Original Paper

Survival Benefit of Germline BRCA Mutation is Associated with Residual Disease in Ovarian Cancer

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Key Words

Ovarian cancer • BRCA1 gene • BRCA2 gene • Mutation • Survival • Residual disease

Abstract

Background/Aims: Prognostic value of germline *BRCA1* or *BRCA2* (*gBRCA1/2*) mutations in epithelial ovarian cancer (EOC) remains controversial, especially in the estimation of long-term survival. We previously reported the largest study of *gBRCA1/2* mutation prevalence in Chinese EOC patients. The aim of this study is to further illustrate the correlation of residual disease and survival in *BRCA*-associated EOC in China. **Methods:** In the current cohort consisting of 615 cases from the Chinese EOC genome-wide association study, we evaluated the association between *gBRCA1/2* mutation and clinical outcomes. **Results:** Overall, we did not find any significant difference between *gBRCA1/2* mutation carriers and non-carriers in both progression-free survival (PFS) and overall survival (OS) (19.3 vs. 18.1 months and 77.2 vs. 73.2 months, $P=0.528$ and 0.147 , HR 0.93 and 0.79, 95%CI 0.74–1.17 and 0.57–1.09, respectively). However, within three years after diagnosis, mutation carriers showed a longer OS than non-carriers ($P=0.018$, HR 0.53, 95%CI 0.31–0.90). Such a survival advantage decreased along with the extension of follow-up time. Quite interestingly, in the subgroup of patients with gross residual disease, mutation carriers had a longer survival than non-carriers (18.5 vs. 15.1 months and 68.5 vs. 54.3 months, $P=0.046$ and 0.038 , HR 0.74 and 0.65, 95% CI 0.55–1.00 and 0.43–0.98, for PFS and OS respectively). **Conclusions:** Our findings provided the evidence that *gBRCA1/2* mutation was not associated with survival in Chinese EOC patients, which possibly attributed to more than 37% of the patients without gross residual disease. Survival benefit of *gBRCA1/2* mutation was prominent in ovarian cancer patients with gross residual disease.

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Introduction

Epithelial ovarian cancer (EOC) is one of the leading fatal gynecologic malignancies worldwide, resulting in 151,900 cancer deaths in 2012 [1]. The incidence of EOC in China has drastically increased, while the mortality rate has not been improved over the past 10 years, up to 52,100 new cases and 22,500 deaths in 2015 [2]. Accumulated data have demonstrated a wide range of inter-individual genetic variability associated with EOC risk, and approximately 20-25% of all EOC patients had germline mutations [3], among which germline *BRCA1* or *BRCA2* (*gBRCA1/2*) mutations are a major risk factor for Hereditary Breast and Ovarian Cancer (HBOC) syndrome [4]. In recent years, recommendations for *BRCA* testing and genetic counseling from the Society for Gynecologic Oncology [5] and from the National Comprehensive Cancer Network [6] have further expanded to any individual who is diagnosed with an invasive ovarian cancer, even in the absence of a family history.

Another important reason for *BRCA* testing in ovarian cancer patients has been further emphasized is that mutation carriers showed an increased sensitivity to PARP (poly [ADP-ribose] polymerase) inhibitors [7]. However, the updated descriptive survival analyses suggested that such a short-term progression-free survival (PFS) advantage of PARP inhibitor maintenance monotherapy did not lead to an overall survival benefit eventually [8], indicating a possible controversy of using *BRCA* mutations as the prognostic factor for long-term survival in ovarian cancer patients. Similarly, amounting evidence from studies including several meta-analyses has demonstrated that EOC patients carrying inherited *BRCA1* or *BRCA2* mutations have a better overall survival, compared with non-carriers [9, 10]. However, more large-scale studies have suggested that the short-term survival advantage would not persist, when the patients were followed up 10 years [11, 12]. To date, there is no agreement on the exact role of *gBRCA1/2* mutations in the prognosis of EOC. More importantly, given the substantial inter-ethnic heterogeneity, to our knowledge, there is still no large-scale study focused on the association between *gBRCA1/2* mutation status and survival in Chinese EOC patients.

We firstly reported a large study of *gBRCA1/2* mutation screening in a population of 916 Chinese EOC patients, and found an overall frequency of 16.7% in the cases harboring *gBRCA1/2* pathogenic mutations [13]. Till now, the relatively long-term survival data have been available for those patients. Herein, we compared the clinical outcomes between EOC patients with and without inherited *BRCA1/2* mutations. Our findings provided evidence on whether *gBRCA1/2* mutation is a prognostic factor for EOC patients during a relatively long-term follow-up period.

Materials and Methods

Study subjects

This study was approved by the Institutional Review Board of Zhongshan Hospital, Fudan University (FDUZH) and Fudan University Cancer Hospital (FUDCH). Each patient signed a written informed consent and provided an additional 10 ml of venous blood sample for DNA extraction.

As described in the previously published study, the *BRCA1/2* mutation testing was performed on whole blood samples from 916 EOC patients based on Shanghai Ovarian Cancer Study that enrolled in the Chinese EOC genome-wide association study [13, 14]. Each patient was followed up for disease progression and survival status, except for 157 cases who were derived from Jiangsu Cancer Hospital. As a result, the current retrospective observational study enrolled 759 EOC patients, among which 144 cases were lost for follow-up after primary cytoreduction, with a lost-follow-up rate of 19%. Therefore, the final cohort included 615 EOC patients with the available data on the follow-up and *gBRCA1/2* mutation status. All the tumors were pathologically reviewed and confirmed independently by two gynecologic pathologists. The detailed clinical and pathological information was extracted from the institutional patients' database, including age at diagnosis, tumor histopathology, grade, International Federation of Gynecology and Obstetrics (FIGO) stage, neoadjuvant chemotherapy, chemotherapeutic response, and residual disease (RD). HBOC-related tumors

were defined as breast, ovarian, pancreatic cancers in women and cancers of breast and prostate in men. For those patients who were diagnosed with both ovarian carcinoma and breast cancer, survival estimations were confirmed by the reason of death or recurrence. As described previously, complete cytoreduction was defined as no grossly visible tumor in overall after surgical procedure [15].

gBRCA1/2 mutation status

Mutation screening was performed by using the next generation sequencing approach confirmed by Sanger DNA sequencing, as described previously [13]. We considered protein-truncating variants, splicing variants, and missense variants referred to be deleterious by public mutation databases as class-5 or pathogenic mutations.

Statistical methods

PFS and overall survival (OS) times were calculated from the date of first treatment to the date of disease recurrence and death, respectively. Progression-free interval (PFI) was defined from the date of last cycle of first-line adjuvant chemotherapy to the date of recurrence. We defined PFI < 6 months and PFI ≥ 6 months as chemoresistant and chemosensitive, respectively. Patients without progression, lost to follow-up or died from other causes were censored at their last date of the records. Kaplan-Meier survival estimate and log-rank test were calculated to evaluate PFS, OS and PFI. We performed the Cox proportional hazards regression analysis to evaluate the effects of *gBRCA1/2* mutation status on the cumulative probability of survival in EOC patients. Life-table approach was used to estimate annual mortality and hazards risk for each one-year period after the date of diagnosis. All analyses were performed using the SPSS Statistics software v16.0, unless stated otherwise. All *P* values were two-sided with a significance level of *P* < 0.05.

Results

Patients' characteristics and gBRCA1/2 mutations

In this observational study, the final analysis included 615 patients who were pathologically confirmed with EOC and had available follow-up data. Despite of potential interests of variants with unknown biological significance, we only took pathogenic mutations (class-5) into consideration. In total, 105 mutations were classified as pathogenic (17.1%), characterized by frameshifts, nucleotide substitutions leading to stop-codon or affecting canonical splicing sites, or missense mutations that were defined as pathogenic by existing mutation databases. Specifically, 81 out of 105 pathogenic mutations occurred in

Table 1. Clinico-pathological characteristics with mutation status. FIGO, International Federation of Gynecology and Obstetrics; HBOC, Hereditary Breast and Ovarian Cancer; RD, residual disease; PFS, progression-free survival; PFI, progression-free interval; OS, overall survival. ^a One is endometrioid/transitional cell, and the other one is endometrioid/serous. ^b HBOC-related tumors were defined as cancers of breast, ovary, pancreatic cancers in women and cancers of breast and prostate in male relatives

	Non-carriers	BRCA1 mutation	BRCA2 mutation	BRCA1/2 mutations
Cases	510 (82.9)	81 (13.2)	22 (3.6)	2 (0.3)
Age at diagnosis, yrs., median (range)	54.0 (20-81)	51.0 (36-69)	55.5 (44-72)	64.5 (62-67)
Histology				
Serous	434 (85.1)	73 (90.1)	21 (95.5)	2 (100)
Clear cell	33 (6.5)	1 (1.2)	0	0
Endometrioid	24 (4.7)	4 (4.9)	0	0
Mucinous	12 (2.4)	0	0	0
Transitional cell	2 (0.4)	1 (1.2)	0	0
Mixed ^a	2 (0.4)	0	0	0
Adenocarcinoma	3 (0.6)	1 (1.2)	1 (4.5)	0
Undifferentiated	0	1 (1.2)	0	0
Grade				
1	8 (1.6)	0	0	2 (100)
2	59 (12.1)	10 (12.7)	0	0
3	421 (86.3)	69 (87.3)	20 (100)	0
FIGO stage				
I	16 (4.8)	0	0	0
II	20 (6.0)	6 (10.7)	0	0
III	253 (76.0)	40 (71.4)	13 (86.7)	1 (100)
IV	44 (13.2)	10 (17.9)	2 (13.3)	0
HBOC-related tumor ^b				
Yes	39 (7.6)	27 (33.3)	5 (22.7)	0
No	471 (92.4)	54 (66.7)	17 (77.3)	2 (100)
Neoadjuvant chemotherapy				
Yes	76 (15.5)	10 (12.3)	1 (4.8)	0
No	413 (84.5)	71 (87.7)	20 (95.2)	2 (100)
Chemotherapeutic sensitivity				
Yes	366 (73.6)	61 (76.2)	18 (85.7)	1 (50.0)
No	131 (26.4)	19 (23.8)	3 (14.3)	1 (50.0)
Residual disease, RD				
RD=0	169 (37.1)	31 (40.3)	8 (38.1)	0
RD>0	287 (62.9)	46 (59.7)	13 (61.9)	2 (100)
Recurrence				
Yes	428 (84.9)	72 (90.0)	18 (81.8)	1 (50.0)
No	76 (15.1)	8 (10.0)	4 (18.2)	1 (50.0)
Cancer-related death				
Yes	232 (45.5)	33 (40.7)	10 (45.5)	1 (50.0)
No	278 (54.5)	48 (59.3)	12 (54.5)	1 (50.0)
PFS, months, median (95% CI)	18.0 (16.5-19.6)	19.0 (14.6-23.4)	20.8 (15.7-26.0)	8.4
PFI, months, median (95% CI)	11.8 (10.4-13.3)	13.4 (10.8-16.0)	15.1 (11.5-18.7)	0.9
OS, months, median (95% CI)	73.2 (63.2-83.1)	109 (56.0-163.4)	53.8 (21.5-86.0)	38.1

BRCA1 only (13.2%) and 22 (3.6%) occurred in *BRCA2* only. Two patients carried variants in both *BRCA1* and *BRCA2* (0.3%) (Table 1). The age at diagnosis ranged from 20 to 81 years with 88.8% of cases aged between 41 and 70 years. The median ages were 54.0, 51.0 and 55.5 years for non-carriers, *BRCA1* only and *BRCA2* only mutation carriers, respectively.

There were no differences in mean ages at diagnosis between pathogenic mutation carriers and non-carriers (54.3 vs. 52.9 years; Student's *t*-test, *P*=0.106). Patients who had family or personal history of HBOC-related tumors had a significantly increased rate of pathogenic *gBRCA1/2* mutations (*P* < 0.001). Among those patients, 10 were diagnosed with personal history of the additional breast cancer. All four deaths were confirmed by the cause of ovarian carcinoma. Except for histology, there were no differences between mutant carriers and non-carriers in other clinico-pathological variables, such as tumor grade, FIGO stage, chemotherapeutic response, and RD.

Clinical outcomes

The follow-up was censored at May 31, 2017, with a median follow-up of 71.3 (interquartile range, IQR 47.9-88.6) months. There were 519 recurrences and 276 cancer deaths, among which 72, 18 and 1 recurrences, as well as 33, 10 and 1 deaths were observed in *BRCA1* only, *BRCA2* only and *BRCA1/2* mutation carriers, respectively (Table 1). The median PFS, OS and PFI were 18.4 (95% CI 17.1-19.8) months, 73.6 (95% CI 64.5-82.8) months, and 12.5 (95%CI 11.1-13.8) months, respectively. Overall, we did not find any significant difference between mutation carriers and non-carriers in PFS and OS (19.3 vs. 18.1 months for PFS; 77.2 vs. 73.2 months for OS, *P*=0.528 and 0.147, HR 0.93 and 0.79, 95%CI 0.74-1.17 and 0.57-1.09, respectively; Fig. 1). Similarly, no significant survival benefit was observed in those patients who carried *BRCA1* or *BRCA2* mutation only (Table 2).

Interestingly, during the short-term follow-up period, within three years after diagnosis, mutation carriers showed a longer overall survival than non-carriers (*P*=0.018, HR 0.53, 95%CI 0.31-0.90; Fig. 2A). Such a survival advantage was decreased along with the extension of follow-up time. As shown in Fig. 2B, the risk of *gBRCA1/2* mutation status was much higher than that of non-carriers at three years of median survival time, and reversed at

Fig. 1. Survival of ovarian cancer patients by *gBRCA1/2* mutation status. A. progression-free survival, B. overall survival.

Table 2. Prognostic factors of epithelial ovarian cancer by Cox proportional hazards regression models. HGSOc, high-grade serous ovarian carcinoma; FIGO, International Federation of Gynecology and Obstetrics; RD, residual disease. ^a Cox proportional hazards regression models, comparing *BRCA1* mutation carriers vs. non-carriers. ^b Cox proportional hazards regression models, comparing *BRCA2* mutation carriers vs. non-carriers

Prognostic factors	Recurrence	Univariate	Multivariate		Death	Univariate	Multivariate			
	N (%)	HR (95% CI)	P	HR (95% CI)	P	N (%)	HR (95% CI)	P	HR (95% CI)	P
All patients	520 (85.5)					277 (45.0)				
Age at diagnosis, yrs										
≤ 54 (median)	271 (85.2)	1.00		1.00		143 (44.5)	1.00		1.00	
> 54 (median)	249 (85.9)	1.14 (0.96-1.35)	0.137	0.88 (0.70-1.10)	0.247	134 (45.6)	1.20 (0.95-1.52)	0.133	0.82 (0.60-1.12)	0.215
Histopathology										
HGSOC	404 (88.2)	1.00		1.00		214 (46.3)	1.00		1.00	
Others	99 (75.0)	0.64 (0.51-0.80)	<0.001	0.82 (0.58-1.16)	0.253	57 (42.2)	0.67 (0.50-0.90)	0.008	0.97 (0.61-1.53)	0.882
FIGO stage										
I-II	29 (74.4)	1.00		1.00		14 (33.3)	1.00		1.00	
III-IV	315 (87.3)	1.36 (1.12-1.65)	0.002	1.29 (1.04-1.61)	0.021	162 (44.6)	1.56 (1.17-2.07)	0.002	1.55 (1.12-2.16)	0.009
Neoadjuvant chemotherapy										
No	425 (85.0)	1.00		1.00		227 (44.9)	1.00		1.00	
Yes	79 (90.8)	1.47 (1.15-1.86)	0.002	1.56 (1.17-2.07)	0.002	43 (49.4)	1.49 (1.17-1.89)	0.003	1.52 (1.01-2.29)	0.044
Residual disease, RD										
RD=0	149 (73.4)	1.00		1.00		64 (30.8)	1.00		1.00	
RD>0	319 (91.9)	2.17 (1.78-2.65)	<0.001	1.87 (1.44-2.44)	<0.001	190 (54.6)	2.63 (1.97-3.51)	<0.001	2.00 (1.37-2.90)	<0.001
gBRCA mutation										
No	428 (84.9)	1.00		1.00		232 (45.5)	1.00		1.00	
Yes	91 (87.5)	0.93 (0.74-1.17)	0.528	0.88 (0.66-1.18)	0.394	44 (41.9)	0.79 (0.57-1.09)	0.140	0.94 (0.63-1.40)	0.766
BRCA1 mutation only ^a	72 (90.0)	0.96 (0.75-1.23)	0.739	1.00 (0.73-1.38)	0.980	33 (40.7)	0.76 (0.53-1.09)	0.130	0.89 (0.57-1.37)	0.586
BRCA2 mutation only ^b	18 (81.8)	0.83 (0.52-1.34)	0.451	0.61 (0.31-1.19)	0.147	10 (45.5)	0.92 (0.49-1.72)	0.783	0.63 (0.25-1.56)	0.315

five years of survival. Annual mortality for the subgroups of *BRCA1*, *BRCA2*, *BRCA1/2* mutation carriers and non-carriers at one-year interval from the time of diagnosis are presented in Table 3. The annual risk of death in the mutation carriers was much lower than that of non-carriers for years 1 and 2, but thereafter was similar or increased. The odds of death of EOC for carriers vs. non-carriers increased over the time since diagnosis.

As shown in Table 2, poor PFS and OS were observed in those patients who were diagnosed with high-grade serous EOC (HG-SOC), or with an advanced stage (III-IV), or received neoadjuvant chemotherapy, or incomplete cytoreduction. Obviously, FIGO stage (III-IV), neoadjuvant chemotherapy and gross residual disease (RD>0) were independently associated not only with disease recurrence but also with cancer death (For recurrence: adjusted HR 1.29, 1.56 and 1.87; 95% CI 1.04-1.61, 1.17-2.07 and 1.44-2.44; $P=0.021$, 0.002 and <0.001, respectively; for death: adjusted HR1.55, 1.52 and 2.00; 95% CI 1.12-2.16, 1.01-2.29 and 1.37-2.90; $P=0.009$, 0.044 and <0.001, respectively).

Subgroup analyses by clinico-pathological variables showed that mutation carriers had a significantly better PFS and OS than non-carriers in the subgroup of incomplete cytoreduction (RD>0, 18.5 vs. 15.1 months and 68.5 vs. 54.3 months; $P=0.046$ and 0.038; HR 0.74 and 0.65; 95% CI 0.55-1.00 and 0.43-0.98; Fig. 3). More interestingly, in the subgroup of non-mutation carriers, complete cytoreduction led to a much longer PFS and OS, compared with incomplete cytoreduction (RD>0) (both $P<0.001$; HR 2.42 and 2.96; 95% CI 1.93-3.03 and 2.13-4.11); while such a strong evidence of survival benefit from complete cytoreduction could not be observed in those patients who carried *BRCA1/2* mutations (Fig. 3).

gBRCA pathogenic mutations

Totally, out of 12 patients with longer than 10-year survival, five *BRCA1* mutations were identified: c.5470_5477del8, c.1058G>A, c.1054G>T, c.4120_4121delAG and c.441+2delT.

Table 3. Annual cancer-related mortality (%) by gBRCA1/2 mutation status. ^a Annual mortality is the ratio of the observed deaths due to ovarian cancer relative to the number of person-years in that specific interval. ^b Odds ratio of death in the one-year interval for women that were alive at the beginning of the same interval, comparing BRCA mutation carriers vs. non-carriers

Year from diagnosis	Non-carriers		BRCA1 mutation		BRCA2 mutation		BRCA1/2 mutations		Odds ratio (95%CI) ^b
	Death	Annual mortality ^a (%)	Death	Annual mortality ^a (%)	Death	Annual mortality ^a (%)	Death	Annual mortality ^a (%)	
≤ 1	20	3.9	0	0	0	0	0	0	—
1 to ≤ 2	53	11.2	3	3.8	0	0	0	0	0.43 (0.13-1.38)
2 to ≤ 3	52	13.3	11	15.6	1	5.0	0	0	0.91 (0.48-1.71)
3 to ≤ 4	37	12.2	6	11.3	5	28.6	1	100	1.18 (0.61-2.26)
4 to ≤ 5	30	13.2	5	12.2	3	26.1	0	0	2.47 (1.10-5.54)
5 to ≤ 6	14	8.9	2	6.5	1	13.3	0	0	0.71 (0.23-2.21)
6 to ≤ 7	14	13.4	3	13.3	0	0	0	0	0.66 (0.15-2.94)
7 to ≤ 8	6	11.2	0	0	0	0	0	0	—
8 to ≤ 9	3	12.8	0	0	0	0	0	0	—
9 to ≤ 10	2	18.2	1	14.3	0	0	0	0	1.03 (0.09-11.55)
> 10	2	13.8	2	21.1	0	0	0	0	3.28 (0.28-38.48)
Overall	233	10.3	33	7.9	10	9.4	1	15.4	0.78 (0.57-1.08)

Fig. 2. A. Overall survival by gBRCA1/2 mutation status within three years from diagnosis, B. The association between gBRCA1/2 mutation status and the risk of survival by the Life-Table analysis.

Fig. 3. Survival of ovarian cancer patients by gBRCA1/2 mutation status and residual disease. A. progression-free survival, B. overall survival.

The mutation c.441+2delT was never reported in the literatures or public databases. Among 111 cases who had less than two-year OS time, three *BRCA1* mutations were identified (c.2216_2217delAA, c.3181delA and c.5095C>T). However, among eight patients with the c.5470_5477del8 mutation, only one case survived longer than 10 years. Likewise, c.5095C>T showed a controversial survival outcome, one with a 18-months OS verses the other with a 109.7-months OS.

Discussion

This is, to our knowledge, the first report with a relatively large sample size to evaluate the prognostic value of *gBRCA1/2* mutations in Chinese EOC patients. In this unfiltered series of EOC patients, we did not find any significant associations between *gBRCA1/2* mutations and survival (carriers vs. non-carriers: 19.3 vs. 18.1 months and 77.2 vs. 73.2 months, for PFS and OS respectively). During the short-term follow-up period, within three years after diagnosis, patients with *gBRCA1/2* mutations showed a longer OS than non-carriers, but such a survival advantage was decreased along with the extension of follow-up time. Further annual cancer-related death by the mutation status confirmed the findings that the annual risk of death in the mutation carriers was much lower than that of non-carriers in the first two years after diagnosis, but the mortality rate stayed similar or reversed in years 3 to 10. Our findings were consistent with several independent large-scale studies in Caucasians [11, 12, 16]. For example, in 2013, McLaughlin first reported their long-term follow-up data that short-term survival advantage of *BRCA* mutations did not provide a long-term survival benefit [12], which led to a controversy on prognostic value of the *BRCA* mutation status. In a larger study with 6, 556 EOC patients, the 10-year survival estimates were similar among *gBRCA1* and *gBRCA2* mutation carriers and non-carriers (25%, 35% and 30%, respectively) [11].

On the contrary, an updated meta-analysis including 18, 396 EOC patients debated that *BRCA1/2* mutations, *BRCA1* or *BRCA2* mutation might only show a certain benefit of OS and PFS [10]. It might be more likely addressed to the better response to platinum-based chemotherapy for mutation carriers [17, 18]. Recently, Bookman reported the impact of primary platinum-free interval and the *BRCA1/2* mutation status on EOC survival in 267 patients [19]. They found that the time to recurrence in mutation carriers was significantly prolonged than that in non-carriers, but the OS did not show the same statistical significance [19]. This might partly explain our findings of the vanishing long-term survival benefit of *gBRCA1/2* mutations. Moreover, the effect of *gBRCA1/2* mutations might be superior on the initial response to chemotherapy, particularly in those with incomplete cytoreduction, leading to a better survival. However, the ultimate probability of long-term survival was more likely to be similar because more than 37% of the patients had no gross residual disease after primary debulking surgery.

More notably, our further subset analyses showed that in the subgroup of non-carriers, complete cytoreduction was associated with a much longer survival, but this association was not prominent in the subgroup of *gBRCA1/2* mutation carriers. Strong evidence has shown that the size of residual disease was one of the strongest prognostic markers in stage III and IV EOC patients, because patients with microscopic (no gross) residual disease had a far better PFS and OS than those with gross lesions, especially those with more than 1.0 cm residual disease [20, 21].

In contrary to our findings, Hyman stated that there were no correlation between the *BRCA* mutation status and the rate of optimal debulking surgery [22], which might be affected by various ethnics and different sample size. Thus, in the current study, we found a discrepancy on the prognostic role of complete cytoreduction between mutation carriers and non-carriers, but the underlying mechanism is unclear. It seems that there was a superior impact of complete cytoreduction on prognostic estimation, compared with hereditary factors, such as *gBRCA1/2* mutations. Therefore, complete cytoreduction was strongly

recommended in primary debulking surgery, especially for EOC patients without *gBRCA1/2* mutations.

In the current study, we further evaluated the impact of clinico-pathological variables on EOC prognosis, and found that complete cytoreduction and FIGO stage were strong predictors for EOC recurrence and death. These findings support that survival is maximized when residual disease is minimized after complete cytoreduction and chemotherapy [23]. Moreover, we found that neoadjuvant chemotherapy was independently associated with OS, which was consistent with our previous retrospective study [15]. Likewise, in 2017, Petrillo *et al.* reported that in the subgroup of *BRCA1/2* non-mutation carriers, patients with neoadjuvant chemotherapy had a worse PFS than those with primary debulking surgery, but no significant difference was found in *BRCA1/2* mutation carriers, nor in the estimation of OS [24].

Quite remarkably, five mutations in *BRCA1* (i.e., c.5470_5477del8, c.1058G>A, c.1054G>T, c.4120_4121delAG and c.441+2delT) were identified in patients with longer survival (> 10 years). In our previous study, c.5470_5477del8, as the top recurrent mutation, was shown to be a Chinese ethnic-related hot-spot alteration in *BRCA1* [13]. Here we suspect that c.5470_5477del8 may be a prognosis-associated mutation for EOC, which has a possible impact on EOC tumorigenesis and progression in Chinese ethnicity. However, the observed controversial survival outcome that one (EOC0314) had a long-term survival and the other two (EOC1199 and 35) had a short OS (< three years) has yielded an uncertain conclusion. Thus, further validation studies with functional experiments in depth are warranted.

Conclusion

In conclusion, we reported for the first time a relatively large-scale study to illustrate the prognostic role of *gBRCA1/2* mutations in Chinese EOC patients. Overall, there were no significant associations between *gBRCA1/2* mutations and survival, especially in long-term survival. Similar result was found in subgroup of patients with complete cytoreduction, but mutation carriers had a better PFS and OS than non-carriers in the subgroup of incomplete cytoreduction (RD>0). Our findings strengthened the evidence that EOC survival did not differ between *gBRCA1/2* mutation carriers and non-carriers, which likely attributed to more than 37% of the patients with complete cytoreduction. Larger prospective studies are warranted to validate our findings in Chinese populations.

Abbreviations

EOC (epithelial ovarian cancer); *gBRCA1/2* (germline *BRCA1* or *BRCA2*); PARP (poly [ADP-ribose] polymerase); PFS (progression-free survival); FDUZH (Zhongshan Hospital, Fudan University); FDUCH (Fudan University Cancer Hospital); FIGO (International Federation of Gynecology and Obstetrics); RD (residual disease); HBOC (Hereditary Breast and Ovarian Cancer); OS (overall survival); PFI (progression-free interval); HGSOC (high-grade serous ovarian cancer); IQR (interquartile range).

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Disclosure Statement

The authors declare that they have no competing interests.

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