Int J Clin Exp Med 2019;12(3):2538-2548
www.ijcem.com /ISSN:1940-5901/IJCEM0085246

Original Article

COX-2 rs689466 polymorphism correlates with increased lung cancer risk

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Received September 8, 2018; Accepted November 10, 2018; Epub March 15, 2019; Published March 30, 2019

Abstract: Background: The aim of this study was to assess, using comprehensive meta-analysis, if there was a significant association between polymorphisms in *cyclooxygenase-2* (*COX-2*) gene and lung cancer risk. Methods: PubMed, MEDLINE, EMBASE, Web of Science, CBM, CNKI, WanFang, and CQVIP were searched for all eligible studies through July 2018. A total of 612 citations were retrieved. Odds ratios (OR) and corresponding 95% confidence intervals (CIs) were utilized to evaluate the strength of association between *COX-2* gene polymorphisms and lung cancer risk. Meta-analysis, sensitivity analysis, Begg's funnel plot, Egger's linear regression, and subgroup analyses were carried out to clarify and validate pooled results. Results: A total of 8 studies met the inclusion criteria and were included in the meta analysis. This current systematic review indicated that *COX-2* rs689466 polymorphism correlates with increased lung cancer risk in the allele model (A vs. G), dominant model (AA vs. GG/AG), and homozygous model (AA vs. GG). According to subgroup-analysis, the AA genotype of *COX-2* gene rs689466 site increased lung cancer risk in Asian populations, population-based, and hospital-based. Conclusion: *COX-2* rs689466 site may moderately increase the risk of lung cancer, especially in Asian populations, PB, and HB studies. In addition, AA homozygotes may contribute to early diagnosis and prevention, providing timely treatments. Results suggest that *COX-2* rs689466 polymorphism may be a potential pathogenic factor in lung cancer.

Keywords: *COX-2* rs689466, gene polymorphism, lung cancer, meta-analysis

Introduction

Lung cancer has become the top cause of cancer-related morbidity and mortality, posing a serious threat to human health [1, 2]. As indicated by many epidemiologic studies, occurrence of lung cancer results from the synergistic effects of multiple factors [3, 4], such as smoking [5, 6], air pollution, and occupational exposure [7-9]. In recent years, the important roles of genetic factors in the occurrence and development of lung cancer have been reported [10]. Correlations between gene polymorphisms and lung cancer susceptibility have been revealed in many studies, with some focusing on *cyclo-oxygenase-2* (*COX-2*) gene [11].

COX is the rate-limiting enzyme in converting arachidonic acid (AA) to prostaglandins (PGs). It has 3 isoenzymes: *COX-1, COX-2,* and *COX-3*. The gene encoding *COX-2* is located in chromosome 1q25.2-25.3 with a full length of approximately 8.3 kb. It is involved in inflammatory reactions through promoting the release of inflammatory substances, raising permeability of tissues and mediating injures to tissues and organs [12]. Increasing studies have focused on the association between gene polymorphisms in *COX-2* and lung cancer susceptibility, aiming to provide a new method of prevention and treatment of lung cancer. Multiple polymorphic sites, such as rs689466, rs689465 and rs20417 [13, 14], have been proven to be closely related to lung cancer susceptibility. Of these sites, rs689466 polymorphism has been shown to be related with lung cancer susceptibility [15], although results remain controversial and require further verification. Moreover,

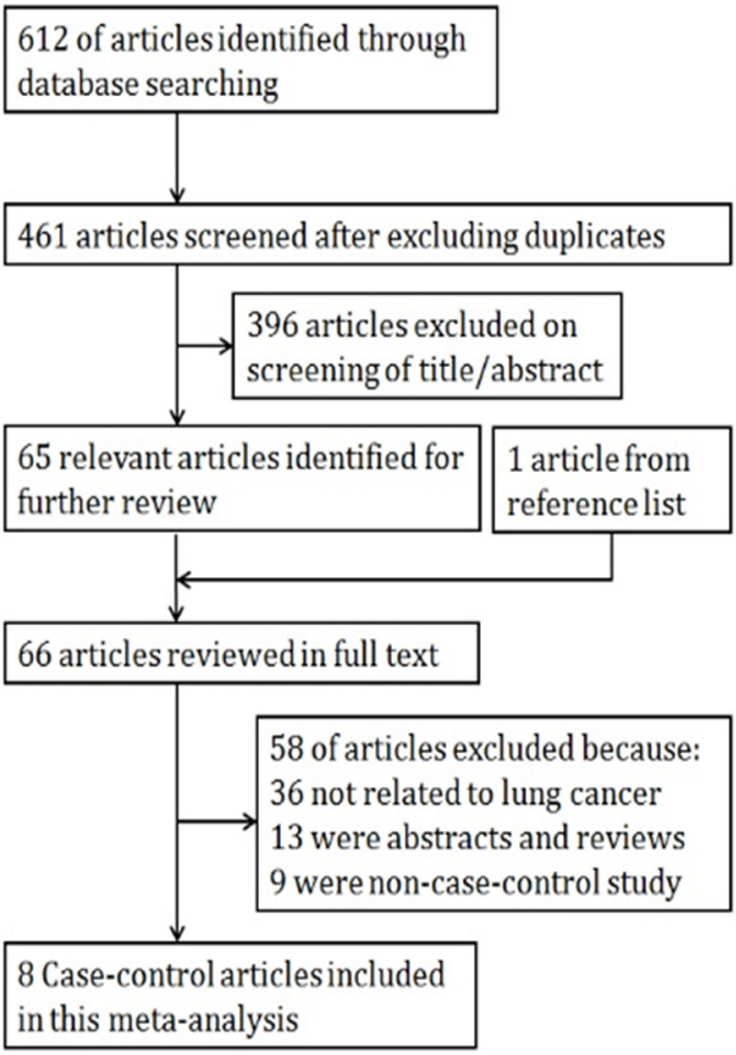

Figure 1. Flow chart showing the selection process for included studies.

the sample size of one single case-control study might limit the efficacy of interpreting the association. Based on these controversial results, the present study conducted an integrated and comprehensive meta-analysis to elucidate the relationship between polymorphisms of *COX-2* rs689466 and susceptibility to lung cancer.

Material and methods

Search strategy

Retrieval was performed using MeSH terms (cyclooxygenase 2 or cyclooxygenase-2 or *COX2* or *COX-2*) and (variant or polymorphism or SNP or mutation) and (lung) and (cancer or carcinoma or tumor or malignancy or neoplasm) in the following databases: PubMed, MEDLINE, EMBASE, Web of Science, CBM, CNKI, WanFang, and CQVIP (up to July of 2018). Related conference articles were obtained by manually retrieving the periodical database of the library in the Third Military Medical University. For example, details of formatting used for the Pubmed search were as follows:

#1, cyclooxygenase 2 OR cyclooxygenase-2 OR COX2 OR COX-2; #2, variant OR polymorphism OR SNP OR mutation; #3, lung; #4, cancer OR carcinoma OR tumor OR malignancy OR Neoplasm; #5, #1 AND #2 AND #3 AND #4.

Inclusion criteria

Studies were included when meeting the following criteria: 1) Case-control study; 2) Case groups in the analysis consisted of patients diagnosed with lung cancer; 3) The study was relevant to association between gene polymorphism of *COX-2* rs689466 and lung cancer susceptibility; and 4) The study provided adequate data of odds ratios (ORs) with corresponding 95% confidence intervals (CIs) for the calculation of genotype data.

Exclusion criteria

Studies were excluded when meeting one of the following criteria: 1) The study was not about the association between gene polymorphism of *COX-2* rs689466 and susceptibility to lung cancer; 2) The study was not a case-control study or it has been published more than once; 3) The study was a summary, review, or case report; and 4) The study had no complete or accessible original data.

Data extraction & quality evaluation

Data were independently extracted by 2 researchers (Jiang Wang and Gaoming Li) using

Table 1. Baseline information of included studies

Author	Year	Ethnicity	Source of controls	Source of genotyping	Histological types of cases	Genotyping method	SNP	Sample size		Cases			Controls			Association	HWE
								Case	Control	AA	AG	GG	AA	AG	GG		
Vogel et al.	2008	Caucasians	Cancer-free controls (age-, sex-matched; PB)	Lymphocytes	138 AC; 70 SCLC; 94 SQCC; 101 others	PCR-probes	rs689466	403	744	262	124	17	467	253	24	NRF	0.143
Coskunpinar et al.	2010	Caucasians	Cancer-free controls (age-matched; PB)	Peripheral whole blood	61 AC; 26 SCLC; 21 others	PCR-RFLP	rs689466	231	118	173	57	1	70	48	0	RF	0.006
Liu et al.	2010	Asians	Healthy controls (age-, gender-, smoking habits-matched, HB)	Peripheral blood leukocytes	NA	PCR-RFLP	rs689466	358	716	102	172	84	193	345	178	NRF	0.337
Guo et al.	2012	Asians	Cancer-free controls (age-matched; HB)	Peripheral whole blood	257 AC; 221 SQCC; 142 SCLC; 64 others	PCR-LDR	rs689466	684	602	230	318	136	161	320	121	RF	0.096
Zhang et al.	2013	Asians	Healthy controls (age-, sex-matched, PB)	Peripheral whole blood	NA	PCR-RFLP	rs689466	956	994	271	502	183	247	530	217	RF	0.034
Zhang et al.	2015	Asians	Healthy controls (HB)	Peripheral blood leukocytes	60 NSCLC	PCR-RFLP	rs689466	60	62	12	28	20	4	31	27	RF	0.209
Cao et al.	2015	Asians	Healthy controls (PB)	Peripheral whole blood	42 NSCLC	PCR-RFLP	rs689466	42	50	8	20	14	3	27	20	RF	0.118
Moraes et al.	2017	Caucasians	Cancer-free controls (PB)	Peripheral blood	51 AC; 41 SQCC; 9 others	RT-qPCR	rs689466	104	200	71	30	3	138	52	10	NRF	0.092

NA: not available; AC: adenocarcinoma; SCLC: small cell lung carcinoma; SQCC: squamous cell carcinoma; NSCLC: non-small cell lung carcinoma. PB: population-based; HB: hospital-based; HWE: Hardy-Weinberg equilibrium; RF: risk factor; NRF: not risk factor.

Table 3. Stratified analysis of the *COX-2* Rs689466 polymorphism with risk of lung cancer

	Allele model (A vs. G)			Dominant model (AA vs. GG/AG)			Recessive model (AA/AG vs. GG)			Homozygous comparison (AA vs. GG)			Heterozygous comparison (AG vs. GG)		
	OR (95% CI)	P_h	Expected power (%)	OR (95% CI)	P_h	Expected power (%)	OR (95% CI)	P_h	Expected power (%)	OR (95% CI)	P_h	Expected power (%)	OR (95% CI)	P_h	Expected power (%)
Total	1.14 (1.06, 1.23)*	0.30	62.2	1.24 (1.11, 1.39)*	0.06	67.8	1.11 (0.96, 1.27)	0.81	18.1	1.26 (1.07, 1.49)*	0.32	45.5	1.02 (0.88, 1.19)	0.74	5.5
Ethnicity															
Asians	1.14 (1.05, 1.24)*	0.47	91.4	1.26 (1.10, 1.44)*	0.12	93.2	1.12 (0.97, 1.30)	0.80	49.7	1.30 (1.09, 1.54)*	0.22	90.2	1.04 (0.89, 1.21)	0.77	14.1
Caucasians	1.14 (0.95, 1.36)	0.09	52.7	1.21 (0.99, 1.48)	0.05	59.5	0.90 (0.52, 1.56)	0.51	6.9	0.93 (0.53, 1.63)	0.59	10.2	0.84 (0.47, 1.48)	0.38	5.2
Source of Controls															
PB	1.14 (1.03, 1.26)*	0.22	11.4	1.22 (1.06, 1.41)*	0.08	12.7	1.15 (0.94, 1.40)	0.67	5.9	1.26 (1.00, 1.60)	0.35	8.1	1.08 (0.87, 1.33)	0.57	5.0
HB	1.14 (1.01, 1.27)*	0.26	70.4	1.29 (1.07, 1.54)*	0.09	82.5	1.07 (0.88, 1.30)	0.58	19.2	1.26 (1.00, 1.58)	0.16	6.50	0.98 (0.79, 1.20)	0.60	5.1

OR: odds ratio; CI: confidence interval; P_h: *p* value for heterogeneity; PB: population-based; HB: hospital-based *: OR with statistical significance.

Table 2. Newcastle Ottawa Scale for quality evaluation of included case-control studies

No.	Study (year)	Selection				Comparability		Exposure			Total No. of stars
		1	2	3	4	1 (a)	1 (b)	1 (a)	2	3	
1	Vogel et al., 2008	*	*	*	*	*	*	*	*	*	9
2	Coskunpinar et al., 2010	*	*	*	*	*	-	*	*	*	8
3	Liu et al., 2010	*	*	-	*	*	*	*	*	*	8
4	Guo et al., 2012	*	*	-	*	*	-	*	*	*	7
5	Zhang et al., 2013	*	*	*	*	*	*	*	*	*	9
6	Zhang et al., 2015	*	*	-	*	-	-	*	*	*	6
7	Cao et al., 2015	*	-	*	*	-	-	*	*	*	6
8	Moraes et al., 2017	*	*	*	*	-	-	*	*	*	7

"-" means no star was assigned.

the same data sheet, including the following data: first author, year published, country, source of control group, histological types of cases, genotyping method, sizes of case group and control group, genotype distribution, and HWE test results of the control group. Discussions involving a third party were conducted to solve disagreements. Furthermore, Newcastle-Ottawa Scale was employed to evaluate the quality of included studies regarding selection of objects, comparability, and exposure.

Statistical approach

ORs and 95% CIs were used as effect indicators in this analysis. $P < 0.05$ indicates statistical significance. Five genetic models, including allele model (A vs. G), recessive model (AA/AG vs. GG), dominant model (AA vs. GG/AG), homozygous model (AA vs. GG) and heterozygous model (AG vs. GG), were compared, respectively. Z test was employed to summarize the statistical significance of OR values and the corresponding significance level was two-sided 0.05. The χ^2 test was used to evaluate the compliance of genotypes of the control groups with HWE. Cochrane Q test was used to analyze heterogeneity among all studies, with $P < 0.10$ indicating a significant difference. The magnitude of heterogeneity was quantitatively assessed with I^2 values, ranging from 0% to 100%. The greater the I^2 value, the higher the heterogeneity. In heterogeneity testing, if $P < 0.10$ or $I^2 > 50\%$, a random effects model (DerSimonian Laird Method) was used. Otherwise, a fixed-effects model (Mantel-Haenszel Method) was applied. In addition, sensitivity analysis was performed by interchanging the combined models, excluding small sample size studies and studies inconsistent with HWE. Begg's funnel plot and Egger's linear regression were employed to analyze publication bias, defined by $P < 0.1$. This meta-analysis was conducted using Revman 5.2.0 and Stata 11.0. Power analysis was performed using the Power and Sample Size Calculation (PS) program [16].

Results

Bibliographic retrieval

A total of 612 studies were retrieved after removing duplicates from the 461 articles. Irrelevant studies were excluded according to titles and abstracts (396 papers irrelevant to the topic) and by reviewing abstracts and full texts intensively (58 papers, 36 irrelevant to lung cancer, 13 abstracts and reviews, and 9 non-case control studies). One additional study was obtained based on reference lists of included literature. A total of 8 studies were eventually included, covering 2,838 lung cancer cases and 3,486 controls (**Figure 1**). Baseline information of included studies is shown in **Table 1**.

Quality evaluation

Quality evaluation revealed that all 8 studies had a definite diagnosis, credible data, and good comparability between the case group and control group. Two studies had a score of 9 points [17, 18], two scored 8 [19, 20], and two scored 7 [21, 22], with two getting 6 [15, 23] (**Table 2**). Results suggest that these included studies were suitable for meta-analysis.

Association between COX-2 rs689466 polymorphism and lung cancer susceptibility

Results of this meta-analysis, along with heterogeneity testing, are displayed in **Figure 2** and **Table 3**.

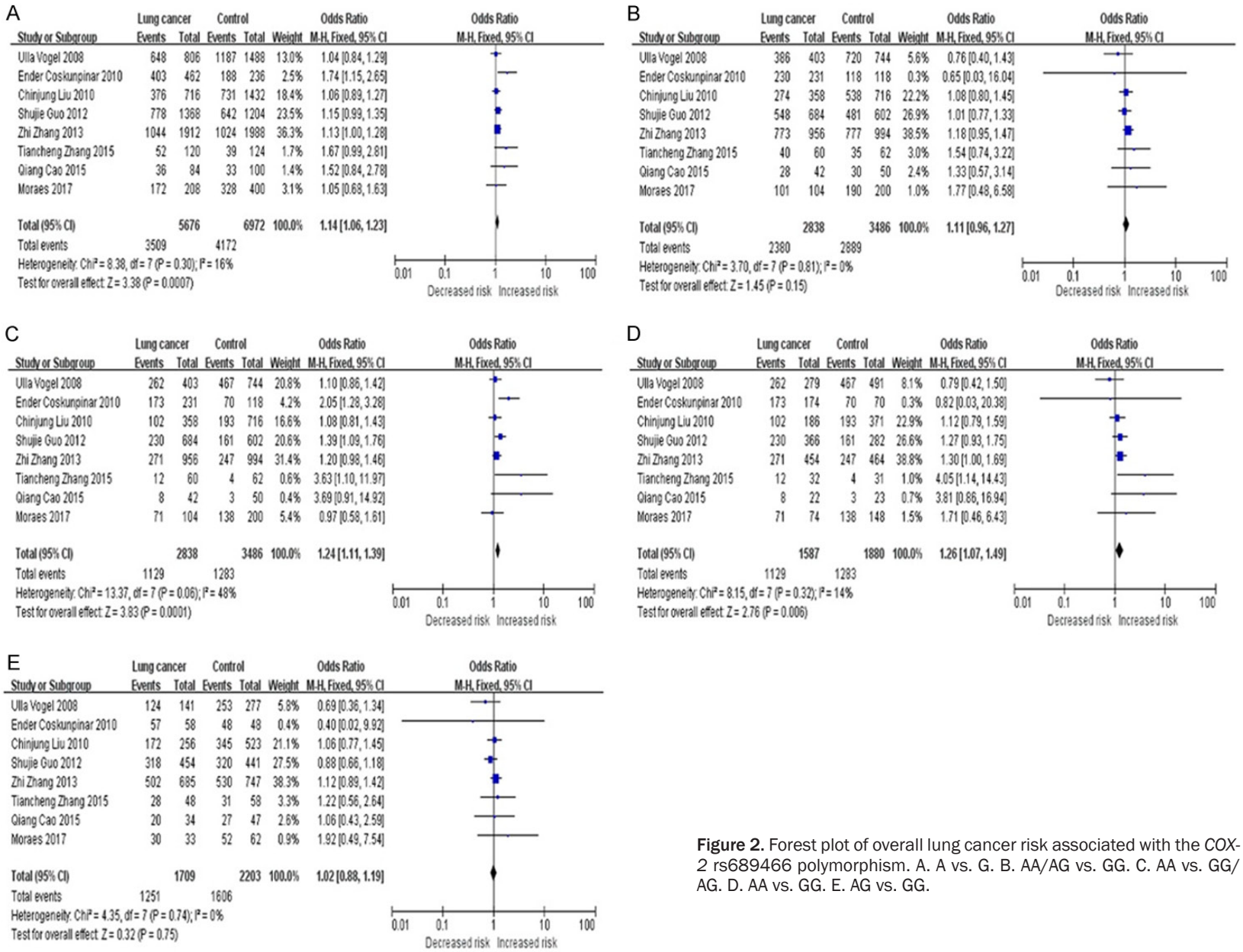

Figure 2. Forest plot of overall lung cancer risk associated with the *COX-2* rs689466 polymorphism. A. A vs. G. B. AA/AG vs. GG. C. AA vs. GG/AG. D. AA vs. GG. E. AG vs. GG.

Table 4. Results of sensitivity analysis in overall analysis under different models

	Mantel-Haenszel Method		DerSimonian Laird Method		Excluding small sample size studies$^{\Delta}$		Excluding not in HWE studies	
	OR	OR (95% CI)	OR	OR (95% CI)	OR	OR (95% CI)	OR	OR (95% CI)
A vs. G	1.14	1.06, 1.23	1.15	1.05, 1.25	1.12	1.04, 1.22	1.12	1.02, 1.23
AA vs. GG/AG	1.24	1.11, 1.39	1.28	1.07, 1.53	1.22	1.09, 1.37	1.21	1.06, 1.40
AA/AG vs. GG	1.11	0.96, 1.27	1.11	0.96, 1.27	1.09	0.94, 1.26	1.06	0.89, 1.27
AA vs. GG	1.26	1.07, 1.49	1.26	1.03, 1.53	1.21	1.03, 1.43	1.24	1.00, 1.53
AG vs. GG	1.02	0.88, 1.19	1.02	0.88, 1.19	1.02	0.87, 1.18	0.97	0.80, 1.17

Δ: Sample size is less than 200.

Heterogeneity testing of A vs. G showed no significant differences in all included studies (I^2 = 16%; P = 0.30). Thus, the overall pooled OR was calculated under a fixed-effects model. Results indicated that increased lung cancer risk was identified in the allele model (A vs. G: OR = 1.14; 95% CI = 1.06-1.23; P = 0.0007) (**Figure 2A**). Subgroup analysis, stratified by ethnicity and source of controls, also showed a significant association between *COX-2* rs689466 polymorphism and lung cancer in the subgroups of Asians (OR = 1.14; 95% CI = 1.05-1.24; P = 0.002), population-based (PB) (OR = 1.14; 95% CI = 1.03-1.26; P = 0.009), and hospital-based (HB) (OR = 1.14; 95% CI = 1.01-1.27; P=0.03). Power calculations on the Asians (91.4%) were more than 80%, revealing adequate sample sizes (**Table 3**).

Heterogeneity testing of AA/AG vs. GG showed no significant differences in all included studies (I^2 = 0%, P = 0.81), thus overall pooled OR was calculated under a fixed-effects model. Results revealed that no significant association was seen in the recessive model (AA/AG vs. GG: OR = 1.11; 95% CI = 0.96-1.27; P = 0.15) (**Figure 2B**). When subgroup analysis was stratified by ethnicity and source of controls, significant association between COX-2 rs689466 and lung cancer susceptibility was not observed (**Table 3**).

Heterogeneity testing of AA vs. GG/AG showed no significant differences between included studies (I^2 = 48%, P = 0.06), thus overall OR was calculated using a fixed-effects model. Results demonstrated that a positive relationship with lung cancer risk was found in the dominant model (AA vs. GG/AG: OR = 1.24; 95% CI = 1.11-1.39; P = 0.0001) (**Figure 2C**). Subgroup analysis, stratified by ethnicity and source of controls, also showed a significant association between *COX-2* rs689466 polymorphism and lung cancer susceptibility in the subgroups of Asians (OR = 1.26; 95% CI = 1.10-1.44; P = 0.0007), PB (OR = 1.22; 95% CI = 1.06-1.41; P = 0.007), and HB (OR = 1.29; 95% CI = 1.07-1.54; P = 0.006). Power calculations on the Asians (93.2%) and HB (82.5%) groups were more than 80%, indicating adequate sample sizes (**Table 3**).

Heterogeneity testing of AA vs. GG showed no significant differences existing among included studies (I^2 = 14%, P = 0.32). A fixed-effects model was used to calculate overall OR, evaluating the risk of lung cancer. Results showed that, in the homozygous model (AA vs. GG: OR = 1.26; 95% CI = 1.07-1.49; P = 0.006), the positive relationship between *COX-2* rs689466 polymorphism and susceptibility to lung cancer was significant (**Figure 2D**). Subgroup analysis, stratified by ethnicity and source of controls, also showed a significant association between *COX-2* rs689466 polymorphism and lung cancer susceptibility in Asian populations (OR = 1.30; 95% CI = 1.09-1.54; P = 0.003). Power calculations on the Asians (90.2%) were more than 80%, demonstrating adequate sample sizes (**Table 3**).

Heterogeneity testing of AG vs. GG also showed no significant differences among included studies (I^2 = 0%, P = 0.74). A fixed-effects model was employed in this meta-analysis. Results showed that a significant association between *COX-2* rs689466 polymorphism and lung cancer risk was not observed in the heterozygous model (AG vs. GG: OR = 1.02; 95% CI = 0.88-1.19; P = 0.75) (**Figure 2E**). When subgroup analysis was stratified by ethnicity and source of controls, results also showed no significant association

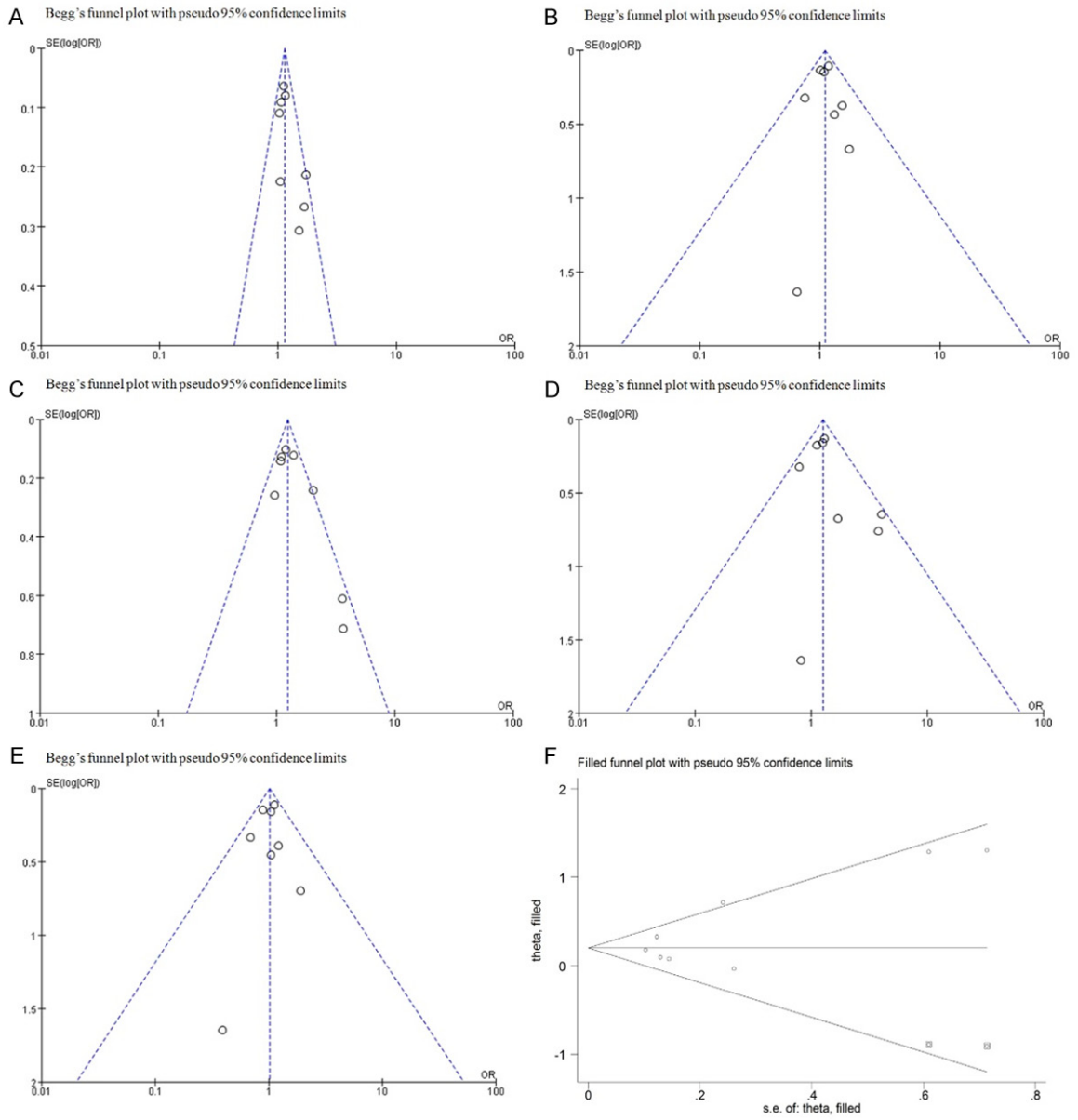

Figure 3. Funnel plot of overall lung cancer risk associated with the *COX-2* rs689466 polymorphism for publication bias. A. A vs. G. B. AA/AG vs. GG. C. AA vs. GG/AG. D. AA vs. GG. E. AG vs. GG. F. Adjusted funnel plot for publication bias in the overall analysis under AA vs. GG/AG model.

between COX-2 rs689466 and lung cancer risk (**Table 3**).

Sensitivity analysis

Small sample sizes and studies not in accordance with HWE may affect overall results. To eliminate these effects, sensitivity analysis was performed by interchanging the combined models, excluding the studies with small sample sizes and the studies inconsistent with HWE. Results of sensitivity analysis are presented in **Table 4**. Analysis revealed no significant changes in pooled ORs, suggesting that results of sensitivity analysis are stable.

Publication bias

Begg's funnel plot and Egger's tests were used to evaluate publication bias. Begg's funnel plots in all genetic models were nearly symmetrical (**Figure 3A-E**). Egger's test results, respectively, were A vs. G, t = 1.90, P = 0.106; AA vs. GG/AG, t = 1.96, P = 0.097; AA/AG vs. GG, t =

0.23, P = 0.828; AA vs. GG, t = 1.00, P = 0.354; AG vs. GG, t = -0.24, P = 0.821. As a result, evidence was found for publication bias (*P* = 0.097 in Egger's test) in the dominant model (AA vs. GG/AG) of *COX-2* rs689466. This publication bias might be a limitation for the present analysis. Using the trim-and-fill method, it was shown that if the publication bias was the only source of the funnel-plot asymmetry, two more studies were required to balance the funnel plot (**Figure 3F**). There was no obvious dissymmetry in the filled funnel plot and the adjusted OR value calculated by the fixed effects model was (OR = 1.221; 95% CI = 1.092-1.364), with no significant changes in the pooled odds ratio. The Egger's test result was P = 0.025, indicating the stability of present results.

Discussion

One of the most common malignancies, lung cancer has long been plagued with high morbidity and mortality. Better understanding of its pathogenesis can help to improve diagnosis and treatment. In this study, an integrated and comprehensive meta-analysis was conducted. A significant association between polymorphism of *COX-2* gene and lung cancer was identified. This study verified that the polymorphism of *COX-2* rs689466 site might moderately increase the risk of lung cancer.

A total of 8 research papers, concerning 2,838 cases and 3,486 controls, were included in this analysis. According to overall meta-analysis results, in the dominant model (AA vs. GG/AG: OR = 1.24; 95% CI = 1.11-1.39) and the homozygous model (AA vs. GG: OR = 1.26; 95% CI = 1.07-1.49), the risk of lung cancer was significantly increased by gene polymorphism of *COX-2* rs689466. Thus, the AA homozygote may be a risk factor of lung cancer. Screening for *COX-2* A/G polymorphisms and premorbid intervention to AA homozygotes in a high-risk population might reduce the risk of lung cancer.

COX-2 is the major rate-limiting enzyme in PGs synthesis. Its primary function is to mediate inflammatory responses. Currently, increasing attention has been paid to its effects on occurrence and development of different cancers and the influence of its genetic polymorphisms on susceptibility to various cancers [24, 25]. For digestive cancers such as colorectal cancer, hepatocellular carcinoma, and stomach cancer, [26-29], *COX-2* gene may increase prevalence risks. However, for breast cancer and prostatic cancer, correlations of *COX-2* with cancers have not been conclusively verified [30, 31]. These findings suggest that the roles of *COX-2* seem to vary in different cancers. The rs689466 site of *COX-2* gene is in 1195 bp upstream of the promoter region. It regulates expression of *COX-2* proteins by activating specific transcription factors, a series of enhancers, and transcriptional regulatory elements [32, 33]. Further research has revealed that the rs689466 site can enhance transcription activity of *COX-2* mRNA expression by binding to c-MYB transcription factor, hence promoting the occurrence and development of cancers, such as esophageal cancer [34]. However, many other studies have shown different results. For example, by analyzing multiple sites of polymorphism, Vogel, Liu, and Wang et al. [13, 17, 20] found that the rs689466 site was neither a risk factor of lung cancer nor closely related to lung cancer susceptibility. Differences in the above results were possibly caused by the limitation of sample sizes in one single study and the inefficiency of statistical tests.

The morbidity and mortality of lung cancer remain high, ranking first in males, second only to breast cancer in females in China [35]. It has been reported that increased expression of *COX-2* gene occurred in invasive and metastatic adenocarcinoma [36]. Furthermore, comparing serums between healthy people and patients with lung cancer in a Chinese population, Zhang et al. [15] found that expression in the AA genotype of rs689466 site was remarkably increased in patients with lung cancer. Thus, they demonstrated that the AA genotype of this site could significantly increase the risk of lung cancer. In addition, rs689466 polymorphism is a marker for the prognosis of first-line chemotherapy of lung cancer in PD stage. Recent studies have suggested that progression-free survival (PFS) and overall survival (OS) of patients carrying the AA genotype were longer than patients carrying the AG or GG genotype [37]. Meanwhile, cigarette smoke can induce expression of *COX-2* genes. High expression of this gene was found in the pathologic tissue of lung cancer patients that smoked [38, 39]. Moreover, *COX-2* inhibitors also play a role in anticancer therapies, such as lung cancer,

breast cancer, and colorectal tumor [40-42]. The present study investigated the association between polymorphism of rs689466 site and lung cancer susceptibility using a comprehensive meta-analysis. Results indicated that gene polymorphisms of lung cancer benefit the development of etiology, providing sole evidence that *COX-2* rs689466 polymorphism correlates with lung cancer.

According to subgroup analysis based on ethnicity, AA genotype of *COX-2* gene rs689466 site increased lung cancer risk in Asian populations, but not in Caucasian populations. One possible reason for this difference is that different ethnicities may have distinct genetic backgrounds which influence tumor susceptibility [43, 44]. In another subgroup analysis based on source of controls, an increased cancer risk was found in PB and HB studies in AA genotype of *COX-2* gene rs689466 site.

However, even though this study was carefully designed and conducted, there were certain limitations. First, only studies published in English and Chinese were involved in the literature retrieval using PubMed, MEDLINE, and WanFang. Therefore, accessibility to other studies published in other languages and unpublished data may have modified results. Second, caution should be taken in interpreting present results. The statistical power of the meta-analysis was calculated in overall, ethnicity, and source of controls groups. Most of them were less than 80%, limited by inadequate sample sizes. Third, this meta-analysis was based on original data of included literature without correcting irrational data or eliminating statistical defects. Subgroup analysis, based on age, gender, use of alcohol, different histological types, tobacco usage, and other factors, was not conducted. Thus, more studies including these factors should be conducted in the future. Fourth, research concerning the mechanisms of COX-2 rs689466 polymorphism increasing lung cancer susceptibility is encouraged in the future. Advanced technologies, such as bioinformatics and luciferase assays, should be used. Moreover, heterogeneity is a usual concern when performing a meta-analysis. In addition to ethnicity and source of controls, other factors, such as number of included studies, selection of controls, race variation, age, gender, histological types, and prevalence of lifestyle factors, may also contribute to heterogeneity. Except for rs689466 polymorphism, *COX-2* polymorphisms also include rs689465 and rs20417 polymorphisms, which have been proven to have a certain relationship with susceptibility to lung cancer. However, due to quantitative restrictions of included case-control studies, interactions among multiple sites, as well as their relationships with susceptibility to lung cancer, were not analyzed. Correlation between the polymorphisms of these sites and lung cancer will be of interest in future studies.

Conclusion

In summary, despite the limitations mentioned above, results of the present meta-analysis, involving 8 case-control studies, verified that polymorphisms of *COX-2* rs689466 site may moderately increase the risk of lung cancer, especially in Asian populations, PB, and HB studies. Further studies with larger sample sizes are necessary to obtain more reliable results. This polymorphism site, especially in AA homozygotes, may contribute to early diagnosis and prevention, providing timely treatment of the disease.

Acknowledgements

The authors would like to show their thankfulness to Mrs. Hongxia Li (Department of Pulmonary, People's Liberation Army General Hospital, China) for kindly providing guidance in writing and to Mr. Yongsheng Li (Institute of Cancer, Xinqiao Hospital, Third Military Medical University, China) for providing comments in revision. This study was supported by the National Natural Science Foundation of China (grant No. 81172070) and the Chongqing Science and Technology Key Projects Fund (grant No. 2011AB5032).

Disclosure of conflict of interest

None.

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