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A meta-analysis of the association between BRAF mutation and nonsmall cell lung cancer

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Abstract

Background: Previous studies investigating the association between BRAF mutations and nonsmall cell lung cancer (NSCLC) remain controversial. To address the issue, we performed an updated meta-analysis of related articles.

Methods: We conducted a comprehensive literature search in the electronic databases including ISI Science Citation Index, EMBASE, PubMed, and CNKI (up to January 2016). The odds ratios (ORs) and 95% confidence interval (CI) were assessed based on random-effects or fixed-effects models according to the heterogeneity of eligible studies.

Results: A total of 16 studies enrolled 11,711 patients with NSCLC were involved in the meta-analysis. The overall BRAF mutation rate was 2.6% (303/11,711). There was a significant association between BRAF mutations and adenocarcinomas (ADCs) in NSCLC compared with non-ADCs (OR=3.96, 95% CI=2.13–7.34, $P < 0.0001$). No significant difference was observed in smoking and stage in patients with BRAF mutations. However, a significant difference of BRAF mutation rate was observed between women and men (OR=0.72, 95% CI=0.55–0.95, $P = 0.02$). In addition, the BRAF^{V600E} mutations were more frequent in women (OR=0.45, 95% CI=0.26–0.77, $P = 0.004$) and never smokers (OR=0.12, 95% CI=0.05–0.29, $P < 0.00001$).

Conclusions: BRAF mutations in ADCS and female significantly increased the risk of NSCLC compared to non-ADCS and male, respectively. BRAFV^{600E} mutation in NSCLC patients was significantly associated with female and nonsmokers.

Abbreviations: ADCs = adenocarcinomas, CI = confidence interval, NSCLC = nonsmall cell lung cancer, ORs = odds ratios.

Keywords: BRAF, meta-analysis, mutation, nonsmall cell lung cancer

1. Introduction

Lung carcinoma is one of the leading causes of cancer-related death universally, and patients with lung carcinoma are often diagnosed at advanced stage with poor prognosis.[1] Nonsmall cell lung cancers (NSCLCs) occupies most of lung carcinoma and 5-year survival rate remain very low.[2,3] Traditional therapeutic methods for lung carcinoma are mainly based on cancer histology. Classifying NSCLC into clinically related molecular subclasses may be helpful for the cure of NSCLC. The classification was constructed depending on mutations of genes, including HER2, KRAS, PIK3CA, BRAF, and others in frequencies more than 1%.[4–6] In addition, the NSCLC subtypes have been successfully established by using an overlap of genomic molecular markers and immunohistochemistry.[7]

BRAF is one of RAF kinase family member and plays a vital role in the mitogen-activated protein kinase signal pathways.[8] BRAF variations have been investigated in multiple cancers, such as colorectal cancer, papillary thyroid cancer, melanoma, and ovarian cancer.[9–12] Moreover, BRAF variations were also observed in NSCLCs.[13]

Gene variations are closely correlated to specific clinic pathologic characteristics, including gender, smoking, tumor histology, and clinical stage.[14,15] Although BRAF mutations have been found in NSCLC for quite a few years, associations between BRAF mutations and NSCLC are still disputable due to the lack of patient cases explored.[16,17] Therefore, we performed a meta-analysis from much more related studies to accurately evaluate the association of BRAF mutations with NSCLC.

2. Materials and methods

2.1. Search strategy and study selection

A computerized literature search was conducted in the PubMed, EMBASE, ISI, and CNKI databases to screen eligible articles. The deadline of retrieval period was up to January 2016. The terms and keywords used for search were as follows: "BRAF or B-RAF," "large cell lung cancer or carcinoma," "squamous-cell lung carcinoma or cancer," "non-small cell lung cancer or carcinoma," "lung adenocarcinoma," and "NSCLC."

Studies were selected if they met the following criteria: studies on the relationship between BRAF mutations and NSCLC; studies available as a full text; the patient number with BRAF mutations was more than one. The excluded standards were as follows: duplicate publications; studies without valuable data; reviews,

letters, case reports, and expert opinions. The institutional review board was approved by the First Affiliated Hospital of Zhengzhou University.

2.2. Data extraction

The following information was extracted by 2 investigators (GC and DL) independently from the eligible studies: author's last name, publication year, number of patient cases, country of origin, gene detection method, number of BRAF mutations, number of BRAF^{V600E} mutations, gender, smoking, histology, and clinical stage of patients. Any disagreement was resolved by discussion among all investigators.

2.3. Statistical analysis

Odds ratios (ORs) and 95% confidence interval (95% CI) were used to estimate the association between BRAF mutations and NSCLC risk by RevMan (version 5.2). The degree of heterogeneity between the studies was evaluated by the Chi-square value and I^2 value. A Chi-square test $P<0.10$ or an I^2 value $>50\%$ indicated a significant heterogeneity.[18] If $I^2 \le 50\%$, a fixed-effects model was chosen for analysis. In contrast, a random-effects model was applied. Potential publication bias was assessed using Begg test. Sensitivity analysis was explored to ensure the reliability of the results.

3. Results

3.1. Search results and study characteristics

The steps of retrieving eligible articles for the meta-analysis are represented in Fig. 1. The main characteristics of 16 eligible studies with 11,711 patients included in the meta-analysis are shown in Table 1.[16,17,19–32] The articles were published from November 2008[22] to January 2016.[31] Overall, 6 studies were performed in Asian, 6 studies from Europe, 2 from USA, 1 from Australia, and 1 from a mixed 4 countries. Different methods, including PCR, PCR+SEQ, PCR+SEQ/MALDI-TOF MS,

PCR+SEQ/SSCP, PCR+SEQ/HRMA, MALDI-TOF MS, HRMA, sAMS-PCR, were used to detect BRAF mutation. The number of patient cases ranged from 80 to 2690. BRAF mutation rate in distinct studies was from 0.9% to 8.9%. Only 303 (2.6%) of these patients with NSCLC harbored BRAF mutations.

3.2. Correlation between BRAF mutations and clinic pathologic characteristics in NSCLC

The associations of BRAF mutations with clinic pathologic characteristics in NSCLC are shown in Fig. 2 and Table 2. Fourteen studies including 7979 patients were analyzed for associations between the mutations of BRAF and gender. The results showed that 107 of 4404 male patients (2.43%) were BRAF mutations positive and 108 (3.02%) of 3575 female patients were BRAF mutations positive, indicating a significant difference of BRAF mutations between female and male (OR = 0.72, 95% CI=0.55–0.95, P=0.02). Eleven studies reported the association of BRAF gene mutations with smoking. The results suggested that 143 (4.13%) of 3465 smokers were detected harboring BRAF mutations and 50 (1.83%) of 2738 never smokers were detected harboring BRAF mutations, indicating that there were no significant differences in BRAF mutations between smokers and never smokers (OR=1.22, 95% CI=0.61–2.46, P=0.57). Ten studies informed the association of BRAF mutation with cancer histology. One hundred forty-one of 5064 ADCs (2.78%) harbored BRAF mutations and 9 (0.58%) of 1546 non-ADCs had BRAF mutations, indicating a significant difference in BRAF mutations between ADCs and non-ADCs (OR=3.96, 95% CI= 2.13–7.34, P<0.0001). Only 5 studies contained the related data on mutations of BRAF and the stage of NSCLC. The results demonstrated that 67 of 3136 stage I/II NSCLCs (2.14%) harbored BRAF mutations and 76 (6.15%) of 1235 stage III/IV NSCLCs had BRAF mutations, indicating there were no significant differences in BRAF mutation between stage I/II and stage III/IV (OR=0.86, 95% CI=0.44–1.68, P=0.65).
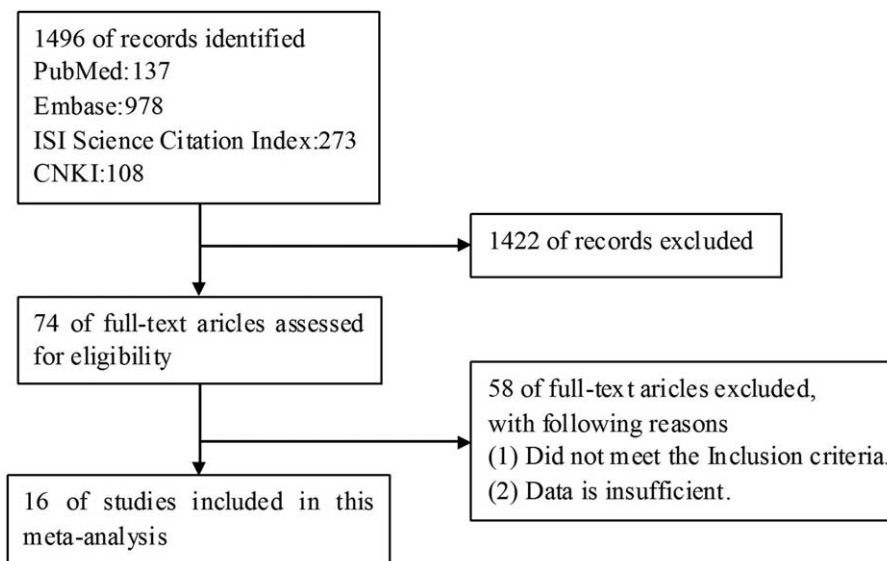

Figure 1. The flow chart for retrieving eligible articles used in the meta-analysis.

Table 1

Characteristics of the studies included in the meta-analysis.

First author	Year	Source of Pts	Methods	No. of Pts	Mut BRAF (%)	Female (%)	Smokers (%)	ADC (%)	Stage III/IV (%)
Pratilas	2008	4 countries	PCR + SEQ/MALDI-TOF MS	916	17 (1.9)	577 (63.0)	614 (67.0)	623 (68.0)	NA
Schmid	2009	Austria	PCR + SEQ	96	2 (2.1)	38 (39.6)	74 (77.1)	NA	NA
Lee	2010	Korea	PCR + SEQ	173	2 (1.2)	60 (34.7)	117 (67.6)	117 (67.6)	NA
Kobayashi	2011	Japan	PCR + SEQ/SSCP	581	5 (0.9)	204 (35.1)	NA	382 (65.7)	124 (21.3)
Marchetti	2011	Italy	PCR + SEQ/HRMA	1046	37 (3.5)	187 (25.3)	542 (73.3)	739 (70.7)	218 (29.5)
Paik	2011	USA	MALDI-TOF MS	697	18 (2.6)	452 (65.8)	386 (56.2)	NA	NA
An	2012	China	HRMA	452	7 (1.5)	NA	192 (42.5)	307 (67.9)	NA
Sasaki	2012	Japan	PCR + SEQ	305	6 (2.0)	148 (56.7)	NA	NA	NA
Cardarella	2013	USA	PCR + SEQ	883	36 (4.1)	148 (50.5)	229 (78.4)	256 (87.4)	237 (80.9)
Ilie	2013	France	PCR + SEQ	450	40 (8.5)	158 (35.1)	403 (89.6)	NA	352 (78.2)
Brustugun	2014	Norway	PCR	979	17 (1.7)	476 (48.6)	NA	646 (66.0)	NA
Kinno	2014	Asian	PCR + SEQ/HRMA	2001	26 (1.3)	935 (46.7)	844 (42.2)	1835 (91.7)	304 (15.3)
Costa	2015	Spain	PCR	80	2 (2.5)	28 (35)	64 (80)	71 (88.7)	NA
Luk	2014	Australia	MALDI-TOF MS	273	7 (2.6)	129 (47.3)	NA	NA	NA
Shao	2015	China	sARMS-PCR	89	1 (1.1)	35 (39.3)	39 (43.8)	88 (98.9)	16 (18.0)
Tissot	2016	France	PCR + SEQ	2690	80 (3.0)	NA	NA	NA	NA

ADC = adenocarcinoma, HRMA = high-resolution melting analysis, MALDI-TOF MS = matrix-assisted laser desorption/ionization time of flight mass spectrometry, Mut BRAF = mutant BRAF, NA = not available, PCR = polymerase chain reaction, Pts = patients, sARMS = scorpion probe amplification refractory mutation system, SEQ = sequencing, SSCP = single strand conformation polymorphism analysis.

3.3. Correlation between BRAF^{V600E} mutation and clinic pathologic characteristics in NSCLC

The association between BRAF^{V600E} mutation and clinic pathologic characteristics in NSCLC is evaluated in Fig. 3. A fixed-effects model was used to systematically analyze the BRAF^{V600E} mutations in NSCLC reported in 6 studies. 51.0% (107/210) were BRAF^{V600E} mutations in all of the BRAF mutations. Forty-seven (32.6%) of 144 male patients were BRAF^{V600E} mutations positive and 60 (62.5%) of 96 female patients were BRAF^{V600E} mutations positive, indicating a significant difference in BRAF^{V600E} mutations between female and male (OR = 0.45, 95% CI = 0.26–0.77, P = 0.004). Sixty-nine (45.1%) of 153 former or current smokers had BRAF^{V600E} mutations and 40 of 46 never smokers (87.0%) harbored BRAF^{V600E} mutation, indicating that there was a significant difference in BRAF^{V600E} mutation between never smokers and smokers (OR = 0.12, 95% CI = 0.05–0.29, P < 0.00001). Twenty-eight (48.3%) of 58 stage I or II patients harbored BRAF^{V600E} mutations and 74 (55.2%) of 134 stage III or IV patients harbored BRAF^{V600E} mutation, indicating no significant difference in BRAF^{V600E} mutation between stage I/II and stage III/IV (OR = 0.65, 95% CI = 0.33–1.28, P = 0.21).

3.4. Sensitivity analysis and publication bias

Sensitivity analysis was performed to assess the stability of the results and Begg funnel plot was conducted to evaluate the reliability of the results. The sensitivity analysis indicated that removal of any one from the eligible articles had no effect on the final results. The funnel plots (Fig. 4) with low asymmetry suggested that there was no strong publication bias in the meta-analysis of BRAF mutations and clinic pathologic characteristics in NSCLC.

4. Discussion

BRAF mutations may be related to BRAF-mediated downstream signaling pathways, which have acquired extensive interest.[33] Several meta-analyses have been performed to study BRAF mutations in papillary thyroid cancer, colorectal cancer, and melanoma.[34–36] BRAF mutations were closely associated with specific pathologic characteristics, including tumor histology, clinical stage, gender, and smoking. Some studies have reported that BRAF mutations played a significant role in the clinical features of NSCLC. However, due to lack of estimated patient cases, a consensus has not been reached. Though one meta-analysis reported the association of BRAF mutations with NSCLC,[37] the number of NSCLC patients was not enough. Therefore, our updated meta-analysis was performed to explore the characteristics of NSCLC patients harboring BRAF mutations.

Sixteen studies, including 11,711 NSCLC patients, were used to systematically review the association between mutations of BRAF and pathologic features of NSCLC. The BRAF mutation rate was about 2.6% (303/11711), consistent with previous published studies.[24,38] In the studies of Marchetti et al and Pratilas et al, BRAF gene mutation rates were reported to be 2% and 3.5%, respectively,[21,22] which were close to the mutation rates found in our study.

In order to improve tumor mutation analysis, the clinical features of NSCLC were investigated in our study. The meta-analysis was performed to evaluate the association of BRAF mutations with four clinic pathologic features. A significant association was found between gender and BRAF mutation rate (OR = 0.72, 95% CI = 0.55–0.95, P = 0.02), which was opposite to previous meta-analysis in Chen's study.[37] An association of BRAF mutations with female was reported in colorectal cancer patients.[35,39] Further, we detected the associations between mutations of BRAF and smoking status. Our analysis showed that no association was observed between BRAF mutations and smoking status, which was the same with the results of previous studies.[32,37]

NSCLC covers three diverse histologic types, including ADC, large-cell carcinoma, and squamous-cell carcinoma, of which more than 50% are ADC. Our meta-analysis indicated that BRAF mutations were more common in ADCs than those in other histology (OR = 3.96, 95% CI = 2.13–7.34, P < 0.0001), which was consistent with a previous study.[21] Clinical stage, as
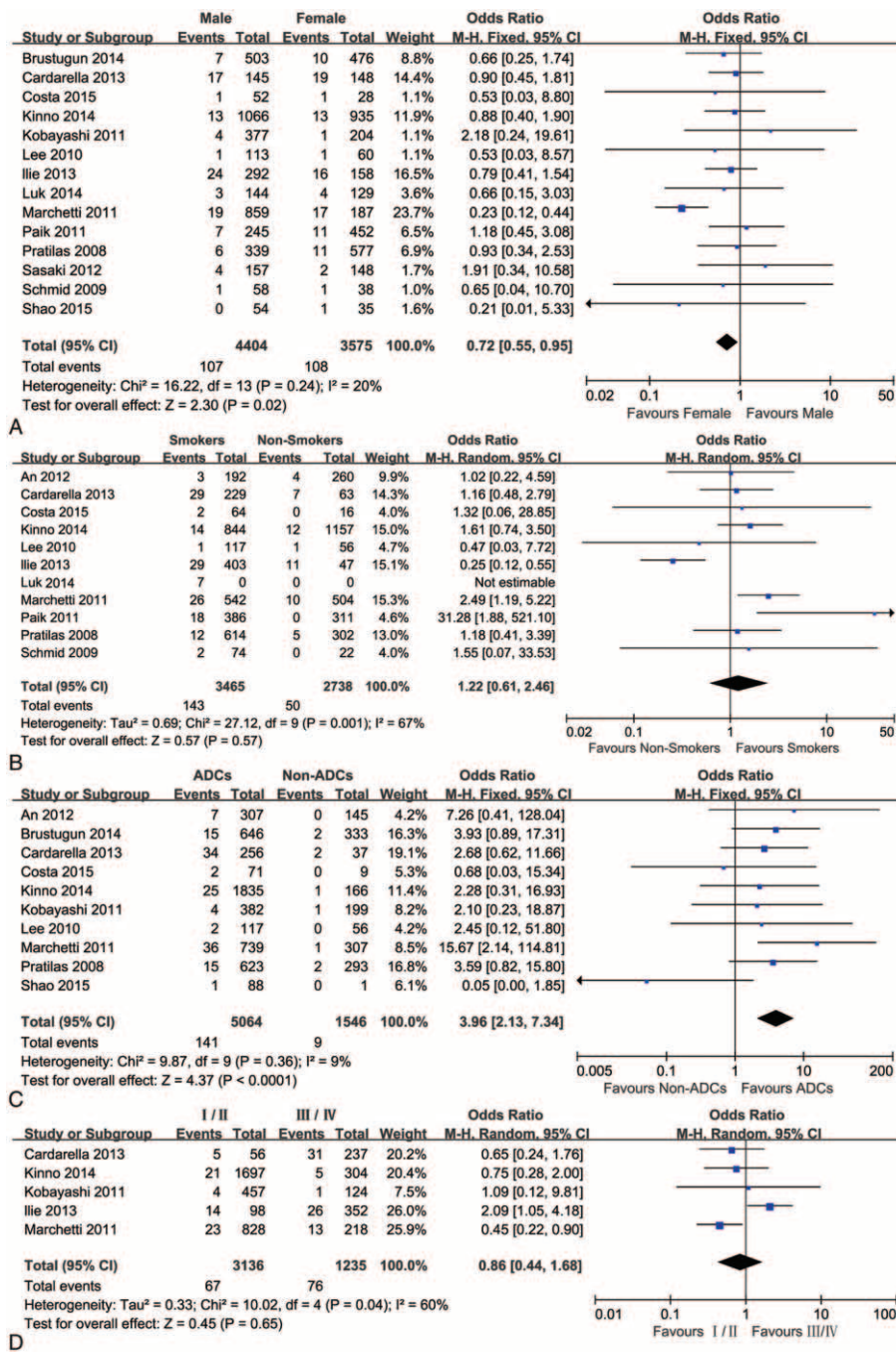
Figure 2. A forest plot for the association between BRAF mutations and gender (A), smoking (B), histology (C), and stage (D).

a vital factor, plays an important role in the prognosis of NSCLC. However, no significant associations between BRAF mutations and stage of NSCLC were demonstrated in our meta-analysis. This result may be caused by lack of a number of patient cases.

BRAF^{V600E} is the most common mutation occurring in the *BRAF* gene.[40] Up to now, 6 studies have involved the association between clinic pathologic features and BRAF^{V600E} mutation.[19,21,27,30–32] Significant differences were found in these studies between the clinical features of NSCLC patients with BRAF^{V600E} and ones with non-BRAF^{V600E}

mutations.[19,21,27] Several reports suggested that BRAF^{V600E} mutations were more frequent in females and never smokers, however, the phenomenon was not observed in other clinic pathologic features.[21,27] Our meta-analysis also indicated that the BRAF^{V600E} mutation was significantly more frequent in females than in males. Compared to smokers, the BRAF^{V600E} mutation was also significantly frequent in never-smokers (OR = 0.12, 95% CI = 0.05–0.29, $P <$ 0.00001). Ilie et al[27] demonstrated that there was a significant association between early-stage tumors and non-BRAF^{V600E} mutations. We also observed a tendency for

Table 2

Association between BRAF mutation and gender, smoking, histology, and stage in NSCLC.

Outcome	Mutant BRAF (%)	Statistical method	Test of association		Heterogeneity test		
			OR (95% CI)	P	χ^2	I^2 (%)	P
Gender							
Male	107/4404 (2.43)	M-H, fixed, 95% CI	0.72 [0.55, 0.95]	0.02	16.22	20	0.24
Female	108/3575 (3.02)						
Smoking							
Former/current	143/3465 (4.13)	M-H, random, 95% CI	1.22 [0.61, 2.46]	0.57	27.12	67	0.001
Never	50/2738 (1.83)						
Histology							
ADC	141/5064 (2.78)	M-H, fixed, 95% CI	3.96 [2.13, 7.34]	<0.0001	9.87	9	0.36
Non-ADC	9/1546 (0.58)						
Stage							
I, II	67/3136 (2.14)	M-H, random, 95% CI	0.86 [0.44, 1.68]	0.65	10.02	60	0.04
III, IV	76/1235 (6.15)						

ADC = adenocarcinoma, CI = confidence interval, NSCLC = nonsmall cell lung cancer, OR = odds ratio.
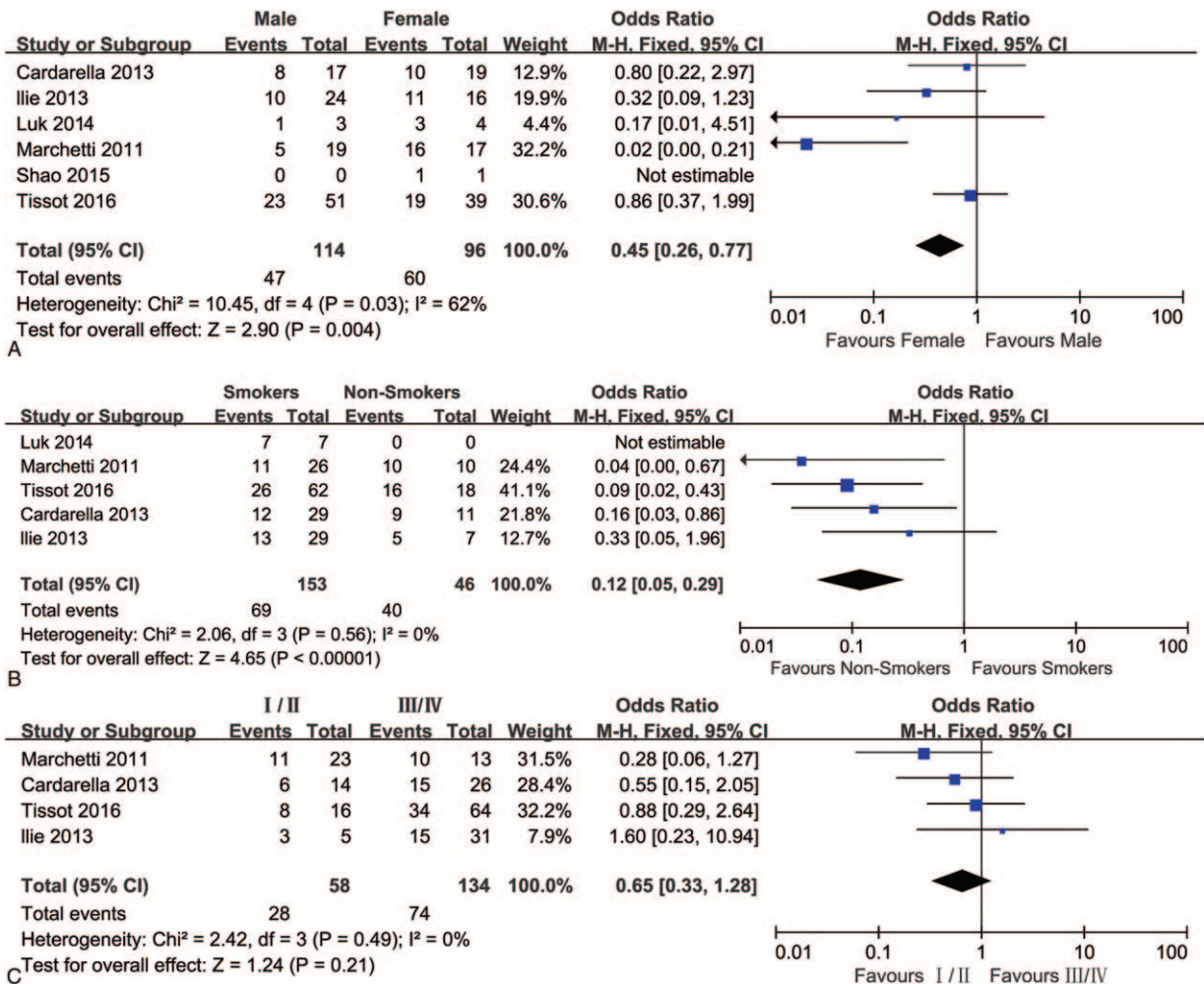

Figure 3. A forest plot for the association between BRAF[V600E] mutations and gender (A), smoking (B), and stage (C).
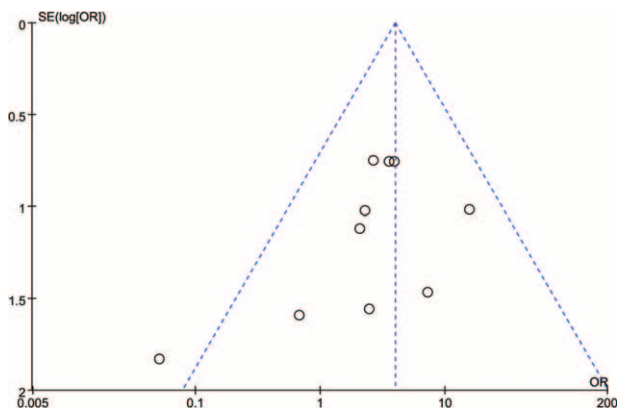
Figure 4. Begg funnel plot for publication bias of BRAF mutations and ADCs risk.

earlier-stage disease but there was no statistical significance, which may result from lack of cases.

Several limitations in our study should be taken into consideration when construing the findings. The number of involved studies on BRAF^{V600E} mutations was not enough. Therefore, additional studies on BRAF^{V600E} mutations are required to extend and approve our results. Moreover, we did not well describe the association of BRAF mutation with clinical stage due to the lack of data.

In conclusion, we found that BRAF mutations in NSCLC patients were significantly associated with ADCs and tend to occur in female. Moreover, BRAFV^{600E} mutation was significantly associated with NSCLC in female and nonsmokers. This may provide a theoretical basis for the diagnosis of NSCLC.

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