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Prevalence and clinical characterization of *BRCA1* and *BRCA2* mutations in Korean patients with epithelial ovarian cancer

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Abstract

This study was performed to investigate the prevalence, clinical characteristics, and treatment response according to *BRCA1* and *BRCA2* (*BRCA*) mutations in Korean patients with epithelial ovarian cancer (EOC). Two-hundred and ninety-eight Korean women diagnosed with high-grade serous and/or endometrioid EOC from 2010 to 2015 were tested for germline and 86 specimens for somatic *BRCA* mutations, regardless of the family history. Clinical characteristics including survival outcomes were compared in patients with and without *BRCA* mutations (NCT02963688). A total of 43 different germline *BRCA* mutations were identified in 78 patients among 298 patients (26.2%). Somatic *BRCA* mutations were identified in 11 (12.8%) patients among patients without germline *BRCA* mutations. Haplotype analysis demonstrated no founder mutations in our Korean patient cohort. Insignificant differences in age at diagnosis, primary site, and residual disease after surgery were observed between patients with and without *BRCA* mutations. In multivariate analysis for overall survival (OS), the presence of *BRCA* mutation was significantly associated with OS ($P = .049$) in addition to platinum sensitivity ($P < .001$), indicating it is an independent prognostic factor for survival regardless of platinum sensitivity to first-line chemotherapy. In addition, a higher response rate to subsequent chemotherapy after recurrence was observed in EOC patients with *BRCA* mutations resulting in better OS. In the current study, the prevalence of *BRCA* mutations in Korean patients with EOC was higher than previously reported in other ethnic groups. We demonstrated characteristics and treatment response in Korean EOC patients with *BRCA* mutations. These findings may provide valuable information to be considered in future clinical trials including Asian patients.

KEYWORDS

BRCA1 genes, *BRCA2* genes, germline mutation, ovarian neoplasm, overall survival

1 | INTRODUCTION

Epithelial ovarian cancer (EOC) is the second leading cause of death related to gynecologic cancers and the eighth most common leading cause of death from cancer in women worldwide.[1] The standard therapy for EOC consists of surgical cytoreduction and adjuvant treatment with taxane and platinum-based chemotherapeutic agents. Despite a positive response to taxane and platinum-based chemotherapeutic agent in patients with advanced EOC, most patients experience relapse.[2] Repeated chemotherapy in recurrent EOC patients diminishes effectiveness and leads to cumulative increased toxicity.[3] Recent trends in treatment for gynecological cancer fields include incorporation of molecular target therapy in chemotherapy. As a result, bevacizumab (humanized monoclonal antibody targeting vascular endothelial growth factor) and poly adenosine diphosphate-ribose polymerase inhibitor (PARPi) maintenance have shown clinical benefits in EOC patients.

The significant activity of PARPi in *BRCA1* and *BRCA2* (*BRCA*) mutation carriers also drew attention in *BRCA* testing early in the management of EOC. In the SOLO-1 study, a phase 3 randomized controlled trial (RCT) in advanced EOC patients with germline *BRCA* mutation (g*BRCA*m) or somatic *BRCA* mutation (*sBRCA*m), olaparib maintenance therapy showed significantly prolonged progression-free survival (PFS).[4] Velaparib and niraparib maintenance therapy in newly diagnosed EOC patients showed survival benefit regardless of the presence of *BRCA* mutations (*BRCA*m),[5,6] but survival benefit for disease progression was clearer in the subgroup with *BRCA*m. PARPi (olaparib, rucaparib, and niraparib) showed its efficacy in EOC patients for the maintenance therapy of relapsed platinum-sensitive EOC.[7-9] In addition, PAPRi, in single or multiple combinations including anti-angiogenic agents and immune check-point inhibitors, is under extensive investigation in clinical trials in patients with first-line setting of EOC as well as in recurrent settings. However, there is still a need for investigation of predictive molecular biomarkers and the best combination for PARPi in the treatment of EOC patients.

Approximate frequency of g*BRCA*m in EOC widely vary from 5% to 30%,[10,11] and less frequent occurrence of s*BRCA*m (2%-8%[12-14]) has been reported in patients with EOC. EOC patients with *gBRCA*m were reported to have better survival outcome compared to patients without *gBRCA*m, and the mechanism underlying this benefit was hypothesized as a high response rate to platinum agents, particularly in patients with high-grade serous type.[10,15] The reason is that patients with *gBRCA*m are impaired in their ability to repair double-stranded DNA breaks through homologous recombination (HR).[16] Despite the discovery of *BRCA* more than 20 years ago, almost all the available data are from women in the United States, Europe, and Australia, and there have only been a few studies, mostly with small sample size, in Asian populations.[12,17-22] Recently, many international clinical trials have been recruiting Asian patients and several clinical trials have exhibited different outcomes between European and Asian EOC patients, for example pazopanib maintenance therapy[23,24] and dose dense weekly paclitaxel plus tri-weekly carboplatin chemotherapy in first-line treatment in ovarian cancer.[25,26] *BRCA*m has recently become known as a prognostic factor in EOC, therefore it is necessary to understand more fully its prevalence and clinical characteristics, including the treatment response of EOC patients with *BRCA*m in Asian populations, through a larger scale study and comprehensive analysis of its clinical characterization.

Thus, we evaluated the clinical characterization and treatment response of EOC patients with the *BRCA* mutation in 298 Korean patients with high-grade serous and/or endometrioid EOC.

2 | METHODS

2.1 | Patients and study design

This study is a result of retrospectively analyzed subgroup data based on the Korean Gynecologic Oncology Group (KGOG) 3019 study, which was a prospective, multicenter observational study conducted in Korea from 2010 to 2015 to identify environmental and personal risk factors for EOC. According to the KGOG 3019 protocol, we collected blood, urine, and tumor samples from patients simultaneously at operation room. Patients were included after histological diagnosis of EOC and were not selected for age or family history. Patient interviews were done in hospital with detailed questionnaires asking about known and suspected ovarian cancer risk factors. A flowchart of the study is shown in Figure 1. We extracted 565 patients from KGOG 3019 data for this study that fitted our inclusion criteria: eligible patients included women 18 years of age and older with previously untreated, high-grade serous and/or endometrioid EOC, fallopian tube or primary peritoneal carcinoma who have consented for *BRCA*m testing. Patients with mucinous, clear cell, low-grade serous or endometrioid, mixed epithelial adenocarcinoma, undifferenciated carcinoma or malignant Brenner's tumor were excluded. A total of 298 patients were tested for *BRCA*m for characterization of *BRCA*m in this population (ClinicalTrials identifier NCT02963688). For a more homogenous group to assess accurate results for survival analysis and treatment response, survival analysis was performed in the patient group after excluding patients who received neoadjuvant chemotherapy or secondary debulking surgery, patients with stages I–II, and patients who did not receive primary chemotherapy. All patients were provided with written informed consent on the protocol approved by the Institutional Review Board.

2.2 | Clinical characteristics assessment

Epithelial ovarian cancer patients routinely underwent primary cytoreductive surgery followed by six to nine cycles of adjuvant intravenous taxane and platinum-based chemotherapy, or patients were treated with three cycles of neoadjuvant chemotherapy followed by interval debulking surgery and an additional three to six cycles of taxane and platinum-based chemotherapy according to the physician's clinical decision. After initial treatment, patients were routinely followed up every 3 months for the first year, then

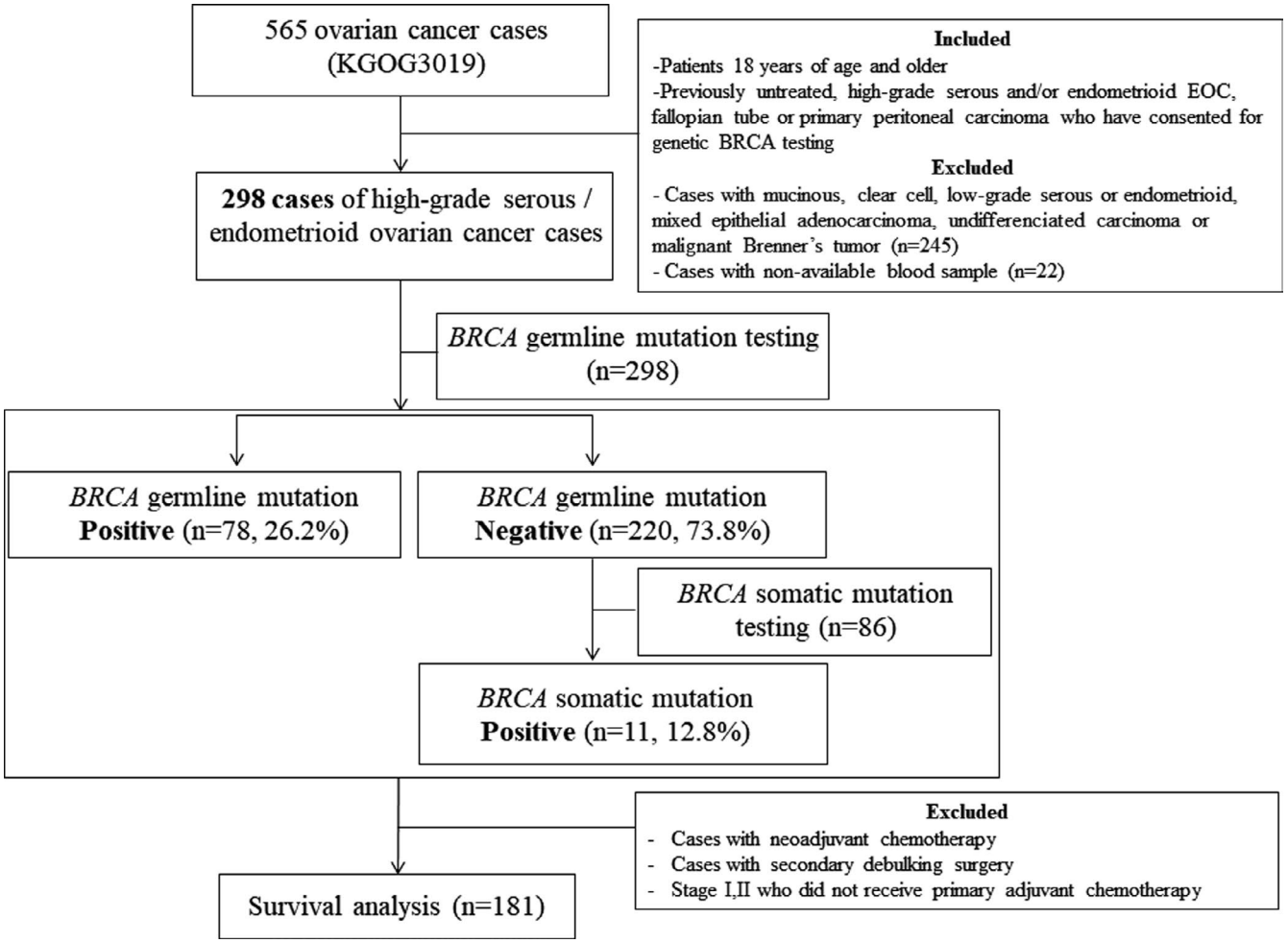

FIGURE 1 Flowchart outlining the study

every 6 months for up to 5 years, and annually thereafter. Patients were monitored based on clinical symptoms, laboratory tests, and imaging examinations. For treatment for recurrent EOC, a taxane and platinum-based regimen was used for the platinum-sensitive group and a nonplatinum-based chemotherapy regimen (topotecan/belotecan, pegylated liposomal doxorubicin, etoposide, and others) was used for the platinum-resistant group. Since PARPi was not used as standard treatment during the period in which the study subjects were being treated, chemotherapy was the main treatment. There was no difference in treatment regimen for recurrence between patients with and without *BRCA*m in this study.

Clinical and pathologic data were collected from the KGOG 3019 database and patient medical records: family cancer history for second-degree relevant, personal cancer history, age at diagnosis, surgical outcome at primary cytoreductive surgery/interval debulking surgery, tumor histology, stage of disease, chemotherapy regimen (first and subsequent lines of treatment), and response assessments including CA-125 level/imaging results.

Surgical staging was assessed according to the International Federation of Gynecologist and Obstetricians (FIGO) staging system when diagnosed. Surgical outcomes were categorized as residual disease of 0-10 mm as optimal and >10 mm as suboptimal after debulking surgery. Platinum sensitivity was classified as two groups: platinum sensitive and platinum resistant. Regarding sensitivity for platinum chemotherapy, platinum sensitive was defined as more than 6 months of platinum-free interval and platinum resistance was defined as less than 6 months of platinum-free interval after the first line of adjuvant chemotherapy.

Progression-free survival was defined as the interval between histologic diagnosis and first progression, death as a result of disease, or last follow-up. Overall survival (OS) was defined as the interval between histologic diagnosis and death as a result of disease, or last follow-up. Death as a result of nondisease-related causes was not considered in the calculation of PFS or OS. Disease progression was determined based on CA-125 levels and imaging results according to Gynaecologic Cancer Inter Group (GCIG) modification of the Response Evaluation Criteria in Solid Tumors (RECIST) guidelines modified for ovarian cancer[27] and RECIST criteria. Overall response rate (ORR) was defined as the proportion of patients who had a partial or complete response to therapy. It does not include stable disease and is a direct measure of drug tumoricidal activity.

2.3 | DNA extraction

DNA was extracted using from the EDTA-anticoagulated whole blood using the Wizard® Genomic DNA Purification Kit according to the manufacturer's instructions (Promega). Surgical snap-frozen fresh tissue was used for *sBRCA*m detection. Genomic DNA was extracted by the concentration of extracted DNA, and it was measured using a Pico-Green dsDNA assay (Quanti-iTTMPicoGreen® dsDNA kit, Invitrogen).

2.4 | Targeted sequencing and variant calling (germline DNA and tumor DNA)

All coding exons and intron sequences of 20 bp around each exon were targeted in the *BRCA1* and *BRCA2* genes, ultimately resulting in a total size of 22 462 bp. Briefly, 30 ng of DNA (10 ng per pool) was amplified using the Ion AmpliSeq *BRCA1* and *BRCA2* Panel (Life Technologies) containing 167 primer pairs and an Ion AmpliSeq kit 2.0. The amplicons were ligated to adapters with barcodes of the Ion Xpress Barcode Adapter Kit (Life Technologies). The libraries with adapters were pooled for multiplexing. The amplicons were clonally amplified through emulsion PCR by using a IT OneTouch Template Kit 2.0 on an IT OneTouch system (Life Technologies) following the manufacturer's instructions. Template-positive Ion Sphere Particles (ISPs) were enriched, and purified ISPs were loaded on an Ion 316 or 318 Chip. Twelve barcoded samples on an Ion 316 Chip and 32 barcoded samples on a 318 Chip were sequenced. Targeted sequencing was performed using the Ion PGM platform using an Ion PGM sequencing 200 kit following the manufacturer's instructions.

2.5 | Bioinformatic analysis and mutation prioritization

Data analysis including signal processing, base calling, read alignment, and coverage analysis was done using Torrent Suite software (ver 4.0.3, Life Technologies). Torrent browser plugin software such as variantCaller (v4.2.1.0) and coverageAnalysis (v4.2.1.4) was used for variant calling and coverage analysis. The variant calling was performed using the "Germ Line – PGM – High Stringency" setting. The variants were functionally annotated using the ANNOVAR tool.[28,29] A number of in silico tools, including SIFT, Polyphen 2, LRT, MutationTaster, MutationAssessor, and FATHMM, GERP score, were used.[29] To prioritize the pathogenic mutations, we applied the criteria for pathogenicity classification according to the American College of Medical Genetics and Genomics (ACMG) guideline, and the prioritized variants were classified as pathogenic variants and likely pathogenic variants.[30] "Disease-causing mutations" (DM) in the Human Genome Mutation Database (HGMD, professional version 2014.01), "pathogenic" mutations in ClinVar (http://www.ncbi.nlm.nih.gov/clinvar/), or causal mutation in UMD (http://www.umd.be/BRCA1/, http://www.umd.be/BRCA2/) were categorized as known mutations.[31,32] The "A" of the ATG translation initiation codon is described as position number 1 in the *BRCA1* (NM_007294.2) and *BRCA2* (NM_000059.3).

2.6 | Sanger sequencing

All of the prioritized mutations were validated with independent Sanger sequencing. The mutated DNA was amplified by PCR using primer pairs designed with Primer3 software. Relevant regions were sequenced using a BigDye Terminator Cycle Sequencing Ready Reaction Kit (Applied Biosystems) and an ABI Prism 3100 Genetic Analyzer (Applied Biosystems Foster City).

2.7 | Statistical analysis

Frequency distributions between categorical variables among the groups were compared using the χ^2 test. The Fisher's exact test was used if the expected frequency was <5. The Kaplan-Meier method with the log-rank test was used to estimate and compare PFS and OS. The Cox proportional hazard model was used to evaluate the association between factors and survival. Statistical analyses were performed by SPSS software (version 21.0). A P value of ≤.05 was considered statistically significant, and all P values were two-sided.

3 | RESULTS

A flowchart outlining the study is shown in Figure 1. A total of 565 patients were enrolled to the KGOG 3019 from 2010 to 2015, and 298 patients were eligible for the current study: patients with EOC, peritoneal or fallopian tube primary tumor with high-grade serous or endometrioid cell type and consent to examine *BRCA* genotyping. Median follow-up for all patients was 28.1 months.

3.1 | Patient characteristics

The patient characteristics of the current study and *BRCA*m status are shown in Table 1. An insignificant association between *BRCA*m(+) and *BRCA*m(-) patients for age, primary site, and FIGO stage was observed in our study. The median age at diagnosis for *BRCA*m(+) EOC patients was 53.0 years (range 38–75 years) and was similar to *BRCA*m(-) patients (median 53.0 years, range 30–79 years). This was different from previous studies, which showed earlier onset of disease with *BRCA*m, in particularly patients with g*BRCA1*m.[10,15,33-35] Most *BRCA*m(+) were found in high-grade serous EOC (98.9%). Sixteen patients had a personal history of breast cancer and this was significantly higher in the *BRCA*m(+) group (10/89, 11.2%) than in the *BRCA*m(-) group (6/209, 2.9%, P = .008; Table 1). This means 62.5% (10/16) showed *BRCA*m(+) among patients with EOC having a personal history of breast

TABLE 1 Patient characteristics

	Total	*BRCA*m(-)	*BRCA*m(+)				*P* value*
				*gBRCA1*m(+)	*gBRCA2*m(+)	*sBRCA*m(+)	
Total cases, *n* (%)	298	209	89	64	14	11	.712
Age at diagnosis, years, median (range)	53 (30-79)	53 (30-79)	53 (38 ~ 75)	53 (38-73)	57 (44-75)	54 (48-71)	
Primary site, *n* (%)							
Ovary	270 (90.6)	188 (90.0)	82 (92.1)	58 (90.6)	13 (92.9)	11 (100)	.438
Peritoneum	14 (4.7)	12 (5.7)	2 (2.2)	2 (3.1)	0	0	
Fallopian tube	14 (4.7)	12 (5.7)	5 (5.6)	4 (6.3)	1 (7.1)	0	
Histology, *n* (%)							
Serous	282 (94.7)	194 (92.8)	88 (98.9)	63 (98.4)	14 (100)	11 (100)	.046
Endometrioid	16 (5.4)	15 (7.2)	1 (1.1)	1 (1.6)	0	0	
FIGO stage, *n* (%)							
I-II	34 (11.4)	28 (13.4)	6 (6.7)	4 (6.3)	1 (7.1)	1 (9.1)	.113
III-IV	264 (94.3)	181 (86.6)	83 (93.3)	60 (93.7)	13 (92.9)	10 (90.9)	
Personal breast cancer history, *n* (%)							
No	282 (94.6)	203 (97.1)	79 (88.8)	56 (87.5)	12 (85.7)	11 (100)	.008
Yes	16 (5.4)	6 (2.9)	10 (11.2)	8 (12.5)	2 (14.3)	0	
Family breast cancer history, *n* (%)							
Unknown	28 (9.4)	23 (11.0)	5 (5.6)	2 (3.1)	3 (21.4)	0	.003
No	234 (78.5)	169 (80.9)	65 (73.0)	46 (71.9)	9 (64.3)	10 (90.9)	
Yes	36 (12.1)	17 (8.1)	19 (21.3)	16 (25.0)	2 (14.3)	1 (9.1)	
Family ovarian cancer history, *n* (%)							
Unknown	28 (9.4)	23 (11.0)	5 (5.6)	2 (3.1)	3 (21.4)	0	<.001
No	249 (83.6)	179 (85.6)	70 (78.7)	49 (76.6)	10 (71.4)	11 (100)	
Yes	21 (7.0)	7 (3.4)	14 (15.7)	13 (20.3)	1 (7.1)	0	
Residual disease after debulking surgery							
0-10 mm	239 (80.2)	170 (81.3)	69 (77.5)	54 (84.4)	9 (64.3)	6 (54.5)	.070
>10 mm	45 (15.1)	33 (15.8)	12 (13.5)	5 (7.8)	2 (14.3)	5 (45.5)	
Missing data	14 (4.7)	6 (2.9)	8 (9.0)	5 (7.8)	3 (21.4)	0	
Platinum sensitivity ($N = 181$), *n* (%)**		n = 126 (100)	n = 55 (100)				.106
Sensitive	98 (54.1)	63 (50.0)	35 (63.6)	24 (37.5)	8 (57.1)	3 (27.3)	
Resistant	83 (45.9)	63 (50.0)	20 (36.4)	14 (21.8)	2 (14.2)	4 (36.4)	

Note: Table shows column percentages.

Abbreviations: *BRCA*m, *BRCA* mutation; FIGO, International Federation of Gynecology and Obstetrics.

**P* value of Fisher's exact test and chi-square test between the *BRCA*m(+)and *BRCA*m(-) groups.; **Platinum sensitivity was assessed from available data of 181patients of advanced ovarian cancer patients who had undergone adjuvant platinum-based chemotherapy.

cancer. Number of breast cancer family history was significant different between *BRCA*m(+) and *BRCA*m(-) patients (19/89, 21.3% vs 17/209, 8.1%, $P = .003$; Table 1), showing a 52.8% (19/36) probability of *gBRCA*m in EOC patients with family breast cancer history. Number of ovarian cancer family history was very strongly associated with *BRCA*m (+), 15.7% (14/89) of *BRCA*m(+) and 3.3%(7/209) of *BRCA*m (-), respectively ($P < .001$), also showing a 66.7% (14/21) chance of *BRCA*m.

In the present study, regarding optimality, described as residual disease after debulking surgery, a residual tumor less than 1 cm after primary debulking surgery was observed in 80.2% of patients. There were no significant differences between *BRCA*m status and optimal primary debulking rate (*BRCA*m(+) vs *BRCA*m(-), 77.5% vs 81.3%, $P = .070$; Table 1) and sensitivity to first-line platinum based combination chemotherapy (*BRCA*m(+) vs *BRCA*m(-), 63.6% vs 50.0, $P = .106$; Table 1), which is not consistent with previous studies.[10,36]

3.2 | Prevalence of *BRCA1/2* mutations

In the present study, germline mutation was observed in 26.2% of patients and somatic mutation in *gBRCA*m(-) specimens was observed in 12.8% (Table 1). All 298 patients were tested for *gBRCAm*. A total of 49 different mutations were identified in 78 patients. The germline mutation profile of 78 patients is shown in Table 2. The ratio of *gBRCA1m*:*gBRCA2m* was 4.6:1 (64 vs 14 patients). Regarding patterns of mutation types in the study population, stopgain was the most common, with 31 patients (39.7%), followed by frameshift insertion (16 patients, 20.5%), frameshift deletion (16 patients, 20.5%), splicing (nine patients, 11.5%), and missense (six patients, 7.7%). Seven of these mutations were novel: p.P1238fs, p.N941fs, p.G394fs, p.G1319fs in *BRCA1* and p.D2110fs, p.S1992fs, p.K3084fs in *BRCA2*. Twelve recurrent mutations were identified: 11 in *BRCA1* and one in *BRCA2*. Five of them (p.Y130X [$n = 5$], p.E1210fs [$n = 9$], p.Q1144X [$n = 3$], p.W1815X [$n = 3$], and c.5467+1G>A [$n = 5$] in *BRCA1*) were found in at least three unrelated patients. Haplotype analysis demonstrated no founder effects in three recurrent mutations such as p.Y130X, p.E1210fs, and c.5467+1G>A in *BRCA1*. All of the haplotypes were exclusively seen only in mutation-containing cases. Frequently occurring BRCA mutation loci are shown in Table S1.

The number of mapped reads and percent base reads on target showed medians of 125 340 and 95%, respectively. The average depth of coverage was 675-fold per sample (range of 264- to 1983-fold). A total of 100% and 99.4% of bases were covered by at least 1-fold and 20-fold of coverage, respectively. A total of 153 variants were found in 298 cases. Among them, a total of 53 variants were prioritized, according to the ACMG criteria. In total, 49 mutant alleles including 36 pathogenic and 13 likely pathogenic mutations were validated by Sanger sequencing (validation rate of 92%).

The s*BRCA*m were tested in 86 patients without *gBRCA*m and available fresh tumor samples (Figure 1.). Eleven (12.8%) patients had s*BRCA*m only among 86 *gBRCA*m negative specimens and the somatic *BRCA* mutation rate was estimated to be 3.7% among all patients. The gene profile of s*BRCA*m patients is shown in Table 2. All s*BRCA*m were found in serous-type only and the ratio of *sBRCA1*m ($n = 8$) to *sBRCA2*m ($n = 3$) was 2.7:1.

3.3 | Survival outcomes

For more a homogenous group to assess the accurate results for survival analysis and treatment response, we excluded patients who had undergone neoadjuvant chemotherapy or secondary debulking surgery, patients with stages I-II, and patients who did not receive primary chemotherapy (Figure 1). We finally analyzed a subset of 181 cases for survival analysis. With a median follow-up duration of 28.1 months (range 1.9-89.7) from initial diagnosis, 45 patients died of EOC (seven patients in the *BRCA*m(+) group and 38 patients in the *BRCA*m(-) group). The estimated 5-year OS was 64.6% using the Kaplan-Meier method.

For survival outcomes, Kaplan-Meier curves for PFS and OS are shown in Figure 2. The *BRCA*m(+) group showed better PFS and OS, but only OS with significance ($P = .004$). In univariate analysis for OS for this cohort, *BRCA*m(-) was associated with significantly worse OS compared to cases with *BRCA*m ($P = .021$, hazard ratio = 10.620, 95% confidence interval [CI] = 1.436-78.555). The other characteristics significantly related to OS were residual disease after debulking surgery ($P = .050$) and platinum sensitivity ($P < .001$). The results for median and 5-year survival for PFS and OS by clinical variables using the log-rank test are shown in Table S2. In multivariate analysis for OS, the presence of *BRCA*m was significantly associated with OS ($P = .049$, hazard ratio = 7.637, CI = 1.010-58.278; Table 3) in addition to platinum sensitivity ($P < .001$, hazard ratio = 11.254, CI = 4.333 ~ 29.232) indicating it is an independent prognostic factor for survival regardless of platinum sensitivity to first-line chemotherapy. The location of *BRCA*m was not associated with survival outcome (Figure S1).

3.4 | Treatment response

The number of patients by the chemotherapy regimen type (platinum-based/non platinum-based) in *BRCA*m(+) and *BRCA*m(-) group is shown in Table S3. There was no difference in treatment regimen between patients with *BRCA*m(+) and *BRCA*m(-) for the second ($P = .272$) and third ($P = .316$) regimens in this study. The ORR of first-line to third-line chemotherapy of patients was assessed by *BRCA*m status (Figure 3 and Table S3). There was no statistical difference in ORR in first-line chemotherapy between *BRCA*m(+) and *BRCA*m(-) patients ($P = .838$; Figure 3). Among these patients, 97 had first recurrent disease and 86 of 97 patients received second-line chemotherapy. Second-line chemotherapy revealed a higher response in *BRCA*m(+) patients compared to *BRCA*m(-) patients (60.0% vs 34.5%, $P = .065$; Figure 3). Among these patients, 52 patients had second recurrent disease and 39 of these 52 patients received third-line chemotherapy. Importantly, third-line chemotherapy showed significantly improved ORR in *BRCA*m(+) patients compared to *BRCA*m(-) patients (66.7% vs 13.3%, $P = .004$; Figure 3). *BRCA*m carriers have been shown to have a better response to platinum-based chemotherapy,[10,36] and our results showed a trend of patients with *BRCA*m maintaining a higher response rate to platinum treatment along the progressed chemotherapy lines compared to patients without *BRCA*m. Thus, the survival benefit of patients with *BRCA*m for OS might be associated with maintained platinum sensitivity after first-line platinum-based treatment. Although the sensitivity to first-line platinum-based chemotherapy was similar in both *BRCA*m(+) and *BRCA*m(-) groups, successive lines showed a trend of better treatment response for *BRCA*m(+) patients in our results.

TABLE 2 Germline mutation profile of 78 patients and somatic mutation profile of 11 patients

Germline mutation profile ($n = 78$)								
Case	**Exon/intron**	**Gene**	**RefSeq**	**Exon**	**NT alteration**	**AA alteration**	**Type**	**Classification**
8	Exonic	*BRCA2*	NM_000059	Exon15	c.7480C>T	p.R2494X	Stopgain	Pathogenic
12	Exonic	*BRCA2*	NM_000059	Exon11	c.6331dupA	p.R2112fs	Frameshift insertion	Likely pathogenic
14	Exonic	*BRCA1*	NM_007294	Exon6	c.390C>A	p.Y130X	Stopgain	Pathogenic
15	Exonic	*BRCA1*	NM_007294	Exon10	c.2433delC	p.K812fs	Frameshift deletion	Pathogenic
22	Exonic	*BRCA1*	NM_007294	Exon22	c.5445G>A	p.W1815X	Stopgain	Pathogenic
24	Exonic	*BRCA1*	NM_007294	Exon10	c.3289delA	p.S1097fs	Frameshift deletion	Pathogenic
25	Exonic	*BRCA1*	NM_007294	Exon10	c.2354T>A	p.L785X	Stopgain	Pathogenic
32	Exonic	*BRCA1*	NM_007294	Exon10	c.2433delC	p.K812fs	Frameshift deletion	Pathogenic
33	Splicing	*BRCA1*	NM_007294	IVS23	c.5467+1G>A	NA	Splicing	Pathogenic
34	Exonic	*BRCA1*	NM_007294	Exon19	c.5266C>T	p.Q1756X	Stopgain	Pathogenic
37	Exonic	*BRCA2*	NM_000059	Exon10	c.1399A>T	p.K467X	Stopgain	Pathogenic
38	Exonic	*BRCA1*	NM_007294	Exon10	c.3710_3711dup	p.P1238fs	Frameshift insertion	Likely pathogenic
44	Splicing	*BRCA1*	NM_007294	IVS19	c.5193+1G>C	NA	Splicing	Pathogenic
52	Exonic	*BRCA1*	NM_007294	Exon6	c.390C>A	p.Y130X	Stopgain	Pathogenic
55	Exonic	*BRCA1*	NM_007294	Exon16	c.5030_5033del	p.T1677fs	Frameshift deletion	Pathogenic
56	Exonic	*BRCA1*	NM_007294	Exon10	c.3627dupA	p.E1210fs	Frameshift insertion	Pathogenic
62	Exonic	*BRCA1*	NM_007294	Exon10	c.3627dupA	p.E1210fs	Frameshift insertion	Pathogenic
64	Exonic	*BRCA1*	NM_007294	Exon21	c.5339T>C	p.L1780P	Missense	Likely pathogenic
65	Splicing	*BRCA1*	NM_007294	IVS23	c.5467+1G>A	NA	Splicing	Pathogenic
69	Exonic	*BRCA2*	NM_000059	Exon11	c.5975_5976dupCA	p.L1993fs	Frameshift insertion	Likely pathogenic
71	Exonic	*BRCA1*	NM_007294	Exon9	c.616C>T	p.Q206X	Stopgain	Pathogenic
78	Exonic	*BRCA1*	NM_007294	Exon10	c.1936delA	p.S646fs	Frameshift deletion	Pathogenic
83	Exonic	*BRCA1*	NM_007294	Exon10	c.3627dupA	p.E1210fs	Frameshift insertion	Pathogenic
90	Exonic	*BRCA1*	NM_007294	Exon10	c.3991C>T	p.Q1331X	Stopgain	Pathogenic
91	Exonic	*BRCA1*	NM_007294	Exon21	c.5339T>C	p.L1780P	Missense	Likely pathogenic
93	Exonic	*BRCA1*	NM_007294	Exon21	c.5339T>C	p.L1780P	Missense	Likely pathogenic
94	Exonic	*BRCA1*	NM_007294	Exon22	c.5445G>A	p.W1815X	Stopgain	Pathogenic
97	Exonic	*BRCA1*	NM_007294	Exon16	c.5030_5033del	p.T1677fs	Frameshift deletion	Pathogenic
99	Splicing	*BRCA1*	NM_007294	IVS23	c.5467+1G>A	NA	Splicing	Pathogenic
107	Exonic	*BRCA1*	NM_007294	Exon17	c.5080G>T	p.E1694X	Stopgain	Pathogenic
115	Exonic	*BRCA1*	NM_007294	Exon6	c.390C>A	p.Y130X	Stopgain	Pathogenic
119	Exonic	*BRCA1*	NM_007294	Exon10	c.3627dupA	p.E1210fs	Frameshift insertion	Pathogenic
128	Exonic	*BRCA2*	NM_000059	Exon11	c.6724_6725del	p.D2242fs	Frameshift deletion	Pathogenic

(Continues)

TABLE 2 (Continued)

Germline mutation profile ($n = 78$)								
Case	Exon/intron	Gene	RefSeq	Exon	NT alteration	AA alteration	Type	Classification
134	Exonic	*BRCA1*	NM_007294	Exon10	c.1480C>T	p.Q494X	Stopgain	Pathogenic
136	Splicing	*BRCA1*	NM_007294	IVS6	c.302-2A>C	NA	Splicing	Pathogenic
137	Splicing	*BRCA1*	NM_007294	IVS23	c.5467+1G>A	NA	Splicing	Pathogenic
140	Exonic	*BRCA1*	NM_007294	Exon10	c.3627dupA	p.E1210fs	Frameshift insertion	Pathogenic
149	Exonic	*BRCA1*	NM_007294	Exon10	c.1831delC	p.L611X	Stopgain	Pathogenic
154	Exonic	*BRCA1*	NM_007294	Exon6	c.390C>A	p.Y130X	Stopgain	Pathogenic
155	Splicing	*BRCA1*	NM_007294	IVS23	c.5467+1G>A	NA	Splicing	Pathogenic
156	Exonic	*BRCA2*	NM_000059	Exon16	c.7673_7674del	p.E2558fs	Frameshift deletion	Pathogenic
159	Exonic	*BRCA1*	NM_007294	Exon10	c.2740G>T	p.E914X	Stopgain	Pathogenic
164	Exonic	*BRCA1*	NM_007294	Exon10	c.3627dupA	p.E1210fs	Frameshift insertion	Pathogenic
165	Exonic	*BRCA1*	NM_007294	Exon10	c.3430C>T	p.Q1144X	Stopgain	Pathogenic
170	Exonic	*BRCA1*	NM_007294	Exon10	c.2354T>A	p.L785X	Stopgain	Pathogenic
177	Exonic	*BRCA1*	NM_007294	Exon10	c.928C>T	p.Q310X	Stopgain	Pathogenic
180	Exonic	*BRCA2*	NM_000059	Exon11	c.2830A>T	p.K944X	Stopgain	Pathogenic
186	Exonic	*BRCA1*	NM_007294	Exon22	c.5445G>A	p.W1815X	Stopgain	Pathogenic
187	Splicing	*BRCA1*	NM_007294	IVS17	c.5074+1G>T	NA	Splicing	Pathogenic
188	Exonic	*BRCA1*	NM_007294	Exon10	c.2821_2822dup	p.N941fs	Frameshift insertion	Likely pathogenic
189	Exonic	*BRCA1*	NM_007294	Exon10	c.1179_1180dupAG	p.G394fs	Frameshift insertion	Likely pathogenic
201	Exonic	*BRCA1*	NM_007294	Exon10	c.3627dupA	p.E1210fs	Frameshift insertion	Pathogenic
202	Exonic	*BRCA1*	NM_007294	Exon17	c.5080G>T	p.E1694X	Stopgain	Pathogenic
213	Exonic	*BRCA1*	NM_007294	Exon21	c.5339T>C	p.L1780P	Missense	Likely pathogenic
217	Exonic	*BRCA1*	NM_007294	Exon10	c.3442delG	p.E1148fs	Frameshift deletion	Pathogenic
223	Exonic	*BRCA1*	NM_007294	Exon21	c.5339T>C	p.L1780P	Missense	Likely pathogenic
225	Exonic	*BRCA1*	NM_007294	Exon10	c.3296delC	p.P1099fs	Frameshift deletion	Pathogenic
228	Exonic	*BRCA1*	NM_007294	Exon10	c.3718C>T	p.Q1240X	Stopgain	Pathogenic
229	Exonic	*BRCA1*	NM_007294	Exon10	c.3627dupA	p.E1210fs	Frameshift insertion	Pathogenic
233	Exonic	*BRCA1*	NM_007294	Exon10	c.2359delG	p.E787fs	Frameshift deletion	Pathogenic
244	Exonic	*BRCA2*	NM_000059	Exon11	c.4471_4474del	p.L1491fs	Frameshift deletion	Pathogenic
245	Exonic	*BRCA1*	NM_007294	Exon11	c.4117G>T	p.E1373X	Stopgain	Pathogenic
249	Exonic	*BRCA2*	NM_000059	Exon11	c.2798_2799del	p.T933fs	Frameshift deletion	Pathogenic
250	Splicing	*BRCA2*	NM_000059	Exon24_IVS24	c.9254_9256+11del	NA	Splicing	Likely pathogenic
254	Exonic	*BRCA1*	NM_007294	Exon10	c.3627dupA	p.E1210fs	Frameshift insertion	Pathogenic
255	Exonic	*BRCA1*	NM_007294	Exon10	c.3954dupT	p.G1319fs	Frameshift insertion	Likely pathogenic

(Continues)

TABLE 2 (Continued)

Germline mutation profile ($n = 78$)								
Case	Exon/intron	Gene	RefSeq	Exon	NT alteration	AA alteration	Type	Classification
256	Exonic	*BRCA1*	NM_007294	Exon10	c.3430C>T	p.Q1144X	Stopgain	Pathogenic
274	Exonic	*BRCA1*	NM_007294	Exon10	c.3430C>T	p.Q1144X	Stopgain	Pathogenic
276	Exonic	*BRCA2*	NM_000059	Exon14	c.7375A>T	p.K2459X	Stopgain	Pathogenic
278	Exonic	*BRCA2*	NM_000059	Exon11	c.6600_6601del	p.S2201X	Stopgain	Pathogenic
280	Exonic	*BRCA1*	NM_007294	Exon23	c.5470_5477del	p.I1824fs	Frameshift deletion	Pathogenic
290	Exonic	*BRCA2*	NM_000059	Exon10	c.1796_1800del	p.S599X	Stopgain	Pathogenic
294	Exonic	*BRCA1*	NM_007294	Exon6	c.390C>A	p.Y130X	Stopgain	Pathogenic
295	Exonic	*BRCA1*	NM_007294	Exon21	c.5339T>C	p.L1780P	Missense	Likely pathogenic
297	Exonic	*BRCA1*	NM_007294	Exon10	c.3895C>T	p.Q1299X	Stopgain	Pathogenic
298	Exonic	*BRCA1*	NM_007294	Exon10	c.3954dupT	p.G1319fs	Frameshift insertion	Likely pathogenic
299	Exonic	*BRCA2*	NM_000059	Exon11	c.2798_2799del	p.T933fs	Frameshift deletion	Pathogenic
302	Exonic	*BRCA1*	NM_007294	Exon10	c.3442delG	p.E1148fs	Frameshift deletion	Pathogenic
Somatic mutation profile ($n = 11$)								
Case	Exon/intron	Gene	RefSeq	Exon	NT alteration	AA alteration	Type	Classification
3	Exonic	*BRCA1*	NM_007294	Exon10	c.3449delC	p.P1150fs	Frameshift deletion	Likely pathogenic
5	Splicing	*BRCA1*	NM_007294	IVS22	c.5404_5406+1del	NA	Splicing	Likely pathogenic
7	Exonic	*BRCA2*	NM_000059.3	Exon11	c.5073delA	p.K1691fs	Frameshift deletion	Pathogenic
19	Exonic	*BRCA2*	NM_000059.3	Exon23	c.8991T>G	p.Y2997X	Stopgain	Pathogenic
40	Exonic	*BRCA1*	NM_007294	Exon21	c.5339T>C	p.L1780P	Missense	Likely pathogenic
43	Exonic	*BRCA2*	NM_000059.3	Exon11	c.5576_5579delTTAA	p.I1859fs	Frameshift deletion	Pathogenic
45	Splicing	*BRCA1*	NM_007294	IVS23	c.5467+1G>A	NA	Splicing	Pathogenic
47	Exonic	*BRCA1*	NM_007294	Exon10	c.2467A>T	p.R823X	Stopgain	Likely pathogenic
67	Exonic	*BRCA1*	NM_007294	Exon4	c.160C>T	p.Q54X	Stopgain	Pathogenic
74	Exonic	*BRCA1*	NM_007294	Exon10	c.3252delT	p.R1085fs	Frameshift deletion	Likely pathogenic

Note: The "A" of the ATG translation initiation codon is described as position number 1 in the *BRCA1* (NM_007294.2) and *BRCA2* (NM_000059.3). According to the American College of Medical Genetics and Genomics (ACMG) guideline, the prioritized variants were classified as pathogenic variants and likely pathogenic variants. "Disease-causing mutations" (DM) in THE Human Genome Mutation Database (HGMD, professional version 2014.01), "pathogenic" mutations in ClinVar, or causal mutation in UMD were categorized as known mutations.

Abbreviations: AA, amino acid; NA, not applicable; NT, nucleotide.

4 | DISCUSSION

This study was a large-scale nationwide next-generation sequencing (NGS)-based germline and somatic *BRCA* mutation prevalence study with clinical outcomes including treatment response in Korean ovarian cancer patients regardless of family history and age at diagnosis. We conducted germline and somatic *BRCA*m testing with whole blood and fresh frozen samples, respectively, using NGS analysis. The combined prevalence of *BRCA* germline and somatic mutation in patients with EOC differed depending on the sample cohort and detection method. The prevalence of germline or somatic *BRCA* mutations in epithelial ovarian cancer with all histologic types is known to vary from 5% to 29% by ethnicity and country.[37] The reported frequency of *BRCA*m in patients with high-grade serous EOC varies between 19% and 30%.[13,14,38,39] Our results showed higher rate of combining g*BRCA*m (26.2%) in high-grade serous EOC patients and s*BRCA*m (12.8%) among patients without germline mutation in Korean patients with high-grade serous EOC compared to previous reports. Although our study had potential selection biases similar to the TCGA ovarian cohort, which may have resulted in various

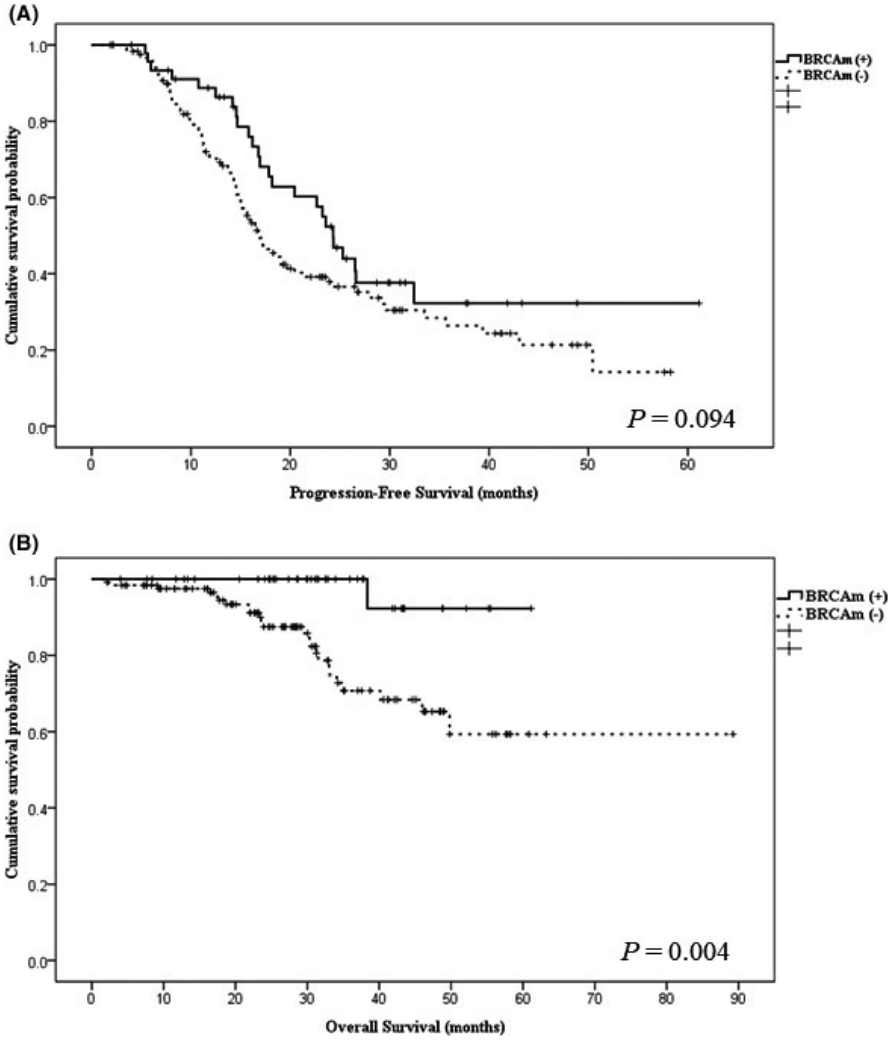

FIGURE 2 Kaplan-Meier survival analysis for progression-free survival and overall survival. (A) Progression-free survival according to *BRCA*m. (B) Overall survival according to *BRCA*m

TABLE 3 Univariate and multivariate Cox proportional hazards analysis for overall survival

	OS			
	Univariate		Multivariate	
Variables	HR (95% CI)	*P* value	HR (95% CI)	*P* value
Age at diagnosis, years, continuous	1.034 (0.995 ~ 1.076)	.092		
BRCA mutation ([+] vs [-])	10.620 (1.436 ~ 78.555)	.021	7.637 (1.010 ~ 58.278)	.049
Residual disease after debulking surgery (0-10 mm vs >10 mm)	2.330 (1.001 ~ 5.422)	.050	2.396 (0.938 ~ 6.118)	.068
Platinum response (sensitive vs resistant)	9.914 (4.094 ~ 24.006)	<.001	11.254 (4.333 ~ 29.232)	<.001

Abbreviations: CI, confidential interval; HR, hazard ratio; OS, overall survival.

estimated for both germline and somatic mutation rates,[40] it gives important message that we should perform tumor *BRCA* testing to provide a chance to use PARPi, even in this *BRCA*m (-) population.

The proportion of g*BRCA1*m to g*BRCA2*m in our cohort was reported as 4.6:1. Previous studies in predominantly Caucasian population-based cohorts showed proportions of 1.7:1 in Australia,[10] 1.9:1 in Canada,[41] and 1.7:1 to in the United States.[42] In Asian populations, most studies have reported that *BRCA1* comprised a higher proportion of *BRCA* mutations than *BRCA2*.[18,19,21,22,43,44] The high ratio for *BRCA1* to *BRCA2* mutation (4.6:1) in this study was interesting, but a larger study may be needed in the future. Founder mutations were shown in various ethnic groups, including Ashkenazi Jews, Icelanders, Russians, and Israelis.[45-47] Until recently, no founder mutations had been reported in Asian populations.[17-20,22,43] In this study, we also did not identify founder mutations. Therefore, genetic testing of *BRCA1m* and *BRCA2m* using full sequencing may

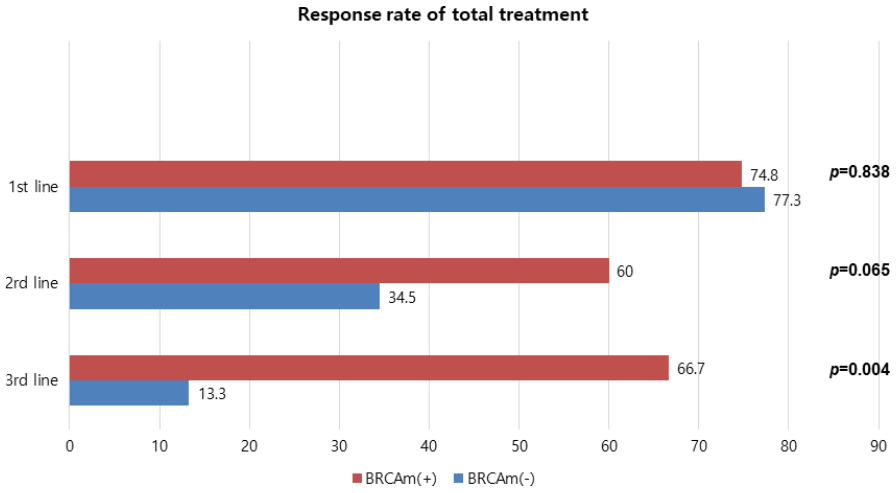

FIGURE 3 Comparison of overall response rate (ORR) in subsequent chemotherapy between *BRCA*m(+) and *BRCA*m(-) patients

be beneficial in Korean patients until highly recurrent founder mutations specific to Koreans have been identified. Wu et al[18] reported that 5% of their observed *gBRCA*m was large genomic rearrangement. Therefore, there is the possibility of undetected genomic rearrangement mutations in our study. However, we confirmed that large genomic rearrangement of the *BRCA* gene was very rare in Korean *BRCA* mutation carriers (<1%) in a previous report and it may not change the mutation rate in this study.

Korean data for *BRCA* mutation in EOC patients have been published and showed the clinical and genetic characteristics of this group.[48] There are substantial differences between the previous and current study that current study provides more information regarding the treatment response of patients' group. While the previous study showed only the characteristics of EOC patients with *BRCA*m, our study also showed the results of survival data and response to first-, second-, and third-line chemotherapies. In the previous study, the frequency of *BRCA*m was 16.5%, which is different to the 26.2% found in our study. It can be inferred that the difference in these results may be related to differences in the histologic type. In our study, only serous-type and endometrioid-type EOC were included, and the serous type was 94.7%, but in the previous study, serous type was 72.4%. In addition, the small number of patients may have caused the differences in the results, and a larger data analysis is needed in the future. In both studies, the age at diagnosis was not significant and the family history was a significant factor between the *BRCA*m(+) and *BRCA*m(-) groups.

Epithelial ovarian cancer patients with *BRCA*m were younger than those without *BRCA*m in previous reports from Western countries.[10] However, our data revealed there was no difference in age at diagnosis between the *BRCA*m(+) and *BRCA*m(-) groups (Table 1). In another Asian study, there were similar results for age characteristics in that Asian ovarian cancer patients without *BRCA* mutation were younger than those in Western countries, and there was no difference in age at diagnosis of ovarian cancer between the *gBRCA*m (+)and *gBRCA*m(-) groups.[17,21,43,18] In our study, 46 (46/78, 59.0%) patients with *gBRCA*m(+) had no family history of breast and/or ovarian cancer. These findings indicate that all ovarian patients should be tested for *BRCA*m for a better treatment decision regardless of their family history.[18] For the same reason *gBRCA* testing is currently recommended by the Society of Gynecologic Oncology and the National Comprehensive Cancer Network for all women diagnosed with EOC regardless of family history. Korean national health insurance also supports *BRCA*m testing in EOC regardless of family history. Although the relationship between *BRCA* mutation and advanced stage at diagnosis is controversial, some investigators have reported that ovarian cancers associated with *BRCA*m are more likely to be diagnosed at advanced stages although other reports[10,20] have shown no difference or a higher positive rate at stage I-II.[12,42,49,50] Our results showed no significant difference in g*BRCA*m rate between patients at stage I-II and stage III-IV.

In our study, the presence of *BRCA*m was associated with significantly better OS for patient with EOC compared to patients without *BRCA*m in univariate and multivariate analysis (Table 3 and Figure 2B), similar to previous reports.[10,11,15,36,51] *BRCA*m is known to be associated with better platinum response.[10,36,52] Several studies reported higher platinum response in the *gBRCA*m patient group even for first-line chemotherapy[10,36] and this effect may persist in subsequent lines of chemotherapy. Interestingly, our results were slightly different. In first-line chemotherapy, there was no difference platinum response between *BRCA*m(+) and *BRCA*m(-) patients (Figure 3). In second-line treatment, the platinum response of *BRCA*m(+) was significantly higher than that of *BRCA*m(-). Third-line chemotherapy showed also a significantly higher response in *BRCA*m(+) patients compared to *BRCA*m(-) patients. Thus, a trend of maintaining platinum sensitivity along successive lines of platinum chemotherapy in *BRCA*m(+) patients compared to acquiring resistance to platinum chemotherapy in *BRCA*m(-) patients was observed. These results are consistent with previous reports apart from no difference of platinum sensitivity at first-line chemotherapy in the current study.

There were several limitations in our study, including a number of limitations regarding gene analysis. First, we did not analyze a large genomic rearrangement (LGA).[12] Hasmad et al[43] reported that LGA was discovered in patients with negative for *BRCA*m using the sequencing mutation test, and the proportion of LGA was approximately 11% of the total *BRCA*m. An increasing number of LGA are being identified.[53] Second, analysis was not done

on whether *BRCA* gene inactivation was by epigenetic silencing.[13] Third, other genes associated with HR deficiency in patients with EOC were not analyzed.[11,13] Consequently, there is a possibility that a proportion of patients with *BRCA*m(-) might have HR-related gene alterations and they might show similar clinical outcomes, such as platinum sensitivity, to *BRCA*m(+) patients. Fourth, somatic BRCA mutation was tested only in patients without *gBRCA*m and with presence of available tissue. The family histories of the patients in this study were retrieved not from a genetic counselling interview but from questionaire and medical records. In addition, underestimation of the presence of actual familial history cannot be excluded due to separation or loss of families. Therefore, the real proportion of family history in Korean EOC patients may be higher than results in the current study.[22] Finally, the duration of follow-up of patients (28.1 months) was too short to provide accurate survival outcome, and not all enrolled patients were used in survival analysis.

The theory has been persistently raised that the penetrance and biology of *BRCA*m in Asian patients with EOC differ from that in the Caucasian population, resulting in different presentation of EOC. Furthermore, there is a suggestion that this depends on ethnicity and country. Currently, there are not sufficient data on the risk of EOC among Asian *BRCA*m carriers, but the risk of breast cancer seems to be lower than in Caucasians.[54] In this study, we demonstrated several differences to Caucasian group, such as comparable or higher prevalence of germline and/or somatic mutations, younger age at diagnosis of ovarian cancer resulting in no difference between age at diagnosis of EOC with or without *BRCA*m, high ratio of *BRCA1*m to *BRCA2*m, and a pattern of platinum sensitivity in the *BRCA*m group. However, the survival benefit and improved overall platinum sensitivity in the *BRCA*m group were similar to previous reports involving other ethnicities. Risk for cancer is affected by a number of factors, such as population incidence of cancer, birth cohort, genetic background, and reproductive and lifestyle factors, and these may alter the risk and presentation of EOC in Asian women.[54] There is therefore is a need to determine the risk of cancer and calibrate risk assessment methods for Asian women. The current study provides valuable insight and information about the role and presentation of *BRCA*m in Asian as well as Korean patients with EOC. In a future international clinical trial for high-grade serous EOC, ethnicity including *BRCA*m and its clinical significance should be considered since this may affect the clinical outcome of investigational treatments.

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CONFLICT OF INTEREST

The authors have no conflicts of interest to declare.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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