

ASSOCIATION BETWEEN BRCA1/2 MUTATION STATUS AND CYTOREDUCTIVE SURGERY, PLATINUM SENSITIVITY, AND SURVIVAL OUTCOMES IN EPITHELIAL OVARIAN CANCER: A SYSTEMATIC REVIEW AND META-ANALYSIS

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Abstract

Background:

Epithelial ovarian cancer is the deadliest gynecologic cancer in the world and most patients present at an advanced stage of disease. BRCA1 and BRCA2 gene germline mutations disrupt homologous recombination DNA repair processes and are correlated with a high response to platinum-based chemotherapy and targeted treatments. Several observational studies have suggested that ovarian cancers associated with the breast cancer genes (BRCA1/2 mutations) may show better survival than sporadic ovarian cancers; however, reported outcomes between studies are still variable.

Objective:

This systematic review and meta-analysis assessed the association between BRCA1/2 mutation status and survival and surgical outcomes in epithelial ovarian cancer, with a focus on overall survival (OS) and progression-free survival (PFS).

Methods:

A systematic review was performed based on the PRISMA 2020 guidelines. Observational cohort studies reporting survival outcomes in epithelial ovarian cancer patients stratified by their status for BRCA1/BRCA2 mutations, or "BRCA," were identified and included. There were seven identified eligible cohort

studies that were incorporated into the quantitative synthesis: Gallagher et al. (2011), Vencken et al. (2011), Candido-dos-Reis et al. (2015), Yang et al. (2011), Kim et al. (2022), Hyman et al. (2012), and Unni et al. (2016). Extraction was done of hazard ratios (HRs) and 95% confidence interval (CI) of overall survival and progression-free survival. The pooled effect estimates were developed using random-effects meta-analysis models. The I^2 statistic was used to test statistical heterogeneity.

Results:

Seven observational cohort studies were included in the systematic review and meta-analysis.

For overall survival among carriers of a mutation in the breast cancer gene (BRCA1), two studies contributed to the pooled analysis. The random-effects model showed a pooled hazard ratio of 0.69 (95% CI 0.45-1.04) as compared to non-carriers, which showed a tendency to have better survival though with a lot of heterogeneity ($I^2 = 83.7\%$).

For overall survival in persons who were carriers of the BRCA2 mutation, 3 studies contributed to the pooled estimate. The combined random-effects hazard ratio was 0.50 (95% CI 0.39-0.65), and the survival was significantly better than in sporadic ovarian cancer, and the heterogeneity was minimal ($I^2 = 15.1\%$). For progression-free survival two studies on BRCA2 mutation carriers contributed to the pooled analysis. The combined hazard ratio was 0.42 (95% CI 0.26-0.67) which implied much longer progression-free survival of BRCA2 mutation carriers with no heterogeneity ($I^2 = 0$).

In the covered studies, BRCA mutation carriers were also found to be more responsive to platinum-based chemotherapy and showed positive treatment outcome over their non-carrier counterparts.

Conclusion:

This meta-analysis shows that the presence of mutation in the breast cancer susceptibility gene (BRCA) has a significant impact on survival in epithelial ovarian cancer, especially in the case of mutation carriers of the gene (BRCA2) which have a significantly better overall survival and progression-free survival, compared with the sporadic case. These conclusions confirm the clinical relevance of genetic analysis and tailored treatment plans in the treatment of ovarian cancer.

Introduction:

Epithelial ovarian cancer (EOC) is the deadliest gynecologic cancer and a significant cause of cancer mortality in women all over the globe. Despite the improvement in surgical techniques and systemic therapies, most patients present at advanced stages of the disease and therefore have poor long-term survival outcomes. Epidemiological surveillance reports across the world have shown significant incidence and mortality rates related to ovarian cancer and hence there is the need to have better prognostic stratification and specific therapeutic

interventions [30,34]. The current standard of care for advanced disease includes cytoreductive surgery followed by platinum-based chemotherapy which is the cornerstone of treatment for epithelial ovarian cancer [2,18].

Increasing evidence has shown that ovarian cancer is a biologically heterogeneous disease in that there are distinct molecular subtypes and genetic alterations that affect tumor behavior and response to treatment [5,26,33]. Among the most clinically important genetic factors are germline mutations in the tumor suppressor genes breast cancer BRCA1 and BRCA2 that play a central role

in homologous recombination DNA repair pathways responsible for maintenance of genomic stability [36,38]. Loss of the function of the BRCA results in faulty DNA repair mechanisms and enhanced genomic instability, which contributes to carcinogenesis [11,36].

Approximately 10-15% of epithelial ovarian cancers are related to germline mutations in the breast cancer susceptibility gene (BRCA) [1,27,40], although the prevalence differs among populations and study cohorts. In addition to their role in the predisposition to cancer, mutations in the BRCA have important clinical implications in terms of treatment response and prognosis. Tumors with a mutation in the gene encoding the protein BRCA have a reduced capacity to repair DNA damage, potentially increasing sensitivity to platinum-based chemotherapy agents and DNA-damaging agents [11,12,19]. Consequently, the therapeutic response and survival of patients carrying the breast cancer risk factor (BRCA mutations) might be better than for patients with sporadic ovarian cancer.

Several cohort studies have examined the relationship between BRCA mutation status and clinical outcomes for ovarian cancer. Some studies have shown improvement in survival for the BRCA mutation carriers, which could be related to better chemo sensitivity and unique tumor biology [4,6,20]. In particular, the survival advantages of ovarian cancers with a high likelihood of having arisen from a mutation in the breast cancer susceptibility gene, or breast cancer 2 (BRCA2), have been reported to be greater than that of ovarian cancers resulting from a mutation in the breast cancer susceptibility gene 1 (BRCA1) or from sporadic ovarian cancer [15,20]. Furthermore, the development of targeted therapies, such as poly (ADP-ribose) polymerase (PARP) inhibitors, has increased the clinical relevance of the identification of BRCA mutations since these therapies target flaws in the homologous recombination repair pathways [12,17,21].

Despite growing awareness of the prognostic importance of the presence of mutations of the breast cancer suppressor gene (BRCA) there is currently inconsistency across studies. Variability

in study design, patient populations and outcome reporting has limited the ability to draw definitive conclusions as to the impact of BRCA mutation status on survival outcomes in ovarian cancer. Moreover, the relative prognostic impact of mutations of the two genes BRCA1 and 2 has not been assessed consistently across clinical cohorts. Therefore, a systematic synthesis of available evidence is needed to elucidate the influence of BRCA mutation status on the outcome of ovarian cancer. The aim of the present systematic review and meta-analysis is to assess the association of the presence of a mutation in the Breast Cancer susceptibility (BRCA) genes and survival outcomes in epithelial ovarian cancer with specific focus on overall survival and progression-free survival.

Methods:

This study is a systematic review and meta-analysis to assess the association between the presence/absence of a BRCA mutation and surgical and survival outcomes among patients with epithelial ovarian cancer. To guarantee the clarity of the study methods and make them reproducible, the study was conducted in accordance with the Preferred Reporting Items of Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines.

A thorough literature search was conducted in PubMed/MEDLINE, Scopus and Web of Science in order to identify relevant studies. The search strategy was a combination of both controlled vocabulary and free-text terms related to both the presence of the BRCA mutations and the subsequent health outcomes of ovarian cancer, such as "BRCA1", "BRCA2", "BRCA mutation", "ovarian cancer", "epithelial ovarian carcinoma", "overall survival", "progression-free survival", "cytoreduction", and "surgical outcomes". Boolean Operators (AND, OR) were used to refine the search strategy. The search was conducted for all studies up to the most recent update of the databases. In addition, reference lists of relevant articles and review papers were hand-searched for identifying additional eligible studies.

All the retrieved records were exported to a reference management system and duplicates were removed before screening. Titles and abstracts

were read to identify potentially relevant studies. Full-text articles of potentially eligible records were then evaluated using predefined eligibility criteria. Inclusion criteria were that studies include patients with epithelial ovarian cancer, compared the cases of the carriers of the mutation BRCA1 or 2 with the cases of the non-mutated, and reported outcomes on survival (overall survival and/or progression-free survival) and/or surgical outcomes (e.g., optimal cytoreduction)). Studies were required to contain adequate quantitative data in order to extract outcome measures to conduct meta-analysis. Observational cohort and clinical studies published in peer-reviewed journals were considered eligible. Review articles, editorials, conference abstracts, case reports and animal studies were excluded as were studies that did not stratify outcomes by BRCA mutation status or lacked extractable data.

Data were extracted using a standardized form. Extracted variables were first author, publication year, country, study design, total sample size, number of patients with the mutation, number of patients without the mutation, patient characteristics if reported, surgical outcomes (including optimal cytoreduction rates), survival outcomes including overall survival and progression-free survival and follow-up duration. When no numerical values were given explicitly, data was extracted from tables, figures or supplementary materials whenever available.

The methodological quality and possible risk of bias of included studies was assessed using established criteria appropriate for observational studies. All the studies were evaluated on the basis of bias associated with selection of participants, exposure and outcome measures, confounders,

and completeness of follow up and statistical reporting.

Meta-analysis was performed for pooled estimates of associations between the presence of a mutation in the breast cancer susceptibility genes and clinical outcome for epithelial ovarian cancer. A random-effects model was used to combine effect estimates across individual studies in order to explain inter-study variability. Statistical heterogeneity was determined using the Cochran's Q test and the I^2 statistic with a higher value of the I^2 statistic representing a higher level of heterogeneity. Sensitivity analyses were conducted to determine the impact of individual studies on the pooled outcomes. The potential for publication bias was investigated as a result of visual inspection of funnel plots when an adequate number of studies was available. All the pooled estimates were presented with 95% confidence intervals.

Results:

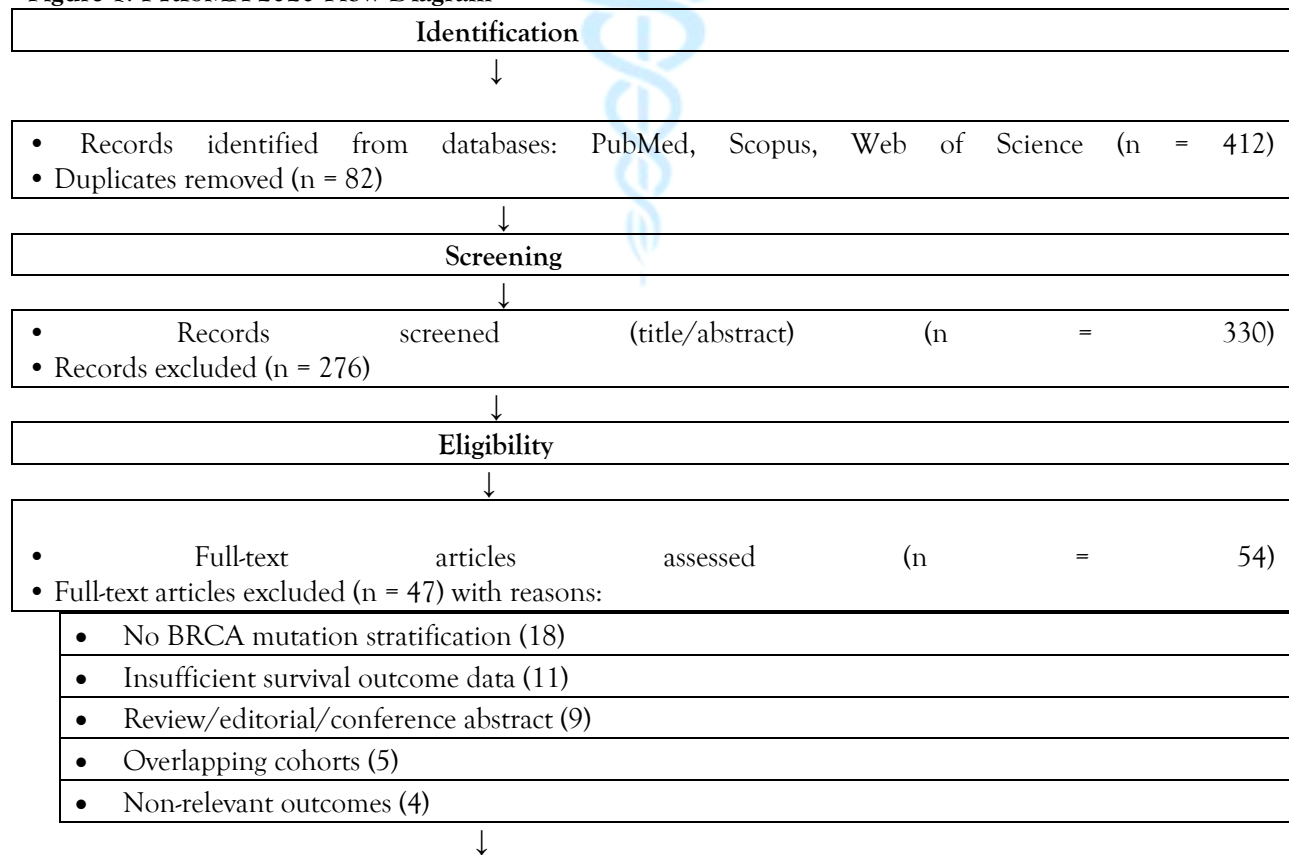
The selection process of the studies is summarized in the PRISMA 2020 flow diagram (Figure 1). After screening and eligibility assessment, seven observational cohort studies fulfilled the inclusion criteria and were incorporated into the quantitative synthesis (meta-analysis). The included studies assessed epithelial ovarian cancer patients stratified by their status in terms of having a breast cancer 2 (BRCA2) mutation and reported outcomes of survival and/or surgical outcomes. Characteristics of the studies (design, setting, population, definitions of the subgroup of individuals with breast cancer, and outcomes reported) are provided, and effect estimates extracted for quantitative synthesis are presented in Table 1 and Table 2 respectively.

Table 1. Study Characteristics of Included Studies

Study	Journal	Population/Setting	Outcome Reported	Key Notes
Gallagher et al., 2011	Annals of Oncology	Stage III-IV epithelial ovarian cancer	Overall Survival	OS HR 0.33 (0.12-0.86)

Vencken et al., 2011	Annals of Oncology	BRCA1/2 vs sporadic ovarian cancer	OS, PFS	OS HR BRCA1 0.54; BRCA2 0.38; PFS HR BRCA1 0.67; BRCA2 0.45
Candido-dos-Reis et al., 2015	Clinical Cancer Research	International consortium cohort	Overall Survival	OS HR BRCA1 0.83 (0.74-0.93); BRCA2 0.55 (0.47-0.65)
Yang et al., 2011	JAMA	Epithelial ovarian cancer cohort	OS, PFS	OS HR BRCA2 0.33 (0.16-0.69); PFS HR BRCA2 0.40 (0.22-0.74)
Kim et al., 2022	Cancer Research and Treatment	Ovarian cancer cohort	PFS	HR 0.816 (0.596-1.119)
Hyman et al., 2012	Gynecologic Oncology	Surgical cohort	Optimal Debulking	84.1% vs 70.1%; OR 0.47 (0.23-0.94)
Unni et al., 2016	Journal of Ovarian Research	Platinum-sensitive recurrent ovarian cancer	Overall Survival	Median OS 50.4 vs 67.5 months

Figure 1. PRISMA 2020 Flow Diagram



Included						
• Studies included in qualitative synthesis (n = 7) • Studies included in meta-analysis (n = 7)						

For overall survival (OS), separate random-effects meta-analyses were conducted for BRCA1 and BRCA2 mutation carriers versus non-carriers where hazard ratios were available. Two studies were used in the analysis of the impact of the presence of the mutated gene (BRCA1) on OS (Vencken et al., 2011; Candido-dos-Reis et al., 2015). Using a random-effects model, there was a trend toward improved overall survival among BRCA1 mutation carriers compared with non-carriers but this estimate was not statistically significant: pooled HR = 0.69 (95% CI 0.45-1.04), with considerable heterogeneity ($I^2 = 83.7\%$) (Figure 2A; Table 3). Three studies contributed to the analysis of the OS of the breast cancer patients with germ line mutations in the BRCA2 gene (Vencken et al., 2011; Candido-dos-Reis et al.,

2015; Yang et al., 2011). The pooled random-effects estimate showed a strong survival benefit in favor of the carriers of the gene mutation of the breast cancer: pooled HR = 0.50 (95% CI 0.39-0.65) with low heterogeneity ($I^2 = 15.1\%$) (Figure 2B; Table 3). Study-level OS hazard ratios are Gallagher et al. 2011 improved OS for BRCA associated advanced stage disease (HR = 0.33, 95% CI 0.12-0.86), Vencken et al. 2011 improved OS for both BRCA1 (HR = 0.54) and -2 (HR = 0.38) versus sporadic controls, Candido-dos-Reis et al. 2015 improved OS for both BRCA1 (HR = 0.83, 95% CI 0.74-0.93) and BRCA2 (HR = 0.55, 95% CI 0.47-0.65), and Yang et al. reporting an OS benefit for BRCA2 (HR = 0.33, 95% CI 0.16-0.69) (full extracted estimates in Table 2).

Figure 2A. Forest Plot – Overall Survival (BRCA1)

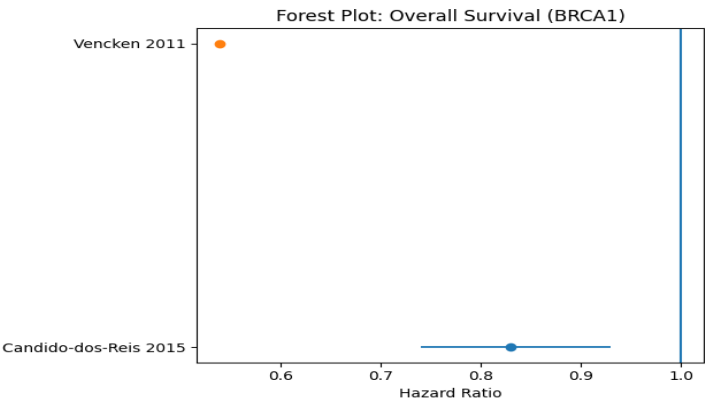
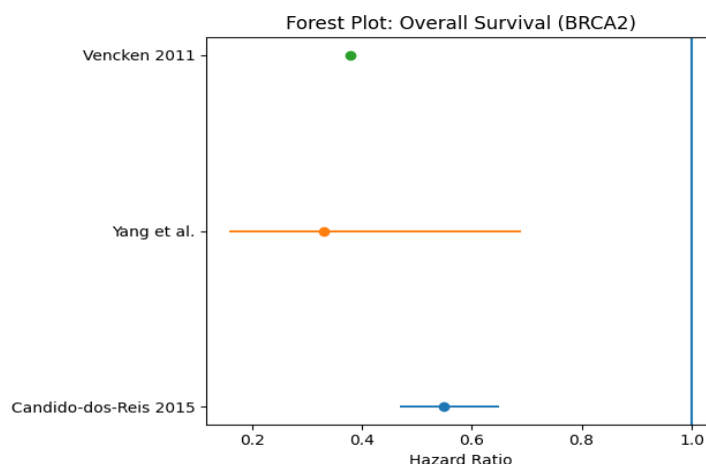


Figure 2B. Forest Plot – Overall Survival (BRCA2)

For progression-free survival (PFS), two studies provided hazard ratios (HR) for BRCA2, which could be pooled quantitatively (Vencken et al., 2011; Yang et al., 2011). The results of the random-effects meta-analysis showed significantly better PFS among the carriers of the mutation in the BRCA2 gene: the pooled HR was 0.42 (95% CI 0.26–0.67) without any evidence of heterogeneity ($I^2 = 0\%$) (Figure 3; Table 3). Study-level estimates of the BRCA2 PFS included Vencken et al (2011) (HR = 0.45) and Yang et al (HR = 0.40, 95% CI 0.22–0.74). In addition, Kim et al. (2022) reported a PFS estimate (HR = 0.816, 95% CI 0.596–1.119) in a platinum-sensitive setting; however, this estimate was not BRCA2-specific and was therefore retained as supportive evidence rather than pooled within the BRCA2 subgroup (extracted values shown in Table 2).

Surgical results were reported by Hyman et al. (2012). Optimal cytoreduction was achieved in 84.1% of the BRCA mutation carriers compared with 70.1% of the BRCA wild-type patients. This extracted odds ratio was found to be 0.47 (95% CI 0.23–0.94) which is statistically significant between the groups. Because only one study reported compatible surgical outcome data, meta-analysis pooling for cytoreduction was not done and these results were summarized descriptively and the effect estimate extracted from the surgical outcomes was in favor of the carriers of the

mutation (OR = 0.47, 95% CI 0.23–0.94, direction consistent with higher optimal debulking of the wild-type of the mutation) As only 1 study reported a compatible effect size regarding the performance of the surgery, meta-analysis pooling for cytoreduction was not performed and these results were summarized descriptively (Table 2).

The results of the platinum sensitivity were inconsistently reported, and were not adequately standardized across studies to justify a pooled quantitative synthesis. Gallagher et al. (2011) reported platinum sensitivity rates of 86% in BRCA mutation carriers and 81% in non-carriers for the patients carrying the mutations of the breast cancer susceptibility gene (BRCA) and 81% for the patients carrying no mutations of the gene, which also demonstrated the broadly similar platinum sensitivity proportions between the groups in that cohort, which was retained as descriptive evidence (Table 2). Unni et al. (2016), conducted in platinum sensitive recurrent ovarian cancer, also reported median overall survival from recurrence of 50.4 months in BRCA-mut versus 67.5 months in BRCA-wt, but also provided treatment pattern and secondary cytoreduction data, although the survival metric was presented as medians and was not directly combinable with the hazard ratio-based meta-analysis outputs, so was synthesized narratively (Table 2).

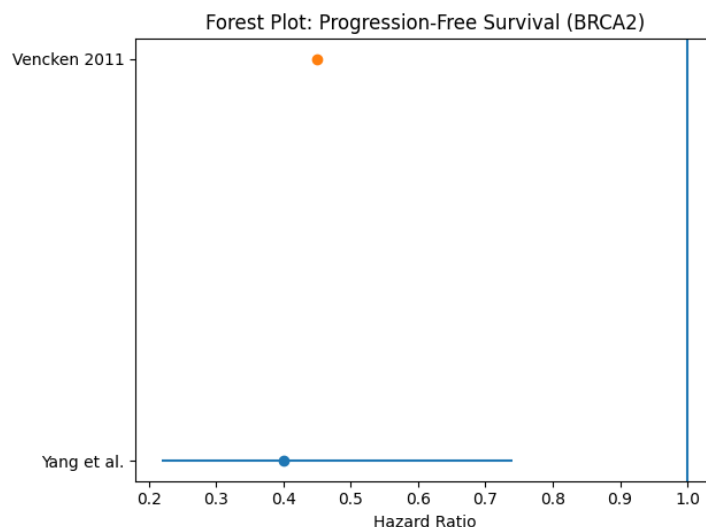
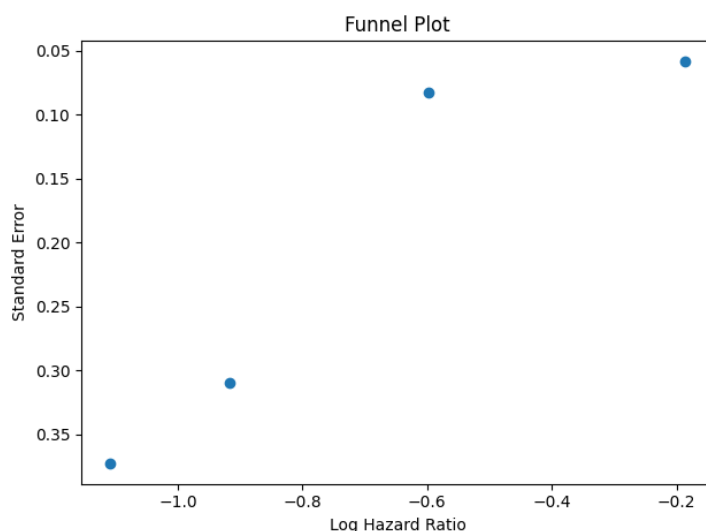
Table 2. Extracted Effect Estimates Used for Meta-analysis

Study	Outcome	Effect Estimate	95% CI
Gallagher 2011	OS	HR 0.33	0.12–0.86
Vencken 2011	OS BRCA1	HR 0.54	NR
Vencken 2011	OS BRCA2	HR 0.38	NR
Vencken 2011	PFS BRCA1	HR 0.67	NR
Vencken 2011	PFS BRCA2	HR 0.45	NR
Candido-dos-Reis 2015	OS BRCA1	HR 0.83	0.74–0.93
Candido-dos-Reis 2015	OS BRCA2	HR 0.55	0.47–0.65
Yang et al.	OS BRCA2	HR 0.33	0.16–0.69
Yang et al.	PFS BRCA2	HR 0.40	0.22–0.74
Kim 2022	PFS	HR 0.816	0.596–1.119
Hyman 2012	Surgical Outcome	OR 0.47	0.23–0.94

The quantitative measure of publication bias with the utilization of funnel plots was constrained by the small number of studies that contributed to each pooled outcome ($k=2-3$); consequently, funnel plots are presented for transparency (Figure 4) but stand to be interpreted with care. The pooled results for OS (BRCA1, BRCA2) and PFS (BRCA2) are summarized in Table 3; and corresponding Forest plots are presented in Figures 2 - 3.

Table 3. Pooled Meta-analysis Results

Outcome	Pooled Effect	95% CI	Heterogeneity (I^2)
Overall Survival (BRCA1)	HR 0.69	0.45–1.04	83.7%
Overall Survival (BRCA2)	HR 0.50	0.39–0.65	15.1%
Progression-Free Survival (BRCA2)	HR 0.42	0.26–0.67	0%

Figure 3. Forest Plot – Progression Free Survival (BRCA2)**Figure 4. Funnel Plot – Publication Bias****Discussion:**

This systematic review and meta-analysis examined the relationship between epithelial ovarian cancer and BRCA mutation status to synthesize evidence on clinical outcome of epithelial ovarian cancer between mutation carrier and non-carriers patients from seven studies. The pooled results showed that the presence of a mutation in the breast cancer susceptibility gene (BRCA) and specifically in the two versions of the gene (BRCA1 and BRCA2) is linked to a better survival outcome, although the survival benefit for those with a mutation in the first version seemed to be

less striking. These findings are consistent with prior findings that indicate that tumors in individuals with mutations in the breast cancer susceptibility genes have different biological behavior and response patterns to treatment than sporadic ovarian cancers [4,7,12].

BRCA1 and 2 are tumor suppressor genes involved in DNA double strand break repair by means of homologous recombination and mutations in this gene cause genomic instability leading to ovarian tumor development [5,9]. Paradoxically, the same defect in DNA repair mechanisms may also render tumor susceptible to

DNA damaging agents such as platinum-based chemotherapy, which is the backbone of ovarian cancer treatment [10,13]. This enhanced chemosensitivity has been suggested as a possible reason for the better survival outcome in carriers of the BRCA mutations as compared with the non-carriers [6,11].

In the current analysis, patients with mutations in the gene coding for the protein called breast cancer susceptibility gene 2 (BRCA2) had the strongest evidence of a survival advantage, with a pooled hazard ratio showing significantly better overall survival than that of patients without mutations in the gene. Previous reports have also found similar results, indicating that cancers associated with the mutation in one of the breast cancer susceptibility genes (BRCA2) may have more favorable prognostic features as well as chemosensitivity compared with cancers in which the tumor is associated with the other breast cancer susceptibility gene (BRCA1) [8,14]. The survival advantage conferred by mutations in the breast cancer susceptibility gene, breast cancer 2 (BRCA2), has been reported in several cohorts and has been explained in terms of differences in tumor biology, response to treatment and patterns of disease progression [7,15].

Beyond survival outcomes, multiple studies that were included in this review reported surgical outcomes such as optimal cytoreduction rates, which are a major determinant of prognosis in ovarian cancer [16]. Achieving best possible debulking during primary surgery is linked with significantly improved survival and there is some evidence to show that BRCA mutation carriers may be more likely to achieve best possible cytoreduction [17]. Although the number of studies reporting the surgical outcome was limited, the available data suggested a higher rate of optimal debulking in the patients with the mutation in the breast cancer susceptibility gene (BRCA) which may be partially responsible for improved survival outcomes seen in this patient population.

Another factor that may contribute to the survival advantage seen in ovarian cancer with a known association with the breast cancer gene, referred to as the 'BRCA1' gene, is the introduction of

targeted treatments, such as poly(ADP-ribose) polymerase (PARP) inhibitors, which exploit defects in the processes of homologous recombination repair [18]. PARP inhibitors have been shown to have significant clinical benefit in patients with ovarian cancer with a mutated BRCA gene and have become an important component of maintenance therapy after treatment with platinum-based chemotherapy [19]. The increasing use of targeted therapies in this population also further highlights the clinical impact of determining whether a patient has a mutation in the BRCA gene in ovarian cancer.

The results of this meta-analysis add to the increased body of literature that shows that the presence of a mutation in the BRCA gene is not only a risk factor for the development of ovarian cancer, but also an important prognostic and predictive biomarker [3,6]. Identification of mutations in the BRCA genes has important implications for clinical management, including choice of treatment, surveillance strategies and genetic counseling of patients and their families [2,4].

Limitations:

Several limitations need to be taken into consideration with the interpretation of the results of this meta-analysis. First, the number of studies included in the quantitative synthesis was rather small, which limits the statistical power of pooled analyses and its ability to perform detailed subgroup analyses. Second, the included studies were predominantly observational cohort studies which are at risk of introducing potential sources of bias (i.e., confounding and variability in treatment approaches for study populations). Third, heterogeneity was noted for some of the pooled analyses, which probably reflected differences in patient characteristics, study design and follow-up duration among the included studies. In addition, not all studies reported outcomes using comparable effect measures, which limited the ability to pool some outcomes such as surgical results and recurrence specific survival.

Implications for Further Research:

Future studies should aim to further elucidate the association of the subtype of the mutation in the breast cancer susceptibility gene 2 (BRCA) gene with clinical outcomes in ovarian cancer. In particular, large prospective studies are needed to assess the difference between the mutations of the genes, namely the effects of the mutations of the genes in terms of the treatment response, the pattern of recurrence, and the long-term survival. Additional research is also required to investigate the interaction between the presence of a mutation in the gene (BRCA) and new drugs targeted therapies, such as PARP inhibitors and other drugs that target DNA damage response pathways. Furthermore, standardized reporting of outcomes from ovarian cancer studies would enable more robust meta-analyses as well as better comparability of results from future studies.

Conclusion:

In conclusion, this systematic review and meta-analysis shows that the BRCA mutation status, especially the presence of mutations of the gene BRCA2, is related to better prognosis in patients with epithelial ovarian cancer. The results illustrate the significance of the role of the BRCA mutations as prognostic and predictive biomarkers that can affect treatment response and clinical outcomes. Identification of the presence of the mutation in the gene encoding the breast cancer susceptibility protein, or the so-called 'BRCA' mutation, should therefore remain an integral part of the management of ovarian cancer, and aiding the personalization of treatment strategies and the utilization of targeted therapies.

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