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Original Article

Association between 1195G>A polymorphism of cyclooxygenase-2 gene with lung cancer risk: a meta-analysis

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Abstract: The studies on the relationship between the 1195G>A polymorphism of cyclooxygenase-2 (COX-2) gene and the risk of lung cancer development have shown conflicting results. A meta-analysis based on accumulated reports was carried out to clarify the relationship. PubMed and Embase databases were searched until January 2017 for the relative references with sufficient information to estimate odds ratios (ORs) and 95% confidence intervals (CIs). We performed a meta-analysis of 2692 lung cancer cases and 3236 controls concerning 1195G>A polymorphism from 6 case-control studies. Compared with controls, the 1195G>A polymorphisms in COX-2 gene increased the lung cancer risk in whole population (GG versus AA: OR=1.235, 95% CI=1.045-1.459, p<0.05; GG+GA versus AA: OR=1.249, 95% CI=1.114-1.402, p<0.001), in Asian population (GG versus AA: OR=1.276, 95% CI=1.073-1.518, p<0.01; GG+GA versus AA: OR=1.245, 95% CI=1.089-1.424, p<0.01) and in European population (GG+GA versus AA: OR=1.261, 95% CI=1.009-1.576, p<0.05). COX-2 1195G>A polymorphism was associated with an increased risk of lung cancer. To our knowledge, this is the first report to reveal the significant relationship between 1195G>A polymorphism and lung cancer risk with a meta-analysis.

Keywords: Lung cancer, cyclooxygenase-2, polymorphism, meta-analysis

Introduction

Lung cancer (LC) is a public health problem worldwide. In 2012, lung cancer is the leading cause of tumor death among females, accounting for 26% in the deaths [1]. Lung cancer is generally divided into two groups: small cell lung cancer (SCLC) and non-small cell lung cancer (NSCLC) [2]. Though the accurate mechanism is still unclear till now, the known risk factors of lung cancer include smoking, exposure to metal, exposure to organochlorine pesticide, environmental pollution and hereditary [3-6]. However, not everyone with those risk factors results in lung cancer since inherited genetic susceptibility factors exist in lung cancer development. Several recent studies investigated the association between lung cancer risk and cyclooxygenase-2 (COX-2) gene polymorphism [7-10].

COX-2 can convert arachidonic acid to prostaglandins. As an inducible enzyme, COX-2 is induced only by some stimuli, which are negative in normal conditions. It was reported that increased expression of COX-2 promotes malignant progression [11-12]. Three single nucleotide polymorphisms of COX-2 gene, rs20417 (765G>C), rs689466 (1195G>A) and rs5275 (8473T>C) are the most extensively studied polymorphisms in lung cancer development. However, few data were obtained for the 1195G>A polymorphism in the COX-2 gene [13-14]. These studies have shown discrepant results compared with the case-control studies. Recently, several new case-control studies on COX-2 1195G>A polymorphism have been reported [7-10]. Therefore, we collected the related data and performed the meta-analysis to estimate this association [7-10, 15-16].

Material and methods

Studies identification

To identify all studies that examined the association between 1195G>A polymorphism of COX-2 with lung cancer, we searched PubMed

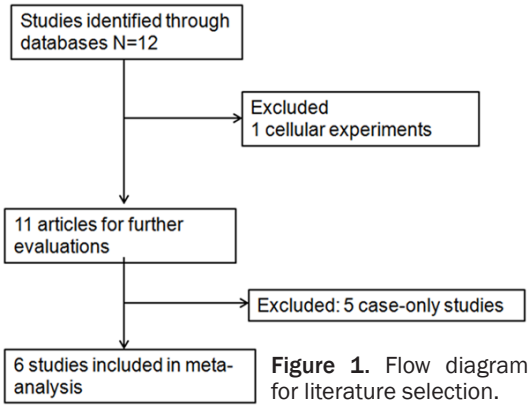

Figure 1. Flow diagram for literature selection.

and Embase databases without language limitation, covering all articles published up to January 2017, using the following key words and subject terms: COX-2, PGHS-2, polymorphism (rs689466 or 1195G>A), lung cancer and their synonyms in MeSH. We evaluated potentially relevant publications by checking their titles and abstracts and then obtained the most relevant publications for a detailed examination. Furthermore, the reference lists of the selected articles were also screened for other potential articles that may have been missed in the initial search.

The following criteria were used for the selection of reports for this meta-analysis: (a) evaluation of the association between the 1195G>A polymorphism of COX-2 and lung cancer risk, (b) case-control study, and (c) sufficient published data for estimating an OR with a 95% CI. After searching, we reviewed all of the articles in accordance with the criteria defined above for further analysis.Some studies were not selected according to these exclusion criteria: (a) review, letter to editor or meta-analysis, (b) research on cellular experiments and (c) case-only studies (**Figure 1**).

Data extraction

The data were extracted from all eligible publications independently by two of the authors according to the above-mentioned inclusion criteria. Disagreement was resolved by discussion between the two authors. If these two authors could not reach a consensus, then another author was consulted to resolve the dispute, and a final decision was made by majority vote. Hardy-Weinberg equilibrium (HWE) was also applied in evaluate the study quality, which was measured with the chi-square test to examine the goodness-of-fit in controls. $p>0.05$ of the control samples was considered in good equilibrium. The following data were extracted from each study: first author's name, publication date, country of origin, ethnicity, genotyping methods, genotype frequency, and information of 1195G>A polymorphism. The ethnicity was divided into Asian and European populations. We did not define any minimum number of patients to include in this meta-analysis.

Statistical analysis

The following statistical analyses in this study were performed using STATA version 11.1 (Stata Corporation, College Station, TX). Crude ORs with 95% CIs were used to assess the strength of the association between the 1195G>A polymorphism of COX-2 and lung cancer risk. For the 1195G>A polymorphism, the pooled ORs were performed for an additive model (GG versus AA), a dominant model (GG+GA versus AA), and a recessive model (AA versus GG+GA), respectively. The chi-square-based Q statistical test was performed to assess heterogeneity among the studies [17]. A *p* value above 0.05 for the Q-test indicates a lack of heterogeneity among the studies, so the pooled OR estimate of each study was calculated by the fixed-effects model [the Mantel-Haenszel method] [18]. Besides, the random-effects model (the M-H heterogeneity method) was used [19]. Meta-regression analyses were performed for the genotyping methods and ethnicity. Subgroup analyses were performed by ethnicity and genotyping methods. A sensitivity analysis was performed to assess the stability of the results. A single study involved in the meta-analysis was deleted each time to reflect the influence of the individual data set on the pooled ORs. An estimate of potential publication bias was assessed by the visual inspection of funnel plots, in which the standard error of the log (OR) of each study was plotted against its log (OR) [20]. An asymmetric plot indicates a possible publication bias. The symmetry of the funnel plot was further evaluated by Egger's linear regression test ($p<0.05$ was considered to be indicative of a significant publication bias) [21].

Table 1. Characteristics of the individual studies in the meta-analysis

Author, Year	Country	Race	Genotyping methods	Cases				Controls				HWE
				Total	GG	GA	AA	Total	GG	GA	AA	
Zhang, 2015	China	Asian	PCR-RFLP	60	20	28	12	62	27	31	4	0.209
Zhang, 2013	China	Asian	PCR-RFLP	956	183	502	271	994	217	530	247	0.034
Guo, 2012	China	Asian	PCR-LDR	684	136	318	230	602	121	320	161	0.096
Coskunpinar, 2011	Turkey	European	PCR-RFLP	231	1	57	173	118	0	48	70	NA
Liu, 2010	China	Asian	PCR-RFLP	358	84	172	102	716	178	345	193	0.337
Vogel, 2008	Denmark	European	TaqMan	403	17	124	262	744	24	253	467	0.135

PCR-LDR, polymerase chain reaction ligase detection reaction; PCR-RFLP, polymorphism chain reaction-reaction-restriction fragment length polymorphism; PCR-PIRA, primer-introduced restriction.

Table 2. Summary of Results of the meta-analysis

Subgroup	N	GG versus AA		(GG+GA) versus AA		GG versus (GA+AA)	
		OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h
Ethnicity							
Asian	4	1.276 (1.073-1.518)**	0.293	1.245 (1.089-1.424)**	0.173	0.894 (0.773-1.035)	0.680
European	2	0.793 (0.424-1.485)	0.983	1.261 (1.009-1.576)*	0.024	1.330 (0.715-2.475)	0.926
Total	6	1.235 (1.045-1.459)*	0.331	1.249 (1.114-1.402)***	0.072	0.913 (0.792-1.052)	0.700

*p<0.05; **p<0.01; ***p<0.001. N: Number of comparison; P_h: *P* value of Q test for heterogeneity test.

Results

Study characteristics

This study focused on the association between COX-2 1195G>A polymorphism and the risk of lung cancer development. From 6 studies which included four Asian populations and two European populations, 2692 lung cancer patients and 3236 control subjects were applied in this study. **Table 1** listed the identified studies and their main characteristics.

Meta-analysis results

Table 2 showed the pooled OR estimates and the corresponding 95% CI of this meta-analysis. There were 5928 subjects for COX-2 1195G>A polymorphism. Meta-regression analyses revealed that both ethnicity and genotyping methods were not related to the risk of lung cancer (all p>0.05). Overall, the data for COX-2 1195G>A polymorphism had no heterogeneity (p>0.05).

Meta-analysis results indicated the association between the COX-2 1195G>A and lung cancer risk in G-allele carriers (GG+GA) and GG versus AA for the fixed-effects model (GG versus AA: OR=1.235, 95% CI=1.045-1.459, p<0.05; GG+GA versus AA: OR=1.249, 95% CI=1.114-1.402, p<0.001), no statistically significant association was observed in GG versus GA+AA: OR=0.913, 95% CI=0.792-1.052, p=0.207 (**Figure 2** and **Figure 3**). Subgroup analysis by ethnicity indicated that COX-2 1195G>A polymorphism was remarkably associated with increased lung cancer risk in Asian population (GG versus AA: OR=1.276, 95% CI=1.073-1.518, p<0.01; GG+GA versus AA: OR=1.245, 95% CI=1.089-1.424, p<0.01) and in European population (GG+GA versus AA: OR=1.261, 95% CI=1.009-1.576, p<0.05).

Sensitivity analysis

Each data set was omitted individually to investigate the impact of a single study on the pooled ORs. The exclusion of any single study did not alter the overall conclusion, indicating that results were stable.

Publication bias

Begg's funnel plots and Egger's tests were applied to assess publication bias of included literature. The shapes of the funnel plots revealed no obvious asymmetry. The Egger's test was used to statistically assess funnel plot symmetry. The results of the overall and subgroup data suggested no evidence of publication bias (p>0.05) (**Figure 4**). The result indicat-

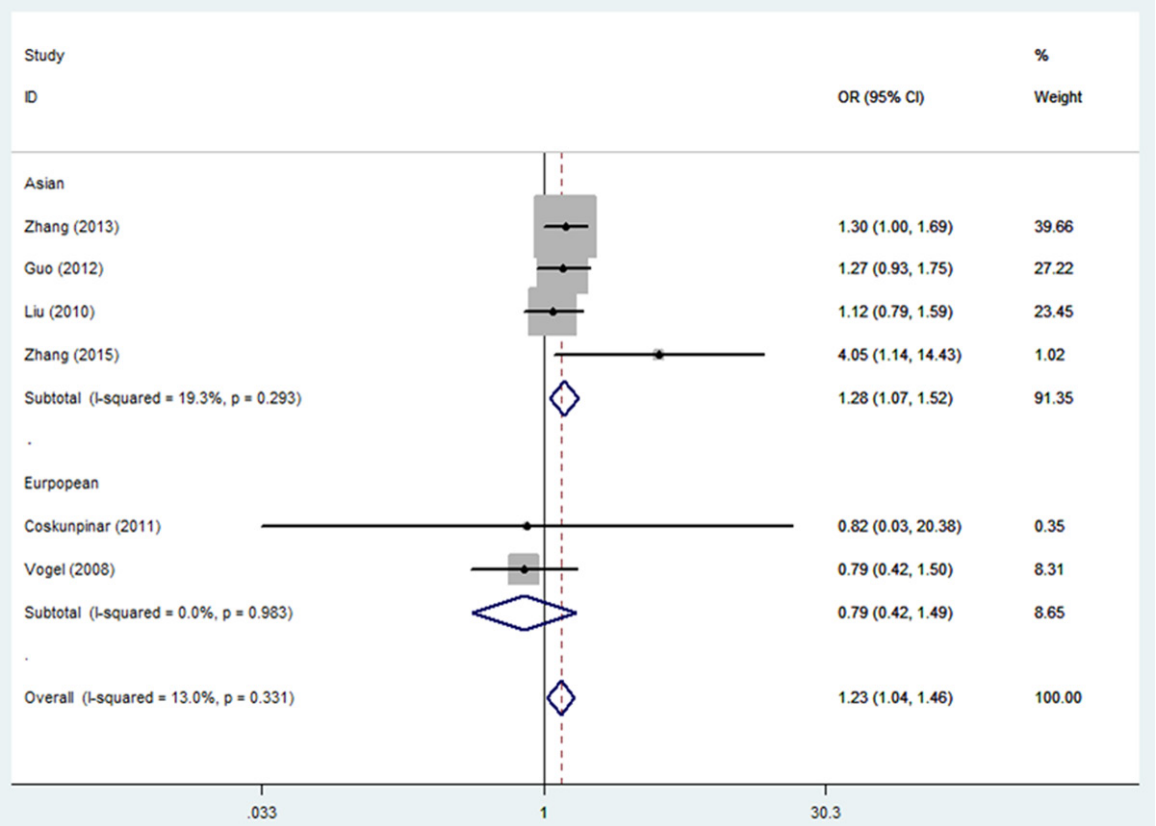

Figure 2. Forest plot of COX-2 1195G>A polymorphism (AA versus GG) with a fixed-effects model.

ed that the results of these meta-analyses were relatively stable and that publication bias was unlikely to affect the results of the meta-analyses.

Discussion

The present meta-analysis identified asignificant association between COX-2 1195G>A polymorphism and increased risk of lung cancer, which included G-allele carriers GG+GA versus AA and GG versus AAin whole population and in Asian population. For European population, GG+GA versus AA of COX-2 1195G>A also showed the statistically significant relationship.

Compared with previous papers, two case-control studies were added [14]. The number of total subjects changed from 3856 to 5928. This is the first meta-analysis report on the significant relationship between COX-2 1195G>A polymorphism and lung cancer development.

Some related studies suggested that COX-2 has correlation with lung cancer development. It was reported that increased COX-2 expression correlated with tumor characteristics [12]. The proliferation, migration and invasion of lung cancer cells were inhibited via directly negative regulation of COX-2 [22]. In this study, the data of selected case-control studies suggested the relationship between COX-2 1195G>A polymorphism and lung cancer. However, the concrete mechanism of COX-2 polymorphisms elevated lung cancer risk is still unknown.

In this study, neither the ethnicity nor genotyping method was significant contributor to the heterogeneity. Subgroup analyses were applied to these two potential risk factors. A publication bias was excluded by Begg's funnel plots and Egger's test. No publication bias was detected, indicating that the pooled results should be reliable. The sensitivity analysis did not change the results.

There were several potential limitations of this study. First, the accuracy of the results may be influenced by relative small samples of the selected studies. Second, lacking information on potential risk factors may cause a confound-

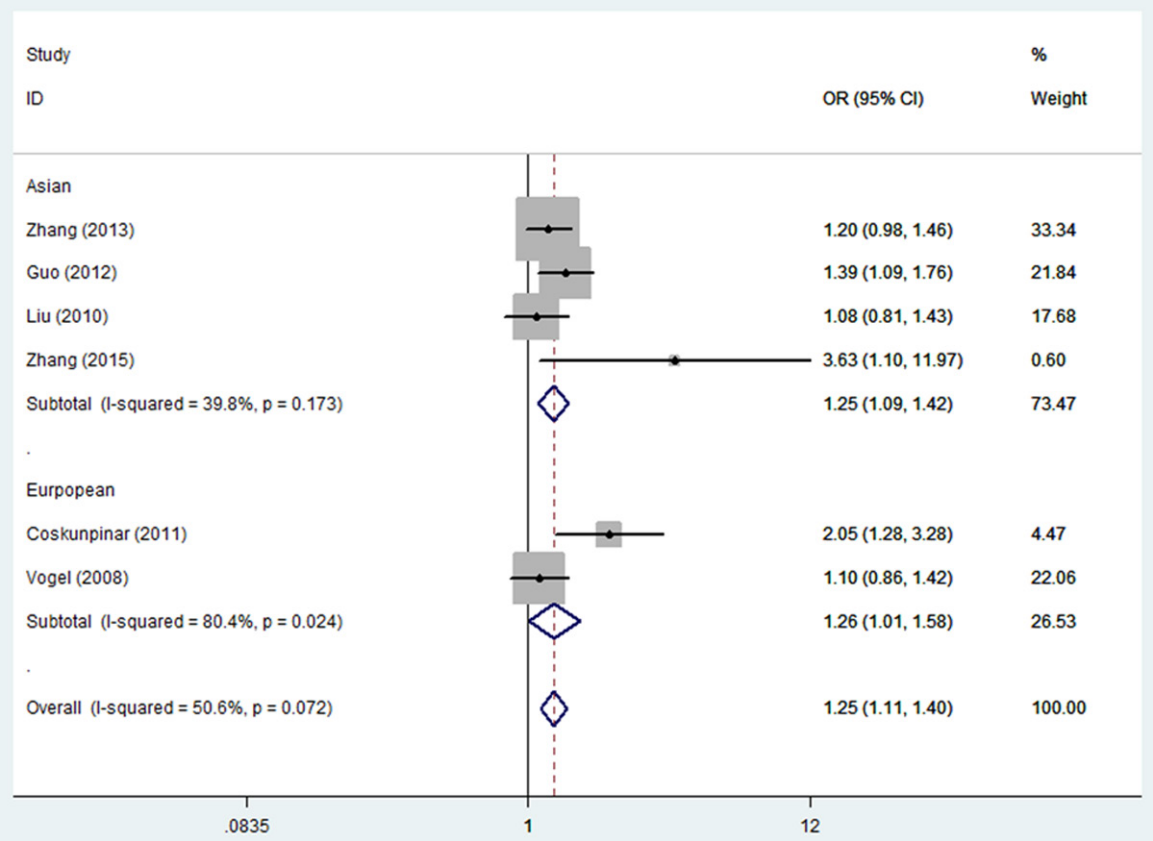

Figure 3. Forest plot of COX-2 1195G>A polymorphism (AA versus GA+GG) with a fixed-effects model.

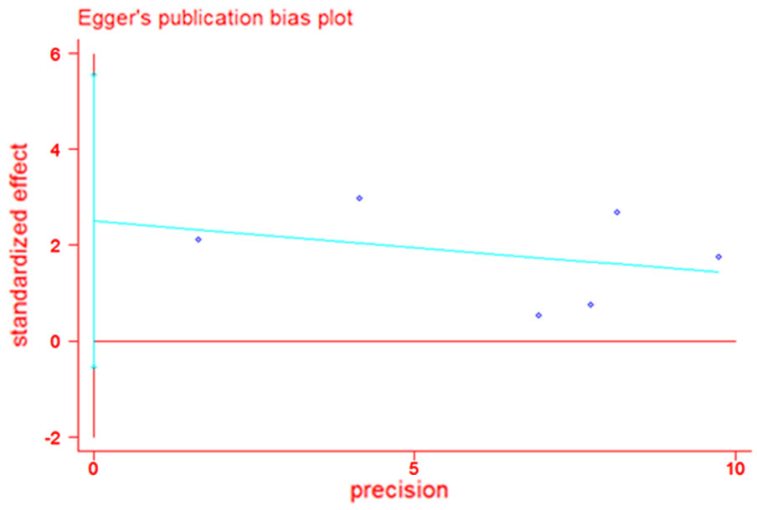

Figure 4. Publication bias plot of COX-2 1195G>A polymorphism.

ing bias. The development of lung cancer is affected by multiple factors, such as smoking, exposure to metal, environmental pollution and polymorphisms of other genes. Prospective studies are suggested for the future to reduce confounding factors. As one possibleetiologic factor in lung cancer development, the role of COX-2 polymorphisms was difficult to confirm. Third, the studies reviewed in this paper were carried out in different population groups. Some caveats are needed in interpreting the present data [13]. The heterogeneity of the data pooled from different studies of COX-2 polymorphisms may weaken the reliability of conclusion for the differences among these different populations. Lack of consistency in definitions and study designs also existed in the pooling published data. This issue may only be resolved ultimately by the establishment of large single or multicenter cohorts using comparable methods.

This meta-analysis provided the possible relationship of 1195G>A polymorphism with lung cancer development. Moreover, large-scale case-control studies still needed in future.

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Disclosure of conflict of interest

None.

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