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META-ANALYSIS

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Association Between *COX-2* Polymorphisms and Lung Cancer Risk

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Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Funds Collection G

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Background: Multiple relevant risk factors for lung cancer have been reported in different populations, but results of previous studies were not consistent. Therefore, a meta-analysis is necessary to summarize these outcomes and reach a relatively comprehensive conclusion.

Material/Methods: STATA 12.0 software was used for all statistical of the relationship between *COX-2* polymorphisms and lung cancer risk. Inter-study heterogeneity was examined with the Q statistic (significance level at $P<0.1$). The publication bias among studies in the meta-analysis was analyzed with Begg's funnel plot and Egger's test. Hardy-Weinberg equilibrium was tested in all controls of the studies.

Results: *COX-2* rs20417 polymorphism had a significant association with reduced risk of lung cancer under homozygous and recessive models, and similar results were observed in white and population-based subgroups under 2 and 3 contrasts, respectively. Additionally, rs2066826 polymorphism manifested a strong correlation with increased risk of lung cancer under 5 genetic models.

Conclusions: In *COX-2* gene, rs20417 may have a certain relationship with reduced risk of lung cancer, while rs2066826 may increase the risk of lung cancer.

MeSH Keywords: **Cyclooxygenase 2 • Lung Neoplasms • Polymorphism, Genetic**

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Background

Lung cancer, also known as bronchogenic carcinoma, generally refers to malignant tumors from epidermal cells of the bronchus or bronchiole, which account for 90–95% of total lung cancer cases [1–3]. Currently, lung cancer is the leading cause of death among all cancers worldwide, and its mortality shows a rising tendency each year, especially in women [4–6]. The precise pathogenesis of lung cancer is not yet clearly understood, but numerous reports have confirmed some risk factors involved in lung cancer, including smoking, air pollution, occupational factors, chronic lung diseases, and human genetic factors [7–11].

An *in vitro* experiment suggested that cigarette smoke exposure could increase the death of lung cancer cells [12]. The study of Wang et al. found that tobacco smoke could promote the development of lung cancer via enhancing CCL20 level [13]. In addition, elevated risk of lung cancer was identified in individuals exposed to silica dust, welding fumes, diesel exhaust, and man-made mineral fibers [14]. Further analysis by Li et al. reported that occupational exposure to welding fumes brought about oxidative stress, telomere alterations, and DNA methylation [15]. In a clinic-based case-control study, family history of lung cancer or any other cancer was confirmed as a risk factor for lung cancer [16]. A growing body of evidence shows the crucial roles of genetic factors, like genetic polymorphisms and abnormal expression, in the pathogenesis of lung cancer [17–21]. All these findings suggest that the development of lung cancer results from the combined effects of genetic and environment factors, which is supported by many studies [22–25].

Cyclooxygenase (COX), also called prostaglandin endoperoxide synthases (PTGs), is a rate-limiting enzyme catalyzing the synthesis of prostaglandins (PGs) and thromboxanesA2 (TXA2) through arachidonic acid (AA) [26]. So far, there are at least 2 types in the COX family – COX-1 and COX-2. As an induced enzyme, COX-2 rarely expresses in normal tissues, but starts its expression after being stimulated by multiple factors, such as cytokines, growth factors (including PD-GF, TNF, EGF, bFGF and IL-1), oncogenes (like ras and V-rsc), tumor promoters, and endotoxins, thus participating in physiological and pathological processes in inflammation and tumors [27,28].

Many studies have explored the relationship between polymorphisms in *COX-2* gene and lung cancer, but contradiction among study results still exists [29]. Moreover, *COX-2* polymorphisms might be influenced by genetic and environmental factors, such as high-fat diets, lifestyle, folate intake, and smoking [30–32]. As a consequence, results of studies on the correlation of *COX-2* polymorphisms with lung cancer risk based on a single population cannot be generalized. Therefore, a meta-analysis was performed among studies on this relationship to extract a more reliable and comprehensive conclusion.

Material and Methods

Literature search

A literature search was performed in the databases of PubMed, EMBASE, CNKI, and Chinese Wanfang Data for potentially relevant studies published in English or Chinese languages. The terms for search included "lung cancer" or "pulmonary cancer" or "lung carcinoma", "*COX-2*", and "polymorphism" or "genetic variant". The reference lists of relevant studies were manually examined for potential articles.

Inclusion criteria

All studies included in this meta-analysis met the following criteria: (1) using case-control study method to assess the relationship of *COX-2* polymorphisms with lung cancer risk; (2) providing sufficient genotype distribution data in cases and controls for calculation of odds ratio (OR) with corresponding 95% confidence interval (95%CI); and (3) with validated genotyping methods. When overlapping data appeared in more than 1 publication, we selected that containing the largest samples.

Data extraction

The data for meta-analysis were extracted independently by 2 authors in accordance with the same standard. No disagreement occurred in this work. From each study included in this analysis, the following information was recorded: first author, year of publication, original country, ethnicity, source of control, genotyping methods, researched polymorphism, and genotype frequencies in cases and controls.

Statistical analysis

The overall pooled ORs and corresponding 95%CIs were calculated to evaluate the relationship between *COX-2* polymorphisms and lung cancer under homozygous, dominant, recessive, allele, and heterozygous models. The chi-square-based Q statistic was used to assess the heterogeneity among included articles. The overall ORs were obtained under the random-effects model when there was significant heterogeneity ($P<0.1$), and under the fixed-effects model when the heterogeneity was not significant. The genotype distribution in controls of each study was measured with the chi-square test to examine the goodness-of-fit in controls to Hardy-Weinberg equilibrium, and $P>0.05$ indicates that the control samples were in good equilibrium. Publication bias was detected by Begg's funnel plot and Egger's linear regression test [33,34]. Sensitivity

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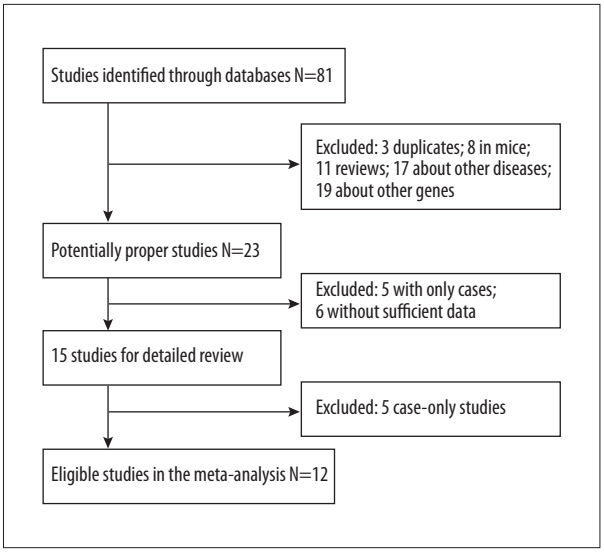

Figure 1. Flow diagram for literature selection.

test was performed through deleting a single included study each time to observe the effect on the overall ORs in this meta-analysis. All data were processed with STATA 12.0 software (Stata Corporation, College Station, TX, USA).

Results

Study characteristics

We retrieved 81 relevant articles following the above search strategy, and 12 qualified ones were included ultimately [35–46]. Figure 1 presents the particular process of literature screening. Table 1 displays the general characteristics of these 12 studies.

Table 1. Principle characteristics of the studies included in the meta-analysis.

First author	Year	Country	Ethnicity	Control source	Genotyping method	SNP	HWE
Bhat	2014	Srinagar	Asian	Hospital-based	PCR-RFLP	rs5275	0.470
Campa	2005	Europe	Caucasian	Population-hospital	Taqman	rs5275	0.285
Campa	2004	Norway	Caucasian	Hospital-based	Taqman	rs20417	0.198
Campa	2004	Norway	Caucasian	Hospital-based	Taqman	rs5277	0.316
Campa	2004	Norway	Caucasian	Hospital-based	Taqman	rs20432	0.071
Campa	2004	Norway	Caucasian	Hospital-based	Taqman	rs5275	0.304
Coskunpinar	2011	Turkey	Caucasian	Population-based	PCR–RFLP	rs20417	0.197
Coskunpinar	2011	Turkey	Caucasian	Population-based	PCR–RFLP	rs689466	0.006
Hu	2005	China	Asian	Population-based	PCR-PIRA	rs5275	0.113
Lim	2010	China	Asian	Hospital-based	Taqman	rs5275	0.984
Liu	2010	China	Asian	Hospital-based	PCR-RFLP	rs20417	0.060
Liu	2010	China	Asian	Hospital-based	PCR-RFLP	rs5275	0.921
Liu	2010	China	Asian	Hospital-based	PCR-RFLP	rs689466	0.337
Liu	2010	China	Asian	Hospital-based	PCR-RFLP	rs2745557	0.358
Liu	2010	China	Asian	Hospital-based	PCR-RFLP	rs16825748	0.910
Liu	2010	China	Asian	Hospital-based	PCR-RFLP	rs2066826	0.588
Ma	2010	China	Asian	Hospital-based	PCR–RFLP	rs3218625	0.858
Park	2006	Korea	Asian	Hospital-based	PCR-PIRA	rs5275	0.552
Sorensen	2005	Denmark	Caucasian	Hospital-based	Taqman	rs5275	0.583
Vogel	2008	Denmark	Caucasian	Population-based	PCR-probes	rs5275	0.959
Vogel	2008	Denmark	Caucasian	Population-based	PCR-probes	rs689466	0.143
Zhang	2013	China	Asian	Hospital-based	PCR-RFLP	rs689466	0.034

PCR – polymerase chain reaction; PCR-RFLP – PCR-restriction fragment length polymorphism; TaqMan – TaqManSNP; PCR-PIRA – PCR-based primer-introduced restriction analysis; HWE – Hardy-Weinberg equilibrium.

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Table 2. *COX-2* polymorphisms and lung cancer risk.

		22 versus 11		22+12 versus 11		22 versus 11+12		2 versus 1		12 versus 11	
		OR (95%CI)	Ph	OR (95%CI)	Ph	OR (95%CI)	Ph	OR (95%CI)	Ph	OR (95%CI)	Ph
rs20417											
Fixed-effects model											
Ethnicity	Asian	/	/	0.87 (0.59, 1.29)	/	/	/	0.87 (0.60, 1.27)	/	0.87 (0.59, 1.29)	/
	Caucasian	0.41 (0.22, 0.77)	0.507	0.91 (0.69, 1.19)	0.500	0.39 (0.22, 0.70)	0.476	0.81 (0.64, 1.02)	0.250	0.95 (0.70, 1.27)	0.537
Source of control	Hospital	0.65 (0.14, 2.95)	/	0.93 (0.70, 1.25)	0.593	0.64 (0.14, 2.90)	/	0.92 (0.70, 1.22)	0.657	0.94 (0.70, 1.27)	0.528
	Population	0.37 (0.19, 0.74)	/	0.84 (0.60, 1.19)	/	0.35 (0.19, 0.67)	/	0.74 (0.55, 0.98)	/	0.88 (0.60, 1.29)	/
Total		0.41 (0.22, 0.77)	0.507	0.89 (0.72, 1.12)	0.787	0.39 (0.22, 0.70)	0.476	0.83 (0.68, 1.01)	0.486	0.92 (0.72, 1.16)	0.784
rs5275											
Fixed-effects model											
Ethnicity	Caucasian	1.00 (0.85, 1.17)	0.014	0.98 (0.90, 1.07)	0.312	1.04 (0.89, 1.22)	0.004	0.99 (0.92, 1.07)	0.006	0.98 (0.89, 1.08)	0.470
	Asian	0.88 (0.60, 1.28)	0.496	0.93 (0.82, 1.05)	0.552	0.90 (0.62, 1.31)	0.616	0.93 (0.83, 1.03)	0.349	0.93 (0.82, 1.05)	0.627
Source of control	Population-Hospital	0.94 (0.77, 1.15)	/	0.97 (0.87, 1.07)	/	0.97 (0.80, 1.18)	/	0.97 (0.89, 1.06)	/	0.96 (0.86, 1.08)	/
	Population	0.74 (0.50, 1.09)	0.814	0.89 (0.75, 1.05)	0.313	0.75 (0.52, 1.09)	0.934	0.87 (0.75, 1.01)	0.345	0.90 (0.75, 1.07)	0.288
	Hospital	1.21 (0.92, 1.58)	0.064	1.00 (0.89, 1.12)	0.423	1.30 (1.00, 1.68)	0.043	1.03 (0.93, 1.14)	0.019	0.99 (0.87, 1.12)	0.596
Total		0.98 (0.84, 1.13)	0.063	0.96 (0.90, 1.03)	0.518	1.02 (0.88, 1.18)	0.027	0.97 (0.92, 1.03)	0.021	0.96 (0.89, 1.04)	0.695
Random-effects model											
Ethnicity	Caucasian	1.01 (0.68, 1.50)	0.014	0.99 (0.89, 1.10)	0.312	1.05 (0.69, 1.60)	0.004	1.03 (0.85, 1.24)	0.006	0.98 (0.89, 1.08)	0.470
	Asian	0.88 (0.61, 1.29)	0.496	0.93 (0.82, 1.05)	0.552	0.91 (0.63, 1.32)	0.616	0.93 (0.82, 1.04)	0.349	0.93 (0.82, 1.05)	0.627
Source of control	Population-hospital	0.94 (0.77, 1.15)	/	0.97 (0.87, 1.07)	/	0.97 (0.80, 1.18)	/	0.97 (0.89, 1.06)	/	0.96 (0.86, 1.08)	/
	Population	0.74 (0.50, 1.09)	0.814	0.89 (0.75, 1.06)	0.313	0.75 (0.52, 1.09)	0.934	0.87 (0.75, 1.01)	0.345	0.89 (0.73, 1.09)	0.288
	Hospital	1.07 (0.68, 1.69)	0.064	1.00 (0.89, 1.12)	0.423	1.11 (0.69, 1.78)	0.043	1.01 (0.85, 1.21)	0.019	0.99 (0.87, 1.12)	0.596
Total		0.97 (0.75, 1.26)	0.063	0.96 (0.90, 1.03)	0.518	1.00 (0.76, 1.33)	0.027	0.97 (0.87, 1.08)	0.021	0.96 (0.89, 1.04)	0.695

Meta-analysis results

The association of each polymorphism in *COX-2* gene with lung cancer is listed in Table 2 under 5 contrasts with corresponding effect models. Among 9 polymorphisms, 7 polymorphisms (rs5275, rs689466, rs2745557, rs3218625, rs20432, rs16825748, and rs5277) had no significant relationship with lung cancer risk, while the other 2 (rs20417 and rs2066826) expressed significant correlations with the cancer. *COX-2* rs20417 polymorphism demonstrated a remarkable relevance to reduced lung

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Table 2 continued. *COX-2* polymorphisms and lung cancer risk.

		22 versus 11		22+12 versus 11		22 versus 11+12		2 versus 1		12 versus 11	
		OR (95%CI)	Ph	OR (95%CI)	Ph	OR (95%CI)	Ph	OR (95%CI)	Ph	OR (95%CI)	Ph
rs689466											
Fixed-effects model											
Ethnicity	Caucasian	1.25 (0.67, 2.33)	0.987	0.86 (0.70, 1.06)	0.100	1.32 (0.71, 2.45)	0.923	0.89 (0.74, 1.07)	0.066	0.83 (0.67, 1.03)	0.117
	Asian	0.89 (0.74, 1.07)	0.660	0.96 (0.86, 1.08)	0.828	0.90 (0.76, 1.07)	0.689	0.95 (0.87, 1.04)	0.718	0.96 (0.84, 1.09)	0.847
Source of control	Population	1.25 (0.67, 2.33)	0.987	0.86 (0.70, 1.06)	0.100	1.32 (0.71, 2.45)	0.923	0.89 (0.74, 1.07)	0.066	0.83 (0.67, 1.03)	0.117
	Hospital	0.89 (0.74, 1.07)	0.660	0.96 (0.86, 1.08)	0.828	0.90 (0.76, 1.07)	0.689	0.95 (0.87, 1.04)	0.718	0.96 (0.84, 1.09)	0.847
Total		0.91 (0.76, 1.10)	0.751	0.94 (0.85, 1.03)	0.298	0.92 (0.78, 1.09)	0.682	0.94 (0.86, 1.02)	0.271	0.92 (0.83, 1.03)	0.288
rs2066826											
Random-effects model		4.36 (1.48, 12.87)	/	1.65 (1.20, 2.26)	/	4.00 (1.36, 11.79)	/	1.76 (1.31, 2.35)	/	1.56 (1.12, 2.16)	/
rs2745557											
Random-effects model		1.40 (0.44, 4.44)	/	0.94 (0.69, 1.27)	/	1.43 (0.45, 4.53)	/	0.96 (0.72, 1.27)	/	0.92 (0.67, 1.25)	/
rs3218625											
Random-effects model		/	/	2.40 (0.83, 6.94)	/	/	/	2.40 (0.84, 6.88)	/	2.40 (0.83, 6.94)	/
rs20432											
Random-effects model		2.45 (0.10, 60.42)	/	0.84 (0.54, 1.31)	/	2.57 (0.10, 63.39)	/	0.86 (0.56, 1.31)	/	0.82 (0.53, 1.29)	/
rs16825748											
Random-effects model		/	/	0.67 (0.13, 3.32)	/	/	/	0.67 (0.13, 3.31)	/	0.67 (0.13, 3.32)	/
rs5277											
Random-effects model		0.86 (0.30, 2.51)	/	1.00 (0.68, 1.48)	/	0.86 (0.30, 2.48)	/	0.99 (0.69, 1.40)	/	1.02 (0.67, 1.53)	/

11 – Wide-type homozygote; 12 – heterozygote; 22 – rare homozygote; *Ph* – *P*-value of heterogeneity test.

cancer risk under AA versus GG (OR=0.41, 95%CI=0.22–0.77) and AA versus GG+GA contrast (OR=0.39, 95%CI=0.22–0.70), as well as in subgroup analysis of white and population-based groups (Figure 2, Figure 3). As for rs2066826, a positive relationship with lung cancer was found in all 5 models [AA versus GG (OR=4.36, 95%=1.48–12.87), AA+GA versus GG (OR=1.65, 95%CI=1.20–2.26), AA versus GG+GA (OR=4.00, 95%CI=1.36–11.79), A versus G (OR=1.76, 95%CI=1.31–2.35), and GA versus GG (OR=1.56, 95%CI=1.12–2.16)] (Figure 4).

Sensitivity analysis

The pooled ORs showed no distinct discrepancy from those obtained after omitting a single study each time, indicating all these studies did not have substantial impact on the whole ORs.

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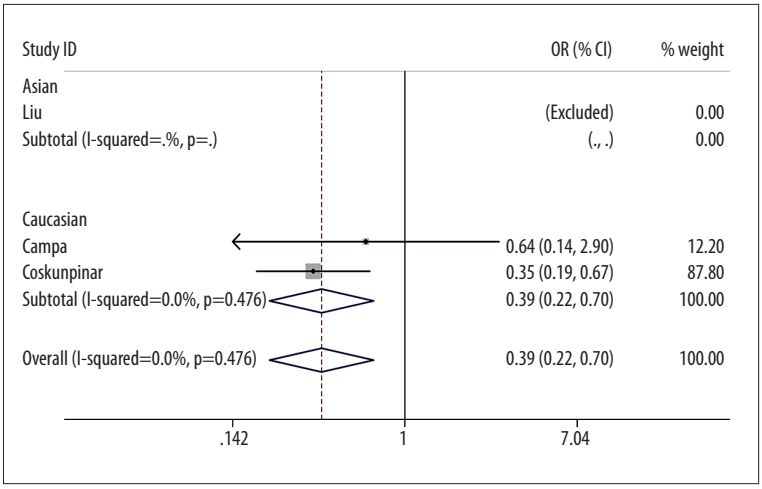

Figure 2. Forest plot for the association of *COX-2* gene rs20417 polymorphism with lung cancer risk in subgroup by ethnicity under AA versus GG+GA model.

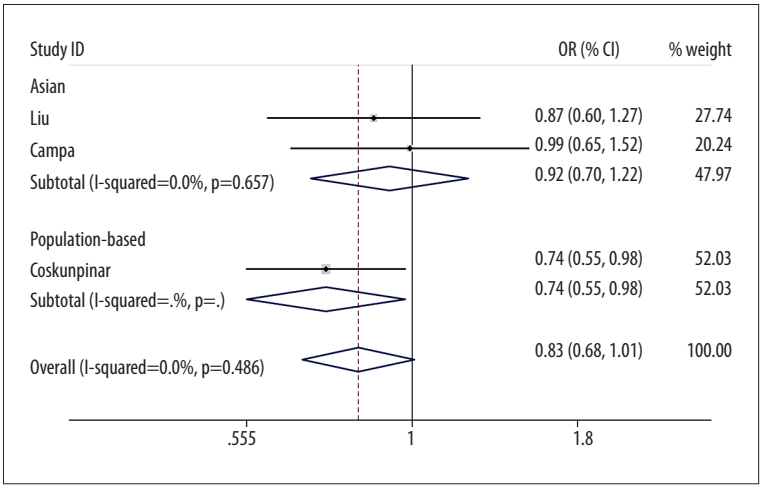

Figure 3. Forest plot for the association of *COX-2* gene rs20417 polymorphism with lung cancer risk in subgroup by source of control under A versus G model.

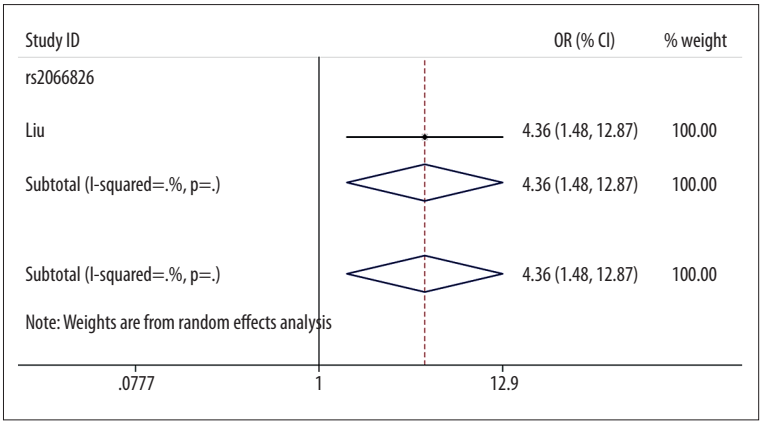

Figure 4. Forest plot for the association of *COX-2* gene rs2066826 polymorphism with lung cancer risk under AA versus GG model.

Publication bias

Begg's funnel plot seemed symmetrical for each polymorphism, which was further proven by Egger's linear regression test (*P*=0.582), implying there was no significant publication bias among studies in our meta-analysis (Figure 5).

Discussion

In spite of the advances in the diagnostic technology, the 5-year overall survival rate of lung cancer is still low, at about 12-15%, because the patients were diagnosed at moderate and advanced stages when clinic symptoms are presented. Statistically, the 5-year survival rate of patients at stage

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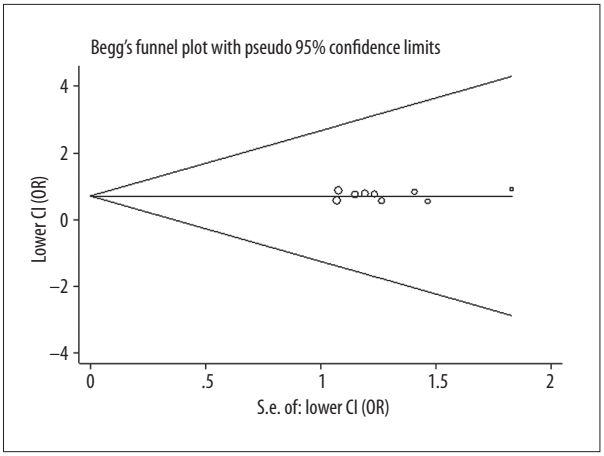

Figure 5. Funnel plot for publication bias.

I reaches more than 70%, so early discovery, diagnosis, and treatment appear to be important to reduce the mortality rate of lung cancer. Currently, only 10% of asymptomatic patients are identified and receive radical treatments. Because of the limited sensitivity and specificity of existing screening methods, the mortality rate of lung cancer is still not reduced. It is urgently important to discover effective means for detection of individuals with high risk of lung cancer.

Human *COX-2* gene is located on chromosome 1q25.2~25.3 with a length of about 8.8kb, and consists of 10 exons and 9 introns [47]. The over-expression of COX-2 is closely related to the metastasis of malignant tumors, and the *COX-2* gene plays an important role in all stages of neoplasm metastasis, such as the decrease of cells' adhesion caused by the changes in cell surface adhesion factors and in extracellular matrix, and the promotion of neovascularization in tumors [48]. Studies of the relationship of *COX-2* polymorphisms with lung cancer are based on various populations in different countries; therefore, varied results may exist even among those on the same polymorphism. We carried out this meta-analysis of the eligible studies in order to reach a more precise conclusion.

As shown in the present analysis, 9 polymorphisms were examined to ascertain their potential relationships with lung cancer risk, of which 7 were not found to have relevance to the risk of lung cancer, including rs5275, rs689466, rs2745557, rs3218625, rs20432, rs16825748, and rs5277. rs2066826 had a significant association with the increased risk of lung cancer under all 5 contrasts, while a distinct correlation was observed between rs20417 polymorphism and the reduced risk of lung cancer under both homozygous and dominant models. Furthermore, in subgroup analysis for rs20417 and lung cancer risk, the same relationship was revealed in the white group under homozygous and dominant contrasts, and in population-based group under homozygous, dominant, and allele models.

There is discrepancy between our meta-analysis and previous studies. The presence of this phenomenon might be attributed to the following aspects: the samples in previous studies and our meta-analysis were not balanced in terms of quantity, or based on different ethnicities in various genetic backgrounds; and the possible interactions among genes and environmental factors were not taken into consideration in this meta-analysis. Therefore, the exact correlations of *COX-2* polymorphisms with lung cancer risk need to be re-examined in future explorations.

Multiple genetic variants in *COX-2* are reportedly associated with lung cancer, so in the present analysis we selected as many polymorphisms as possible from eligible studies to explore the relationship between these polymorphisms and lung cancer risk. As in previous studies, the present analysis also had its own shortcomings affecting the exactitude of the ultimate results. In this study, we only discussed the association of *COX-2* polymorphisms with lung cancer in Asian and white populations, ignoring other populations. Moreover, for some polymorphisms, the number of involved studies and samples was relatively small. Although a meticulous literature search was performed and relevant reference lists were manually examined, the limitation in study language may lead to possible publication bias which cannot be shown by Begg's funnel plot and Egger's test. In addition, the interactions between genetic and environmental factors were not taken into account in this analysis. Therefore, the results in this meta-analysis should be interpreted with caution, and need to be verified by well-designed studies in future.

Conclusions

COX-2 rs20417 polymorphism is associated with reduced risk of lung cancer, but rs2066826 polymorphism may increase the risk of lung cancer. These results will contribute to detecting individuals with high risk of lung cancer and providing timely treatments.

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