Systematic Review and Meta-Analysis

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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; $P = .039$). *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 *BCRA1/2* 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.[1–4] 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.[5,6] 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

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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.[18] Briefly, the tool assess bias in 6 domains; study participation, study attrition, prognostic factor measurement, outcome measurement, confounding measurement and account, and 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 χ^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

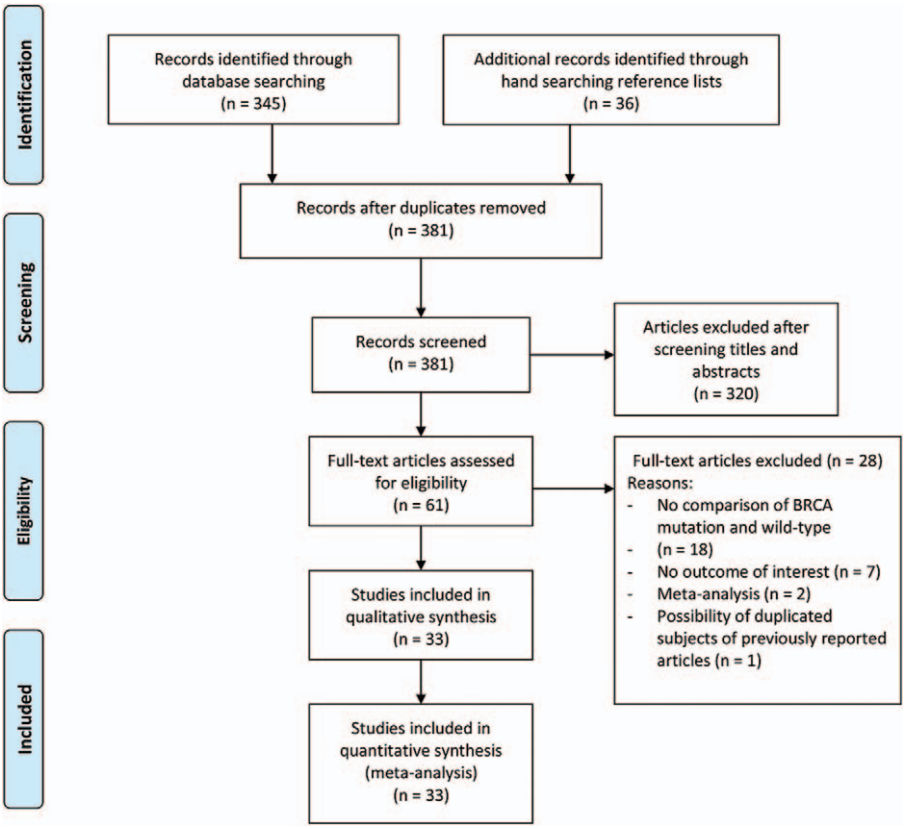


Figure 1. PRISMA flow diagram of study selection.

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)	Age, y	Stage, % (I/II/III/IV)	Histopathology, % (Serous/Endometrioid/ Clear cell/Mucinous)	Primary/ recurrent	Follow-up, mo
Biglia[46]	Retrospective	BRCA1/2	24	54*	17/21/46/8	71/4/0/0	Primary	46*
		Wild-type	64	54*	19/5/56/20	53/11/6/6		
Harter[21]	Retrospective	BRCA1/2	51	52*	0/6/80/14	76/4/2/4	Primary	NA
		Wild-type	278	58*	0/9/72/19	75/4/3/6		
Sabatier[47]	Retrospective	BRCA1/2	33	52	9/0/73/9	42/9/3/0		67
		Wild-type	71	52	21/11/52/6	58/9/6/3	NA	71
Synowiec[48]	Retrospective	BRCA1	17	47*	11/8/68/12	54/26/4/7	Primary	NA
		Wild-type	108	56*				
Unni[22]	Retrospective	BRCA1/2	15	56	I-II: 13/ III-IV:67	67/0/0/0	Recurrent	NA
		Wild-type	25	56	I-II: 20/ III-IV: 60	72/4/0/0		
Kotsopoulos[15]	Retrospective	BRCA1	109	51	6/17/60/14	74/16/1/0	NA	97
		BRCA2	68	57	3/4/71/16	78/9/2/0		91
		Wild-type	1244	58	20/18/47/14	52/22/8/9		116
Rudaitis[10]	Prospective	BRCA1/2	55	48*	0/0/78/22	98/2/0/0	NA	35*
		Wild-type	52	54*		87/6/6/2		25*
Safra[23]	Retrospective	BRCA1/2	69	53	I-II: 10/74/16	51/42/0/0	Recurrent	42*
		Wild-type	187	63	I-II: 9/74/17	46/46/0/0		42*
Alsop[8]	Retrospective	BRCA1	88	53	5/8/67/10	84/8/5/0	NA	NA
		BRCA 2	53	60	8/4/60/15	83/6/0/0		
		Wild-type	777	61	13/7/56/11	69/13/7/0		
Dann[24]	Retrospective	BRCA1	12	NA	0/8/92/0	67/33/0/0	NA	NA
		BRCA2	3		0/0/100/0	100/0/0/0		
		Wild-type	38		0/0/79/21	74/11/13/0		
Hyman[25]	Retrospective	BRCA1/2	69	NA	NA	NA	NA	NA
		Wild-type	298	NA	NA	NA		
Adams[26]	Retrospective cohort study	BRCA1/2	23	≥ 55: 43.5%	I-II: 14/III-IV: 86	87/0/0/0	Recurrent	NA
		Wild-type	41	≥ 55: 53.6%	I-II: 10/III-IV: 90			
Hyman[27]	Retrospective	BRCA1/2	9	57	0/11/78/11	NA	Recurrent	7*
		Wild-type	41	61	0/3/89/8	NA		
Lacour[28]	Retrospective	BRCA1/2	95	55	0/0/88/12	62/4/0/0	Primary	43*
		Wild-type	183	55	0/0/88/11	71/8/2/2		38*
Safra[29]	Retrospective	BRCA1/2	40	53	0/0/90/10	85/15/0/0	Recurrent	NA
		Wild-type	115	60	0/0/78/22	87/13/0/0		
Vencken[9]	Retrospective	BRCA1	99	52	8/14/63/15	70/14/2/4	NA	NA
		BRCA2	13	55	23/8/69/0	63/0/0/15		
		Wild-type	222	53	13/9/58/21	64/11/5/9		
Yang[30]	Retrospective	BRCA1	35	56	0/6/77/17	NA	NA	NA
		BRCA2	27	61	0/4/92/4	NA		
		Wild-type	219	62	0/4/77/19	NA		
Gallagher[11]	Retrospective	BRCA1/2	36	58*	0/0/86/14	86/6/0/0	Primary	41*
		Wild-type	74	62*	0/0/95/5	78/8/1/0		41*
Hennessy[31]	Retrospective	BRCA1/2	44	60*	5/2/61/23	89/0/0/0	NA	35.7*
		Wild-type	191		5/7/68/12	77/0/0/0		
Tan[32]	Retrospective	BRCA1/2	22	50*	0/9/77/14	68.2/27/5/0	NA	42*
		Wild-type	44	50*	0/9/77/14	89/7/5/0		

(*continued*)

Table 1

(continued).

First author	Study design	Comparison group	Number of patients (total: 7745)	Age, y	Stage, % (I/II/III/IV)	Histopathology, % (Serous/Endometrioid/ Clear cell/Mucinous)	Primary/ recurrent	Follow-up, mo
Pal[33]	Retrospective	BRCA1	20	53	5/15/65/15	70/5/0/0	NA	NA
		BRCA2	12	58	33/8/50/8	50/17/0/0		
		Wild-type	200		21/8/59/12	58/14/5/10		
Chiang[34]	Retrospective	BRCA1	22	48*	I-II: 0/ III-IV: 82	77/0/0/0	NA	64.9*
		Wild-type	30	63*	I-II: 0/ III-IV: 83	70/0/0/0		61.2*
Majdak[35]	Retrospective	BRCA1	18	< 50 y: 83%	I-II: 11/ III-IV: 89	83/0/0/17	Primary	NA
		BRCA1/2	16	< 50 y: 44%	I-II: 19/ III-IV: 81	69/0/0/31		
		Wild-type	171	< 50 y: 34%	I-II: 12/ III-IV: 88	63/0/0/37		
Cass[36]	Retrospective	BRCA1/2	34	50*	I-II: 15/ III-IV: 85	Serous invasive: 91	Primary	142*
		Wild-type	37	59*	I-II: 16/ III-IV: 68	Serous invasive: 78		72*
Buller[37]	Retrospective	BRCA1	24	NA	NA	NA	Primary	NA
		Wild-type	24	NA	NA	NA		
David[38]	Retrospective	BRCA1/2	234	56.5*	NA	NA	NA	60*
		Wild-type	662	59*	NA	NA		
Ramus[39]	Retrospective	BRCA1	15	52*	I-II: 7/ III-IV: 93	93/0/0/0	NA	NA
		BRCA2	12	73*	I-II: 8/ III-IV: 92	73/0/0/0		
		Wild-type	71	67*	I-II: 21/ III-IV: 79	73/0/0/0		
Zweemer[40]	Retrospective	BRCA1/2	23		NA	NA	NA	NA
		Wild-type	17		NA	NA		
Boyd[41]	Retrospective cohort study	BRCA1/2	88	56	3/5/77/15	68/14/2/0	NA	57*
		Wild-type	101	63	0/1/85/14	60/13/7/5		59*
Pharoah[42]	Retrospective	BRCA1	127	NA	NA	Invasive epithelial ovarian cancer	NA	NA
		BRCA2	24	NA	NA			
		Wild-type	119	NA	NA			
Aida[43]	Retrospective	BRCA1	13	54*	0/0/100/0	92/0/0/0	NA	54.8
		Wild-type	29	60*	0/0/100/0	69/7/3/10		NA
Rubin[44]	Retrospective	BRCA1	43	NA	0/0/III-IV: 100	NA		
		Wild-type	43	NA		NA	Primary	NA
Johannsson[45]	Retrospective	BRCA1	38	51	5/26/45/24	50/18/0/7		
		Wild-type	97	53	6/22/52/21	57/10/2/9	NA	NA

NA = not available.

Age and length of follow-up are presented as mean, unless otherwise indicated.

* Median.

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 *BCRA1* or *BCRA2* 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).

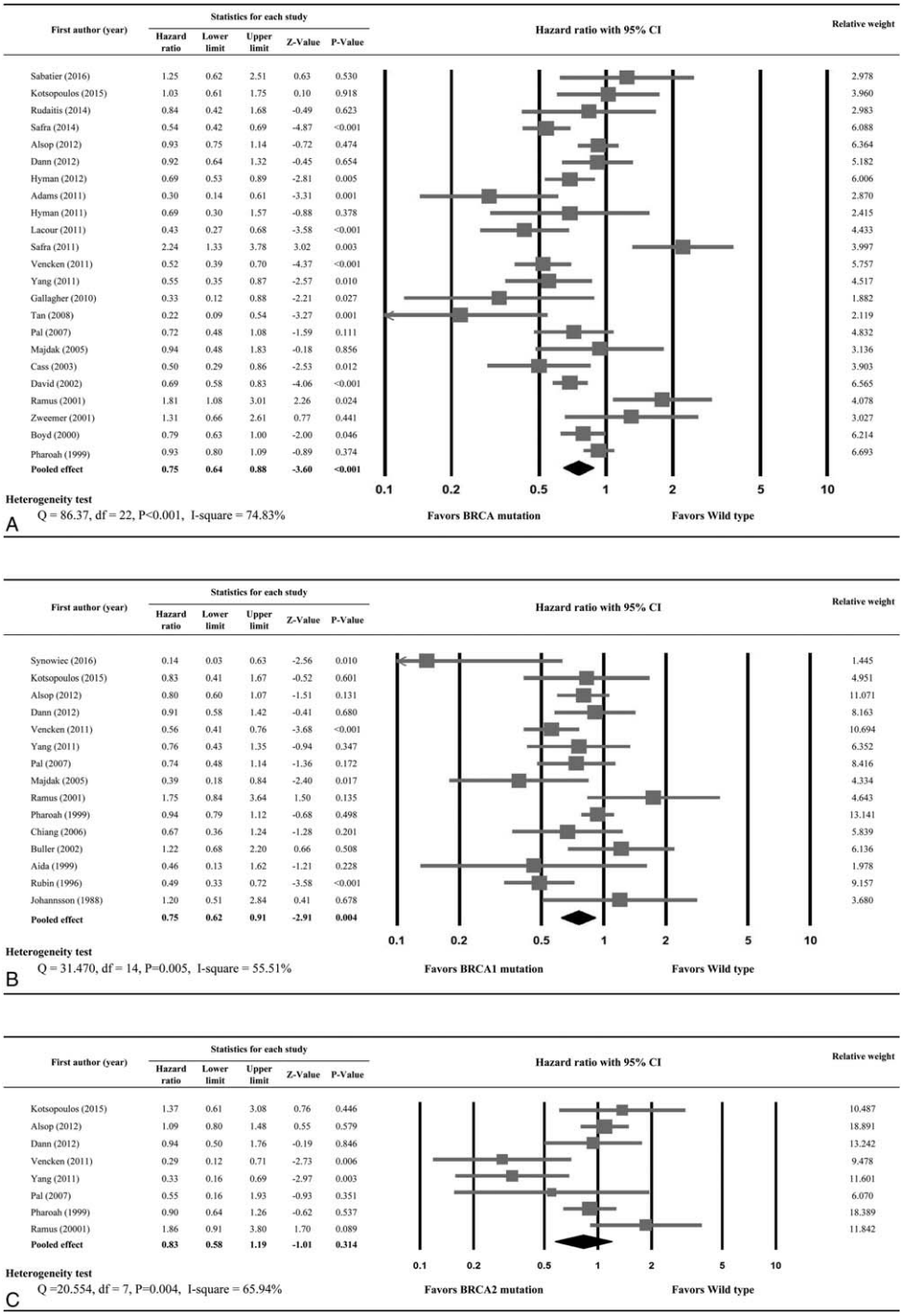


Figure 2. Forest plots of overall survival by (A) *BRCA1/2* mutations, (B) *BRCA1* mutations only, and (C) *BRCA2* mutations only. Hazard ratios represent comparison of patients with *BRCA* mutations and wild-type gene.

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.

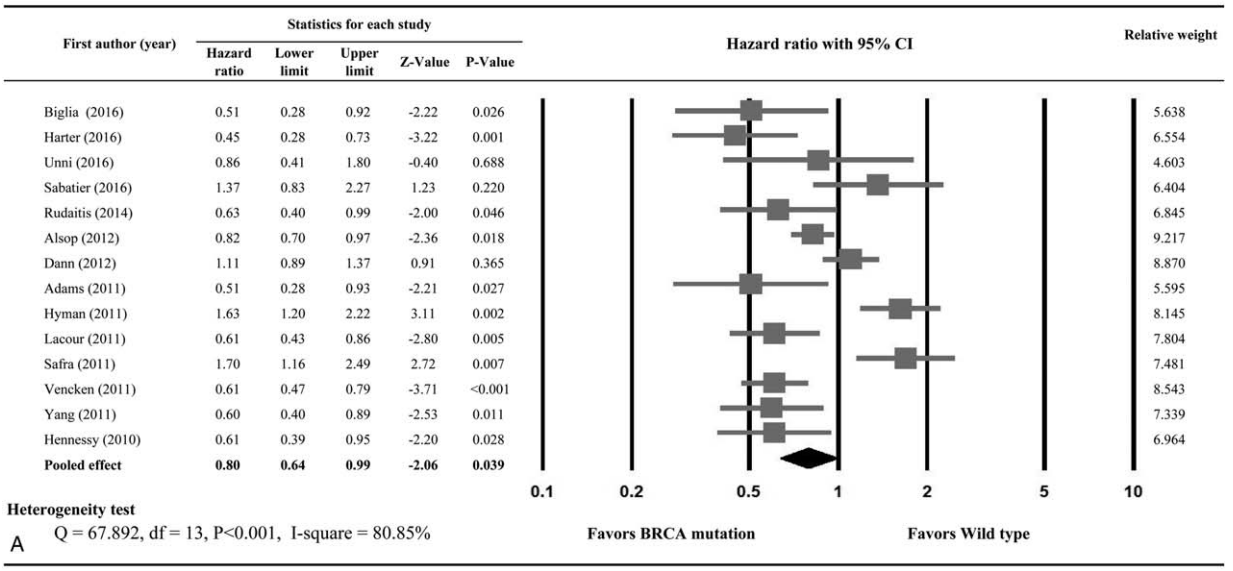
Upon review of the individual study results, it was apparent that 3 studies had a strong signal and low OR, and potentially may have had the following biases which may have overly influenced the results: Rubin (1996): outcome measure and

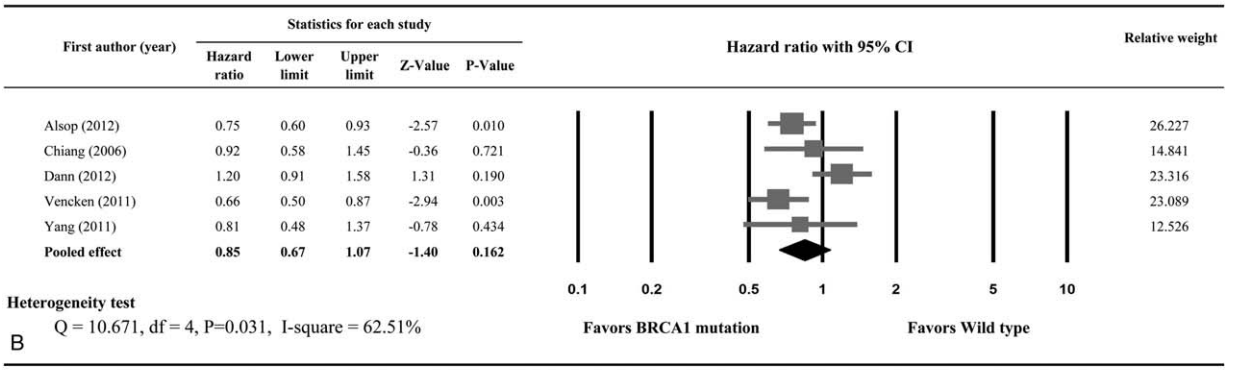
Table 2

Subgroup analysis of primary, recurrent, and advanced-stage disease.

	Heterogeneity test			Pooled effect	
	Number of studies	Q statistic	I^2	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.





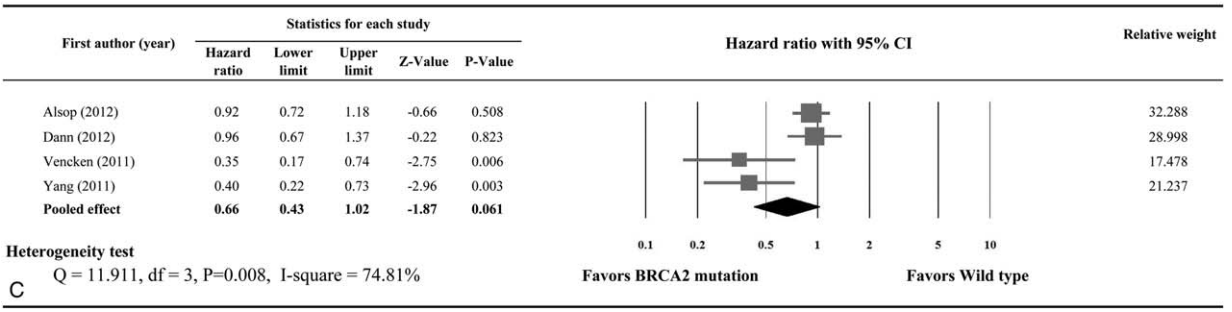


Figure 3. Forest plots of progression-free survival by (A) *BRCA1/2* mutations, (B) *BRCA1* mutations only, and (C) *BRCA2* mutations only. Hazard ratios represent comparison of patients with *BRCA* mutations and wild-type gene.

Table 3

Meta-analysis for treatment response.

	Heterogeneity test			Pooled effect	
	Number of studies	Q statistic	I^2	OR (95% CI)	*P*
BRCA1 or 2 mutants vs wild-type					
Complete response	4	5.08	40.90%	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)	.828
Overall response rate	3	9.1	78.01%	1.30 (0.31, 5.44)	.722
BRCA2 vs wild-type					
Complete response	1	NA	NA		
Partial response	1	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.

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.[49] 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,[50,51] and poly (ADP-ribose) polymerase (PARP) inhibitors that inhibit DNA repair mechanisms.[52–54]

Studies have generally shown that *BRCA1/2* mutations are associated with an improved response to platinum-based chemotherapy.[9,12,32,33,36,41] However, how an improved response translates into survival benefits is unclear. Kotsopoulos et al[15] 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[13] 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[23] reported that an OS advantages was only seen in patients with *BRCA2* mutations, and not those with *BRCA1* mutations. Similarly, a study by Sun et al[55] 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.[56]

Other meta-analyses have examined the influence of BRCA1/2 mutations on survival of patients with ovarian cancer. In 2015 Zhong et al[57] 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 but similar PFS as compared with noncarriers, and BRCA2 was not associated with breast cancer prognosis. A recent meta-analysis by Xu et al[58] found that BRCA1 and BRCA2 mutations were associated with improved OS and PFS; however, that analysis did perform subgroup analysis based on disease stage or examine treatment response. Another meta-analysis of 34 evaluable studies showed that *BRCA* 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:

0.63, 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 *BRCA* promotor methylation was associated with a poorer prognosis (HR = 1.59, 95% CI: 0.72, 3.50, $P = .077$). 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* promotor 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, promotor 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 chemotherapies were platinum-based and some were not. The number of studies that analyzed *BRCA1* alone and *BRCA2* alone was markedly difference, and the reason may be that in ovarian cancer patients the *BRCA1* mutation occurs at a higher frequency that 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 is 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 previously reported studies were used for comparison which might duplicate data from other studies and for this reason the study was not included in the analysis.

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 state 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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