Clinical significance of breast cancer susceptibility gene 1 expression in resected non-small cell lung cancer: A meta-analysis

Yang Gao, Xiao-Di Luo, Xiao-Li Yang, Dong Tu

BACKGROUND
The clinical significance of breast cancer susceptibility gene 1 (BRCA1) in non-small cell lung cancer (NSCLC) patients undergoing surgery remains unclear up to now.

AIM
To explore the relation of BRCA1 expression with clinicopathological characteristics and survival in patients with resected NSCLC.

METHODS
EMBASE, PubMed, Web of Science, and The Cochrane Library databases were searched to identify the relevant articles. To assess the correlation between the expression of BRCA1 and clinicopathological characteristics and prognosis of patients with resected NSCLC patients, the combined relative risks or hazard ratios (HRs) with their corresponding 95% confidence intervals [CIs] were estimated.

RESULTS
Totally, 11 articles involving 1041 patients were included in the meta-analysis. The results indicated that the expression of BRCA1 was significantly correlated with prognosis of resected NSCLC. Positive BRCA1 expression signifies a shorter overall survival (HR = 1.60, 95%CI: 1.25-2.05; P < 0.001) and disease-free survival (HR = 1.78, 95%CI: 1.42-2.23; P < 0.001). However, no significant association of BRCA1 expression with any clinicopathological parameters was observed.

CONCLUSION
BRCA1 expression indicates a poor prognosis in resected NSCLC patients. BRCA1 might serve as an independent biomarker to predict clinical outcomes and help to customize optimal adjuvant chemotherapy for NSCLC patients who had received...
surgical therapy.

**Key Words:** Breast cancer susceptibility gene 1; Non-small cell lung cancer; Clinicopathological characteristics; Prognosis; Surgery; Meta-analysis

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**Core Tip:** Based on 11 included articles involving 1041 patients, we demonstrated that the expression of the breast cancer susceptibility gene 1 (BRCA1) was significantly correlated with prognosis of resected non-small cell lung cancer (NSCLC). Furthermore, positive BRCA1 expression signified a shorter overall survival and disease-free survival. However, no significant association of BRCA1 expression with any clinicopathological parameters was observed. Overall, BRCA1 expression indicates a poor prognosis in resected NSCLC patients. BRCA1 might serve as an independent biomarker to predict clinical outcomes and help to customize optimal adjuvant chemotherapy for NSCLC patients who had received surgical therapy.

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**INTRODUCTION**

Lung cancer has become the leading cause of cancer death among men and women globally[1-3]. According to the pathology, lung cancer is classified into two subgroups: Small-cell lung cancer (SCLC) and non-small-cell lung cancer (NSCLC). And approximately 85% of all lung cancer cases belong to NSCLC. For most NSCLC patients, surgical resection is still the most important therapy. Although the diagnosis and treatment techniques have been improved greatly in recent years, the overall 5-year survival rate for NSCLC in China was only 19.8%[4].

The tumor-node-metastasis (TNM) staging remains the most popular tool to assess the progression and predict the prognosis of NSCLC patients. However, a number of indicators have been reported to be significantly associated with clinicopathological characteristics and survival of NSCLC patients in recent years, including many genetic markers[5,6]. Increasing evidence indicates that DNA repair genes can be used as predictive and prognostic markers in NSCLC[7]. Breast cancer susceptibility gene 1 (BRCA1) is a 220-kD multifunctional nuclear phosphoprotein that has a vital role in DNA repair[8]. As a member of the DNA repair genes, BRCA1 plays an important role in the pathway to repair fractured double-stranded DNA. It interacts with the MRE1/RAD50/NBS1 complex which is related to homologous recombination repair and non-homologous recombination repair[9].

BRCA1 is expressed in about 40% of inherited breast cancers and more than 80% of inherited ovarian cancers[10]. As for NSCLC, the proportion of BRCA1 positive cases ranged from 13.1% to 66.7%[11,12]. Meanwhile, several studies have explored the clinicopathological and prognostic significance of BRCA1 expression in NSCLC patients who received surgical therapy. Nevertheless, their results were inconclusive and inconvinclable because of limited data.

Therefore, we aimed to conduct the current meta-analysis to further investigate the correlation of BRCA1 expression with clinicopathological parameters and long-term outcomes in resected NSCLC.

**MATERIALS AND METHODS**

**Literature retrieval**

A systematic research was conducted in EMBASE, Web of Science, Cochrane Library,
and PubMed for relevant studies published from the inception of the databases to July 4, 2020 using the following terms: BRCA1, breast cancer susceptibility gene 1, breast cancer 1, lung, pulmonary, cancer, neoplasm, tumor, and carcinoma. The specific search strategy was: (breast cancer susceptibility gene 1 OR BRCA1) AND (lung OR pulmonary) AND (tumor OR cancer OR carcinoma OR neoplasm). The references listed in the included articles were also reviewed for eligibility. The literature retrieval was conducted by two independent authors (Gao Y and Luo XD).

Inclusion and exclusion criteria
The inclusion criteria were as follows: (1) Patients who were diagnosed with NSCLC pathologically and received surgical therapies; (2) Articles that assessed the correlation of BRCA1 expression with prognosis; (3) The interest outcomes included overall survival (OS) or progression-free survival (PFS) with hazard ratios (HRs) and corresponding 95% confidence intervals (CIs); (4) Enough data like Kaplan-Meier curves were provided to calculate the HRs with 95%CIs for OS or PFS when they were not reported directly; (5) Articles were published in English with full-texts; and (6) Newcastle–Ottawa scale score ≥ 6[13].

The exclusion criteria were as follows: (1) Expert opinions, reviews, meeting abstracts, letters, case reports, and animal trials; (2) The HRs with 95%CIs could not be calculated because of the lack of relevant information; and (3) Duplicated or overlapped studies.

The literature selection was performed by two investigators independently (Gao Y and Luo XD).

Data extraction and quality assessment
The following information was extracted from each included study: The name of the first author, publication year, country, sample size, number of patients with positive BRCA1 expression, TNM stage, end-point events, source of HR, HRs with corresponding 95%CIs, and other necessary data to calculate the association of BRCA1 expression with several clinicopathological parameters including gender, age, tumor size, TNM stage, differentiation status, and histological type.

The quality of included studies was assessed using the Newcastle-Ottawa scale score and studies that earned a score of 6 or higher were regarded as high-quality studies[13].

Statistical analysis
All statistical analyses were conducted using STATA 12.0 software (StataCorp, College Station, TX, United States). The relation of BRCA1 expression with the clinicopathological characteristics and prognosis was assessed by the pooled relative ratios or HRs with 95%CIs. HRs with 95%CIs from multivariable models were used whenever available. If the articles did not report them directly, they would be estimated from the Kaplan-Meier curves using the method reported by Tierney et al[14]. The χ²-based Q-test and the I² statistic were applied to calculate the heterogeneity among the included studies[15]. If there was significant heterogeneity (P < 0.10 and/or I² > 50%), the random-effects model was used; otherwise, the fixed-effects model was used[16]. The stability of pooled results was assessed by sensitivity analysis. Potential publication bias was detected using Begg’s funnel plot and Egger’s test[17]. A log-rank P value < 0.05 was considered statistically significant.

RESULTS
Characteristics of included studies
As shown in Figure 1, initially 3609 records were identified through database searching. After removing the duplicates, 2836 records were left. Then 29 publications were reviewed with full-texts for eligibility after excluding 2807 irrelevant records. Finally, 11 articles involving 1041 patients were included in the meta-analysis [11,12, 18-26]. The sample sizes ranged from 32 to 221 and the proportion of patients with BRCA1 expression ranged from 13.1% to 66.7%. Furthermore, Gachechiladze et al[21] performed subgroup analysis based on the TNM stage and provided sufficient data of the two groups, so we considered them as two studies during the process of statistical analyses. Other specific information is summarized in Table 1.
Table 1 Basic characteristics of included studies

| Ref.          | Year | Country | Sample size | Positive, n (%) | TNM stage | Outcome | Source of HR | NOS score |
|---------------|------|---------|-------------|-----------------|-----------|---------|--------------|-----------|
| Rosell et al[18] | 2007 | Spain   | 123         | 40 (32.5)       | IB-III A  | OS      | R            | 6         |
| Bartolucci et al[11] | 2009 | Italy   | 54          | 36 (66.7)       | IB-III B  | OS/DFS  | R            | 7         |
| Ma et al[19]   | 2010 | China   | 89          | 53 (59.6)       | III A     | OS/DFS  | E            | 8         |
| Leng et al[20] | 2012 | China   | 85          | 14 (16.5)       | I- IV     | OS/DFS  | R            | 7         |
| Gachechiladze et al[21] | 2013 | Israel  | 32          | 9 (28.1)        | I- II     | OS/DFS  | E            | 7         |
| Gachechiladze et al[21] | 2013 | Israel  | 58          | 15 (25.9)       | III-IV    | OS/DFS  | E            | 7         |
| Yu et al[22]   | 2013 | China   | 80          | 36 (45)         | I- IV     | OS/DFS  | E            | 7         |
| Grossi et al[23] | 2015 | Italy   | 81          | 45 (55.6)       | I A-III B | OS      | R            | 6         |
| Lafuente-Sanchis et al[24] | 2015 | Spain   | 64          | 30 (46.9)       | I         | DFS     | R            | 7         |
| Huang et al[12] | 2016 | China   | 84          | 11 (13.1)       | II-III    | DFS     | R            | 8         |
| Wang et al[25] | 2017 | China   | 70          | NR              | II-III    | OS      | R            | 6         |
| Lefavette et al[26] | 2017 | France  | 221         | 129 (58.4)      | I- IV     | OS/DFS  | R            | 8         |

TNM: Tumor-node-metastasis; OS: Overall survival; DFS: Disease-free survival; HR: Hazard ratio; R: Reported; E: Estimated; NOS: Newcastle-Ottawa quality assessment scale.

Association of BRCA1 expression with clinicopathological parameters in patients with resected NSCLC

Based on the information provided by included studies, we explored the relationship of BRCA1 expression with gender, age (≥ 60 vs < 60 years), tumor size (T3/4 vs T1/2), TNM stage (IV/III vs I/II), histology (adenocarcinoma vs squamous cell carcinoma), differentiation (poor vs moderate/well). However, no significant association between BRCA1 expression and these parameters was observed (Table 2).

Association between BRCA1 expression and OS

Totally ten studies of 893 patients compared OS between the BRCA1-positive group and BRCA1-negative group. The fixed-effects model was adopted because of the low
Table 2 Correlations of breast cancer susceptibility gene 1 (BRCA1) expression with clinicopathological characteristics in resected non-small cell lung cancer

| Ref. | Gender (M vs F) | Age (≥ 60 vs < 60) | Tumor size (T3/4 vs T1/2) | TNM stage (II/IV vs I/II) | Histology (AC vs SCC) | Differentiation (poor vs moderate/well) |
|------|----------------|-------------------|--------------------------|--------------------------|----------------------|----------------------------------------|
| Rosell et al [18] | - | - | - | - | - | - |
| Bartolucci et al [11] | - | - | - | - | - | - |
| Ma et al [19] | 1.050 (0.740-1.489) | - | 1.046 (0.734-1.489) | - | 0.916 (0.636-1.319) | 1.204 (0.860-1.687) |
| Leng et al [20] | - | - | - | - | - | - |
| Gachechiladze et al [21] | - | - | - | 0.920 (0.454-1.861) | - | - |
| Gachechiladze et al [21] | 0.857 (0.608-1.210) | 1.273 (0.917-1.768) | - | 1.020 (0.727-1.433) | 0.990 (0.704-1.392) | 1.238 (0.890-1.723) |
| Yu et al [22] | - | - | - | - | - | - |
| Grossi et al [23] | - | - | - | - | - | - |
| Lafuente-Sanchis et al [24] | 0.829 (0.265-2.592) | 0.367 (0.050-2.678) | - | 3.375 (0.776-14.678) | 1.660 (0.383-7.204) | - |
| Huang et al [12] | - | - | - | - | - | - |
| Wang et al [25] | 0.948 (0.735-1.224) | 0.889 (0.711-1.112) | - | - | - | - |
| Overall | 0.94 (0.79-1.12), P = 0.04; P = 0.532; I² = 0.0; P = 1.01 (0.72-1.42), P = 0.948; I² = 51.2, P = 0.739; I² = 22.7, P = 0.076; I² = 0.0, P = 0.732 | - | 1.05 (0.78-1.42), P = 0.739; I² = 22.7, P = 0.076; I² = 0.0, P = 1.05 (0.78-1.42), P = 0.076; I² = 0.0, P = 1.22 (0.97-1.55), P = 0.097; I² = 0.0, P = 0.908 |

M: Male; F: Female; TNM: Tumor-node-metastasis; AC: Adenocarcinoma; SCC: Squamous cell carcinoma.

The results of the current meta-analysis which summarized 11 studies involving 1041 patients showed that positive BRCA1 expression was associated with a shorter OS and DFS without regional disparities. The conclusion was consistent with the results of the previous studies [18, 21, 25, 26]. BRCA1 expression status could serve as a novel indicator for the assessment of prognosis and formulation of therapy strategy for resected NSCLC patients. No significant correlation between BRCA1 expression and clinicopathological characteristics was observed in our study. However, more than heterogeneity (I² = 0.0%, P = 0.794) among those studies included. The pooled HR was 1.60 (95% CI: 1.25-2.05, P < 0.001), which indicated that BRCA1 positive expression was an independent risk factor for OS of resected NSCLC patients (Figure 2A). The results of subgroup analysis stratified by the country was similar with the overall pooled results (Table 3).

Association between BRCA1 expression and disease-free survival

In total, nine studies of 767 patients explored the impact of BRCA1 expression on the disease-free survival (DFS). The patients with BRCA1 negative expression had a significantly prolonged DFS compared to patients with BRCA1 positive expression (HR = 1.78, 95% CI: 1.42-2.23, P < 0.001) with no heterogeneity (I² = 0.0%, P = 0.781) (Figure 2B). Subgroup analysis based on the country further verified the above result (Table 3).

Sensitivity analysis and publication bias

The sensitivity analysis performed by excluding each study individually signified that the results of our meta-analysis were stable (Figure 3). We conducted Begg’s funnel plot and Egger’s test to identify potential publication bias. As a result, Begg’s funnel plot was symmetrical (Figure 4) and the P value for Egger’s test was 0.451, which both indicated that no significant publication bias existed.

DISCUSSION

The results of the current meta-analysis which summarized 11 studies involving 1041 patients showed that positive BRCA1 expression was associated with a shorter OS and DFS without regional disparities. The conclusion was consistent with the results of the previous studies [18, 21, 25, 26]. BRCA1 expression status could serve as a novel indicator for the assessment of prognosis and formulation of therapy strategy for resected NSCLC patients. No significant correlation between BRCA1 expression and clinicopathological characteristics was observed in our study. However, more than
Table 3 Meta-analysis for association of breast cancer susceptibility gene 1 expression with survival of resected esophageal squamous cell carcinoma patients

| Analysis                        | No. of studies | HR (95%CI)  | Log-rank P value | F (%) | P value |
|---------------------------------|----------------|-------------|------------------|-------|---------|
| Overall survival                | 10             | 1.60 (1.25-2.05) | < 0.001          | 0     | 0.794   |
| Country                         |                |             |                  |       |         |
| Non-Asian countries             | 4              | 1.57 (1.15-2.15) | 0.005            | 0.0   | 0.798   |
| Asian countries                 | 6              | 1.66 (1.12-2.45) | 0.011            | 7.5   | 0.495   |
| Disease-free survival           | 9              | 1.78 (1.42-2.23) | < 0.001          | 0.0   | 0.781   |
| Country                         |                |             |                  |       |         |
| Non-Asian countries             | 3              | 1.58 (1.13-2.20) | 0.007            | 22.3  | 0.276   |
| Asian countries                 | 6              | 1.97 (1.44-2.69) | < 0.001          | 0.0   | 0.936   |

HR: Hazard ratio.

Half of included studies did not report the relation of BRCA1 expression with clinicopathological parameters including gender, age, tumor size, TNM stage, histology type, and differentiation. Therefore, we believe that more investigations are still needed to further determine the association between BRCA1 expression status and these parameters.

Cellular DNA is continuously attacked by intracellular active substances and environmental factors. Toxicity and mutagenesis are minimized by different repair pathways. Approximately 130 known human genes are involved during DNA repair process[27]. As a part of them, the BRCA1 gene was identified to have normal cellular functions, such as replication, transcription regulation, cell cycle regulation, and higher chromatin hierarchical control[8]. Furthermore, BRCA1 plays a crucial role in DNA damage response (DDR) through direct interaction with DDR proteins[28].

BRCA1 mutation is known as a risk factor for breast and ovarian cancers. And breast cancer patients with BRCA1 mutation account for 51% to 75% of all cases[29]. It has also been reported that prostate carcinomas with BRCA1 positive expression showed a high tumor proliferation index due to the cell-cycle regulation, and signified a worse prognosis compared to BRCA1 negative tumors[30]. Although BRCA1 mutations have not been found in NSCLC, the downregulation of BRCA1 mRNA and protein expression was found in 30% of NSCLC cases (mostly adenocarcinoma)[31].

One of the main targets of BRCA1 was the DNA damage-responsive gene GADD45. Expression of BRCA1 could trigger apoptosis through the c-Jun N-terminal kinase/stress-activated protein kinase pathway (JNK/SAPK)[32], which is activated by GADD45. Nevertheless, the JNK/SAPK pathway could mediate a physiological response to cisplatin-induced DNA damage[33]. It was plausible that the absence of BRCA1 increased a high sensitivity to cisplatin and there was a survival advantage for patients with a low level of BRCA1 mRNA treated with platinum-based drugs[34,35], which was consistent with our conclusion.

About the clinical significance of BRCA1 in NSCLC, there are still some fields which deserve further investigations. First of all, the inner mechanisms of the platinum-resistance in NSCLC patients with positive BRCA1 expression are still not clear. It is necessary and valuable to seek more potent agents to reverse platinum resistance in platinum-resistant NSCLC patients. It has been published that curcumin may serve as a chemosensitizer to enhance cisplatin-induced proliferation inhibition and apoptosis of A549/cisplatin cells by inhibiting DNA repair in the FA/BRCA pathway[36], which is a DNA cross-link damage repair pathway that regulates cellular resistance to DNA cross-link agents[37]. More rigorous and well-designed studies are warranted to investigate the possibility and feasibility of agents to reverse platinum resistance. Second, as mentioned above, only five of included studies did not report the association of BRCA1 expression with clinicopathological characteristics, which led to an indistinct relationship between BRCA1 expression and tumor development and progression in NSCLC. Third, BRCA1 is usually expressed in breast and ovarian cancers[10], so is there any difference in the clinical significance of BRCA1 expression between men and women?

There were some limitations in our meta-analysis. First of all, only 11 studies with small sample sizes were included. Second, the methods (reverse transcription-
CONCLUSION

In conclusion, the level of BRCA1 expression is associated with a poor prognosis in resected NSCLC. BRCA1 may be a promising and independent prognostic factor in NSCLC. This information could be useful to customize the adjuvant chemotherapy for NSCLC patients who received surgical therapy.
ARTICLE HIGHLIGHTS

Research background
The clinical role of breast cancer susceptibility gene 1 (BRCA1) expression in non-small cell lung cancer (NSCLC) patients undergoing surgery remains unclear.

Research motivation
This study explored the clinical value of BRCA1 expression in resected NSCLC patients.
Research objectives
This study aimed to explore the relation of BRCA1 expression with clinicopathological characteristics and survival in patients with resected NSCLC.

Research methods
Several electronic databases were searched to identify the relevant articles. The combined relative risks or hazard ratios with their corresponding 95% CIs were estimated.

Research results
The expression of the BRCA1 was significantly correlated with the prognosis of resected NSCLC. Positive BRCA1 expression signified a shorter overall survival and disease-free survival. However, no significant association of BRCA1 expression with any clinicopathological parameters was observed.

Research conclusions
BRCA1 expression indicated a poor prognosis in resected NSCLC patients. BRCA1 might serve as an independent biomarker to predict clinical outcomes and help to customize optimal adjuvant chemotherapy for NSCLC patients who received surgical therapy.

Research perspectives
BRCA1 could serve as a novel biomarker in resected NSCLC for the evaluation of prognosis and formulation of treatment strategy.

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