BRCA1/2 Mutation Status Is an Independent Factor of Improved Survival for Advanced (Stage III–IV) Ovarian Cancer

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Objective: The aim of this study was to explore *BRCA* mutation frequency and to evaluate its impact on prognosis of advanced-stage ovarian cancer patients treated with debulking surgery and platinum-based chemotherapy.

Methods: Patients with advanced-stage epithelial ovarian cancer were enrolled in a prospective, single-center study from September 2008 to December 2011. All cases were screened for *BRCA1* and *BRCA2* gene mutations. Progression-free survival (PFS) was assessed between *BRCA1/2* mutation carriers and *BRCA1/2* wild-type patients.

Results: One hundred seven patients were enrolled and screened for *BRCA1* and *BRCA2* mutations; 51.4% patients were positive for *BRCA1/2* gene mutation, 63.6% of which carried a single Baltic mutation, and 98.2% of them had serous histology. Older age (hazard ratio [HR], 1.032; 95% confidence interval [CI], 1.010–1.055; $P = 0.0047$), nonoptimal cytoreduction (HR, 3.170; 95% CI, 1.986–5.060; $P < 0.0001$), and *BRCA1/2* wild type (HR, 1.625 [1.003–2.632]; $P = 0.0486$) were significantly associated with shorter PFS in multivariate Cox regression analysis. Only the nonoptimal cytoreduction was a statistically significant risk factor for shorter overall survival (HR, 2.684; 95% CI, 1.264–5.701; $P = 0.0102$).

Conclusions: Advanced ovarian cancer patients harboring *BRCA1/2* mutation treated with debulking surgery and platinum-based adjuvant chemotherapy have a longer PFS.

Key Words: *BRCA1*, *BRCA2*, Cytoreductive surgery, Founder mutation

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Thirteen percent to 18% of all ovarian cancers are associated with autosomal dominant genetic predisposition due to germ-line mutations in *BRCA1* and *BRCA2* genes.[1–4] Certain ethnicities (eg, Ashkenazi Jewish, Polish, French Canadians) have been reported to have as high as 30% to 40% *BRCA1/2* mutation prevalence rates in epithelial ovarian cancer (EOC) due to founder effect.[5] In Lithuania, *BRCA1/2* mutational profile is complex and is also influenced by significant founder effect.[1,6] A single study (n = 43) from Lithuania showed 19% prevalence rate of 3 *BRCA1* founder mutations in unselected ovarian cancer cases.[7] However, the authors did not report histology or other clinical variables, and no comprehensive genetic testing was performed.

Cytoreductive surgery is the key toward prolonged survival in advanced EOC.[8–11] Many studies as well as Cochrane Gynecological Cancer Group meta-analysis indicated

cytoreduction to the lowest residual disease resulting in better survival.[12]

Another important factor influencing advanced EOC patient survival is the use of adjuvant chemotherapy. Until recently, a combination of taxane-based and platinum-based chemotherapy administered intravenously had been a criterion standard in treatment of advanced EOC.[13] International Collaborative Ovarian Neoplasm 7 and Gynecology Oncology Group-0218 trials, which added bevacizumab to the standard adjuvant chemotherapy, showed the best survival rates for high-risk EOC patients. Unfortunately, this regimen is not universally available due to its high cost. In addition, intraperitoneal chemotherapy is another treatment option for optimally debulked advanced ovarian cancer showing the highest progression-free survival (PFS) and overall survival (OS) rates.[14]

Biological factors including *BRCA* gene mutations can be prognostic in EOC. According to some studies, *BRCA* mutation carriers had longer PFS and responded better to platinum-based treatment.[15–18] However, there were studies that revealed no additional benefit of harboring a *BRCA* mutation influencing OS or PFS to already mentioned clinical factors previously.[19,20] These results could have been influenced by variability in study design, sample size, and different mutations, and the confounding effects of other well-established prognostic factors, such as extent of optimal debulking surgery, chemotherapy, and age, may have influenced these results.

The aim of our study was to evaluate *BRCA1/2* mutation frequency and influence of *BRCA1/2* mutation status on PFS in patients with advanced EOC, treated with debulking surgery and platinum-based chemotherapy.

MATERIALS AND METHODS

Patient Selection and Data Definition

Patients were recruited into the study at Vilnius University Hospital Santariskiu Klinikos (VUHSK) between September 2008 and December 2011. Eligible patients were women aged 18 years or older who had histologically confirmed nonmucinous primary or recurrent stage III to IV EOC and who were treated with debulking surgery and platinum-based chemotherapy. The study protocol was approved by the Vilnius Regional Biomedical Research Ethics Committee. All patients signed a written informed consent form. The date of diagnosis, tumor histology, age, ascites, level of cytoreduction, treatment type (chemotherapy, surgery), date of the first relapse, subsequent treatment modalities, and deaths were recorded. Cytoreduction to less than 5 mm or nonvisible or palpable residual tumor was considered as optimal (R0) cytoreduction. Cytoreduction to more than 5 mm, but less than 2 cm of residual tumor, was considered as suboptimal (R1), and cytoreduction to more than 2 cm of residual tumor was considered as nonoptimal (R2). Prospective follow-up was carried out at VUHSK by clinical oncologists or gynecologists every 2 to 3 months after the disease diagnosis. In case of suspicion of relapse, the gynecological examination with pelvic and abdominal ultrasound was performed followed by body computed tomography and/or magnetic resonance imaging. After the review of medical and pathology records, surgical stage, histological tumor type, and grade of differentiation were defined according to the International Federation of Gynecology and Obstetrics nomenclature[21] and World Health Organization standards. Performance status was evaluated according to the Eastern Cooperative Oncology Group (ECOG) criteria. The date of progression was determined based on CA-125 levels, and the imaging results were determined according to Response Evaluation Criteria in Solid Tumors.[22] Progression-free survival was defined as the time interval between the end of first-line chemotherapy and first confirmed sign of disease progression or recurrence. Progression-free survival was considered to be 0 months if disease progression manifested during treatment. Overall survival was defined as the time interval between the date of diagnosis and date of death from any cause.

BRCA1 and *BRCA2* Genetic Analysis

Comprehensive *BRCA1* and *BRCA2* (*BRCA1/2*) genetic testing was accomplished in the Laboratory of Molecular Medicine, Hematology, Oncology, and Transfusion Medicine Center, VUHSK. Genomic DNA for molecular analysis was extracted from peripheral blood leukocytes of EOC patients by using column-based kits (QIAamp Mini Kit, Qiagen, or GeneJET Kit, Fermentas) according to the manufacturer's instructions.

First, genetic screening for mutations in *BRCA1/2* genes was performed by high-resolution melting screening strategy on 96-well plate Light Cycler 480 (LS480; Roche Diagnostics) and 384-well plate LightScanner (LS; Idaho Technology) by using M13-tagged primers described previously[23] with optimized conditions for Maxima HotStartTaq and SYTO9 (Invitrogen) fully saturating dye. LC480 was used to perform the initial rapid screening for the identified 5 frequent mutations in Lithuania [ie, *BRCA1*: c.4035delA (4154 delA), c.5266dupC (5382insC), c.181 T > G (300 T > G), c.1687C > T (1806C > T), and *BRCA2*: c.658 659del (220delGT)] and LS for the full *BRCA1/2* screen of samples negative for the initial screen of common mutations. Gene Scanning Software (version 1.5; Roche) and LightScanner software (version 2.0; Idaho Technology) were used for analysis of melting curves obtained on the LC480 and LS, respectively. Automated bidirectional sequencing on ABI 3500 genetic analyzer (Life Technologies) was performed for the observed aberrant melting curve samples from the independent polymerase chain reaction product. NTI 10 (Invitrogen) software was used for the generated sequencing electropherogram data alignment and analysis.

Second, large genomic rearrangements were assessed by Multiplex ligation-dependent probe amplification method by using SALSA *BRCA1* P002 and *BRCA2* P045 probemix kits (MRC Holland, the Netherlands) according to the manufacturer's instructions for the samples negative for small *BRCA1/2* mutations. The fragment analysis of the amplified probes was implemented on an ABI 3500 genetic analyzer, and generated data were analyzed by visual inspection. Mutations of *BRCA1/2* genes were classified according to Human Genome Variation Society nomenclature at genomic level, and Breast Cancer Information Core nomenclature was used for consistency.

Finally, all EOC patients, identified with pathogenic *BRCA1/2* mutations, received cancer genetic counseling during their medical follow-up.

Statistical Analysis

Descriptive statistics was used to describe demographic characteristics. The normality of the distribution was assessed by using Kolmogorov-Smirnov test. Student *t* and Mann-Whitney *U* tests were used to evaluate the differences between the 2 independent normally and nonnormally distributed data sets, respectively. The differences between the independent 2 qualitative data groups were evaluated by Fisher exact test. Risk factors for PFS and OS were assessed by Cox regression analysis. The factors found to be significant in the univariate Cox regression analysis were entered into multivariate Cox model with stepwise model selection process. Survival trends were evaluated by Kaplan-Meier method. A 2-tailed *P* value less than 0.05 was considered to be significant. Statistical analysis was performed using the Statistical Analysis System package version 9.2.

RESULTS

Clinical Characteristics and Mutations

Between September 2008 and December 2011, 107 eligible patients (88 with primary and 19 with recurrent advanced EOC) were enrolled. Stage distribution was presented

TABLE 1. Clinical characteristics of advanced (stage III–IV) EOC patients, n = 107

	BRCA Mutation Positive		*BRCA* Wild Type		
Characteristic	**n**	**%**	**n**	**%**	
Total	**55**	**51.4**	**52**	**48.6**	***P***
Primary debulking status					
R0	32	58.2	28	53.9	0.6994*
R1	9	16.4	6	11.5	
R2	14	25.4	18	34.6	
Histological subtype					
Serous	54	98.2	45	86.5	0.0286†
Endometrioid	1	1.8	3	5.8	
Clear cell carcinoma	0	0.0	3	5.8	
Small cell carcinoma	0	0.0	1	1.9	
First-line chemotherapy					
Platinum with paclitaxel	39	70.9	41	78.8	0.3803
Platinum and cyclophosphamide	16	29.1	11	21.2	
Chemotherapy upfront surgery					
Performed	9	16.4	19	36.5	0.0270
Not performed	46	83.6	33	63.5	
ECOG					
0–1	52	94.5	42	80.8	0.0386
≥2	3	5.5	10	19.2	
Family history					
Breast-ovarian family history	37	67.3	6	11.5	<0.0001
No history of breast-ovarian cancer	18	32.7	46	88.5	
Age at the diagnosis of ovarian cancer, y					
Median	48		54		0.0349
Range	37–73		23–82		
Time from diagnosis to *BRCA* genes testing, mo					
Median	6		2		0.4571
Range	0–155		0–191		
Follow-up for all patients, mo					
Median	35		25		0.3433
Range	1–169		8–210		

*R0 vs non-R0.
†Serous vs nonserous.

TABLE 2. *BRCA* mutation types of advanced (stage III–IV) EOC patients, n = 107

BRCA Genes Status	n	%
BRCA wild type	52	48.6
BRCA mutated	55	51.4
BRCA1 c.4035delA (4154 delA)	35	63.6
BRCA1 c.5266DUP (5382 insC)	11	20.0
BRCA1 c.181 T > G (300 T > G)	3	5.6
BRCA1 c.1687C > T (1806C > T)	2	3.6
BRCA1 c.5258G > C (5377G > C)	1	1.8
BRCA1 c.3700_3704del5 (3819del5)	1	1.8
BRCA2 c.658 659del (8ex) (220delGT)	1	1.8
BRCA2 c.3975_3978dup (4206ins4)	1	1.8

as follows: IIIA, 3 (2.8%); IIIB, 2 (1.9%); IIIC, 78 (72.9%); and IV, 24 (22.4%). At diagnosis, the median age of all patients was 50 (range, 23–82) years. Fifty-five patients (51.4%) were carriers of *BRCA1/2* germ-line mutations (Table 1). Compared with the *BRCA1/2* wild-type patients, *BRCA1/2* mutant patients were diagnosed at a younger age (48 vs 54 years), more often had serous histology (98.2% vs 86.5%), had a better (ECOG 0-1) performance status (94.5% vs 80.8%), and had more often surgery upfront chemotherapy (16.4% vs 36.5%). The differences in clinical characteristics between *BRCA1/2* carriers and *BRCA* wild type were statistically not significant. Between the mutation and wild-type groups, optimal cytoreduction was not different. The median follow-up time of all patients was 29 (range, 1–210) months and was not different between the *BRCA* carriers and wild-type groups.

Among the *BRCA1/2* mutation patients, 35 (63.6%) had Lithuanian founder mutation c.4035delA (Table 2), which together with c.5266DUP and c.181 T > G accounted for 89.2% of all germ-line mutations. The prevalence of the remaining mutations was 10.8%. The prevalence of the Baltic mutation in advanced EOC trial population was 32.7%. Four *BRCA1/2* mutation-positive patients and 1 sporadic EOC patient had previously been diagnosed with breast cancer.

Survival Outcomes

Univariate Cox regression analysis identified 4 potential risk factors for a shorter PFS as follows: older age, nonoptimal cytoreduction, poorer performance status, and *BRCA1/2* wild type (Table 3). In multivariate analysis, older age (hazard ratio [HR], 1.032; 95% confidence interval [CI], 1.010-1.055; $P = 0.0047$), nonoptimal cytoreduction (HR, 3.170; 95% CI, 1.986-5.060; $P < 0.0001$), and *BRCA* wild type (HR, 1.625 [1.003-2.632]; $P = 0.0486$) remained independently statistically associated with shorter PFS. The median PFS was 19 (95% CI, 13-25) months in *BRCA1/2* mutated compared with 13 (95% CI, 10-16) months in *BRCA1/2* wild type ($P = 0.0390$) patients (Fig. 1).

At the last data check, 30 patients have died. All deaths were caused by disease progression. The deaths were equally distributed in both groups; 15 deaths were recorded in the *BRCA1/2* mutation group, and 15 were in the *BRCA1/2* wild-type group. Nonoptimal cytoreduction was the only significant factor for shorter OS (HR, 2.684; 95% CI, 1.264-5.701; $P = 0.0102$). The median OS was 92 (95% CI, 44-140) and 94 (95% CI, 45-143) months in *BRCA1/2* mutated and wild type ($P = 0.6256$) patients, respectively (Fig. 1).

DISCUSSION

We present a comprehensive analysis of clinical, demographic, and *BRCA1/2* genes analysis of 107 advanced ovarian cancer patients. Specifically, we evaluated the

TABLE 3. Cox regression analysis for PFS and OS of advanced (stage III-IV) EOC patients, n = 107

	Univariate			Multivariate		
	HR			HR		
Factor	Estimate	95% CI	*P*	Estimate	95% CI	*P*
PFS						
Age, y	1.032	1.010–1.054	0.0044	1.032	1.010–1.055	0.0047
Nonoptimal cytoreduction	2.801	1.769–4.434	<0.0001	3.170	1.986–5.060	<0.0001
ECOG ≥2	2.520	1.263–5.028	0.0088	Nonsignificant		
Nonserous histology	2.043	0.931–4.483	0.0747			
BRCA negative	1.590	1.010–2.504	0.0454	1.625	1.003–2.632	0.0486
OS						
Age, y	1.016	0.981–1.052	0.3709			
Nonoptimal cytoreduction	2.684	1.264–5.701	0.0102	2.684	1.264–5.701	0.0102
ECOG ≥2	0.899	0.270–2.993	0.8620			
Nonserous histology	1.174	0.351–3.924	0.7946			
BRCA negative	1.189	0.591–2.393	0.6268			

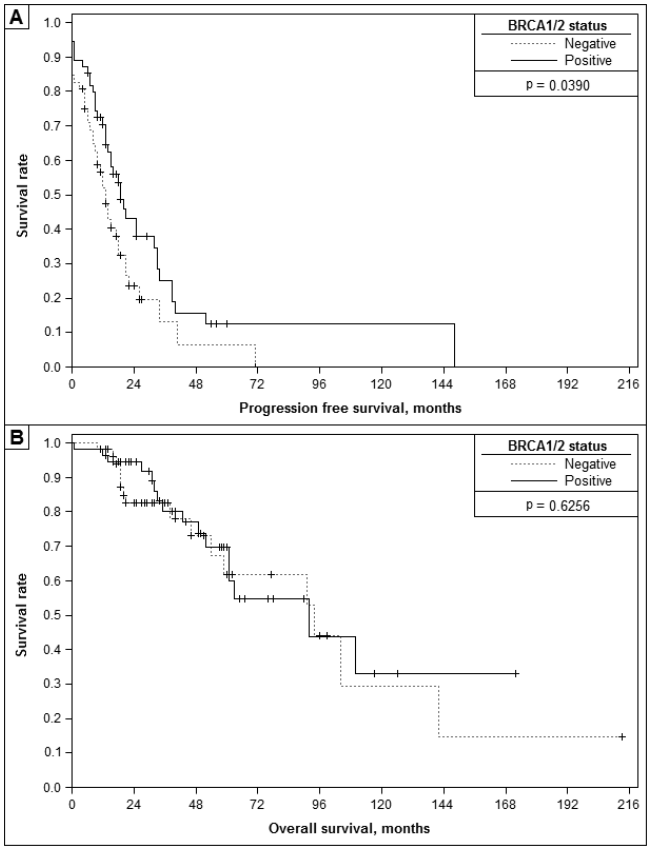

FIGURE 1. Kaplan-Meier PFS (A) and OS (B) survival curves for *BRCA 1/2* mutation positive and *BRCA 1/2* mutation negative patients.

influence of *BRCA1/2* mutation positivity on PFS in cases of advanced-stage ovarian cancer cohort in uniformly treated patient group. Our analysis was mainly focused on PFS after primary treatment because it represents better the effect of residual disease, optimal cytoreduction, and the efficacy of adjuvant chemotherapy. *BRCA1/2* status remained statistically significant for longer PFS despite other well-established strong confounding clinical factors such as debulking surgery, age, and performance status.[8,10,16]

Undisputable factor toward prolonged survival is the remaining tumor burden after cytoreductive surgery.[8,24] In a retrospective study of 194 patients, Aletti et al[11] concluded that a residual disease was the only independent predictor of poorer survival and that aggressive surgery to minimize the residual disease was justified. We can hardly argue about that, but what is extremely provoking is that in the recent and most comprehensive prospective trial that was conducted by the Australian Ovarian Cancer study apart from optimal cytoreduction, *BRCA1/2* mutation status was an independent prognostic factor toward longer PFS and OS.[18] Interestingly, patients with *BRCA1/2* mutation and nonoptimal cytoreduction had similar survival compared with optimally debulked nonmutant patients.

According to the cancer statistics at diagnosis, the average ovarian cancer patient age was 63 years.[25] In our study group, the median age at diagnosis of *BRCA1/2* mutation-positive patients was 48 years compared with 54 years in *BRCA1/2* wild-type group. Early onset of the disease in the study group was attributed to the high prevalence of *BRCA1/2* mutations. Mutation carriers presented with EOC at an earlier age of onset compared with noncarriers, which is consistent with earlier penetrance for *BRCA1/2* carriers.[5] A younger age could be an attributing factor toward better survival for patients with advanced ovarian cancer.[26] Some retrospective studies supposed that because of their age and comorbidities, elderly ovarian cancer patients did not receive standard treatment.[26,27]In our prospectively enrolled patients cohort, the age seemed to be an independent factor toward better PFS, but the difference in years between *BRCA* mutant and control group (median age, 48 vs 54; $P = 0.0349$) was statistically nonsignificant.

Residual disease and age are the 2 factors closely related to 1 another, probably because surgeons are willing to perform more aggressive surgery on younger patients to achieve optimal cytoreduction and thus improve survival. In our study, *BRCA1/2* wild-type patients were older, but the difference of optimal cytoreduction was not statistically significant compared with *BRCA1/2* mutation-positive patients (53.9% vs 58.2%, $P = 0.6994$).

About half of our study population were *BRCA1/2* mutation carriers, which could be attributed to several factors; 43 patients (40%) had family history of breast or ovarian cancer, and 86% of them were carriers. In the subgroup without family history, mutations were found in 18 patients (28%), which is comparable with the upper prevalence range of other inland white populations.[28] More than 60% of patients carrying a *BRCA1/2* mutation had a single Baltic founder mutation *BRCA1* c.4035delA; therefore our results could be more readily applied to EOC populations that have high prevalence of this mutation.

Our analysis has several strengths; unlike many previous studies, we restricted our analysis only to advanced stage(III-IV) EOC that accounts for the major morbidity and mortality from EOC; over 90% of the study group had serous histology and high-grade tumors. Such restriction allowed us to reveal the impact of *BRCA1/2* mutations in the most cases of advanced EOC. Furthermore, all of our trial group EOC patients were tested for *BRCA1/2* genes mutations and confirmed as *BRCA1/2* wild type (noncarriers) rather than matched untested controls, which was the case in most previous studies. In addition, we accounted for possible survivorship bias due to the time elapsed from the date of diagnosis and genetic testing; therefore time from the diagnosis to genetic testing was recorded and proved to be not different between mutated and nonmutated patients. Finally, our study was limited to the patients who were treated in the single institution with common medical and surgical standards and had detailed clinical analysis with a careful follow-up, thus minimizing variability in the treatment strategies that could affect outcomes.

However, our study has limitations; due to the small sample size we, were unable to differentiate outcomes between *BRCA1 and BRCA2* mutation carriers. In our study, 19 patients were recruited after their first recurrence or after they came seeking for a second opinion into a tertiary

clinic, which could be a bias on PFS analysis. We performed subanalyses in that group to minimize bias by enrolling only *BRCA* mutation positive or only optimally debulked patients. As a result of this analysis, we found that there were no differences in terms of enrollment of only *BRCA* positive or only patients without residual disease. In conclusion, our data provide an additional line of evidence of better outcome of BRCA-mutant advanced EOC patients after debulking surgery and platinum chemotherapy. This can have important clinical implications for counseling, medical management, and enrolling patients into new trials. It is well known that ovarian cancer cells that lost the ability to repair deoxyribonucleic acid double strand break due to alkylating medications are more sensitive to platinum medications and commonly respond to the second-line or third-line of chemotherapy with platinum.[16] Because of this, we could suspect that patients with *BRCA1/2* mutations should have not only longer PFS but OS as well. This response can be dependent on tumor type, with breast and ovarian cancer cell lines preferentially showing this effect. Although the therapeutic implications of *BRCA1/2* mutations remains unproven in these patient groups, initial clinical evidence suggests that there could be higher effect of DNA damaging agents such as heavy metals (cisplatin, carboplatin).

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