateral	12	31,6
Histopathological diagnosis		
Serous	31	81,6
Sexcord	2	5,3
Endometrioid	1	2,6
Clearcell	2	5,3
Undifferentiated	1	2,6
Carsinosarcom	1	2,6
Metastasis at diagnosis		
No	16	42,1
Yes	22	57,9
Marital Status		
Single	2	5,3
Married	33	86,8
Widow	3	7,9
Number of children		
No children	6	15,7
<3	17	44,7
≥3	15	39,6
The number of relatives with cancer		
No	19	50,0
1	12	31,6
≥2	7	18,4
HBOC associated cancer type		
Breast	14	66,7
Ovarian	3	14,3
Prostate	3	14,3
Pancreas	1	4,8
Menstrual Periods		
Irregular	4	10,5
Regular	34	89,5
Age at first labor (years)		
Nulliparity	6	15,8
<20	7	18,4
≥20	25	65,8
BMI		
Weak	3	7,9
Normal	15	39,4
Overweight	12	31,6
Obese	8	21,1
Breast feding duration		
No	6	15,8
<1 year	10	26,3
≥1 year	22	57,9

In assessment of smoking status, women who had smoked at least 10 cigarettes a day for at least 10 years or more were included in the positive group. Chronic diseases were recognized as conditions requiring periodic monitoring and supportive care for hypertension, diabetes mellitus, goiter, etc. Surgical history of groups were included, such as appendectomy, cholecystectomy, hemorrhoidectomy, etc. In the evaluation of cancer history in relatives, HBOC associated cancers diagnosed in many organs such as breast, ovary, prostate, and pancreas was included. When calculating BMI (kg/m^2), 18.5 to 24.9 were healthy, 25.0–29,9 were considered as overweight and 30 and over were mentioned as obese. Patients carrying *BRCA1/2* pathogenic variants and not carry them were grouped separately for statistical comparison. No statistically significant relationship was found between these groups in the aspect of such as age, age of diagnosis, presence of secondary primary cancer, age of first menstrual, metastasis status at the time of diagnosis. The present age and ovarian cancer diagnosis age of these patients with pathogenic *BRCA1/2* variant carriers in these two groups were statistically significantly higher than the group in Tab. 2.

Table 2: Comparison of age parameters in groups according to *BRCA1/2* carrying status

Variable	***BRCA1/2* non-carriers (n = 29)**		***BRCA1/2* carriers (n = 9)**		**Statistical analysis***
	$\bar{X} \pm S.S.$	**Median [Min–Max]**	$\bar{X} \pm S.S.$	**Median [Min–Max]**	**Probability**
Age (years)	50,28 ± 10,80	52,0 [27,0–65,0]	59,11 ± 11,14	60,0 [46,0–76,0]	t = –2,129 **p = 0,040**
Age at diagnosis	46,24 ± 11,14	46,0 [18,0–64,0]	55,44 ± 13,47	48,0 [40,0–76,0]	t = –2,062 **p = 0,046**

*"Independent Sample-*t*" test (*T-table* value) statistics were used to compare the measurement values of two independent variables in the normal distribution data.

The mean age of 38 patients with ovarian cancer was 52.37 ± 11.38 (years) and the average age of diagnosis of patients was 48.42 ± 12.20 (years). Patients mostly applied to the doctor for complaining of swelling in the abdominal region and were subsequently diagnosed with ovarian cancer (39.5%). The majority of patients were over 40 years old (76.3%) and 7 patients (18.4%) had another primer cancer. Six patients with second primary cancer seen as breast cancer, one had renal cell cancer. Pathogenic mutation in the *BRCA2* gene was detected in 3 of these patients diagnosed with breast cancer and one of the patient was bilateral breast cancer.

As a result of *BRCA1/2* gene analysis, among 9 (23.7%) out of 38 patients had a pathogenic variant causing disease. Eight of nine (88.9%) of these pathogenic variants were detected in the *BRCA2* gene and 1 (11.1%) in the *BRCA1* gene. While 8 of these variants were obsebed frameshift, 1 of them produced a loss of function in the gene with the nonsense mechanism. Variants were mostly observed in 11th exonic region in the *BRCA2* gene. Two of the *BRCA2* pathogenic mutation carriers, carried the c.6634_6637delTGTT (p.Cys2212Leufs*16) variant of the frameshift showed no consanguinity between them. Serous carcinoma was one of the histological Ovarian cancer carrier type, while the other type carcinosarcoma was a rare tumor; it was also interesting that an ovarian tumor of this type was caused by an inherited gene mutation [9]. After the analysis, these 9 patients were diagnosed with HBOC associated with *BRCA1* and *BRCA2* and they were given genetic counseling (Tab. 3).

A statistically significant relationship was found between the disease status and the number of relatives with HBOC associated cancer between these two groups (χ^2 = 6,167; p = 0.046). It was determined that the number of relatives having cancer 2 or more patients, mostly in the *BRCA1*/2 mutation genes carrier group, other patients with 1 relatives having HBOC associated cancer to the other group givenin Tab. 4.

Table 3: *BRCA1* and *BRCA2* genes analysis results and details

Patient ID	Gene	Nucleotide Change/ AA Change	Exon/ Intron	Function	Acmg Scoring	AGE	Age at diagnosis of OC	OC Histotypes	Other Primer Cancer(S)/ Age at Diagnosis	Cancer History on Relatives	
P1	*BRCA2*	c.5722_5723delCT (p.Leu1908Argfs*2)	Exon 11	Frameshift	PAT	49	45	Epithelial (Serous)	-	1^0	1 Stomach, 1 Breast
										2^0	2 Leukemia, 1 Breast
										3^0	1 Colon, 1 Stomach
P8	*BRCA2*	c.7217_7218delTT (p.Phe2406Cysfs*5)	Exon 14	Frameshift	PAT	65	65	Epithelial (Serous)	-	1^0	1 Endometrium
										2^0	-
										3^0	-
P11	*BRCA2*	c.1773_1776delTTAT (p.Ile591Metfs*22)	Exon 10	Frameshift	PAT	60	46	Epithelial (Serous)	Bilateral Breast Cancer/ 50	1^0	-
										2^0	1 Breast
										3^0	3 Breast
P14	*BRCA2*	c.5969delA (p.Asp1990Valfs*14)	Exon 11	Frameshift	PAT	74	74	Epithelial (Serous)	Breast Cancer/ 51	1^0	1 Leukemia
										2^0	1 Endometrium
										3^0	-
P23	*BRCA2*	c.5791C>T (p.Gln1931*)	Exon 11	Nonsense	PAT	62	59	Epithelial (Serous)	Breast Cancer/ 45	1^0	1 Lung
										2^0	-
										3^0	2 Breast
P27	*BRCA2*	c.6468_6469delTC (p.Gln2157Ilefs*18)	Exon 11	Frameshift	PAT	49	48	Epithelial (Serous)	-	1^0	1 Lung, 1 Breast
										2^0	1 Colon
										3^0	1 Pancreas
P32	*BRCA2*	c.6634_6637delTGTT (p.Cys2212Leufs*16)	Exon 11	Frameshift	PAT	51	46	Epithelial (Serous)	-	1^0	1 Prostat, 1 Breast,1 Lymphoma
										2^0	-
										3^0	-
P35	*BRCA1*	c.2952delT (p.Ile986SerfsTer14)	Exon 10	Frameshift	PAT	46	40	Epithelial (Serous)	-	1^0	1 Lung
										2^0	1 Brain, 1 Breast
										3^0	1 Stomach
P38	*BRCA2*	c.6634_6637delTGTT (p.Cys2212Leufs*16)	Exon 11	Frameshift	PAT	76	76	Carcinosarcoma (Malignant mixed mesodermal tumor)	-	1^0	1 Prostate
										2^0	-
										3^0	1 Colon

Table 4: Relationship between *BRCA1/2* carrier status and the number of relatives with HBOC related cancer

Variable	***BRCA1/2* non-carriers (n = 29)**		***BRCA1/2* carriers (n = 9)**		**Statistical analysis***
	n	**%**	**n**	**%**	**Probability**
The number of relatives HBOC associated cancer					
None	17	58,6	2	22,2	
1	9	31,0	3	33,3	$\chi^2 = 6,167$
≥2	3	10,4	4	44,5	**p = 0,046**

*" χ^2-cross tables" were used to examine the relationships between the two qualitative variables.

A logistic regression model was applied according to the disease risk status. As a result of this analysis; in the current model, it was determined that there were important variables in terms of the number of relatives with HBOC-related cancer and *BRCA1/2* mutation carrier status ($p < 0.05$). Based on this model, those who have relatives with 2 or more HBOC-related cancers will have a 12.844-fold increased risk of having *BRCA1/2* mutation carriers compared to the other group (OR = 12.844; 95% CI = 1.289–128.026) (Tab. 5).

Table 5: Logistic Regression model based on *BRCA1/2* carrier risk status

Variable	B	S.H.	Wald	sd	p	OR	95% Confidence Interval (OR)*	
							Min	Max
The number of relatives with HBOC associated cancer								
None			4,737	2	0,094			
1	1,280	1,129	1,284	1	0,257	3,595	0,393	32,869
≥2	2,553	1,173	4,735	1	**0,030**	12,844	1,289	128,026
Constant	–7,438	3,386	4,826	1	0,028	0,001		
CCR = 76,3%					$\chi^2_{(8)} = 4,685$, p = 0,791			

* Binary logistic regression, Backward: LR model was used.

4 Discussion

Among all cancers ovarian cancer constitutes 3.7% for all female cancers and 4.2% causes of death in this gender [10]. Approximately 90% of all ovarian cancers are of epithelial origin. Of the remaining part, 5–6% of sex cord-stromal tumors and 2-3% of germ cell tumors are held responsible. Epithelial ovarian cancers occur in 5 histological types: high-grade serous (70%), endometrioid (10%), clear cell (10%), mucinous (3%), and low-grade serous (<5%) [11]. Serous ovarian tumors tend to be more bilateral compared to other malignant histological subtypes of the ovary [12]. In many epidemiological studies in the literature, it has been suggested that the increase in the number of labor, the use of oral contraceptives, and the increase in the duration of breastfeeding, created a protective effect from ovarian cancer due to suppression of ovulation [13]. In the literatures [14–16], contradictory results were obtained in studies investigating the relationship between first gestational age and ovarian cancer. The most of patients with this type of cancer are asymptomatic. The most common clinical presentation is chronic or acute onset abdominal pain. With the progression of cancer, the complaints of swelling in the abdomen, weight loss and fatigue become evident [17]. In addition, it has been reported that the effect of parameters such as family cancer history, tubal ligation, education, body mass index and current smoking on ovarian cancer risk may vary according to histological subtypes [18]. About 23% of this cancer type is known as hereditary until today, many genes have been identified for the cause. Approximately 65-85% of hereditary ovarian cancers occurs due to disease-related variants of *BRCA1/2* genes [19]. These genes are inherited as autosomal dominant disease characterized (HBOC), and *BRCA* proteins. These genes are involved in the maintenance of genomic stability by regulating homologous recombination and repairing DNA double chain fractures in this way. These proteins play an important role in transcriptional regulation of the cell cycle, chromatin remodeling and epigenetic regulation of gene expression [20]. *BRCA1/2* genes are responsible for causes of increasing the risk in some cancer types such as breast, ovarian, fallopian tube, peritoneal cancers, pancreas, prostate and melanoma [21].

The rate of *BRCA1/2* mutation carrier was found to be 23.6% in 38 ovarian cancer patients in our study. The mean age for 9 patients diagnosis were 48 and other 29 patients were 46 years old. Statistically comparison shows that 9 patients with BRCA*1/2* mutation carriers was statistically significant, with other 29 patients with *BRCA1/2* normal (t = –2.062; p = 0.046). *BRCA2* gene mutation carriers (8/38, 21%) were more numerous than *BRCA1* mutation carriers (1/38, 2.6%).

Literatures studies have shown that the *BRCA1/2* mutation rate of patients with ovarian cancer has range from 5% to 29% [21]. Although different results can be seen in different populations, studies of comparing hereditary and sporadic ovarian cancer cases may be diagnosed earlier than expected in those area or among populations [22]. The studies of sporadic and hereditary ovarian cancer in America and Europe seen that the diagnosis starts early as 5–10 years compare to others and the *BRCA1* mutation carrier was an important part of this. Studies showed that mutations in the *BRCA1* gene were observed more frequently compared to *BRCA2* hence, ovarian cancer is diagnosed earlier age [23,24]. Study from Japan, women with ovarian cancer did not show significant difference compared to their age of diagnosis according to the *BRCA1/2* mutation carrier status. It was determined that *BRCA2* mutation carriers tended to develop ovarian cancer in a more elderly age compared to *BRCA1* [25]. In a multicenter cohort study conducted by Shi et al. with 1000 ovarian cancer patients, found that the *BRCA* gene mutation carriage rate was 16.7% and mostly found out the *BRCA1* gene. Study shows that the mean age of the patients did not differ significantly between mutation carriers (53.7 years old) and those who did not carry (54.3 years old). *BRCA1* mutation carriers were diagnosed earlier than BRCA2 mutation carriers [26].

In our study, the mean age of 8 patients with *BRCA2* mutation carriers was 57.37 years old and a patient with *BRCA1* mutation carriers was 40 years old. Earlier studies conducted in Turkey to investigate *BRCA1* and *BRCA2* genes in breast and/or ovarian cancer patients shows different results. Study conducted by Egeli et al. [27] with 87 Turkish female patients were with breast and/or ovarian cancer diagnosis, 3 of the patients were detected with *BRCA1*and 2 with *BRCA2* and the average diagnosis age was 44.6 of the group.

Yazici et al.'s study found out that mean age was 49.3 among *BRCA1/2* carriers and 53.2 for non-carriers. Their study had more women with ovarian cancer [28]. In another study of Yazici et al., among young women with breast and or ovarian cancer diagnosed with *BRCA1/2* gene mutation was earlier compare to non-carriers [29]. Similar to this study, in our patient group, the mean diagnosis of ovarian cancer was significantly higher in patients with normal *BRCA* than *BRCA* mutation carriers. The patients in the group with detected *BRCA1/2* mutation were diagnosed over 40 years old, but those who did not carry the *BRCA1/2* mutation gene, ovarian cancer patients were diagnosed at young age.

The statistically significant situation can not be explained clearly due to limited no of patients studied to investigate cancer-related genes other than *BRCA1/2* genes. Apart from *BRCA1/2*, there are many genes that predispose to ovarian cancers. The best known of these are; the mismatch repair (MMR) genes responsible for Lynch syndrome, tumor suppressor *TP53* gene which is responsible for Li-Fraumeni syndrome double chain breaks. Also, genes associated with some histopathological ovarian cancer types and prognosis have been identified, such as *PTEN, KRAS, BRAF, PIK3CA, ERBB2, CTNNB1*and *CHEK2, RAD51C, RAD51D, BRIP1,* and *PALB2* genes which play a role in the repair of DNA*, ARID1A, PPP2R1A* [19]. Apart from these, it is also known that many putative modifier genes are specific to different populations. In our study group; since these susceptibility genes, other than *BRCA1/2*, were not studied, it was not possible to illuminate the genetic background that could be responsible for the disease.

Eight of nine mutations (88.9%) detected in our patients were detected in the *BRCA2* gene and 1 of the mutations (11.1%) was *BRCA1* gene. While 8 of these variants were frameshift, 1 of them produced a loss of function in the gene with the unrelated mechanism. Studies in the literature have revealed that mutation types and localizations in *BRCA1* and *BRCA2* genes may lead to variability in the genotype-phenotype correlation of the disease. Exon10 in the *BRCA1* gene and exon11 in the *BRCA2* gene are defined as hot spot regions in the literature [30]. In hereditary breast and ovarian cancer cases, it has been shown that mutations located in the central region of both genes, especially in exon 11as a result it increase the risk of ovarian cancer and decrease the risk of breast cancer [31]. *BRCA2* in exon 11 region mutations have been associated with a higher risk of breast and ovarian cancer compared to other regions of the BRCA1 gene [32]. It has been reported that the risk of ovarian cancer caused by mutations in the sections of the *BRCA1* gene between exon 1–11, is 20% higher compared to the mutations in the sections after exon 11 [33]. In our study, the single mutation with *BRCA1* gene was detected in exon 10, and the

mutations in the *BRCA2* gene were found at exon 11 (75%, 6/8), and these results were found to be compatible with the literature.

All patients in our study were grouped as *BRCA1/2* mutation carriers and non-carriers, and a comparative study of relatives with HBOC-related cancers (breast, ovarian, prostate, pancreas, etc) was performed. A logistic regression analysis was performed to determined the relatonship. There are significant variables in terms of disease development of relatives with cancer in the current model ($p < 0.05$). Those who have 2 or more relatives with cancer will have a 12.844-fold increasing risk of being *BRCA1/2* mutation carriers than those without cancer relatives (OR = 12,844; 95% CI = 1,289–128,026). Although the importance of the family cancer history of these individuals is already a known fact, the effect of the cancer relatives on the risk of cancer gene carriers increasing. If it could be quantitatively predicted would be better for the selection of the patients for gene analysis. We think that this risk assessment model obtained from the study will be useful in order to evaluate individuals, relatives with cancer and to direct them for gene analysis. Rational data from these and similar studies in large-scale patient groups in different populations can assist in elucidating the etiopathogenesis of this disease.

4.1 Study Limitations

This study has some methodological limitations. These are the case series is relatively small, segregation analysis could not be done to all cancerous individuals in pedigree analysis, environmental factors, and possible somatic mutations were not investigated. Also in this study, many identified genes and candidate genes that could predispose to ovarian cancer could not be investigated.

5 Conclusion

BRCA1 and *BRCA2*; are important tumor suppressor genes that are prone to hereditary ovarian cancers and are responsible for about 15% of all ovarian cancers. In our study, the germline mutation carrying a rate of *BRCA1/2* genes in Turkish ovarian cancer patients was found to be 23.6%. When the number of cancer relatives with HBOC associated with *BRCA1/2* was 2 or more, the risk of being a mutation carrier of these genes would increase to 12.844 times compared to others. Apart from the *BRCA1/2* genes, many genes that can predispose to ovarian cancer are known, and many candidate genes are waiting to be investigated. In future studies, large-scale research to determine for those genes in ovarian cancer will help to enable and illuminate the genetic background of this cancer by discovering new supposed modifying genes in our society.

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A Data Availability Statement: The data are available on special request.

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