Prognostic significance of BRCA mutations in ovarian cancer: an updated systematic review with meta-analysis

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ABSTRACT

There is no consensus on the syntheses concerning the impact of BRCA mutation on ovarian cancer survival. A systematic review and meta-analysis of observational studies was conducted that evaluated the impact of BRCA mutations on the survival outcomes of patients with ovarian cancer. The primary outcome measure was overall survival (OS) and secondary outcome was progression-free survival (PFS). We presented data with hazard ratios (HRs) and 95% confidence interval (CI) and pooled them using the random-effects models. From 2,624 unique records, 34 eligible studies including 18,396 patients were identified. BRCA1/2 mutations demonstrated both OS and PFS benefits in patients with ovarian cancer (OS: HR = 0.67, 95% CI, 0.57 to 0.78, I² = 76.5%, P < 0.001; PFS: HR = 0.62, 95% CI, 0.53 to 0.73, I² = 18.1%, P = 0.261). For BRCA1 mutation carriers, the HRs for OS and PFS benefits were 0.73 (95% CI, 0.63 to 0.86) and 0.68 (95% CI, 0.52 to 0.89), respectively. For BRCA2 mutation carriers, the HRs for OS and PFS benefits were 0.57 (95% CI, 0.45 to 0.73) and 0.48 (95% CI, 0.30 to 0.75), respectively. The results of subgroup analyses for OS stratified by study quality, tumor stage, study design, sample size, number of research center, duration of follow-up, baseline characteristics adjusted and tumor histology were mostly constant across BRCA1/2, BRCA1 and BRCA2 mutation subtypes. In summary, for patients with ovarian cancer, BRCA mutations were associated with improved OS and PFS. Further large-scale prospective cohort studies should be conducted to test its benefits in specific patients.

INTRODUCTION

As two tumor suppressor genes, BRCA1 and BRCA2 mutation are reported to have been associated with increased risk of developing ovarian cancer and breast cancer [1–3]. Both of them are involved in DNA damage repair through homologous recombination, contributing to genomic instability and malignant transformation [4–6]. Meanwhile, they also involved in cell growth inhibition, gene transcription regulation, apoptosis and other related cellular regulation processes. Previous study reported that patients with BRCA-deficient ovarian cancer had improved survival rates as these patients were reported sensitive to platinum-based chemotherapy [7, 8].

Currently, numerous studies have reported the association between BRCA mutations and ovarian cancer mortality, and the results are conflicting. Some investigators have found that ovarian cancer patients with BRCA mutations have more favorable outcomes [9–18], whereas others have indicated null results [7, 19–23].

Two previous published meta-analyses have reported the prognostic impact of BRCA mutations on ovarian cancer mortality [24, 25]. Sun et al. found that patients with ovarian cancer with BRCA dysfunction...
status tended to have a better outcome [24]. However, this study investigated the effects of BRCA dysfunction status including mutations, protein expression and its promoter methylation, which did not perform the detailed analyses of BRCA mutations. In the meta-analysis by Zhong et al. they only examined the BRCA1 and BRCA2 mutation separately with limited statistical power without examining BRCA1/2 mutation [25]. Therefore, the purpose of this study was to update the meta-analysis on the impact of BRCA mutation carriers versus noncarriers on mortality in patients with ovarian cancer.

RESULTS

Literature search and study characteristics

From the initial literature search, we yielded 3595 citations. After exclusion of duplicate publications, 2624 citations remained for further review. 45 potentially eligible reports were selected when irrelevant studies were removed. After reading each full manuscript, we finally identified the 34 studies for meta-analysis. As is shown in Figure 1, we follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram to conduct this meta-analysis.

Characteristics of included studies

Table 1 summarizes the baseline characteristics of the included studies. A total of 18,396 patients were included with 32 studies reporting the primary outcome of OS and 13 studies reporting the secondary outcome of PFS. BRCA1, BRCA2 mutation and BRCA1/2 mutation were reported in 15, 14 and 34 studies, respectively. All studies were published between 1996 and 2016. The mean study sample size was 541 (range 40 to 6556) with a percentage of serous cancer ranging from 24.2% to 100%. 32% (11/34) of the included study were conducted in Europe, 50% (17/34) in USA or Canada and 9% (3/34) in Asia, from which 13 were multicenter studies.

As shown in Supplementary Table S1, the quality of the 34 included studies was generally high with 17 studies being more than 7 points.

Survival analysis for BRCA1/2-mutation carriers with ovarian cancer

OS analysis

32 studies of 17,497 patients with either BRCA1 or BRCA2-mutation (BRCA1/2-mutation) were identified in this analysis. Patients with BRCA1/2-mutation had significant OS benefit (HR = 0.67, 95% CI, 0.57 to 0.78, I² = 76.5%, P < 0.001; Figure 2A).

Subgroup analyses revealed that studies with adequate adjusted variables, but not with inadequate adjusted variables, had statistically significant OS benefit in ovarian cancer patients with BRCA1/2-mutation (adequate adjusted variables, HR = 0.63, 95% CI, 0.53 to 0.75, I² = 80.7%, P < 0.001; inadequate adjusted variables, HR = 0.89, 95% CI, 0.72 to 1.10, I² = 0, P = 0.992). OS benefits were also indicated in other subgroups and the HRs for all of the different subgroups are summarized in Table 2A.

PFS analysis

We identified 13 studies involving 3,485 patients with BRCA1/2-mutation for analysis of PFS [7, 10, 13, 20, 26–34]. Patients with BRCA1/2-mutation had significant PFS benefit (HR = 0.62, 95% CI, 0.53 to 0.73, I² = 18.1%, P = 0.261; Figure 2A). The results of subgroup analyses for the association between BRCA1/2-mutation and PFS are demonstrated in Table 3A. In summary, BRCA1/2-mutation was significantly associated with improved PFS for studies stratified according to study quality, study design, number of research center, tumor histology and study region. The trend toward an improved PFS was also observed when studies were stratified by tumor stage, sample size, duration of follow-up and optimal debulking ratio.

No evident publication bias was observed by funnel plot asymmetry (Figure 3A) or through Begg’s test (OS, P = 0.72; PFS, P = 0.58) or Egger’s test (OS, P = 0.23; PFS, P = 0.93). The trim and fill method applied to further conduct the sensitivity analysis indicated 8 and 5 missing studies in the funnel plot for OS and PFS, respectively (Figure 3). However, imputing these hypothesized studies did not substantially alter the primary pooled estimates (OS, adjusted HR = 0.49, 95% CI 0.41 to 0.59; PFS, adjusted HR = 0.48, 95% CI 0.40 to 0.58).

Survival analysis for BRCA1-mutation carriers with ovarian cancer

OS analysis

15 studies involving 12,995 patients with BRCA1-mutation were identified for meta-analysis [12, 13, 27, 28, 32, 34–43]. Patients with BRCA1-mutation had significant OS benefit (HR = 0.73, 95% CI, 0.63 to 0.86, I² = 34.8%, P < 0.001; Figure 2B).

The results of subgroup analyses for the association between BRCA1-mutation and PFS are presented in Table 2B. We found that ovarian cancer patients with BRCA1-mutation had significantly longer OS than noncarriers, regardless of study quality, sample size, research center or duration of follow-up. Such trend was also noted in studies with cohort study design, adequate baseline characteristics adjusted, all histologic types or conducted in USA or Canada.
| Authors and published years | Study design | No. in study (cases/controls) | Inclusion period | Country of origin | Stage | Histology | serum cancer (%) | Mutation detection method | BRCA status | Germ /Soma | Single or multizenter | Follow-up Duration | Adjusted variables | Mutation ratio | Optimal debulking(%) |
|-----------------------------|--------------|------------------------------|------------------|------------------|-------|-----------|-----------------|--------------------------|-------------|------------|---------------------|-------------------|-----------------|----------------|-------------------|
| Synowiec (2016)             | BC           | 17/108                       | 2002-2008        | Poland           | I-IV  | all       | 54.4            | PCR, seq                | BRCA1       | Germ       | single              | NR                | 13.00           | 61.6           |                    |
| Sautier (2016)              | BC           | 33/71                        | 1994-2011        | France           | I-IV  | all       | 52.9            | MLPA, DHPLC, Seq        | BRCA1/2     | Germ       | single              | Mean 69.8 months with an s.d. of 58.4 months | Age, stage, grade, histology, chemotherapy regimen, surgery, grade | 31.70           | 67.2              |
| Kotelesopoulos (2016)       | BC           | 177/1244                     | 1995-1999, 2002-2004 | Canada          | I-IV  | all       | 55.1            | NR                      | BRCA1/2     | NR         | single              | BRCA1 Mutation: 8.1 years (range:94.20-2) BRCA2 Mutation: 7.6 years (range:2.88-19.9) WI: 9.7 years (range:0.59-20.3) | Age, stage, grade, histology, chemotherapy, surgery | 12.50           | NR                |
| Harter (2015)               | BC           | 97/567                       | NR               | Germany         | II-IV | all       | 73.6            | PCR, seq                | BRCA1/2     | Germ       | single              | NR                | Age, stage, grade, histology               | 15              | NR                |
| Chen (2015)                 | BC           | 63/195                       | NR               | Finland         | NR    | NR        | NR              | PCR, Seq                | BRCA1/2     | NR         | multizenter         | NR                | Age, grade, stage, residual disease, neoadjuvant therapy, primary therapy outcome | 23.82           | NR                |
| Candido-deo-Reis (2015)     | BC           | 1496/5060                    | U.S.A            | 1992-2011       | U.S.A | all       | 73              | PCR, seq                | BRCA1/2     | Germ/Soma | single              | Median 4.5 years (range:0.01-10) | Age, stage, grade, debulking status, ascites present at surgery, menopausal status | 22.80           | NR                |
| Cunningham (2014)           | BC           | 70/993                       | 2012             | U.S.A           | II-IV | all       | 73              | PCR, seq                | BRCA1/2     | Germ       | single              | NR                | Age, grade, stage, residual tumor size, response to chemotherapy therapy | 6.6             | 85                |
| Zhang (2014)                | BC           | 75/250                       | 2012             | NR              | II-IV | NR        | NR              | PCR, seq                | BRCA1/2     | NR         | single              | NR                | Age, grade, stage, residual tumor size | 23.10           | 67.1              |
| Radzevits (2014)            | BC           | 55/52                        | 2008-2011        | Lithuania       | III-IV | seromucinous | 92.5            | PCR, seq                | BRCA1/2     | Germ       | single              | BRCA1/2 Mutation: Median 15 months (range:1.10) BRCA2 Mutation: Median 25 months (range:8-210) | Age, follow-up, ECOG, histology, subtype, residual tumor size, neoadjuvant therapy, Family history | 51.40           | NR                |
| Finnstrom (2014)            | BC           | 91/276                       | NR               | U.S.A           | I-IV  | all       | 70.3            | PCR, seq                | BRCA1/2     | Germ/Soma | multizenter         | NR                | Age, size, grade, stage, residual tumor size | 24.8            | 66                |
| Saha (2013)                 | BC           | 90/100                       | 1995-2009        | U.S.A, Israel, India | I-IV  | all       | 69.5            | PCR, Seq                | BRCA1/2     | multizenter | single              | Median 56 months (range 9.3-214) | Age, stage, residual tumor size, Ethnicity, Institution | 47.40           | NR                |
| Authors | BC | Year | Country | Grade | Method | Test | Tumor | Ethnicity | Age, Histology, Stage,多 | Follow-up | PR | CT | RT | NR |
|---------|----|------|---------|-------|--------|------|-------|----------|-------------------------|------------|----|----|----|----|
| Pittard et al. (2013) | 218/1408 | 1995-1999, 2002-2004 | U.S.A. | II-IV | serous | 100 | PCR, seq | IBCA1/2 | Germ | single | Mean 6.9 years (range 0.3-15.7) | Age, histology, grade, stage | 13.4 | NR |
| Hymon et al. (2012) | 47/143 | 1996-2011 | U.S.A. | II-IV | serous | 100 | PCR, seq | IBCA1/2 | Germ | single | Mean 2.5 years | Age, stage, Optimal debulking, DTI | 24.70 | 76.3 |
| Dunc et al. (2012) | 15/38 | 1999-2007 | U.S.A. | II-IV | all | 73.6 | PCR, seq | IBCA1/2 | Germ+Serum | single | NR | Age, grade, histology, residual disease, chemotherapy, Platinum response | 28.50 | 83.7 |
| Chen et al. (2012) | 69/246 | NR | U.S.A. | II-IV | serous | 100 | PCR, seq | IBCA1/2 | Germ+Serum | single | Mean 15.4 months (range 1-225) | Age, grade, histology, residual disease, Efficacy | 21.80 | 63.8 |
| Alto et al. (2012) | 141/560 | 2002-2006 | Australian | I-V | all | 70.8 | PCR, seq | IBCA1/2 | Germ | single | Mean 63.4 months | Age, stage, grade, debulking, primary site, chemotherapy, Efficacy | 14.10 | 62.4 |
| Yang et al. (2011) | 62/232 | 2009-2010 | U.S.A. | II-IV | serous | 100 | PCR, seq | IBCA1/2 | Germ+Serum | single | NR | Age, stage, grade, debulking, Efficacy | 19.70 | 63.8 |
| Lacor et al. (2011) | 95/183 | 1996-2007 | U.S.A. | II-IV | all | 68 | PCR, seq | IBCA1/2 | Germ | single | BCRCA Mutation: median 42.6; BCRCA WT: median 27.5 | Age, stage, grade, histology, debulking, response to chemotherapy, Institution, Efficacy | 34.20 | 70.1 |
| Gallagher et al. (2011) | 36/74 | 1996-2006 | U.S.A. | II-IV | all | 80.9 | PCR, Seq | IBCA1/2 | Germ | single | Mean 41 months | Age, stage, histology, debulking, platinum response, CA125, secondary cytoreduction | 32.70 | 60.9 |
| Hennessey et al. (2010) | 44/191 | 1996-2006 | U.S.A. | I-V | all | 79.1 | PCR,Seq | IBCA1/2 | Germ+Serum | multivariate | Median 107days (range 19-6241) | Age, grade, stage, residual disease, surgery, chemotherapy | 18.70 | 58.7 |
| Tan et al. (2008) | 22/44 | 1993-1995 | UK | II-IV | all | 83.8 | SSCP, seq | IBCA1/2 | Germ | multivariate | NR | Age, stage, histology | 33.30 | NR |
| Cherit et al. (2008) | 252/554 | 1994-1999 | Israel | I-V | all | 57.1 | PCR, seq | IBCA1/2 | Germ | single | Mean 6.2 years (range 0.2-9.4) | Age, stage, grade, menstrual status | 28.90 | NR |
| Pal et al. (2007) | 32/200 | 2000-2003 | U.S.A. | I-V | all | 57.9 | PCR, seq | IBCA1/2 | Germ | single | NR | Age, grade, stage, histology | 13.80 | NR |
| Majchrzak et al. (2005) | 18/187 | 1994-2002 | Poland | I-V | all | 64.9 | F-CSR, PCR, Seq | IBCA1/2 | Germ | single | NR | Age, stage, grade, histology, residual disease, fertility | 8.8 | 52.2 |
| Cass et al. (2003) | 54/57 | 1990-1998 | U.S.A. | I-V | all | 84.5 | PCR, SSCP, seq | IBCA1/2 | Germ | single | Median 72months | Age, stage, grade, histology, CA125, optimal cytoreduction, Primary chemotherapy | 47.90 | NR |
We identified 3 studies involving 1,640 patients with BRCA1-mutation for analysis of PFS [13, 27, 28]. Patients with BRCA1-mutation had significant PFS benefit (HR = 0.68, 95% CI, 0.52 to 0.89, I² = 0, P < 0.001; Figure 2B). The results of subgroup analyses for the association between BRCA1-mutation and PFS are demonstrated in Table 3B.

No evident publication bias was observed by funnel plot asymmetry (Figure 3B) or through Egger’s test (P = 0.84) or Begg’s test (P = 0.83) for OS. The trim and fill method applied to further conduct the sensitivity analysis indicated one missing study in the funnel plot for OS (Figure 3). However, imputing this hypothesized study did not alter the primary pooled estimates (adjusted HR = 0.66, 95% CI, 0.56 to 0.78). We did not investigate the publication bias for PFS due to the limited number of studies.

PFS analysis

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| David (2002)     | RC | 254/662 | 1994–1999 | Israel | NR | all | NR | SCCP/seq | BRCA1/2 | Germ | single | Median 39.5 months (range 20–64) | age, stage, family history | 26.10 | NR |
|------------------|----|---------|-----------|--------|----|-----|----|---------|---------|------|--------|---------------------------------|--------------------------|-------|----|
| Butler (2002)    | NCC| 24/48   | NR        | U.S.A. | I-IV | all | 74.6 | PCR, PTT, seq, SCCP | BRCA1 | Germ | Soma | single | NR | / | 23.60 | NR |
| Zveizer (2001)   | NCC| 23/17   | NR        | Netherlands | I-IV | all | 55 | PCR, PTT | BRCA1/2 | Germ | single | Mean 47 months (range 6–168) | age, stage, grade | 57.50 | NR |
| Kamen (2001)     | RC | 27/71   | 1992–1997 | Israel | I-IV | all | 77.6 | RCR, SCCP, seq | BRCA1/2 | Germ | single | NR | / | 27.60 | NR |
| Boyd (2000)      | RC | 88/101  | 1986–1998 | U.S.A. | I-IV | all | 64 | PCR, Seq | BRCA1/2 | Germ | multilcenter | BRCA Mutation; median 57 months; BRCA W/ median 59 months | Histology, grade, stage, cytoreductive surgery, chemotherapy | 46.60 | 50.8 |
| Pharoah (1999)   | NCC| 38/127  | NR | UK | I-IV | all | 24.2 | PTT, SCCP, Seq | BRCA1/2 | Germ | multilcenter | NR | / | 56 | NR |
| Johansson (1998) | NCC| 38/97   | 1983–1995 | Sweden | I-IV | all | NR | PTT, SCCP, Seq | BRCA1 | Germ | multilcenter | NR | / | 28.15 | NR |
| Miki (1998)      | NCC| 13/49   | 1993–1997 | Japan | III | all | 83.9 | SCCP, PCR, Seq | BRCA1 | Germ | multilcenter | Mean 54.8 months | Age, histology, stage, chemotherapy, response | 57.80 | NR |
| Rubin (1996)     | NCC| 43/44   | 1998–1996 | U.S.A | III-IV | all | 81.1 | SCCP, PCR, Seq | BRCA1 | Germ | multilcenter | Mean 71 months | / | 0 | NR |

Abbreviations: DGGE = Denaturing gradient gel electrophoresis; DRFLP = Dideoxy fingerprinting; F = Fluorescence-based Conformation Sensitive Gel Electrophoresis; Germ = Germline mutation; I-IV = Intersubject and intrapatient therapy; I-IV = Intersubject therapy alone; MLPA = Multiplex ligation-dependent probe amplification; NCC = Nested case-control study; NR = Not reported; PTT = Protein truncation test; RC = Retrospective cohort; RFPL = Restriction fragment length polymorphisms; Seq = Sequencing; Soma = Somatic mutation; SCCP = Single Strand Conformation Polymorphism.

Figure 1: Flowchart of the study selection.

Identified studies from the databases using keywords and bibliographies of relevant articles (N = 3595): PubMed (n = 1305), EMBASE (n = 2290)

Excluded duplicate studies (n = 971)

Studies remaining after excluding duplicates (n = 2624)

Excluded upon reading the title and/or abstract (n = 2537)

Remaining studies (n = 87) evaluated in detail

Excluded studies (n = 42):
- Shared an identical population (n = 1)
- No relevant outcomes (n = 23)
- Letter, comments, correspondence (n = 15)
- Small sample size (n = 3)

Studies eligible for inclusion: (n = 45)

Excluded for insufficient data: (n = 11)

Studies included in final analyses: (n = 34)
Survival analysis for BRCA2-mutation carriers with ovarian cancer

OS analysis

14 studies including 12,933 patients with BRCA2-mutation were involved for meta-analysis [12, 13, 27, 28, 32, 35–43]. Patients with BRCA2-mutation had significant OS benefit (HR = 0.57, 95% CI, 0.45 to 0.73, \( I^2 = 50.3\% \), \( P < 0.001 \); Figure 2C).

The results of subgroup analyses for the association between BRCA2-mutation and OS are presented in Table 2C. We found that ovarian cancer patients with BRCA2-mutation had significantly longer OS than non-carriers, regardless of research center, duration of follow-up or histologic type. Such trend was also noted in studies with high quality, II-IV disease stage, cohort study design, sample size larger than 200, adequate baseline characteristics adjusted or conducted in USA or Canada.

Table 2A: Subgroup analyses stratified by some of the baseline characteristics for associations between BRCA1/2 mutation and overall survival

|                          | HR   | 95% CI          | Degree of heterogeneity \( (I^2 \) statistics; %) | \( P \)  | No. of included Studies |
|--------------------------|------|-----------------|---------------------------------------------------|--------|------------------------|
| Total                    | 0.67 | 0.57 to 0.78    | 76.5                                              | < 0.001| 32                     |
| Study quality            |      |                 |                                                   |        |                        |
| Score > 7                | 0.67 | 0.56 to 0.80    | 74.4                                              | < 0.001| 15                     |
| ≤ 7                      | 0.66 | 0.50 to 0.87    | 79.2                                              | < 0.001| 17                     |
| Stage of disease         |      |                 |                                                   |        |                        |
| I-IV                     | 0.79 | 0.66 to 0.94    | 76.5                                              | < 0.001| 19                     |
| II-IV                    | 0.47 | 0.37 to 0.59    | 0                                                 | 0.423  | 5                      |
| III-IV                   | 0.64 | 0.49 to 0.83    | 43.2                                              | < 0.091| 8                      |
| Study design             |      |                 |                                                   |        |                        |
| Cohort                   | 0.67 | 0.56 to 0.79    | 80.1                                              | < 0.001| 24                     |
| Case-control             | 0.65 | 0.44 to 0.96    | 56.7                                              | 0.024  | 8                      |
| Sample size              |      |                 |                                                   |        |                        |
| ≥ 200                    | 0.68 | 0.56 to 0.83    | 85.5                                              | < 0.001| 5                      |
| < 200                    | 0.67 | 0.54 to 0.83    | 45.7                                              | 0.021  | 17                     |
| Research center          |      |                 |                                                   |        |                        |
| Single                   | 0.67 | 0.53 to 0.84    | 76.7                                              | < 0.001| 20                     |
| Multicenter              | 0.70 | 0.57 to 0.86    | 75.5                                              | < 0.001| 11                     |
| Duration of follow-up    |      |                 |                                                   |        |                        |
| Months                   |      |                 |                                                   |        |                        |
| > 60                     | 0.77 | 0.65 to 0.91    | 77.7                                              | < 0.001| 20                     |
| ≤ 60                     | 0.58 | 0.49 to 0.68    | 40.7                                              | 0.069  | 12                     |
| Adequate baseline         |      |                 |                                                   |        |                        |
| characteristics adjusted  |      |                 |                                                   |        |                        |
| Yes                      | 0.63 | 0.53 to 0.75    | 80.7                                              | < 0.001| 26                     |
| No                       | 0.89 | 0.72 to 1.10    | 0                                                 | 0.922  | 6                      |
| Histology                |      |                 |                                                   |        |                        |
| All                      | 0.68 | 0.58 to 0.79    | 76.2                                              | < 0.001| 31                     |
| High-grade serous        | 0.62 | 0.43 to 0.90    | 84                                                 | < 0.001| 4                      |
| Mutation ratio           |      |                 |                                                   |        |                        |
| > 25%                    | 0.70 | 0.60 to 0.81    | 36.3                                              | 0.068  | 17                     |
| ≤ 25%                    | 0.65 | 0.51 to 0.82    | 85.5                                              | < 0.001| 15                     |
| Region                   |      |                 |                                                   |        |                        |
| Europe                   | 0.65 | 0.48 to 0.88    | 64.8                                              | 0.002  | 10                     |
| America/Canada           | 0.72 | 0.59 to 0.89    | 80.3                                              | < 0.001| 16                     |
| Asia                     | 0.69 | 0.51 to 0.93    | 12.0                                              | 0.321  | 3                      |
| Optimal debulking ratio  |      |                 |                                                   |        |                        |
| > 65%                    | 0.58 | 0.48 to 0.72    | 41.6                                              | 0.090  | 9                      |
| ≤ 65%                    | 0.53 | 0.35 to 0.79    | 60.9                                              | 0.037  | 5                      |

Abbreviations: HR = hazard ratio; CI = confidence interval.

The survival analysis for BRCA2-mutation carriers with ovarian cancer resulted in a significant OS benefit (HR = 0.57, 95% CI, 0.45 to 0.73, \( I^2 = 50.3\% \), \( P < 0.001 \); Figure 2C).
We identified 3 studies involving 1,640 patients with BRCA2-mutation for analysis of PFS [13, 27, 28]. Patients with BRCA2-mutation had significant PFS benefit (HR = 0.48, 95% CI, 0.30 to 0.75, I² = 0, P < 0.001; Figure 2C). The results of subgroup analyses for the association between BRCA2-mutation and PFS are demonstrated in Table 3C.

No evident publication bias was observed by funnel plot asymmetry (Figure 3C) or through Egger’s test (P = 0.54) or Begg’s test (P = 0.96) for OS. The trim and fill method applied to further conduct the sensitivity analysis indicated 4 missing studies in the funnel plot for OS (Figure 3). However, imputing these hypothesized studies did not alter the primary pooled estimates (adjusted HR = 0.38, 95% CI 0.29 to 0.50). We did not investigate the publication bias for PFS due to the limited number of studies.

**DISCUSSION**

The aim of this meta-analysis was to examine the association between BRCA mutation status and ovarian cancer survival (OS and PFS). By pooling the outcomes of 18,396 ovarian cancer patients from 34 individual studies, we found that BRCA mutation (BRCA1/2, BRCA1 and BRCA2) carriers had significantly improved OS and PFS benefits in ovarian cancer patients. Subgroup analysis revealed that this survival benefits remained constant.
irrespective of study quality, tumor stage, study design, sample size, number of research center, duration of follow-up, baseline characteristics adjusted and tumor histology.

This meta-analysis showed that patients who were BRCA mutation carriers had a 33%, 27% and 43% reduction in all-cause mortality for BRCA1/2, BRCA1 and BRCA2 mutants respectively, while patients had a 38%, 32% and 52% reduction in progression-free mortality for BRCA1/2, BRCA1 and BRCA2 mutants, respectively. Individually, however, some of the studies had reported contradictory findings [7, 19–22]: some studies have indicated significantly reduced all-cause mortality or progression-free mortality among BRCA mutation carriers [9–14], whereas Kotsopoulos et al. reported that the mortality risk in ovarian cancer patients was significantly poorer for BRCA mutation carriers than for non-carriers (HR = 1.67; 95% CI 1.34 to 2.08) [19]. The present meta-analysis with the largest number of patients investigated both survival (OS) and progression outcomes (PFS) for ovarian cancer, incorporating not only the general BRCA mutation status but also two subtypes, including BRCA1 and BRCA2 mutation status.

It has been reported that germline BRCA1/2 mutations occur in approximately 10 to 20% of patients with invasive epithelial ovarian cancers [7, 9–14, 19–22], and more than 20% of patients with high-grade serous ovarian cancer [12]. BRCA1/2 tumor suppressor genes are reported to be involved in DNA repair through homologous recombination, through which pathway genes are unable to repair DNA double-strand, resulting

### Table 2C: Subgroup analyses stratified by some of the baseline characteristics for associations between BRCA2 mutation and overall survival

|                                | HR    | 95%CI     | Degree of heterogeneity (I² statistics; %) | P       | No. of included Studies |
|--------------------------------|-------|-----------|---------------------------------------------|---------|------------------------|
| **Total**                      | 0.57  | 0.45 to 0.73 | 50.3                                        | 0.016   | 14                     |
| Study quality                  |       |           |                                             |         |                        |
| Score > 7                      | 0.53  | 0.40 to 0.70 | 50.2                                        | 0.034   | 10                     |
| ≤ 7                            | 0.71  | 0.41 to 1.21 | 46.7                                        | 0.131   | 4                      |
| Stage of disease               |       |           |                                             |         |                        |
| I–IV                           | 0.56  | 0.43 to 0.74 | 39.6                                        | 0.103   | 9                      |
| II–IV                          | 0.46  | 0.21 to 0.97 | 37.2                                        | 0.207   | 2                      |
| III–IV                         | 0.64  | 0.32 to 1.28 | 64.0                                        | 0.062   | 3                      |
| Study design                   |       |           |                                             |         |                        |
| Cohort                         | 0.56  | 0.43 to 0.72 | 48.3                                        | 0.030   | 12                     |
| Case-control                   | 0.54  | 0.13 to 2.14 | 70.7                                        | 0.065   | 2                      |
| Sample size                    |       |           |                                             |         |                        |
| ≥ 200                          | 0.54  | 0.41 to 0.73 | 51.4                                        | 0.036   | 9                      |
| < 200                          | 0.63  | 0.38 to 1.04 | 52.9                                        | 0.075   | 5                      |
| Research center                |       |           |                                             |         |                        |
| Single                         | 0.52  | 0.39 to 0.70 | 24.6                                        | 0.224   | 9                      |
| Multicenter                    | 0.65  | 0.43 to 0.89 | 71.5                                        | 0.007   | 5                      |
| Duration of follow-up          |       |           |                                             |         |                        |
| Months                         |       |           |                                             |         |                        |
| > 60                           | 0.59  | 0.44 to 0.78 | 55.8                                        | 0.016   | 10                     |
| ≤ 60                           | 0.52  | 0.28 to 0.94 | 45.4                                        | 0.139   | 4                      |
| Adequate baseline characteristics adjusted |     |           |                                             |         |                        |
| Yes                            | 0.52  | 0.40 to 0.68 | 48.7                                        | 0.029   | 12                     |
| No                             | 0.92  | 0.61 to 1.39 | 0                                           | 0.881   | 2                      |
| Histology                      |       |           |                                             |         |                        |
| All                            | 0.56  | 0.44 to 0.72 | 36.7                                        | 0.097   | 12                     |
| High-grade serous             | 0.54  | 0.32 to 0.93 | 79.8                                        | 0.002   | 4                      |
| Region                         |       |           |                                             |         |                        |
| Europe                         | 0.61  | 0.34 to 1.07 | 59.0                                        | 0.087   | 3                      |
| America/Canada                 | 0.51  | 0.34 to 0.76 | 66.5                                        | 0.006   | 7                      |
| Asia                           | 0.88  | 0.44 to 1.75 | /                                           | /       | 1                      |

Abbreviations: HR = hazard ratio; CI = confidence interval.
Figure 2: (A) Forest plot for the association between BRCA1/2 mutation and ovarian cancer (1) overall survival and (2) progression-free survival. (B) Forest plot for the association between BRCA1 mutation and ovarian cancer overall survival and progression-free survival; (C) Forest plot for the association between BRCA2 mutation and ovarian cancer overall survival and progression-free survival.
Figure 3: Funnel plot for (A) BRCA1/2, (B) BRCA1, (C) BRCA2 mutation and ovarian cancer overall survival and/or progression-free survival.
in genomic instability and having a tendency to malignant transformation [3]. On the other hand, the impairment of this pathway can also influence DNA cross-links by tumor cells, which can be induced by cisplatin, a chemotherapy agent for ovarian cancer. It has been indicated that BRCA-deficient patients can have better survival outcomes through the increase in the response rate to platinum-based chemotherapy [7, 8].

Table 3A: Subgroup analyses stratified by some of the baseline characteristics for associations between BRCA1/2 mutation and progression-free survival

|                           | HR      | 95%CI    | Degree of heterogeneity (I² statistics; %) | P      | No. of included Studies |
|---------------------------|---------|----------|---------------------------------------------|--------|-------------------------|
| Total                     | 0.62    | 0.53 to 0.73 | 18.1                                     | 0.261  | 13                      |
| Study quality             |         |          |                                             |        |                         |
| Score > 7                 | 0.65    | 0.52 to 0.81 | 40.9                                      | 0.118  | 7                       |
| ≤ 7                       | 0.59    | 0.46 to 0.75 | 0                                          | 0.523  | 6                       |
| Stage of disease          |         |          |                                             |        |                         |
| I–IV                      | 0.74    | 0.47 to 1.15 | 63.0                                      | 0.044  | 4                       |
| II–IV                     | 0.55    | 0.43 to 0.69 | 0                                          | 0.520  | 5                       |
| III–IV                    | 0.60    | 0.48 to 0.76 | 0                                          | 0.996  | 4                       |
| Study design              |         |          |                                             |        |                         |
| Cohort                    | 0.64    | 0.55 to 0.74 | 15.9                                      | 0.296  | 10                      |
| Case-control              | 0.44    | 0.22 to 0.86 | 4                                          | 0.271  | 3                       |
| Sample size               |         |          |                                             |        |                         |
| ≥ 200                     | 0.61    | 0.51 to 0.72 | 0                                          | 0.996  | 6                       |
| < 200                     | 0.62    | 0.37 to 1.04 | 60.7                                      | 0.026  | 6                       |
| Research center           |         |          |                                             |        |                         |
| Single                    | 0.65    | 0.54 to 0.78 | 24                                         | 0.230  | 9                       |
| Multicenter               | 0.56    | 0.42 to 0.75 | 10.7                                      | 0.340  | 4                       |
| Duration of follow-up     |         |          |                                             |        |                         |
| Months                    |         |          |                                             |        |                         |
| > 60                      | 0.60    | 0.30 to 1.18 | 74.6                                      | 0.005  | 4                       |
| ≤ 60                      | 0.60    | 0.51 to 0.70 | 42.2                                      | 0.995  | 7                       |
| Adequate baseline         |         |          |                                             |        |                         |
| characteristics adjusted  |         |          |                                             |        |                         |
| Yes                       | 0.62    | 0.53 to 0.73 | 18.1                                      | 0.261  | 13                      |
| No                        | /       | /        | /                                          | /      | 0                       |
| Histology                 |         |          |                                             |        |                         |
| All                       | 0.64    | 0.52 to 0.78 | 28.4                                      | 0.175  | 11                      |
| High-grade serous         | 0.60    | 0.40 to 0.89 | /                                         | /      | 1                       |
| Mutation ratio            |         |          |                                             |        |                         |
| > 25%                     | 0.60    | 0.51 to 0.71 | 0                                          | 0.987  | 6                       |
| ≤ 25%                     | 0.63    | 0.43 to 0.92 | 55.6                                      | 0.036  | 7                       |
| Region                    |         |          |                                             |        |                         |
| Europe                    | 0.63    | 0.40 to 0.98 | 70.7                                      | 0.008  | 5                       |
| America/Canada            | 0.59    | 0.48 to 0.73 | 0                                          | 0.985  | 5                       |
| Asia                      | 0.75    | 0.08 to 6.90 | /                                         | /      | 1                       |
| Optimal debulking ratio   |         |          |                                             |        |                         |
| > 65%                     | 0.70    | 0.50 to 1.00 | 55.1                                      | 0.063  | 5                       |
| ≤ 65%                     | 0.63    | 0.50 to 0.79 | 0                                          | 0.938  | 3                       |

Abbreviations: HR = hazard ratio; CI = confidence interval.
As a matter of fact, 11 recent published cohort studies were involved in the analyses. Second, three mutation subtypes (BRCA1/2, BRCA1 and BRCA2) were thoroughly investigated in contrast to the earlier two meta-analyses (including only BRCA1 and BRCA2 subtypes). Thirdly, we did detailed subgroup analyses under a broader range of study level circumstances to examine the potential sources of heterogeneity. However, our findings concur with the previous meta-analyses. Inter-study heterogeneity was found very high for a number of analyses, which was probably due to the very variation in population characteristics and BRCA mutation detection methods.

Thus, caution is required when interpreting these findings. Moreover, one important advantage of this meta-analyses lies in that we have thoroughly tested the influence of publication bias through Begg’s test, Egger’s test and sensitivity analysis and confirmed the robustness of the findings.

Several limitations of this meta-analysis are required to be addressed. We acknowledge that the results of this meta-analysis were derived from published data rather than from studies of individual patient data. Thus, we could not obtained the detailed characteristics of each individual from the involved studies including patient age, tumor stage, sample size, and follow-up period, which to

| Table 3B: Subgroup analyses stratified by some of the baseline characteristics for associations between BRCA1 mutation and progression-free survival |
|---------------------------------|-----------------|-------------------------|-------------------|-----------------|
|                                 | HR              | 95%CI                   | Degree of heterogeneity (I^2 statistics; %) | P                | No. of included Studies |
| Total                           | 0.68            | 0.52 to 0.89            | 0                  | 0.750           | 3                      |
| Study quality                   |                 |                         |                    |                 |                        |
| Score > 7                       | 0.78            | 0.48 to 1.27            | 0                  | 0.709           | 2                      |
| ≤ 7                             | 0.64            | 0.46 to 0.88            | /                  | /               | 1                      |
| Stage of disease                |                 |                         |                    |                 |                        |
| I–IV                            | 0.64            | 0.46 to 0.88            | /                  | /               | 1                      |
| II–IV                           | 0.78            | 0.48 to 1.27            | 0                  | 0.709           | 2                      |
| III–IV                          | /               | /                       | /                  | /               | 0                      |
| Study design                    |                 |                         |                    |                 |                        |
| Cohort                          | 0.68            | 0.52 to 0.89            | 0                  | 0.750           | 3                      |
| Case-control                    | /               | /                       | /                  | /               | 0                      |
| Sample size                     |                 |                         |                    |                 |                        |
| ≥ 200                           | 0.68            | 0.52 to 0.89            | 0                  | 0.750           | 3                      |
| < 200                           | /               | /                       | /                  | /               | 0                      |
| Research center                 |                 |                         |                    |                 |                        |
| Single                          | 0.68            | 0.52 to 0.89            | 0                  | 0.750           | 3                      |
| Multicenter                     | /               | /                       | /                  | /               | 0                      |
| Duration of follow-up           |                 |                         |                    |                 |                        |
| Months                          |                 |                         |                    |                 |                        |
| > 60                            | 0.64            | 0.46 to 0.88            | /                  | /               | 1                      |
| ≤ 60                            | 0.78            | 0.48 to 1.27            | 0                  | 0.709           | 2                      |
| Adequate baseline characteristics adjusted |                 |                         |                    |                 |                        |
| Yes                             | 0.68            | 0.52 to 0.89            | 0                  | 0.750           | 3                      |
| No                              | /               | /                       | /                  | /               | 0                      |
| Histology                       |                 |                         |                    |                 |                        |
| All                             | 0.70            | 0.59 to 0.83            | 35.5               | 0.099           | 2                      |
| High-grade serous               | 0.81            | 0.48 to 1.37            | /                  | /               | 1                      |
| Region                          |                 |                         |                    |                 |                        |
| Europe                          | /               | /                       | /                  | /               | 0                      |
| America/Canada                  | 0.81            | 0.48 to 1.38            | /                  | /               | 1                      |
| Asia                            | /               | /                       | /                  | /               | 0                      |

Abbreviations: HR = hazard ratio; CI = confidence interval.
some extent were contributory factors to the heterogeneity, but an attempt was made to account for this variation by conducting subgroup analyses. Another potential limitation of the study is that we also include some conference abstracts in the analysis. It is likely that the results may differ to certain extent between the conference abstracts and future updated full publication. However, we proposed that such differences are very likely to be relatively mild. Moreover, the method for the detection of $BRCA$ mutation varied among studies, which may also a source of substantial heterogeneity. Some of the included studies did not report complete data for analysis, and could have potentially affected the results of multivariate analysis. Most of the included studies adequately adjusted for some known confounders, in particular patients age, tumor stage and grade or chemotherapy. However, some studies did not assess these factors and we acknowledge this limitation. As these were all studies with small sample size, it is unlikely to have affected the results of the analysis substantially. Although no obvious evidence of publication bias was noted in each subset of meta-analysis, it was still a major concern. Due to the time taken to conduct this meta-analysis, further relevant studies concerning this topic may have been published. However, given the relative paucity of suitable studies identified through the last 20 years from 1996 to 2016, we proposed

| Table 3C: Subgroup analyses stratified by some of the baseline characteristics for associations between $BRCA2$ mutation and progression-free survival |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|
|                                  | HR              | 95%CI           | Degree of heterogeneity ($\chi^2$ statistics; %) | $P$              | No. of included Studies |
| Total                            | 0.48            | 0.30 to 0.75    | 0               | 0.590           | 3                 |
| Study quality                    |                 |                 |                 |                 |                   |
| Score $> 7$                      | 0.41            | 0.24 to 0.70    | 0               | 0.895           | 2                 |
| $\leq 7$                        | 0.68            | 0.30 to 1.55    | /               | /               | 1                 |
| Stage of disease                 |                 |                 |                 |                 |                   |
| I–IV                            | 0.68            | 0.30 to 1.55    | /               | /               | 1                 |
| II–IV                           | 0.41            | 0.24 to 0.70    | 0               | 0.895           | 2                 |
| III–IV                          | /               | /               | /               | /               | 0                 |
| Study design                     |                 |                 |                 |                 |                   |
| Cohort                           | 0.48            | 0.30 to 0.75    | 0               | 0.590           | 3                 |
| Case-control                     | /               | /               | /               | /               | 0                 |
| Sample size                      |                 |                 |                 |                 |                   |
| $\geq 200$                      | 0.48            | 0.30 to 0.75    | 0               | 0.590           | 3                 |
| < 200                            | /               | /               | /               | /               | 0                 |
| Research center                  |                 |                 |                 |                 |                   |
| Single                           | 0.48            | 0.30 to 0.75    | 0               | 0.590           | 3                 |
| Multicenter                      | /               | /               | /               | /               | 0                 |
| Duration of follow-up            |                 |                 |                 |                 |                   |
| Months                           |                 |                 |                 |                 |                   |
| $> 60$                           | 0.68            | 0.30 to 1.55    | /               | /               | 1                 |
| $\leq 60$                       | 0.41            | 0.24 to 0.70    | 0               | 0.895           | 2                 |
| Adequate baseline characteristics adjusted | | | | | |
| Yes                              | 0.48            | 0.30 to 0.75    | 0               | 0.590           | 3                 |
| No                               | /               | /               | /               | /               | 0                 |
| Histology                        |                 |                 |                 |                 |                   |
| All                              | 0.40            | 0.22 to 0.73    | /               | /               | 1                 |
| High-grade serous                | 0.60            | 0.30 to 1.20    | 0               | 0.576           | 2                 |
| Region                           |                 |                 |                 |                 |                   |
| Europe                           | /               | /               | /               | /               | 0                 |
| America/Canada                   | 0.40            | 0.22 to 0.74    | /               | /               | 1                 |
| Asia                             | /               | /               | /               | /               | 0                 |

Abbreviations: HR = hazard ratio; CI = confidence interval.
that there were probably very few studies in number and they would not substantially affect the general conclusions of this study.

Despite all of these limitations, however, our meta-analysis with a large sample size of over 18,396 participants, and used the appropriate analyses to investigate the heterogeneity and publication bias among the different studies, showed that in patients with ovarian cancer, BRCA mutation (irrespective of its subtypes) carriers had better OS and PFS than non-carriers. Whether the results may have therapeutic implications remains to be elucidated with further larger, well-designed studies in specific ovarian cancer patients.

MATERIALS AND METHODS

Literature search and study selection

PubMed and EMBASE were searched for studies published up to February 2016 for the following searching terms: (ovary/ovarian/oophor* and cancer/neoplas*/tumor*/tumour*/cancer/carcinoma*/malignan*/neoplasms) and (BRCA1/2 and mutation*/mutated) and mortality/survival/prognosis. Mesh (Pubmed) and Emtree (Embase) terms combined with free text words were used for searching. Detailed search terms and strategies for the two databases are presented in Supplementary Appendix 1. In addition, we also conducted the manual searches of references in all eligible studies to identify potential missing publications that were not identified during the preliminary literature searches. We did not place any restrictions on the searches.

Studies were considered eligible if they met the following inclusion criteria: observational studies (cohort or case-control studies) that investigated patients with ovarian cancer assessed for BRCA mutation status (BRCA1 or BRCA2 mutation status). The outcome measures included OS and PFS, measured as the relative risk (RR), the odds ratio (OR), or the hazard ratio (HR) along with the 95% confidence interval (CI) (or sufficient data for calculating them). We did not include studies with unpublished data. If multiple reports contained the duplicated datasets, the report with the largest or the most recent data was included for analysis. Two investigators independently conducted the literature review (KX and SHY) and any discrepancies were resolved by discussion or by a senior investigator (YCY).

Data extraction and quality assessment

Two investigators independently extracted data from each included study using a predefined standardized data extraction form including the pertinent issues that concerned the characteristics and survival outcomes of the ovarian cancer patients. For each article, the following information was extracted: authors and published years, study design, sample size, inclusion period, research country, disease stage, tumor histology, BRCA mutation detection methods, research center involved, duration of follow-up and adjusted variables. The extracted data were crosschecked and any disagreements were resolved by discussion.

Outcome measures

The primary outcome measure was OS defined as the time from initial ovarian cancer diagnosis to death due to any causes. Secondary outcome was PFS defined as the time from diagnosis to the first confirmed sign of cancer recurrence, or progression (disease relapse or metastasis) or death from any cause.

Quality assessment

The nine-star Newcastle-ottawa Scale (NOS) [44] was used to assess the study quality for each study. Three domains associated with the selection of study population, data comparability and exposure (case-control studies) or outcome (cohort studies) assessment were evaluated. The NOS score ranged from 0 to 9 with a score ≥ 7 indicating high quality. Two investigators scored each study, and any discrepancies were resolved by a third investigator.

Statistical analysis

All statistical analyses were performed using Stata statistical software (version 12.0; Stata Corporation, College Station, TX, USA). Pooled HRs for OS and PFS with 95% CIs were calculated using random-effects model due to the potential substantial heterogeneity between studies [45]. Heterogeneity across studies was examined by I² statistic with an I² ≥ 50% indicating the presence of significant heterogeneity [46]. We further investigated potential heterogeneity by subgroup analyses stratified by study quality, tumor stage, study design, sample size, number of research center, duration of follow-up, baseline characteristics adjusted, mutation ratio and tumor histology for OS and PFS across BRCA1/2, BRCA1 and BRCA2 mutation subgroups. Publication bias was evaluated by observing the asymmetry of funnel plots and using the Begg-Mazumdar rank correlation test and Egger’s test [47, 48]. The Duval and Tweedie trim-and-fill method was also applied to conduct sensitivity analysis [49]. A two-sided P ≤ 0.05 was considered statistically significant.

Abbreviations

CI: 95% confidence interval; HR: hazard ratios; NOS: Newcastle-ottawa Scale; OS: overall survival; PRISMA: the Preferred Reporting Items for Systematic
Reviews and Meta-Analyses; PFS: progression-free survival.

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CONFLICTS OF INTEREST

The authors indicated no financial relationships.

Authors’ contributions

Conception/Design: Yingchao Zhao. Provision of study materials or patients: Kai Xu, Shouhua Yang, Yingchao Zhao. Collection and/or extract data: Kai Xu, Shouhua Yang, Yingchao Zhao. Data analysis and statistical guidance: Kai Xu, Shouhua Yang, Yingchao Zhao. Manuscript writing: Kai Xu, Shouhua Yang, Yingchao Zhao. Final approval of the manuscript: Kai Xu, Shouhua Yang, Yingchao Zhao.

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