

RESEARCH ARTICLE

BRCA1 and BRCA2 mutations in Turkish familial and non-familial ovarian cancer patients: a high incidence of mutations in non-familial cases

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Ovarian cancer is a clinically important cancer in Turkey. The contribution of BRCA1 and BRCA2 to ovarian cancer in Turkish patients has not previously been described. In this study we investigated the presence of BRCA1 and BRCA2 mutations in 102 consecutively ascertained, hospital-based, ovarian cancer cases. Four out of 15 (26.7%, 95% confidence interval (CI), 7.8%–55.1%) familial cases were found to carry mutations in BRCA1. Thirteen of the 87 (14.9%, 95% CI, 7.5%–22.4%) non-familial cases had BRCA1 and BRCA2 mutations, six in BRCA1, and seven in BRCA2. We have further studied the non-familial ovarian cancer cases to determine which subgroups have a likelihood of carrying clinically important mutations. Our study shows that those Turkish ovarian cancer patients with serous histopathology harbor a high proportion of mutations (12/58, 20.7%, 95% CI, 10.3%–31.1%) compared to all non-familial cases (14.9%) regardless of pathology. Within the serous sub-group, those that were also diagnosed below age 50 have an even greater percentage of mutations (8/28, 28.6%, 95% CI, 11.8%–45.3%). Our findings demonstrate that a substantial proportion of Turkish ovarian cancer patients, both with and without a family history, carry BRCA1 and BRCA2 mutations, demonstrating the importance of BRCA1 and BRCA2 in the development of ovarian cancer in this population. *Hum Mutat* 20: 28–34, 2002. © 2002 Wiley-Liss, Inc.

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DATA BASES:

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BRCA2 – OMIM: 600185; GDB: 387848; Genbank: U43746

www.nhgri.nih.gov/intramural_research/lab_transfer/bic/ (breast cancer information core (BIC) database)

INTRODUCTION

For individuals with ovarian cancer, the presence of additional breast and/or ovarian cancer family history is a strong indicator of the presence of a mutation in either of the cancer predisposition genes BRCA1 (MIM# 113705) or BRCA2 (MIM# 600185). However, studies utilizing distinct ethnic populations have demonstrated that some families with isolated cases of ovarian cancer may also harbor BRCA1 and BRCA2 gene mutations [Janezic et al., 1999; Modan et al.,

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1996; Beller et al., 1996; Moslehi et al., 2000; Tonin et al., 1999].

In addition to family history, other characteristics have been investigated to determine their roles in predicting the presence of predisposition mutations in ovarian cancer cases, with or without family history of cancer. These characteristics include age at diagnosis, histopathology, and grade of the tumor [Boyd et al., 2000; Moslehi et al., 2000; Rish et al., 2001].

Ovarian cancer is a clinically important cancer in Turkey. It is the second most common malignancy among woman, accounting for 7.07% of all cancers [Turkish Ministry of Health Statistics, 1994]. The incidence of ovarian cancer in 1994 was 1.88/100,000. Although two studies have investigated the presence of BRCA1 and BRCA2 gene mutations in the Turkish population of women with breast cancer [Yazici et al., 2000; Ozdag et al., 2000], the spectrum and frequency of these mutations in the Turkish ovarian cancer patients has not previously been described.

To investigate the contribution of BRCA1 and BRCA2 germline mutations to ovarian cancer in the Turkish population, we have studied a series of 102 consecutively ascertained, hospital-based, ovarian cancer cases unselected for age or family history of cancer. The types of BRCA1 and BRCA2 mutations and their correlation with the presence or absence of family history, as well as a number of individual tumor characteristics were investigated.

MATERIALS AND METHODS

Ovarian Cancer Cases

The 102 ovarian cancer patients unselected for age at diagnosis or family history of cancer have been recruited between 1995 and 1999. Patients were recruited from the Oncology Institute and the Departments of Gynecology and Surgery of the Istanbul University Medical Faculty. These two clinics are among those with the highest referral rate in Istanbul. Consecutive patients with ovarian cancer were approached for inclusion to this study. Approximately 60% of these individuals agreed to participate. Those who did not participate cited a suspicion of research in general and a concern over possible negative outcomes for themselves as major concerns. The extent of the non-participants' family history of cancer was not known. The detailed personal and family cancer history information was obtained by personal interview with the index cases. In some instances, additional family members supplied information where there was uncertainty as to relative's cancer diagnosis. Detailed family history of cancer was pursued on first and second-degree relatives only. Pathological confirmation of cancer diagnosis was obtained for the index cases but not their relatives.

The educational status of the patients who participated in the study varied from no education at all (21.1%) to elementary school (37.4%), high-school (21.7%), and university (19.3%). None of the index cases were related by blood. Eighty-seven of the 102 (85.3%) had no additional family history of breast or ovarian cancer in first or second-degree relatives (non-familial). The remaining 15 (14.7%) had a positive family history of breast or ovarian cancer in first- or second-degree relatives (familial). Blood samples were obtained

from all patients and genomic DNA and cellular RNA were obtained using conventional nucleic acid extraction methods.

Mutational Analysis

Genomic DNA from 102 ovarian cancer cases was initially analyzed for mutations in exon 11 of BRCA1 and exons 10 and 11 of BRCA2 using the Protein Truncation Test (PTT) as described previously [Ozcelik et al., 1996; Ozcelik et al., 1997; Hakansson et al., 1997]. These exons cover approximately 60% of each gene. Complete analysis of the entire coding regions of BRCA1 and BRCA2 was carried out using PTT analysis in 38 out of the 102 (37.3%) cases where sufficient RNA was available. Molecular analysis of all BRCA1 and BRCA2 coding regions was complete in seven out of 15 (46.7%) and 31 out of 87 (35.6%) of the familial and non-familial cases respectively. For the remainder of the cases approximately 60% of the coding regions were analyzed. All samples with positive PTT products were analyzed further by automated sequencing (ABI, Foster City, CA) and the exact nature of all sequence changes was identified.

Since the Ashkenazi Jewish mutation, 5382insC, has been identified previously in a group of Turkish breast cancer patients [Yazici et al., 2000], we also studied all three Ashkenazi Jewish mutations in the current study. All 102 cases were analyzed for the presence of 185delAG and 5382insC in BRCA1 and 6174delT in BRCA2, utilizing heteroduplex and PTT analysis, respectively [Yazici et al., 2000].

RESULTS

A total of 17 mutations were found among 102 patients (16.7%), including 10 in BRCA1 and seven in BRCA2 (Table 1). Out of 17 mutations, 15 were detected through PTT and two (5382insC) were detected by heteroduplex analysis. All but one of the 17 mutations are predicted to result in a frameshift in the protein sequence. Seven of 10 BRCA1 mutations were deletions (1815delA, 2073delA, 2137delA, 2476delT, 3870delTGTC(2), 5055delG), two were insertions (5382insC(2)), and one was a nonsense substitution (5563G>A). Four of seven BRCA2 mutations were deletions (3693delTT, 4391delT, 5950delCT, 6630delTAACT) and three were insertions (3976insA, 5295insA, 8643insA). Two out of 10 mutations in BRCA1 (1815delA, 2476delT) and five out of seven in BRCA2 (3693delTT, 3976insA, 4391delT, 5295insA, 8643insA) represent novel mutations (Table 1).

Of the 102 ovarian cancer cases in our study, 15 (14.7%) were categorized as familial due to the presence of at least one first- or second-degree relative with a breast and/or ovarian cancer. Six of the 15 familial cases have an additional first- or second-degree relative with ovarian cancer and no breast cancer (site-specific ovarian cancer families). The remaining nine had a first- or second-degree relative with breast cancer with or without additional ovarian cancer history (breast/ovarian cancer families). Four out of 15 (26.7%, 95% confidence interval (CI), 7.8%–55.1%) families were

TABLE 1. Carriers of BRCA1 and BRCA2 Mutations

Case	Age	Gene	Exon	Mutation	BIC	Fhx of cancer ^a	Phx of other cancers
BR 374	43	BRCA1	11	1815delA	No	No	None
BR 251	40	BRCA1	11	2073delA	Yes	No	None
BR 33	38	BRCA1	11	2137delA	Yes	No	None
BR 249	54	BRCA1	11	2476delT	No	Yes	None
BR 370	44	BRCA1	11	3870delTTGTC	Yes	No	None
BR 347	47	BRCA1	11	3870delTTGTC	Yes	Yes	None
BR 294	28	BRCA1	16	5055delG	Yes	Yes	Breast
OK 4	50	BRCA1	20	5382insC	Yes	No	None
OK 9	61	BRCA1	20	5382insC	Yes	No	None
BR 384	45	BRCA1	23	5563G>A	Yes	Yes	None
BR 234	55	BRCA2	11	3693delTT	No	No	None
BR 314	61	BRCA2	11	3976insA	No	No	None
BR 323	37	BRCA2	11	4391delT	No	No	None
BR 236	49	BRCA2	11	5295insA	No	No	None
OK 13	44	BRCA2	11	5950delCT	Yes	No	None
BR 353	45	BRCA2	11	6630delTAACT	Yes	No	Breast
BR 277	68	BRCA2	19	8643insA	No	No	None

^a Family history with first or second degree relative with breast or ovarian cancers.

Novel mutations are presented in bold. BIC, breast cancer information core; Fhx, family history; Phx, personal history.

found to carry mutations in BRCA1 (Table 2). No BRCA2 mutations were identified in this familial group. Two mutations were found in site-specific ovarian cancer families and two were identified in breast/ovarian families. Three of the four carrier probands mentioned above had grade 2 or 3 serous adenocarcinomas of the ovary. The fourth, from a breast/ovarian cancer family, had a borderline endometrioid cystadenocarcinoma.

Non-familial cases were defined as ovarian cancer cases without a breast or ovarian cancer diagnosis in a first- or second-degree relative. Thirteen of the 87 (14.9%, 95% CI, 7.5%–22.4%) non-familial cases had mutations (six BRCA1, seven BRCA2) (Table 2). The distribution of pathological features among the non-familial ovarian cancer group is shown in Table 3. Serous adenocarcinoma was the most common histopathological sub-type in our study, comprising 58 out of 87 (66.7%) of all non-familial cases. Twelve mutations (five BRCA1, seven BRCA2) were identified out of the group of 58 (20.7%, 95% CI, 10.3%–31.1%) patients with a serous histopathological sub-type, whereas only one mutation was identified out of 29 (3.5%) patients with other pathologic subtypes (p -value=0.05, Fisher's exact test). One additional BRCA1 mutation (7.1%) was detected out of the 14 patients with an ovarian tumor displaying an endometrioid histopathological sub-type. No other

mutations were identified in any of the tumors with other histopathologies.

The mean age of diagnosis of all 58 cases in the non-familial, serous adenocarcinoma histopathology group was 52.4 years with an age range of 25 to 75. The mean age of diagnosis of the 12 BRCA1 and BRCA2 carriers was 49.3 years with a range of 35 to 68, whereas the mean age of the 49 non-carriers was 53.2 years with a range of 25 to 75. The average age for the five BRCA1 carriers was 46.4 with a range of 38 to 61 and was 51.3 years for the seven BRCA2 carriers with a range of 37 to 68.

Twenty-eight out of 58 non-familial serous cases were diagnosed below 50 years of age and 30 were diagnosed above 50 years of age (Table 4). Eight out of 28 (28.6%, 95% CI, 11.8%–45.3%) cases diagnosed before 50 years of age were found to carry BRCA1 and BRCA2 mutations. Four mutations in this group were found in BRCA1 and four in BRCA2. Four out of 30 (13.3%, 95% CI, 3.8%–30.7%) cases diagnosed above 50 years of age were found to carry BRCA1 and BRCA2 mutations. The difference in carrier proportion between those under 50 and those over was not significant, due to the small sample size. One mutation in this group was identified in BRCA1 and three in BRCA2. Four out of five (80%) BRCA1 carriers were found in women with an age of diagnosis below 50, while four out of seven (57.1%) BRCA2

TABLE 2. BRCA1 and BRCA2 Carriers in Familial and Non-familial Ovarian Cancer Cases

	Cases n	BRCA1 n (%)	BRCA2 n (%)	BRCA1 and BRCA2 n (%)	95% confidence intervals (%)
Familial	15	4 (26.7)	–	4 (26.7)	7.8–55.1
Non-familial	87	6 (6.9)	7 (8.1)	13 (14.9)	7.5–22.4
Total	102	10 (9.8)	7 (8.1)	17 (16.7)	9.4–23.9

TABLE 3. BRCA1 and BRCA2 Carriers and Histopathological Type in Non-familial Ovarian Cancer Cases

Histopathological type (adenocarcinoma)	Non-familial cases n	BRCA1 n (%)	BRCA2 n (%)	BRCA1 and BRCA2, n (%)
Serous	58	5 (8.6)	7 (12.1)	12 (20.7)
Endometrioid	14	1 (7.1)	-	1 (7.1)
Mucinous	2	-	-	-
Borderline	4	-	-	-
Other subtypes	9	-	-	-

carriers were found in women diagnosed below 50 years. The age distribution of all non-familial serous ovarian cases was: seven women between the ages of 21 and 40, 21 between 41 and 50, 12 between 51 and 60, and 18 between 61 and 80. There were three (two BRCA1, one BRCA2), five (two BRCA1, three BRCA2), one (BRCA2), and three (one BRCA1, two BRCA2) mutations detected in these age groups, respectively. Histopathological grade information was available on 49 out of 58 cases in the non-familial serous group: three (all BRCA2) out of five (60%) grade 1, five (three BRCA1, two BRCA2) out of 27 (18.5%) grade 2, and three (two BRCA1, one BRCA1) out of 17 (17.7%) grade 3 cases had mutations.

Table 5 demonstrates the number of BRCA1 and BRCA2 mutations in the familial group and the various subgroups of the non-familial ovarian cancer cases. The prevalence of BRCA1 and BRCA2 mutations in the entire non-familial cohort is 14.9% (95% CI, 7.5%–22.4%). This proportion increases to 20.7% (95% CI, 10.3%–31.1%) (five BRCA1, seven BRCA2) when we consider only the non-familial cases with serous histopathology. The BRCA1 and BRCA2 mutation prevalence is 28.6% (95% CI, 11.8%–45.3%) (four BRCA1, four BRCA2) when considering only the non-familial, serous histopathological subgroup diagnosed under 50 years of age.

DISCUSSION

This study involves the molecular analysis of BRCA1 and BRCA2 mutations in consecutively ascertained Turkish women with ovarian cancer, unselected for family history, and is the largest study series to date in the Turkish population. In 102 ovarian cases analyzed, we have identified a total of 17 (16.7%) truncating mutations, including 10 in BRCA1 and seven in BRCA2. We have studied the entire coding region of BRCA1 and BRCA2 in

approximately 37% of the cases in this study. However, due to specimen limitation, the rest of the cases were analyzed for approximately 60% of the coding region. If the distribution of mutations throughout the coding region of the gene is roughly uniform, then we would estimate that approximately 60 to 75% of protein truncation mutations were detected by this approach.

Two out of 10 BRCA1 and five out of seven BRCA2 mutations have not been previously identified in Breast Cancer Information Core (BIC) and represent novel mutations. Further analysis will indicate whether these mutations are specific to the Turkish population. Some of the known mutations detected in this study have been also reported in individuals of Dutch, Italian, Russian, Polish, German, and Ashkenazi Jewish ancestry. The presence of these mutations in other surrounding geographical locations may be due to ancestral genetic admixture of the population studied [Tadmouri et al., 1998]. We have identified 13 distinct mutations (six BRCA1, seven BRCA2) in this study. Two mutations (5382insC and 3870delTGTC) in BRCA1 were identified twice. Given the heterogeneous distribution of BRCA1 and BRCA2 mutations in this cohort there is no evidence of a strong founder effect.

It has been shown that families with a high proportion of ovarian cancers, relative to breast cancers, tended to have mutations located within a 3.3 kb region in exon 11 of BRCA2 [Gayther et al., 1997; Thompson et al., 2001]. This region bounded by nucleotides 3035 and 6629 has been termed the “ovarian cancer cluster region” (OCCR). In our study, six out of seven BRCA2 mutations fall in this region supporting the clustering of ovarian cancers within this region. However this observation can be biased since in 63% of the cases the mutational analysis was limited to exons 10 and 11 of BRCA2 bounded by nucleotides 1021–7070.

TABLE 4. Age Distribution of BRCA1 and BRCA2 Carriers With Non-familial Serous Adenocarcinoma

Age of diagnosis	Non-familial, serous cases	Non-carriers	BRCA1 n (%)	BRCA2 n (%)	BRCA1 and BRCA2 n (%)	95% confidence intervals (%)
Below age 50	28	20	4 (14.3)	4 (14.3)	8 (28.6)	11.8–45.3
50 and above	30	26	1 (3.3)	3 (10.0)	4 (13.3)	3.8–30.7

TABLE 5. Mutation Frequency in Non-familial Ovarian Cancer Cases Based on Serous Pathological Subtype and Age of Diagnosis Below 50

Sub-groups	Cases	BRCA1 n (%)	BRCA2 n (%)	BRCA1, and BRCA2 n (%)	95% confidence intervals (%)
Familial	15	4 (26.7)	–	4 (26.7)	7.8–55.1
Non-familial, all	87	6 (6.9)	7 (8.1)	13 (14.9)	7.5–22.4
Non-familial, serous	58	5 (8.6)	7 (12.1)	12 (20.7)	10.3–31.1
Non-familial, serous, below 50	28	4 (14.3)	4 (14.3)	8 (28.6)	11.8–45.3

Two of the four BRCA1 mutations in familial ovarian cases were identified in ovarian site-specific and two in breast and ovarian cancer families. The frequent occurrence of BRCA1 mutations in families with similar cancer histories has been demonstrated in other studies using different geographic and ethnic populations [Easton et al., 1995; Moslehi et al., 2000; Tonin et al., 1999; Gayther et al., 1999]. All but one of the carriers had grade 2 or 3 serous adenocarcinoma histopathological sub-type. The remaining BRCA1 carrier had a borderline ovarian endometrioid cystadenocarcinoma. Previous studies have shown the rare occurrence of germline BRCA1 mutations in borderline ovarian tumors [Rubin et al., 1996; Stratton et al., 1997]. This study demonstrates that mutations in BRCA1 may account for a substantial proportion of Turkish individuals with ovarian cancer and a family history of breast and/or ovarian cancer.

The vast majority of our study cohort (87 out of 102, 85.3%) is non-familial and mutations were identified in 13 out of 87 (14.9%) individuals in this group. Other studies have attempted to determine the proportion of BRCA1 and BRCA2 mutations in non-familial ovarian cancer cases [Janezic et al., 1999; Modan et al., 1996; Beller et al., 1996; Moslehi et al., 2000; Tonin et al., 1999; Risch et al., 2001]. Three of these studies, focusing on the Ashkenazi Jewish population, reported frequencies of mutations in non-familial ovarian cancer cases from 13 to 27%. The study with the lowest frequency of mutations screened only for the 185delAG mutation in BRCA1 [Modan et al., 1996], while the other two studies, with frequencies of 23% and 28%, screened for all three common mutations in both BRCA1 and BRCA2 [Beller et al., 1996; Moslehi et al., 2000]. A study investigating the common mutations in a French Canadian group of 61 non-familial ovarian cancer cases identified only one BRCA2 mutation [Tonin et al., 1999], whereas another Canadian study of ovarian cancer patients recruited from the province of Ontario identified 22 carriers (10 BRCA1, 12 BRCA2) out of 504 (4.4%) cases [Rish et al., 2001]. An American study could not find any mutations in a group of 73 consecutive cases of non-familial ovarian cancer [Janezic et al., 1999]. The differences in the proportion of mutations between our study and others

may be due to actual differences in the attributable risk of BRCA1 and BRCA2 mutations in non-familial ovarian cancer in the various populations. However, this difference also may be the result of the various mutational screening strategies employed. The proportion of mutations in our group, even utilizing a limited molecular analysis, demonstrates that Turkish ovarian cancer patients without a family history should be considered as good candidates for genetic testing in the clinical setting.

BRCA1 mutations were found in both the familial and non-familial groups in our study. However, BRCA2 mutations were found only in the non-familial group. The studies mentioned above also have found both BRCA1 and BRCA2 mutations in isolated cases of ovarian cancer. Perhaps the observation of higher proportions of BRCA2 carriers in our non-familial ovarian cancer cases may be due to the lower penetrance of BRCA2 [Ford et al., 1998].

Approximately 21% of the non-familial cases with serous histopathology carried BRCA1 and BRCA2 mutations compared to 3.5% cases with other histopathologies (p -value = 0.05, Fisher's exact test). Along with other studies [Tonin et al., 1999; Moslehi et al., 2000; Tobias et al., 2000], our data support the notion that the presence of BRCA1 and BRCA2 mutations is significantly associated with serous histopathological sub-type. Among non-familial cases with serous tumors, 28.6% were diagnosed before age 50, whereas 13.3% were diagnosed above age 50. Although this association is not statistically significant, it suggests that non-familial ovarian cases with serous histopathology diagnosed before age 50 may be more likely to be mutation carriers than those diagnosed above age 50. Also, in the carriers diagnosed below age 50, there is a trend toward a greater proportion of BRCA1 mutations (14.3%) compared to BRCA2 mutations (3.3%). BRCA2 mutations were relatively evenly distributed in both age categories (14.3% vs. 10%). This suggests that BRCA1 mutations may lead to earlier onset ovarian cancer when compared to BRCA2. In the non-familial serous histopathology group, BRCA1 and BRCA2 mutations were detected in all nuclear grade categories. However, we did not observe a relationship between the carriers and the grade, possibly because of the small sample size.

Determining which ovarian cancer patients, without a family history, have the highest likelihood of carrying predisposing mutations is of great clinical utility. Our study shows that those Turkish ovarian cancer patients with serous histopathology harbor a high proportion of mutations compared to all non-familial cases regardless of the pathology. Within this sub-group, those that were also diagnosed below age 50 have even a greater percentage of BRCA1 and BRCA2 mutations.

CONCLUSION

Our findings illustrate that a substantial proportion of Turkish ovarian cancer patients, both with and without a family history, carry BRCA1 and BRCA2 mutations. It appears that tailoring the BRCA1 and BRCA2 analysis to those individuals with serous adenocarcinoma diagnosed under the age of 50 years would provide the maximum number of carriers per test in the non-familial cohort. These findings demonstrate the importance of BRCA1 and BRCA2 in the development of ovarian cancer in this population and has implications for the clinical ascertainment of those at risk for the disease.

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