Association of BRCA1/2 mutations with ovarian cancer prognosis

An updated meta-analysis

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Abstract
Objective: A meta-analysis was performed to determine if BRCA1/2 mutations are associated with improved overall survival (OS) and progression-free survival (PFS) in patients with ovarian cancer.

Research design and methods: Studies of patients with primary or recurrent ovarian cancer that examined the relationship between BRCA1/2 mutation status and outcomes were included.

Main outcome measures: The primary outcomes were OS and PFS of patients with and without BRCA1 and BRCA2 mutations. The secondary outcome was treatment response: complete response, partial response, and overall response.

Results: Overall analysis revealed BRCA1/2 mutations were associated with improved OS [hazard ratio (HR)=0.75; 95% confidence interval (CI): 0.64, 0.88; P < .001] and PFS [HR=0.80; 95% CI: 0.64, 0.99; P=0.039]. BRCA1 mutations were significantly associated with improved OS (HR=0.75) but not PFS, and BRCA2 mutations alone were not associated with either improved OS or PFS. The presence of BRCA1/2 mutations was associated with a better overall response rate, higher complete response rate, and lower partial response rate; however, BRCA1 or BRCA2 alone was not associated with overall response rate.

Conclusions: BRCA1 mutations appear to be associated with improved OS in patients with ovarian cancer. However, the effect of BRCA1 mutations on PFS and BRCA2 mutations alone on OS and PFS is less clear.

Abbreviations: CI = confidence interval, CR = complete response, EFS = event-free survival, HR = hazard ratio, OR = odds ratio, ORR = overall response rate, OS = overall survival, PARP = poly (ADP-ribose) polymerase, PFS = progression-free survival, PR = partial response, QUIPS = Quality in Prognostic Studies.

Keywords: BRCA, meta-analysis, mutation, ovarian cancer, survival

1. Introduction

Ovarian cancer is a leading cause of death from gynecological malignancies, with 5-year survival rates of only 5% to 30% for patients with advanced disease despite cytoreductive surgery and platinum- and taxane-based chemotherapy.[14–16] Although the majority of ovarian cancer cases represent sporadic disease, it is now recognized that BRCA1 and BRCA2 mutations confer a genetic susceptibility to ovarian cancer, and females with mutations in these genes have a lifetime risk of 36% to 60% and 16% to 27% respectively, of developing ovarian cancer.[15,6] Elective salpingo-oophorectomy after completion of childbearing can significantly reduce, though not completely eliminate the risk.[7]

Determining the most appropriate treatment for ovarian cancer includes an analysis of risk factors and disease characteristics. Interestingly, whereas BRCA1/2 mutations are associated with an increased risk of ovarian cancer, some studies have indicated that mutation carriers respond better to platinum-based chemotherapy and exhibit longer progression-free survival (PFS).[8–12] Other studies, however, have shown that the presence of BRCA1/2 mutations has no effect on response to chemotherapy and overall survival (OS) or PFS.[13–15] Differences in study results can be because of a multitude of factors including study design, patient population, other prognostic factors, degree of debulking surgery, age, and mutation characteristics. It has been postulated that an improved response to chemotherapy in patients with BRCA1/2 mutations may be because of inhibition of a DNA-repair pathway that sensitizes tumor cells to the DNA-damaging effects of chemotherapies.[16]

The purpose of this study was to perform an updated meta-analysis to determine if BRCA1/2 mutations are associated with improved OS and PFS in patients with ovarian cancer.

2. Methods

2.1. Literature search strategy and study selection

This systematic review and meta-analysis was conducted in accordance with PRISMA guidelines.[17] Medline, Cochrane, EMBASE, and Google Scholar databases were searched from...
inception until May 12, 2017 using the keywords: BRCA, BRCA1, BRCA2, ovarian cancer, overall survival, progression-free survival, prognosis, and response. Reference lists of relevant studies were hand-searched to identify additional potential articles of interest. Meta-analysis inclusion criteria were: prospective, retrospective, and cohort studies; patients with primary or recurrent ovarian cancer; examined the relationship between BRCA1/2 mutation status and OS, PFS, and treatment response to chemotherapy; and provided quantitative outcome data. Letters, comments, editorials, case reports, proceedings, personal communications, and one-arm studies were excluded.

The following information/data were extracted from studies that met the inclusion criteria: the name of the first author, year of publication, study design, number of patients in each group, patient age, cancer stage, histopathological type, treatment, follow-up time, OS, PFS, and response rate to treatment.

The ethical approval and informed consent were not necessary, because meta-analysis does not involve human subjects and does not require IRB review.

2.2. Quality assessment

The Quality in Prognostic Studies (QUIPS) tool was used to assess the quality of the studies included in the meta-analysis.

2.3. Outcome measures and data analysis

The primary outcomes for this meta-analysis were OS and PFS of patients with and without BRCA1 and BRCA2 mutations. The secondary outcome was treatment response; complete response (CR), partial response (PR), and overall response (ORR). Hazard ratios (HR) and 95% confidence intervals (CIs) were extracted for each individual study, and calculated for studies combined. If a HR with a 95% CI was not available, the HR and its variance was estimated using methods described by Parmar et al.[19] and Williamson et al.[20] A HR < 1 indicated that BRCA1/2 mutations were associated with a longer OS or PFS. Treatment response rates were extracted for each individual study and odds ratios (ORs) were calculated for the studies combined. A $\chi^2$-based test of homogeneity was performed, and the inconsistency index ($I^2$) and Q statistics were determined. A Q statistic value of $P < .10$ or an $I^2 > 50\%$ were considered to indicate statistically significant heterogeneity. If significant heterogeneity was detected a random-effects model of analysis was used; otherwise, a fixed-effects model was employed. Pooled effects were calculated, and a 2-sided value of $P < .05$ was considered statistically significant. Publication bias was assessed by constructing funnel plots for OS and PFS and by Egger test. The absence of publication bias was indicated by the data points forming a symmetric funnel-shaped distribution, and a value of $P > .10$ in Egger test. All analyses were performed using Comprehensive Meta-Analysis statistical software, version 2.0 (Biostat, Englewood, NJ).

3. Results

3.1. Literature search

A flow diagram of study selection is shown in Figure 1. A total of 381 potentially relevant articles were identified in the database searches. After screening by title and abstract, 320 were
excluded. Of the 61 remaining articles that underwent a full text review, 28 were excluded, the reasons for which are shown in Figure 1. Thus, ultimately 33 articles were included in the meta-analysis.[8-11,15,21-48]

The basic characteristics of the 33 studies are summarized in Table 1.[8-11,15,21-48] The 33 studies enrolled a total of 7745 patients with primary or recurrent ovarian cancer. One study was prospective, and the others were retrospective. Patient age ranged from 48 to 73 years, and more than 80% of patients had advanced stage disease (stage III or IV). The most common pathological type was serous carcinoma.

### 3.2. Meta-analysis of BRCA1/2 mutations

Twenty-three studies provided OS data and were included in the analysis. Heterogeneity was observed among the 23 studies ($I^2=74.83\%$, $Q$ statistic $=86.37$, $P<.001$); therefore, a random-effects model was used. The analysis revealed a significant OS advantage in ovarian cancer patients with BRCA1/2 mutations (HR = 0.75; 95% CI: 0.64, 0.88; $P<.001$) (Fig. 2A). In addition, primary ovarian cancer patients with BRCA1/2 mutations had significantly longer OS than noncarriers (HR = 0.513; 95% CI: 0.381, 0.689; $P<.001$) as did recurrent ovarian cancer patients (HR = 0.652; 95% CI: 0.530, 0.802; $P<.001$). However,

### Table 1

Characteristics of studies included in the meta-analysis[8-11,15,21-48]

| First author     | Study design            | Comparison group | Number of patients (total: 7745) | Stage, % (I/II/III/IV) | Histopathology, % (Serous/Endometrioid/Clear cell/Mucinous) | Primary/ recurrent | Follow-up, mo |
|------------------|-------------------------|------------------|-----------------------------------|------------------------|----------------------------------------------------------------|-----------------------|---------------|
| Biglia[46]       | Retrospective BRCA1/2   | Wild-type        | 24                                | 54*                    | 17/21/46/8                                                      | 71/4/0               | Primary       | 46*          |
| Harter[21]       | Retrospective BRCA1/2   | Wild-type        | 64                                | 54*                    | 19/5/56/20                                                     | 53/1/6/6             | Primary       | NA           |
| Sabatier[47]     | Retrospective BRCA1/2   | Wild-type        | 51                                | 52*                    | 0/6/80/14                                                      | 76/4/2               | Primary       | NA           |
| Synowiec[48]     | Retrospective BRCA1     | Wild-type        | 71                                | 52*                    | 0/9/73/9                                                       | 42/9/3               | Primary       | 67           |
|                  |                         |                  | 17                                | 47*                    | 21/11/52/6                                                     | 58/6/0               | Primary       | 73           |
| Unni[22]         | Retrospective BRCA1/2   | Wild-type        | 108                               | 56*                    | 11/86/3                                                       | 54/26/4              | Primary       | Primary      |
| Kotsopoulos[15]  | Retrospective BRCA1     | Wild-type        | 109                               | 52*                    | 0/6/70/14                                                     | 74/16/1              | Primary       | 97           |
| Sabatier[47]     | Retrospective BRCA1     | Wild-type        | 68                                | 57*                    | 3/4/71/16                                                     | 78/2/7               | Primary       | 94           |
|                  |                         |                  | 1244                              | 56*                    | 20/18/47                                                      | 52/22/8              | Primary       | 116          |
| Rudolfs[14]      | Prospective BRCA1/2     | Wild-type        | 55                                | 48*                    | 0/78/22                                                       | 98/2/0               | NA            | 35*          |
|                  |                         |                  | 52                                | 54*                    | 21/11/52                                                      | 87/6/2               | NA            | 25*          |
| Safra[23]        | Retrospective BRCA1/2   | Wild-type        | 69                                | 53*                    | 1-13/III IV                                                   | 54/2/0               | Recurrent     | 42*          |
|                  |                         |                  | 187                               | 63*                    | 1-16/II IV                                                   | 46/6/0               | Recurrent     | 42*          |
| Alsup[30]        | Retrospective BRCA1/2   | Wild-type        | 86                                | 53*                    | 5/86/7           | 84/8/50             | NA            | NA           |
|                  |                         |                  | 777                               | 61*                    | 8/4/60/15                                                    | 83/6/0               | NA            | NA           |
| Dann[34]         | Retrospective BRCA1     | Wild-type        | 12                                | NA                    | 0/0/20                                                       | 67/3/3               | NA            | NA           |
|                  |                         |                  | 38                                | NA                    | 0/0/100                                                      | 100/0/0              | NA            | NA           |
| Hyman[25]        | Retrospective BRCA1/2   | Wild-type        | 69                                | NA                    | 0/0/70/21                                                    | 74/11/130            | NA            | NA           |
|                  |                         |                  | 296                               | NA                    | 0/0/100                                                      | 100/0/0              | NA            | NA           |
| Adams[30]        | Retrospective cohort study | Wild-type      | 23                                | ≥ 55: 43.5%          | 1-11/II IV                                                   | 67/0/0               | Recurrent     | NA           |
| Hyman[27]        | Retrospective BRCA1     | Wild-type        | 41                                | ≥ 55: 33.6%          | 0/11/78/11                                                   | NA                   | Recurrent     | 7*           |
| Lacour[30]       | Retrospective BRCA1/2   | Wild-type        | 41                                | 57*                    | 0/3/89/8                                                     | 62/4/0               | Primary       | 43*          |
| Safra[23]        | Retrospective BRCA1/2   | Wild-type        | 95                                | 55*                    | 0/0/88/12                                                   | 62/4/0               | Primary       | 38*          |
| Vencken[9]       | Retrospective BRCA1     | Wild-type        | 115                               | 60*                    | 0/9/73/9                                                      | 85/15/0              | Recurrent     | NA           |
|                  |                         |                  | 99                                | 52*                    | 8/14/63/15                                                   | 70/4/24              | NA            | NA           |
| Yang[30]         | Retrospective BRCA1     | Wild-type        | 35                                | 56*                    | 0/8/77/17                                                   | NA                   | NA            | NA           |
| Gallager[11]     | Retrospective BRCA1/2   | Wild-type        | 219                               | 62*                    | 0/8/77/17                                                   | 56/2/0               | Primary       | 41*          |
| Hennessy[31]     | Retrospective BRCA1/2   | Wild-type        | 74                                | 62*                    | 0/9/55                                                       | 71/0/10              | 41*          |
|                  |                         |                  | 36                                | 52*                    | 5/2/61/23                                                    | 81/0/0               | NA            | 35.7*        |
| Tan[32]          | Retrospective BRCA1/2   | Wild-type        | 44                                | 50*                    | 0/9/77/14                                                   | 68/2/75              | NA            | 42*          |

(continued)
BRCA1/2 mutations were not associated with OS in patients with advanced-stage ovarian cancer (HR = 0.743; 95% CI: 0.302, 1.828; \( P = .518 \)) (Table 2).

Fourteen studies provided data with respect to PFS. A random-effects model was used because significant heterogeneity was noted (\( I^2 = 80.85\% \), Q statistic = 67.892, \( P < .001 \)). The presence of BRCA1/2 mutations was associated with improved PFS (HR = 0.80; 95% CI: 0.64, 0.99; \( P = .039 \)) (Fig. 3A).

Results of the meta-analysis of treatment responses between patients with and without BRCA1 and BRCA2 mutations are shown in Table 3. Seven studies provided ORR data, and were included in the meta-analysis. A random-effects model of analysis was used because heterogeneity was present (\( I^2 = 68.80\% \), Q statistic = 18.07). Ovarian cancer patients with BRCA1/2 mutations were more sensitive to treatment compared with wild-type patients (OR = 2.64; 95% CI: 1.38, 5.05; \( P = .003 \)). Compared with patients with sporadic disease, BRCA-positive patients had a higher CR rate (OR = 2.14; 95% CI: 1.49, 3.08; \( P < .001 \)), but lower PR rate (OR = 0.60; 95% CI: 0.39, 0.91; \( P = .017 \)). The presence of BRCA1 or BRCA2 mutations (vs wild-type) did not affect the CR, PR, or ORR; however, only 3 or fewer studies provided data available for the analysis (Table 3). A summary of the treatments and the response rates reported in all of the studies included in the meta-analysis is shown in Supplemental Table 1, http://links.lww.com/MD/C50.

### 3.3. Meta-analysis of BRCA 1 or BRCA 2 mutations alone

BRCA1 mutation remained significantly associated with improved OS (n = 15 studies; HR = 0.75; 95% CI: 0.62, 0.91; \( P = .004 \)) (Fig. 2B), but BRCA2 mutation alone was not associated with increased OS (n = 8 studies; HR = 0.83; 95% CI: 0.58, 1.19; \( P = .314 \)) (Fig. 2C). BRCA1 mutation alone was not significantly associated with improved PFS (n = 5 studies; HR = 0.85; 95% CI: 0.67, 1.07; \( P = .162 \)) (Fig. 3B), nor was BRCA2 mutation alone significantly associated with improved PFS (n = 4 studies; HR = 0.66; 95% CI: 0.43, 1.02; \( P = .061 \)) (Fig. 3C).

Only 3 studies provided ORR data for BRCA1 mutations alone, and 2 studies for BRCA2 mutations alone. The analysis revealed that BRCA1 mutations alone and BRCA2 mutations alone were not associated with ORR (BRCA1 mutations alone: OR = 1.30, 95% CI: 0.31, 5.44, \( P = .722 \); BRCA2 mutations alone: OR = 3.48, 95% CI: 0.49, 12.90, \( P = .063 \)) (Table 3).
3.4. Publication bias and quality assessment

Results of the analysis of publication bias are shown in Supplemental Figure 1, http://links.lww.com/MD/C50. The funnel plots of OS and PFS had a symmetrical distribution, and Egger’s test indicated no evidence of publication bias ($P = .312$ for OS, and $P = .225$ for PFS).

As shown in Supplemental Figure 2, http://links.lww.com/MD/C50, all included studies had low risk of bias in study participation, study attrition, and analysis. However, 7 studies had high risk, and 1 study had unclear risk of bias in prognostic factor measurement, and the major limitation is in outcome measurement. Overall, the included studies had low risk of bias in study participation, study attrition and analysis, but relatively high risk of bias in prognostic factor and outcome measurement.

Upon review of the individual study results, it was apparent that 3 studies had a strong signal and low OR, and potentially may have had the following biases which may have overly influenced the results: Rubin (1996): outcome measure and publication bias.
Table 2
Subgroup analysis of primary, recurrent, and advanced-stage disease.

| Subgroup                  | Number of studies | Q statistic | I² | Effect size (95% CI) | P |
|---------------------------|-------------------|-------------|----|----------------------|---|
| Primary cancer only       | 4                 | 4.513       | 33.53% | 0.513 (0.381, 0.689) | <.001 |
| Recurrent cancer only     | 4                 | 28.168      | 89.35% | 0.652 (0.530, 0.802) | <.001 |
| Advanced-stage only       | 4                 | 24.921      | 87.96% | 0.743 (0.302, 1.828) | .518 |

CI = confidence interval.

Figure 3. Forest plots of progression-free survival by (A) BRCA1/2 mutations, (B) BRCA1 mutations only, and (C) BRCA2 mutations only. Hazard ratios represent comparison of patients with BRCA mutations and wild-type gene.
confounding measure and account; Venchen (2001): prognostic factor measurement; and Majdak (2005): outcome measure. For this reason, we performed the meta-analysis with the exclusion of these 3 studies, and the results remained the same as indicated in Figure 2. The overall analysis excluding the 3 studies revealed BRCA1/2 mutations and BRCA1 mutations were associated with improved OS (HR = 0.76; 95% CI: 0.64, 0.90; P = .001 and HR = 0.88; 95% CI: 0.78, 1.00; P = .045, respectively), and BRCA2 mutations alone was not associated with OS (Supplemental Figure 3, http://links.lww.com/MD/C50).

4. Discussion

The purpose of this study was to perform an updated meta-analysis examining the influence of BRCA1/2 mutations on OS and PFS in patients with ovarian cancer. The overall results indicated that the presence of BRCA1/2 mutations were associated with improved OS and PFS, but the improved OS was only seen in patients with primary and recurrent disease, not in those with advanced stage disease. BRCA1/2 mutations were associated with a better ORR, though BRCA-positive patients had a higher CR rate but lower PR rate than did patients with sporadic disease. When examined separately, BRCA1 mutations remained significantly associated with improved OS but not PFS, and BRCA2 mutations alone were not associated with either improved OS or PFS. In addition, neither BRCA1 nor BRCA2 mutations alone were associated with ORR, though these findings were limited by a very small number of studies.

BRCA1/2 function as tumor suppressor genes, and their proteins play an important role in repairing damaged DNA through homologous recombination. [16] The majority of BRCA1/2-associated carcinomas have deletions in the genes, resulting in deficiency of the gene protein. [16] Deficiency of the protein results in a carcinoma with a diminished capacity to repair DNA, which is the mechanism by which the mutations lead to an increased susceptibility to cancer. [16] Protein deficiency also results in sensitivity to platinum-based chemotherapy agents, presumably as a result of an inability to repair double-strand DNA breaks caused by chemotherapy. [30–31] and poly (ADP-ribose) polymerase (PARP) inhibitors that inhibit DNA repair mechanisms. [32–54]

Studies have generally shown that BRCA1/2 mutations are associated with an improved response to platinum-based chemotherapy. [9,12,33,36,41] However, how an improved response translates into survival benefits is unclear. Kotsopoulos et al. [31] studied 1421 patients with epithelial ovarian cancer of whom 109 had BRCA1 mutations and 68 had BRCA2 mutations, and found that although mutation carriers exhibited an initial survival advantage, the presence of a mutation was not associated with survival status at 10 years. The study also reported that the strongest predictor of 10-year survival was no residual disease at resection.

The current analysis found that when examined separately BRCA1 mutations remained significantly associated with improved OS but not PFS, and BRCA2 mutations alone were not associated with either improved OS or PFS. A few studies have examined differences between BRCA genotypes. Liu et al. [33] compared event-free survival (EFS) and OS between BRCA1 and BRCA2 patients, and found no difference in the 2 measures between the 2 genotypes, though there was a nonsignificant trend towards improved OS in BRCA2 patients with advanced-stage disease. A study by Yang et al. [34] reported that an OS advantage was only seen in patients with BRCA2 mutations, and not those with BRCA1 mutations. Similarly, a study by Sun et al. [35] suggested that the HR for OS for patients with BRCA2 mutations was lower than that for BRCA1 mutations. This may be because BRCA2 mutations result in more significant homologous recombination defects than BRCA1 mutations. [16]

Other meta-analyses have examined the influence of BRCA1/2 mutations on survival of patients with ovarian cancer. In 2015 Zhong et al. [37] studied patients with ovarian and breast cancer and identified 14 studies examining ovarian cancer and 13 examining breast cancer. The analysis showed that both BRCA1 and BRCA1 mutations were associated with better OS and PFS regardless of tumor stage, grade, or histological subtype. With respect to breast cancer, BRCA1 mutation carriers had worse OS regardless of tumor stage, grade, or histological subtype. Another meta-analysis of 34 evaluable studies showed that BRCA2 mutations was a favorable prognostic factor for OS (HR = 0.69, 95% CI: 0.61, 0.79, P < .001), and analysis of 18 evaluable studies showed that mutations were associated with longer PFS (HR = 0.69, 95% CI: 0.62, 0.76, P < .001).

Table 3

| Table 3 | Meta-analysis for treatment response. | Heterogeneity test | Pooled effect |
|---------|--------------------------------------|-------------------|--------------|
|         | Number of studies | Q statistic | I² | OR (95% CI) | P |
| BRCA1 or 2 mutants vs wild-type | Complete response | 4 | 5.08 | 40.00% | 2.14 (1.49, 3.08) | < .001 |
|         | Partial response | 4 | 0.32 | 0.00% | 0.60 (0.39, 0.91) | .017 |
|         | Overall response rate | 7 | 18.07 | 68.80% | 2.64 (1.38, 5.05) | .003 |
| BRCA1 vs wild-type | Complete response | 3 | 7.1 | 71.83% | 1.18 (0.33, 4.23) | .802 |
|         | Partial response | 3 | 3.4 | 41.14% | 0.93 (0.50, 1.75) | .628 |
|         | Overall response rate | 3 | 9.1 | 78.01% | 1.30 (0.51, 5.44) | .722 |
| BRCA2 vs wild-type | Complete response | 1 | NA | NA | NA |
|         | Partial response | 1 | NA | NA | NA |
|         | Overall response rate | 2 | 0.08 | 0.00% | 3.48 (0.94, 12.90) | .063 |

CI = confidence interval, NA = not available, OR = odds ratio.
0.63, 0.76, P = .118).\(^{[55]}\) When the studies were categorized into BRCA1/2 mutation and low protein/mRNA expression, both categories were found to be favorable prognostic factors, whereas BRCA1 promoter methylation was associated with a poorer prognosis (HR = 1.59, 95% CI: 0.72, 3.30, P = .077). There are some differences between our study and the aforementioned analysis by Sun et al.\(^{[55]}\) in that the prior study examined the role of BRCA status on prognosis of patients with epithelial ovarian cancer, and the BRCA status included BRCA mutation, BRCA methylation, BRCA1 promoter methylation, BRCA1 mRNA level, and BRCA1 protein expression by immunohistochemistry. The objective of the current was to only examine the role of BRCA mutation status with respect to the prognosis of patients with ovarian cancer. Differences in the study results may be because of the purposes of the studies, the study inclusion criteria, and/or the outcome measures examined.

There are a number of limitations to the current analysis. Not all of the included studies examined both BRCA1 and BRCA2, nor did they all examine OS and PFS. Although most of the included studies had a follow-up time > 36 months, many did not report follow-up length, and one study reported a follow-up of only 7 months.\(^{[27]}\) Importantly, there was marked heterogeneity between studies with respect to treatment, disease stage, and histopathological cancer type. Levels of BRCA expression, promoter methylation, epigenetic alterations, histopathological type, and other risk factors may all affect response to therapy, and these were not taken into consideration in the analysis. The subgroup analyses of BRCA1 and 2 for OS and PFS contained a small number of studies, as did the analysis of ORR, and whereas most chemotherapy regimens were platinum-based and some were not. The number of studies that analyzed BRCA1 alone and BRCA2 alone was markedly different, and the reason may be that in ovarian cancer patients the BRCA1 mutation occurs at a higher frequency than the BRCA2 mutation.\(^{[8]}\) The finding that BRCA1/2 was associated with ovarian cancer prognosis, whereas BRCA1 alone or BRCA2 alone was generally not is likely also because of the small numbers of studies that examined the 2 mutations individually (e.g., for analysis of OS, there were 15 articles included in BRCA1 subgroup, and 8 articles in BRCA2 subgroup; however, for analysis of PFS there were only 5 articles in BRCA1 subgroup and 4 articles in BRCA2 subgroup). It would have been valuable if other subgroup analyses could have been performed (e.g., retrospective vs prospective studies, promotor status, or geographical region); however, only 1 prospective study was included in the analysis, and data for other subgroup analyses were limited.

It should also be mentioned that many studies used in the analysis were published in 2011, and this may raise the concern of duplicate data; however, review of the articles excluded the possibility of duplicate patients. For example, Candido-dos-Reis et al.\(^{[59]}\) extracted unpublished data from 2 case-controlled study datasets, and extended survival-time data for 4314 patients from the small numbers of studies that examined the 2 mutations alone and these were not taken into consideration in the analysis. The subgroup analyses were limited.

In conclusion, BRCA1/2 mutations were associated with improved OS and PFS, but the improved OS was only seen in patients with primary and recurrent disease, not in those with advanced disease. BRCA1/2 mutations were associated with a better ORR, though BRCA-positive patients had a higher CR rate, but lower PR rate than did patients with sporadic disease. When examined separately, BRCA1 mutations remained significantly associated with improved OS, but not PFS, and BRCA2 mutations alone were not associated with either improved OS or PFS. In addition, neither BRCA1 nor BRCA2 mutations alone were associated with ORR, though these findings were limited by a small number of studies. Further elucidation of mutation characteristics and their effect on survival and response to therapy may lead to a more individualized approach to the treatment of ovarian cancer and improved outcomes.

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