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Contents

Thrice Monthly Volume 9 Number 30 October 26, 2021

REVIEW

- 8953 Endothelial progenitor cells and coronary artery disease: Current concepts and future research directions
Xiao ST, Kuang CY

MINIREVIEWS

- 8967 Regulation of bone metabolism mediated by β -adrenergic receptor and its clinical application
Zhong XP, Xia WF
- 8974 Tricuspid valve endocarditis: Cardiovascular imaging evaluation and management
Fava AM, Xu B

ORIGINAL ARTICLE

Case Control Study

- 8985 Novel application of multispectral refraction topography in the observation of myopic control effect by orthokeratology lens in adolescents
Ni NJ, Ma FY, Wu XM, Liu X, Zhang HY, Yu YF, Guo MC, Zhu SY

Retrospective Cohort Study

- 8999 Uncertainty in illness and coping styles: Moderating and mediating effects of resilience in stroke patients
Han ZT, Zhang HM, Wang YM, Zhu SS, Wang DY

Retrospective Study

- 9011 Development and validation of a prognostic nomogram model for Chinese patients with primary small cell carcinoma of the esophagus
Zhang DY, Huang GR, Ku JW, Zhao XK, Song X, Xu RH, Han WL, Zhou FY, Wang R, Wei MX, Wang LD
- 9023 Preliminary establishment of a spinal stability scoring system for multiple myeloma
Yao XC, Shi XJ, Xu ZY, Tan J, Wei YZ, Qi L, Zhou ZH, Du XR
- 9038 Effect of intrauterine perfusion of granular leukocyte-colony stimulating factor on the outcome of frozen embryo transfer
Zhu YC, Sun YX, Shen XY, Jiang Y, Liu JY
- 9050 "An integrated system, three separated responsibilities", a new fever clinic management model, in prevention and control of novel coronavirus pneumonia
Shen J, He Q, Shen T, Wu ZQ, Tan MM, Chen YL, Weng Q, Nie LM, Zhang HF, Zheng B, Zhang J

Clinical Trials Study

- 9059** Single dose dexamethasone prophylaxis of postembolisation syndrome after chemoembolisation in hepatocellular carcinoma patient: A randomised, double-blind, placebo-controlled study

Sainamthip P, Kongphanich C, Prasongsook N, Chirapongsathorn S

Observational Study

- 9070** Serum calcium, albumin, globulin and matrix metalloproteinase-9 levels in acute cerebral infarction patients

Zhong TT, Wang G, Wang XQ, Kong WD, Li XY, Xue Q, Zou YA

SYSTEMATIC REVIEWS

- 9077** Neoadjuvant radiotherapy dose escalation for locally advanced rectal cancers in the new era of radiotherapy: A review of literature

Delishaj D, Fumagalli IC, Ursino S, Cristaudo A, Colangelo F, Stefanelli A, Alghisi A, De Nobili G, D'Amico R, Cocchi A, Ardizzoia A, Soatti CP

META-ANALYSIS

- 9090** Clinical significance of breast cancer susceptibility gene 1 expression in resected non-small cell lung cancer: A meta-analysis

Gao Y, Luo XD, Yang XL, Tu D

CASE REPORT

- 9101** Particular tumor of the pancreas: A case report

Zhu MH, Nie CF

- 9108** Dynamic changes in the radiologic manifestation of a recurrent checkpoint inhibitor related pneumonitis in a non-small cell lung cancer patient: A case report

Tan PX, Huang W, Liu PP, Pan Y, Cui YH

- 9114** Spontaneous rupture of a mucinous cystic neoplasm of the liver resulting in a huge biloma in a pregnant woman: A case report

Kośnik A, Stadnik A, Szczepankiewicz B, Patkowski W, Wójcicki M

- 9122** Diagnosis and laparoscopic excision of accessory cavitated uterine mass in a young woman: A case report

Hu YL, Wang A, Chen J

- 9129** Unusual cervical foreign body - a neglected thermometer for 5 years: A case report

Yang L, Li W

- 9134** Long-term survival of a patient with pancreatic cancer and lung metastasis: A case report and review of literature

Yang WW, Yang L, Lu HZ, Sun YK

- 9144** Synchronous diagnosis and treatment of acute myeloid leukemia and chronic lymphocytic leukemia: Two case reports

Chen RR, Zhu LX, Wang LL, Li XY, Sun JN, Xie MX, Zhu JJ, Zhou D, Li JH, Huang X, Xie WZ, Ye XJ

- 9151** Conversion therapy of hepatic artery ligation combined with transcatheter arterial chemoembolization for treating liver cancer: A case report
Feng GY, Cheng Y, Xiong X, Shi ZR
- 9159** Hemophagocytic lymphohistiocytosis secondary to composite lymphoma: Two case reports
Shen J, Wang JS, Xie JL, Nong L, Chen JN, Wang Z
- 9168** Fatal visceral disseminated varicella-zoster virus infection in a renal transplant recipient: A case report
Wang D, Wang JQ, Tao XG
- 9174** Choriocarcinoma misdiagnosed as cerebral hemangioma: A case report
Huang HQ, Gong FM, Yin RT, Lin XJ
- 9182** Rapid progression of colonic mucinous adenocarcinoma with immunosuppressive condition: A case report and review of literature
Koseki Y, Kamimura K, Tanaka Y, Ohkoshi-Yamada M, Zhou Q, Matsumoto Y, Mizusawa T, Sato H, Sakamaki A, Umezu H, Yokoyama J, Terai S
- 9192** Temporary pacemaker protected transjugular intrahepatic portosystemic shunt in a patient with acute variceal bleeding and bradyarrhythmia: A case report
Yao X, Li SH, Fu LR, Tang SH, Qin JP
- 9198** Recurrent pyogenic liver abscess after pancreatoduodenectomy caused by common hepatic artery injury: A case report
Xie F, Wang J, Yang Q
- 9205** Transient ventricular arrhythmia as a rare cause of dizziness during exercise: A case report
Gao LL, Wu CH
- 9211** Successful management of infected right iliac pseudoaneurysm caused by penetration of migrated inferior vena cava filter: A case report
Weng CX, Wang SM, Wang TH, Zhao JC, Yuan D
- 9218** Anterior abdominal abscess - a rare manifestation of severe acute pancreatitis: A case report
Jia YC, Ding YX, Mei WT, Xue ZG, Zheng Z, Qu YX, Li J, Cao F, Li F
- 9228** Monteggia type-I equivalent fracture in a fourteen-month-old child: A case report
Li ML, Zhou WZ, Li LY, Li QW
- 9236** Diagnosis and treatment of primary pulmonary enteric adenocarcinoma: Report of Six cases
Tu LF, Sheng LY, Zhou JY, Wang XF, Wang YH, Shen Q, Shen YH
- 9244** Choroidal metastatic mucinous abscess caused by *Pseudomonas aeruginosa*: A case report
Li Z, Gao W, Tian YM, Xiao Y
- 9255** Diagnosis and treatment of acute graft-versus-host disease after liver transplantation: Report of six cases
Tian M, Lyu Y, Wang B, Liu C, Yu L, Shi JH, Liu XM, Zhang XG, Guo K, Li Y, Hu LS

- 9269** Hepatic portal venous gas without definite clinical manifestations of necrotizing enterocolitis in a 3-day-old full-term neonate: A case report
Yuan K, Chen QQ, Zhu YL, Luo F
- 9276** Emergence of lesions outside of the basal ganglia and irreversible damage to the basal ganglia with severe β -ketothiolase deficiency: A case report
Guo J, Ren D, Guo ZJ, Yu J, Liu F, Zhao RX, Wang Y
- 9285** Skeletal muscle metastasis with bone metaplasia from colon cancer: A case report and review of the literature
Guo Y, Wang S, Zhao ZY, Li JN, Shang A, Li DL, Wang M
- 9295** Biopsy-confirmed fenofibrate-induced severe jaundice: A case report
Lee HY, Lee AR, Yoo JJ, Chin S, Kim SG, Kim YS
- 9302** Missense mutation in *DYNC1H1* gene caused psychomotor developmental delay and muscle weakness: A case report
Ding FJ, Lyu GZ, Zhang VW, Jin H
- 9310** Isolated hepatic tuberculosis associated with portal vein thrombosis and hepatitis B virus coinfection: A case report and review of the literature
Zheng SM, Lin N, Tang SH, Yang JY, Wang HQ, Luo SL, Zhang Y, Mu D

ABOUT COVER

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

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Abstract

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 signified 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

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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 MRE11/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 inconvincible 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 χ^2 -based Q-test and the I^2 statistic were applied to calculate the heterogeneity among the included studies[15]. If there was significant heterogeneity ($P < 0.10$ and/or $I^2 > 50\%$), 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

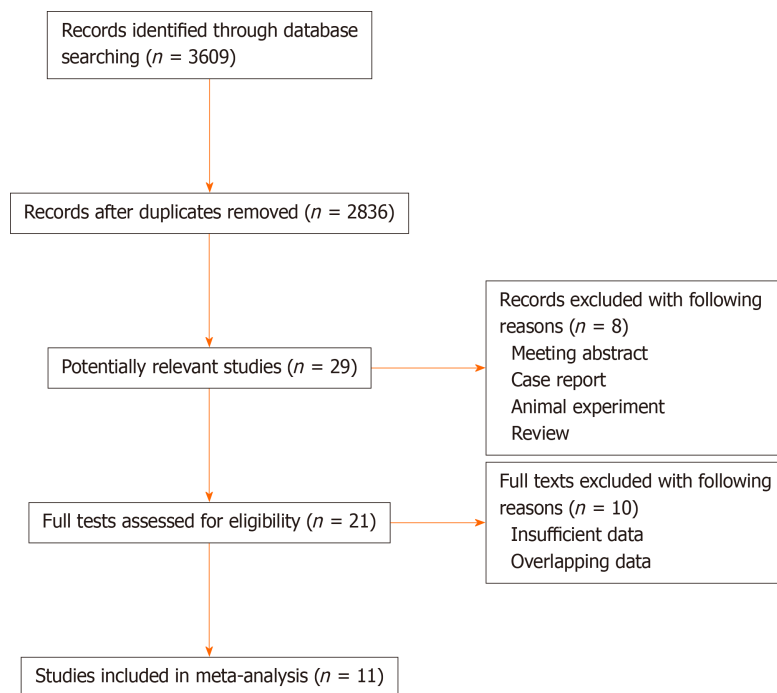
Characteristics of included studies

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 <i>et al</i> [18]	2007	Spain	123	40 (32.5)	IB-III A	OS	R	6
Bartolucci <i>et al</i> [11]	2009	Italy	54	36 (66.7)	IB-II B	OS/DFS	R	7
Ma <i>et al</i> [19]	2010	China	89	53 (59.6)	III A	OS/DFS	E	8
Leng <i>et al</i> [20]	2012	China	85	14 (16.5)	I- IV	OS/DFS	R	7
Gachechiladze <i>et al</i> [21]	2013	Israel	32	9 (28.1)	I- II	OS/DFS	E	7
Gachechiladze <i>et al</i> [21]	2013	Israel	58	15 (25.9)	III- IV	OS/DFS	E	7
Yu <i>et al</i> [22]	2013	China	80	36 (45)	I- IV	OS/DFS	E	7
Grossi <i>et al</i> [23]	2015	Italy	81	45 (55.6)	I A-III B	OS	R	6
Lafuente-Sanchis <i>et al</i> [24]	2015	Spain	64	30 (46.9)	I	DFS	R	7
Huang <i>et al</i> [12]	2016	China	84	11 (13.1)	II-III	DFS	R	8
Wang <i>et al</i> [25]	2017	China	70	NR	II-III	OS	R	6
Levallet <i>et al</i> [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.

**Figure 1** Flow diagram of literature review.

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 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 (III /IV vs I/II)	Histology (AC vs SCC)	Differentiation (poor vs moderate/well)
Rosell <i>et al</i> [18]	-	-	-	-	-	-
Bartolucci <i>et al</i> [11]	-	-	-	-	-	-
Ma <i>et al</i> [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 <i>et al</i> [20]	-	-	-	-	-	-
Gachechiladze <i>et al</i> [21]	-	-	-	0.920 (0.454-1.861)	-	-
Gachechiladze <i>et al</i> [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 <i>et al</i> [22]	-	-	-	-	-	-
Grossi <i>et al</i> [23]	-	-	-	-	-	-
Lafuente-Sanchis <i>et al</i> [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 <i>et al</i> [12]	-	-	-	-	-	-
Wang <i>et al</i> [25]	0.948 (0.735-1.224)	0.889 (0.711-1.112)	-	-	-	-
Overall	0.94 (0.79-1.12), $P = 0.522$; $I^2 = 0.0$, $P = 0.871$	1.01 (0.72-1.42), $P = 0.948$; $I^2 = 51.2$, $P = 0.129$	-	1.05 (0.78-1.42), $P = 0.739$; $I^2 = 22.7$, $P = 0.274$	0.97 (0.76-1.24), $P = 0.806$; $I^2 = 0.0$, $P = 0.732$	1.22 (0.97-1.55), $P = 0.097$; $I^2 = 0.0$, $P = 0.908$

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

heterogeneity ($I^2 = 0.0\%$, $P = 0.794$) 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 ($I^2 = 0.0\%$, $P = 0.781$) (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-

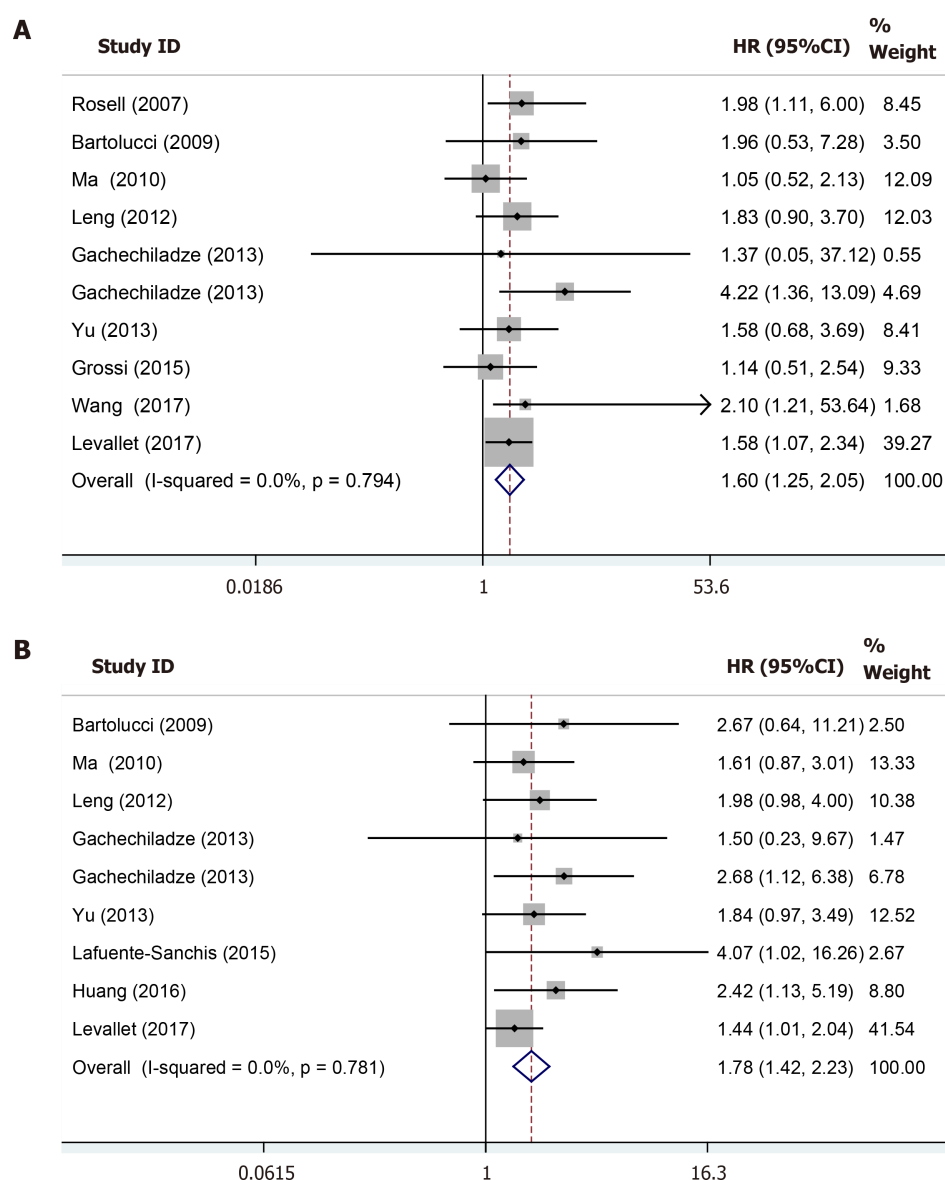


Figure 2 Forest plot of association of breast cancer susceptibility gene 1 expression with overall survival and disease-free survival. A: Association between breast cancer susceptibility gene 1 (BRCA1) expression and overall survival; B: Association between BRCA1 expression and disease-free survival.

polymerase chain reaction and immunohistochemistry) to calculate BRCA1 expression were inconsistent in the studies involved. Lastly, we were unable to conduct subgroup analysis based on age, sex, and TNM stage due to the lack of original data.

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.

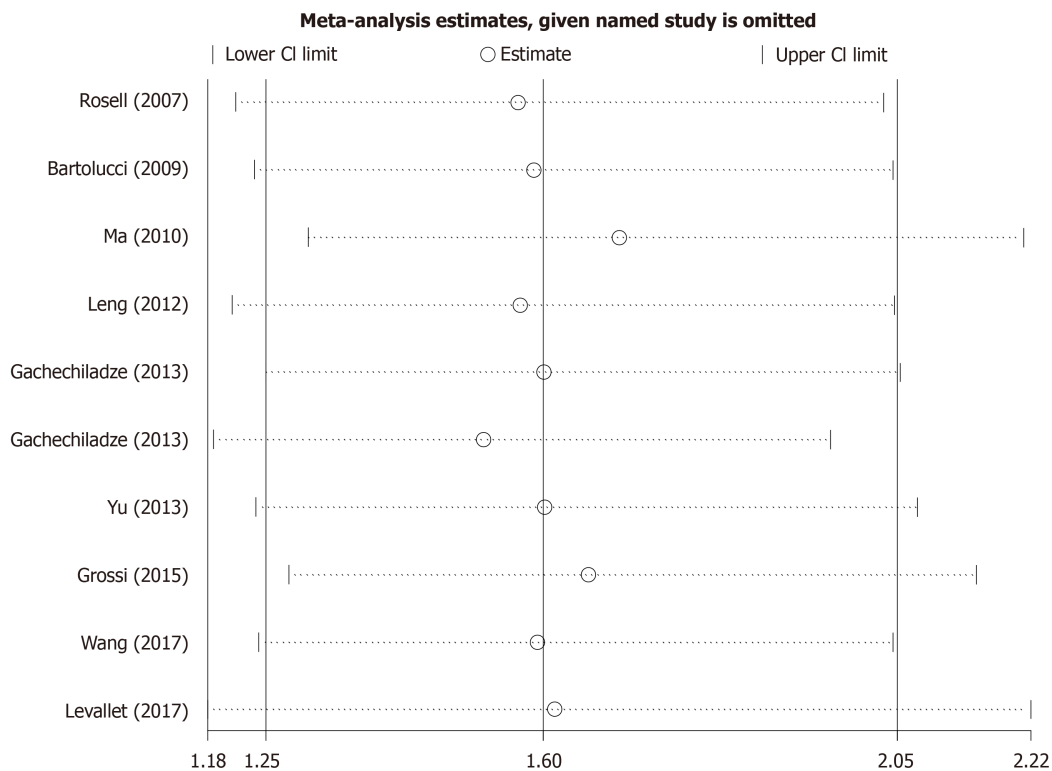


Figure 3 Sensitivity analysis of association between breast cancer susceptibility gene 1 expression and overall survival.

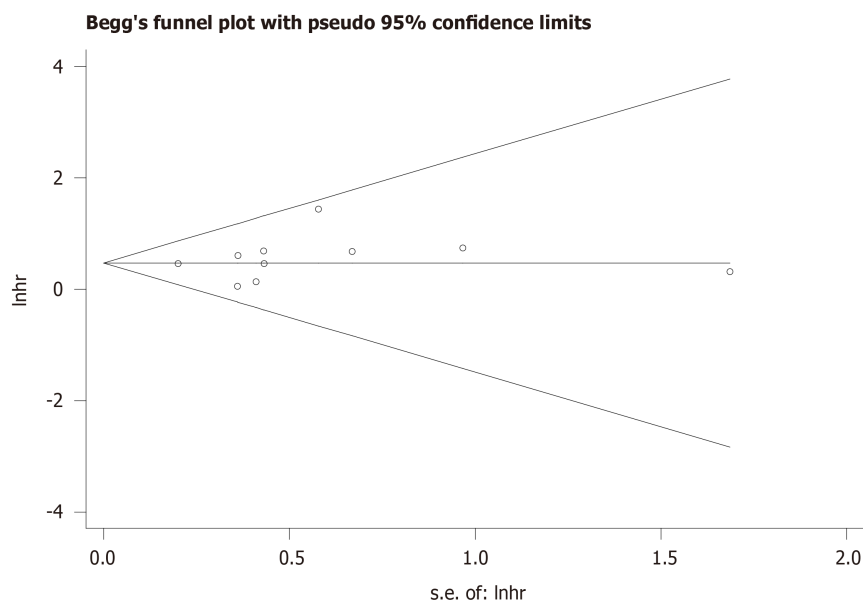


Figure 4 Begg's funnel plot of association between breast cancer susceptibility gene 1 expression and overall survival.

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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