Clinical and genetic characteristics of *BRCA1/2* mutation in Korean ovarian cancer patients: A multicenter study and literature review

Byung-Su Kwon¹, Sul Lee¹, Eun-Hee Yu¹, Ki-Hyung Kim¹

¹Department of Obstetrics and Gynecology, Medical Research Institute, Pusan National University Hospital, Busan, Korea

Introduction

Defects in *BRCA1/2* tumor suppressor genes are the most frequently identified genetic changes associated with ovarian cancer. A *BRCA1/2* germline mutation is associated with poor prognostic factors, including early - onset cancer, serous histology, and advanced cancer stages. Although there have been several reports of *BRCA1/2* mutation analyses in ovarian and breast cancer cases from Asian populations, there is relatively limited data for the Korean ovarian cancer (KoOC) population. Furthermore, there has been no spectrum study of *BRCA1/2* mutations in KoOC patients, such as nation-wide the Korean Hereditary Breast Cancer (KOHBRA) study. Thus, we performed comprehensive analyses to estimate the prevalence, clinicopathological significance, spectrum, and penetrance of *BRCA1/2* mutations in a large cohort of KoOC patients.

Materials and Methods

1. Patients and ethical statement

A total of 279 EOC patients unselected for family history were enrolled between May 2012 and December 2017 from three investigational sites in Korea: the Pusan National University Hospital, Inje University Paik Hospital, and Kosin University Gospel Hospital (PIKO). Genetic testing of *BRCA1/2* genes in all three investigational hospitals was carried out by the Green Cross Company (Yongin, Korea) during the study period. Clinical and pathological data were collected for all patients: age at diagnosis, EOC grade, lymph node metastasis, FIGO stage (International Federation of Gynecology and Obstetrics, 2013), and personal and family history of cancer.

2. Direct sequencing

Genomic DNA was obtained from peripheral blood leukocytes and was extracted using the Promega DNA purification kit (catalog no. LA1620) according to the manufacturer's instructions.

3. Statistical analyses

The Human Genome Variation Society nomenclature system was used for describing sequence variations, and the Breast Cancer Information Core (BIC) database was used for evaluating results.

Results

1. Prevalence of *BRCA1/2* mutations

Figure 1. Prevalence of *BRCA1/2* mutations in unselected 279 Korean ovarian cancer (KoOC) patients. (A) The overall prevalence and (B) prevalence according to Family history of breast/ovarian cancer (FHBOC)

Figure S1. Prevalence of *BRCA1/2* mutations in specific subgroups according to tumor histology (serous vs. non-serous) and FIGO stage (I/II vs. III/IV) in unselected 279 Korean ovarian cancer (KoOC) patients.

2. Clinical characteristics of *BRCA1/2* mutations

Characteristic	Total	<i>BRCA1/2</i> mutation -	<i>BRCA1/2</i> mutation +	p-value ^{a)}
	No. (%)	No. (%)	No. (%)	
Total No.	279 (100.0)	233 (83.5)	46 (16.5)	
Age, mean $\pm$ SD (years)	54.15 $\pm$ 10.7	54.2 $\pm$ 10.9	53.7 $\pm$ 9.6	0.765
Age, early-onset (age < 50)				
< 50	93 (33.3)	71 (30.5)	18 (39.1)	0.223
$\geq$ 50	186 (66.7)	162 (69.5)	28 (60.9)	
FHBOC ^{b)}				
No	219 (78.5)	194 (83.3)	25 (54.3)	< 0.001
Yes	60 (21.5)	39 (16.7)	21 (45.7)	
FH of other cancers				
No	218 (78.1)	190 (81.5)	28 (58.7)	< 0.001
Yes	61 (21.9)	43 (18.5)	18 (41.3)	
Tumor histology				
Serous	202 (72.4)	160 (68.6)	42 (91.3)	0.002
Non-serous	77 (27.6)	73 (31.4)	4 (8.7)	
FIGO stage				
I/II	96 (34.4)	90 (38.6)	6 (13.1)	0.007
III/IV	183 (65.5)	143 (61.4)	40 (86.9)	
LN metastasis				
No	190 (68.1)	166 (71.2)	24 (51.2)	0.011
Yes	89 (31.9)	67 (28.8)	22 (48.8)	

Table 1. Association of *BRCA1/2* mutation status with clinicopathological characteristics in Korean ovarian cancer (KoOC) patients (n=279)

Characteristics	OR (95% CI)	p-value
Age (yr) (<50 vs. $\geq$ 50)	1.762 (0.861-3.605)	0.121
FHBOC ^{a)} (Yes vs. No)	9.089 (3.204-25.783)	< 0.001
FH of other cancers (Yes vs. No)	1.223 (0.861-2.653)	0.747
Tumor histology (Serous vs. Non-serous)	3.834 (1.035-14.201)	0.044
FIGO stage (III/IV vs. I/II)	3.738 (1.258-11.106)	0.018
LN metastasis (Yes vs. No)	1.143 (0.538-2.427)	0.729

Table 2. Multivariate logistic regression in Korean ovarian cancer (KoOC) patients between *BRCA1/2* mutation status and clinicopathological characteristics

3. Spectrum of *BRCA1/2* mutations

Figure 2. Spectrum analysis of 111 (55 distinct) *BRCA1/2* mutations detected in Korean ovarian cancer (KoOC) patients. (A) The ratio of *BRCA1* to *BRCA2* mutations and most frequent mutation in KoOC patients, (B) and the corresponding values in in Korean breast cancer (KoBC) patients as analyzed in the Korean Hereditary Breast Cancer (KOHBRA) study. (C) The proportions of Korean population-specific mutation to non-Korean population-specific mutation and (D) recurrent mutation to non-recurrent mutation.

Gene	Site	Mutation ^{a)}	Type	Citation No. (%) in KoOC	Citation No. (%) in KOHBRA
<i>BRCA1</i>	11	c.3627insA	FS	14 (12.6)	9 (2.3)
<i>BRCA1</i>	7	c.390C>A	NS	8 (7.2)	21 (5.5)
<i>BRCA1</i>	11	c.922_924AGCinsT	NS	5 (4.5)	13 (3.4)
<i>BRCA1</i>	22	c.5339T>C ^{b)}	MS	5 (4.5)	0 (0.0)
<i>BRCA1</i>	11	c.3442delG	FS	5 (4.5)	2 (0.5)

Table 4. Spectrum of highly frequent *BRCA1/2* mutations in Korean hereditary breast and ovarian cancer (HBOC) patients

Discussion

The overall frequency of *BRCA1/2* mutations in unselected KoOC patients was 16.5%, which was comparable to the frequency of 13% to 15% in western cohorts. In addition, the frequency of *BRCA1/2* mutations observed in the present study was comparable to the frequencies reported in other recent Asian reports, ranging from 11% to 17%. These data suggest that there are no marked ethnic differences in the frequency of *BRCA1/2* mutations.

In terms of the age-of-onset, patients with *BRCA1/2* mutation are characterized by developing EOC at a younger age, based on a report of western cohorts. Unlike the data for western cohorts, in this study, the mean age of patients with *BRCA1/2* mutation was not significantly lower than that of those without *BRCA1/2* mutation. There were no significant differences in the proportion of patients with early age-of-onset (< 50 years) of ovarian cancer between *BRCA1/2* mutation carriers and non-carriers in KoOC patients.

Regarding the clinicopathological findings, patients with *BRCA1/2* mutations are characterized by serous histology and advanced stage with unfavorable outcomes. In the present study, 91.3% (42/46 *BRCA1/2* mutation cases) had serous histology. Our study also found that *BRCA1/2* mutations were significantly associated with an advanced FIGO stage of III/IV and LN metastasis ; in case of LN metastasis, it was not significant in multivariate logistic regression.

Recently, two relatively large population-based studies including 95 and 916 women with unselected ovarian cancer were performed in Japan and China, respectively, which are geographically close to Korea. On comparing three studies of East Asian populations, including the present Korean study, we found no marked ethnic differences in the *BRCA1/2* mutation frequency among the studies . These East Asian studies showed no significant difference in the mean age-of-onset between *BRCA1/2* mutation carriers and non-carriers. In addition, these three studies revealed significant associations between *BRCA1/2* mutation and clinicopathological characteristics, including serous histology and advanced FIGO stage.

Among the 2403 index patients, 378 were found to carry *BRCA1/2* mutations. Overall, 153 distinct mutations were identified, including 63 in *BRCA1* and 90 in *BRCA2*. When the *BRCA1/2* mutation spectrum was compared between KoOC and KoBC patients, the *BRCA1*-to-*BRCA2* ratio was 3.6:1.0 in KoOC and 1.0:1.4 in KoBC patients, representing that *BRCA1* mutations (78.4%) were predominant in KoOC, whereas *BRCA2* mutations (59.2%) were predominant in KoBC. In the KOHBRA study, a replacement mutation, c.7480C>T, in the *BRCA2* gene, which was identified as a Korean founder mutation through haplotype analysis by Seong et al., was the most commonly detected mutation, accounting for 10.1% of all *BRCA1/2* mutations. In the present study of KoOC patients, c.3627insA, in the *BRCA1* gene, was the most commonly detected mutation, accounting for 12.6% of all *BRCA1/2* mutations, and c.7480C>T was identified in only four unrelated EOC patients, accounting for 3.6% of all *BRCA1/2* mutations. In our study, the *BRCA1/2* mutation spectrum varied according to the cancer type (ovarian and breast cancers) among the Korean HBOC population. The inconsistency of the *BRCA1/2* mutation spectrum between ovarian cancer and breast cancer in Korean HBOC was an unexpected result.

Conclusion

We demonstrated herein that KoOC patients with *BRCA1/2* mutation were significantly associated with several clinicopathologic factors, such as serous histology and an advanced FIGO stage. However, KoOC patients with *BRCA1/2* mutation were not characterized by an early age-of-onset (age < 50) of ovarian cancer. An analysis of the *BRCA1/2* mutation spectrum in KoOC patients showed that the *BRCA1*-to-*BRCA2* ratio and the most commonly detected mutation were different from those of KoBC patients. Owing to the different mutation spectra of KoOC and KoOC patients among Korean HBOC, there were might be presence of possible penetrance tendency leading to breast cancer or ovarian cancer by mutation sequence-specific manner. Taken together, our observations may provide an insight for better genetic counseling and clinical surveillance for the at-risk relatives of KoOC patients.