Int J Clin Exp Med 2016;9(3):5584-5592
www.ijcem.com /ISSN:1940-5901/IJCEM0019229

Original Article

Association between the *cyclooxygenase-2* rs5275T>C polymorphism and lung cancer susceptibility: a meta-analysis involving 11,682 subjects

Hao Ding[1*], Yafeng Wang[2*], Heping Jiang[3*], Sheng Zhang[4], Chao Liu[5], Weifeng Tang[5]

Departments of [1]Respiratory Disease, [5]Cardiothoracic Surgery, Affiliated People's Hospital of Jiangsu University, Zhenjiang, Jiangsu Province, China; [2]Department of Cardiology, The People's Hospital of Xishuangbanna Dai Autonomous Prefecture, Jinghong, Yunnan Province, China; [3]Department of Emergency, Affiliated Jintan People's Hospital of Jiangsu University, Jintan, China; [4]Department of General Surgery, Changzhou No. 3 People's Hospital, Changzhou, Jiangsu Province, China. [*]Equal contributors.

Received November 5, 2015; Accepted February 10, 2016; Epub March 15, 2016; Published March 30, 2016

Abstract: The possible correlation of *cyclooxygenase-2* (*COX-2*) rs5275T>C polymorphism with lung cancer risk has been widely investigated. However, the results remain controversial. To identify the relationship more precisely, we carried out a pooled analysis of ten publications involving a total of 11,682 subjects. In this study, ten publications were recruited by extensive searching PubMed and EMBASE databases up to September 14, 2015. The lung cancer risk correlated with the *COX-2* rs5275T>C variants was evaluated by odds ratios (ORs) with 95% confidence intervals (95% CIs). Publication bias, heterogeneity and sensitivity analysis were also assessed. The results showed that the *COX-2* rs5275T>C variants were not associated with overall lung cancer susceptibility. In a stratified analysis by histology, the relationship between *COX-2* rs5275T>C polymorphism and decreased lung cancer susceptibility was significant in mixed histology lung cancer. In summary, our study demonstrated that the *COX-2* rs5275T>C polymorphism may be a lung cancer susceptibility factor.

Keywords: Lung cancer, polymorphism, *COX-2*, susceptibility, meta-analysis

Introduction

It is estimated that 1.8 million new lung cancer (LC) cases occurred worldwide in 2012, which account for about 13% of total malignancy diagnoses [1, 2]. Accumulating evidence demonstrates that LC results from complex mutual effect between multi-genetic and multi-environmental factors [2-4]. The pathogenesis of LC is extremely complicated and has not been clarified clearly, although a number of clinical and experimental investigations have kept a watchful eye on the important role of the chronic infection, inflammation and immune system [5-7]. Recently, evidence highlights that tumor immunosurveillance may be impaired in COPD, which may contribute to the increased susceptibility of LC [6].

Cyclooxygenase (COX), a key rate-limiting enzyme, plays an important role in the process of synthetic prostaglandins (PGs). The COX family of enzymes contains two isozymes (COX-1 and COX-2). COX-1 expresses in most of normal tissues stably and influences PG synthesis, then further maintains normal physiological functions [8]. However, COX-2 is an inducible form and rarely expressed in cells, but it may be induced by pro-inflammatory and mitogenic stimuli [9]. The *COX-2* genes locate on chromosome 1q25.2-q25.3 and contain 10 exons [10]. The *COX-2* promoter region contains some cis-acting elements including stimulatory protein 1, suggesting involvement of a complex array of factors in its regulation and thus influences COX-2 expression [11]. Some functional polymorphisms of *COX-2* have been identified to influence its expression through transcriptional and/or post transcriptional mechanisms.

COX-2 rs5275T>C (T8473C), a common single nucleotide polymorphism (SNP) in the 3' un-

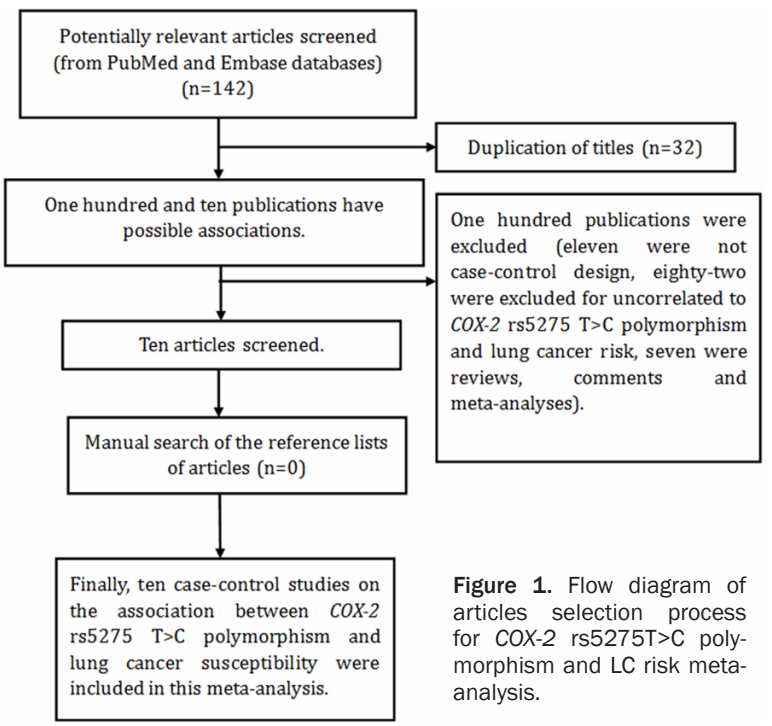

Figure 1. Flow diagram of articles selection process for *COX-2* rs5275T>C polymorphism and LC risk meta-analysis.

translated region (UTR) of the *COX-2* gene, has been identified to be correlated with the alteration of mRNA level of the gene, then influence its expression [12]. In the prior study, it was reported that the *COX-2* rs5275CC genotype was correlated with a decreased susceptibility of LC [12]. However, an individual case-control study may have insufficient power to obtain a conclusive result. To further address the potentially important role of the *COX-2* rs5275T>C variants in the development of lung cancer, we performed this pooled analysis including all eligible publications. To the best of our knowledge, this meta-analysis is the most comprehensive analysis considering the *COX-2* rs5275T>C polymorphism and its relationship with LC susceptibility.

Materials and methods

Search strategy

We searched EMBASE and PubMed databases (updated to September 14, 2015) using the following search terms: 'cyclooxygenase-2' or 'cyclooxygenase-2' or 'COX2' or 'COX-2' and 'genetic variant' or 'polymorphism' or 'SNP' and 'lung' and 'cancer' or 'carcinoma' or 'tumor' or 'malignance' or 'neoplasm'. All the searched publications were retrieved, and their bibliographies were manually screened as well for other relevant papers. Reviews were also checked to find additional papers. Only those publications in English language were included.

Inclusion and exclusion criteria

The major selection criteria were: (1) evaluating the *COX-2* rs5275T>C polymorphism and LC susceptibility, (2) a case-control study design, (3) containing sufficient available data on genotype or allele frequency in case groups and control groups to estimate an odds ratio (OR) with its 95% confidence interval (95% CI). Accordingly, papers without usable data, reviews, letters, comments, not case-control study and overlapping data were excluded.

Data extraction

The three reviewers (H. Ding, Y. Wang and H. Jiang) independently collected data and reached consensus on all items. If they generated conflicting evaluations, they would screen the data again and have a discussion until reaching conformity on items among all reviewers. The following data was extracted: (1) the surname of first author, (2) the histology of LC, (3) published year, (4) country, (5) race, (6) case and control number, (7) numbers of cases and controls of different allele and genotype frequency and (8) genotyping method.

Statistical analysis

The HWE in controls was tested using a web-based HWE calculator (http://ihg.gsf.de/cgi-bin/hw/hwa1.pl). The ORs with their 95% CIs were calculated to determine the strength of correlation between *COX-2* rs5275T>C polymorphism and LC susceptibility. A $P < 0.05$ (two-tailed) was defined as significant. A Chi-square-based I^2 test was harnessed to examine the heterogeneity across the studies and an $I^2 < 25\%$ indicates low heterogeneity, $25\% \leq I^2 \leq$

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

Study	Publication year	Ethnicity	Country	Histology	Sample size (case/control)	Genotype method
Zhang et al.	2015	Asians	China	NSCLC	60/62	PCR-RFLP
Bhat et al.	2014	Asians	India	NSCLC	190/200	PCR-RFLP
Lim et al.	2011	Asians	Singapore	Mixed	433/1375	RT-PCR
Liu et al.	2010	Asians	China	Mixed	358/716	PCR-RFLP
Vogel et al.	2008	Caucasians	Denmark	Mixed	428/800	TaqMan
Park et al.	2006	Asians	Korea	Mixed	582/582	PIRA
Sorensen et al.	2005	Caucasians	Denmark	Mixed	265/272	TaqMan
Hu et al.	2005	Asians	China	Mixed	322/323	PIRA
Campa et al.	2005	Caucasians	Romania	Mixed	2135/2115	Taqman
Campa et al.	2004	Caucasians	Norway	NSCLC	250/214	Taqman

NSCLC: Non-small cell lung cancer. PCR-RFLP: polymerase chain reaction-restriction fragment length polymorphism. PIRA: primer-introduced restriction analysis.

Table 2. Distribution of *COX-2* rs5275T>C polymorphisms genotype and allele among lung cancer cases and controls

Study	Year	Case			Control			Case		Control		HWE
		TT	TC	CC	TT	TC	CC	C	T	C	T	
Zhang et al.	2015	23	26	11	28	32	2	48	72	36	88	No
Bhat et al.	2014	133	53	4	128	66	6	61	319	78	322	Yes
Lim et al.	2011	182	100	15	462	228	28	130	464	284	1152	Yes
Liu et al.	2010	239	119	0	468	248	0	119	597	248	1184	No
Vogel et al.	2008	182	183	38	310	341	93	259	547	527	961	Yes
Park et al.	2006	352	205	25	330	220	32	255	909	284	880	Yes
Sorensen et al.	2005	127	111	18	115	126	27	147	365	180	356	Yes
Hu et al.	2005	234	83	5	209	107	7	93	551	121	525	Yes
Campa et al.	2005	855	886	224	805	904	228	1334	2596	1360	2514	Yes
Campa et al.	2004	31	107	112	65	99	50	331	169	199	229	Yes

HWE: Hardy-Weinberg equilibrium.

50% indicates moderate heterogeneity, and I^2 > 50% indicates large heterogeneity [13]. I^2 > 50% or P < 0.10 (two-sided) shows heterogeneity among the studies, the random-effects model (the DerSimonian-Laird method) [14] was used to calculate the data, otherwise the fixed-effects model (the Mantel-Haenszel method) was harnessed [15]. Sub-group analyses were carried out according to the histology of LC and ethnicity to check the source of heterogeneity. Galbraith radial plot test was harnessed to identify the major source of heterogeneity. Publication bias across the studies was examined by Begg's funnel plot [16] and Egger's linear regression [17]. One-way sensitivity analysis was used to check the stability of our findings. Additionally, for publication bias, P < 0.1 (two-sided) was considered as statistical significance. All statistical analyses in our study were performed using STATA version 12.0 software (Stata CorporationLP, College Station, TX).

Results

Characteristics

The detailed selecting of literatures was shown in **Figure 1**. In total, there were ten eligible studies included in our study [12, 18-26], involving 5,023 LC cases and 6,659 controls. As for the histology of LC, three investigated non-small cell LC (NSCLC) [18-20] and seven investigated mixed histology LC [12, 21-26]. As for subjects, four were Caucasians [20, 23, 25, 26] and six were Asians [12, 18, 19, 21, 22, 24]. **Table 1** summarizes the main characteristics of the included studies. The distribution of the *COX-2* rs5275T>C variants and allelesis summarized in **Table 2**.

Table 3. Summary of results of the meta-analysis

	No. of study	C vs. T			CC vs. TT			CC+TC vs. TT			CC vs. TC+TT		
		OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)	OR (95% CI)	*P*	*P* (Q-test)
Total	10	1.01 (0.85-1.20)	0.934	< 0.001	1.12 (0.70-1.77)	0.639	< 0.001	0.97 (0.81-1.16)	0.731	< 0.001	1.09 (0.74-1.59)	0.667	< 0.001
Ethnicity													
Asians	6	0.94 (0.79-1.12)	0.489	0.054	1.06 (0.58-1.94)	0.862	0.073	0.90 (0.79-1.02)	0.112	0.208	1.10 (0.61-1.96)	0.758	0.089
Caucasians	4	1.09 (0.77-1.54)	0.623	< 0.001	1.16 (0.56-2.40)	0.698	< 0.001	1.11 (0.76-1.63)	0.594	< 0.001	1.08 (0.62-1.87)	0.794	< 0.001
Histology													
Non-small cell lung cancer	3	1.43 (0.71-2.86)	0.312	< 0.001	2.77 (0.74-10.35)	0.131	0.015	1.46 (0.58-3.66)	0.422	< 0.001	2.26 (0.83-6.16)	0.111	0.064
Mixed lung cancer	7	0.92 (0.86-0.98)	0.012	0.245	0.86 (0.73-1.01)	0.062	0.405	0.90 (0.83-0.98)	0.013	0.360	0.90 (0.77-1.05)	0.164	0.526
HWE													
Yes	8	0.98 (0.81-1.19)	0.849	< 0.001	1.01 (0.64-1.59)	0.967	0.920	0.96 (0.78-1.18)	0.713	< 0.001	1.00 (0.70-1.44)	0.988	< 0.001
No	2	1.18 (0.70-1.98)	0.532	0.071	6.70 (1.35-33.31)	0.020	N/A	0.98 (0.76-1.26)	0.873	0.382	6.73 (1.42-31.83)	0.016	N/A

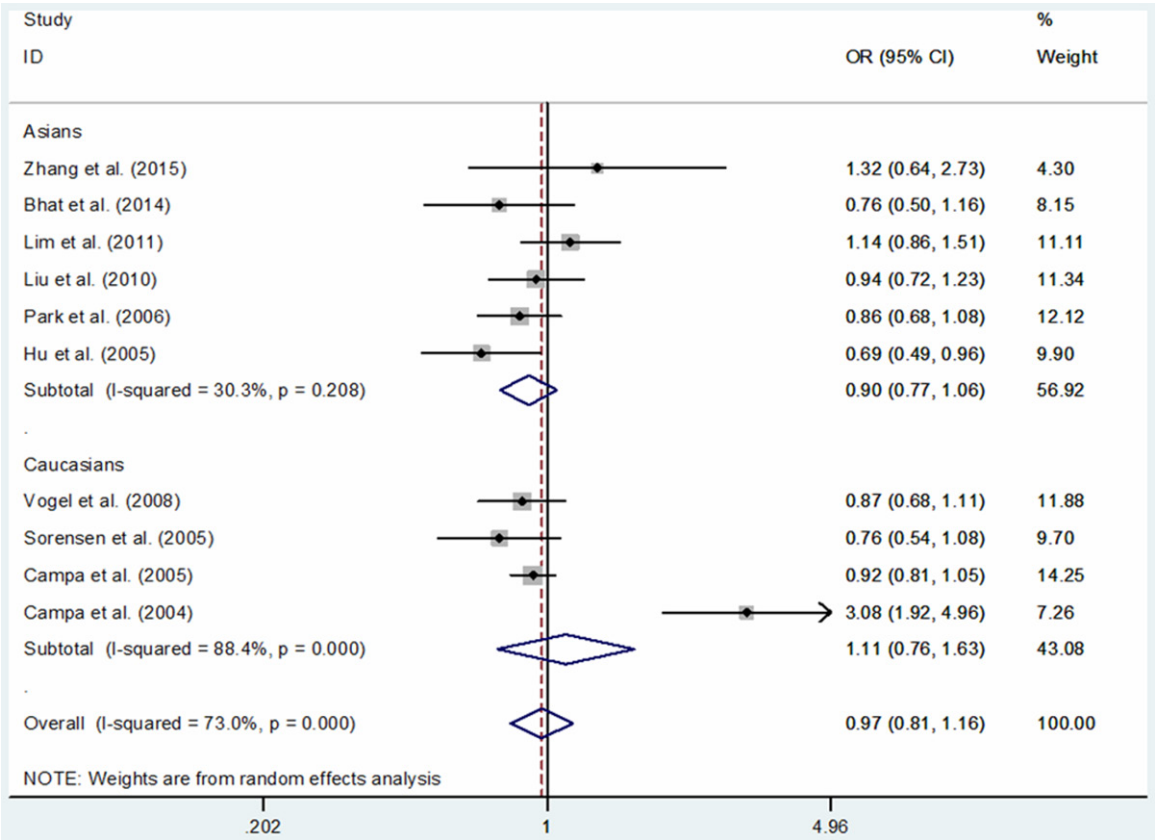

Figure 2. Meta-analysis with a random-effects model for the association between *COX-2* rs5275T>C polymorphism and LC risk (CC+TC vs. TT genetic model).

Quantitative synthesis

A total of 11,682 subjects (5,023 LC cases and 6,659 controls) from ten studies [12, 18-26] were included to examine the correlation of *COX-2* rs5275T>C polymorphism with LC susceptibility. After combining these eligible publications, there was null association between-*COX-2* rs5275T>C polymorphism and overall LC susceptibility (**Table 3** and **Figure 2**). In a stratified analysis by different ethnicity, the relationship of *COX-2* rs5275T>C polymorphism with LC was also non-significant. While in a stratified analysis by the histology of LC, a significant decrease in mixed histology LC risk was detected in allele genetic model: C vs. T (OR, 0.92; 95% CI, 0.86-0.98; *P* = 0.012) and dominant genetic model (OR, 0.90; 95% CI, 0.83-0.98; *P* = 0.013), but not NSCLC (**Table 3** and **Figure 3**).

Tests for publication bias, sensitivity analyses, and heterogeneity

In our study, Begg's funnel plot and Egger's test highlighted that there was no evidence for significant publication bias (C vs. T: Begg's test *P* = 0.721, Egger's test *P* = 0.579; CC vs. TT: Begg's test *P* = 0.251, Egger's test *P* = 0.592; CC+TC vs. TT: Begg's test *P* = 0.592, Egger's test *P* = 0.441; CC vs. TC+TT: Begg's test *P* = 0.175, Egger's test *P* = 0.742) (**Figure 4**).

One-way sensitivity analyses were also carried out by excluding an individual study at a time. The pooled ORs and CIs did not alter the final results but influenced statistical efficacy, suggesting the stability of our findings (**Figure 5**) (data not shown).

Significant heterogeneity was found in current meta-analysis. Thus, we examined the sources of heterogeneity by the histology of LC and ethnicity (**Table 3**). The findings indicated that NSCLC and Caucasians might contribute to the major sources of heterogeneity. In additional, Galbraith radial plot was also used to access the heterogeneity (**Figure 6**) and the result showed that one outlier might lead to the significant heterogeneity [20].

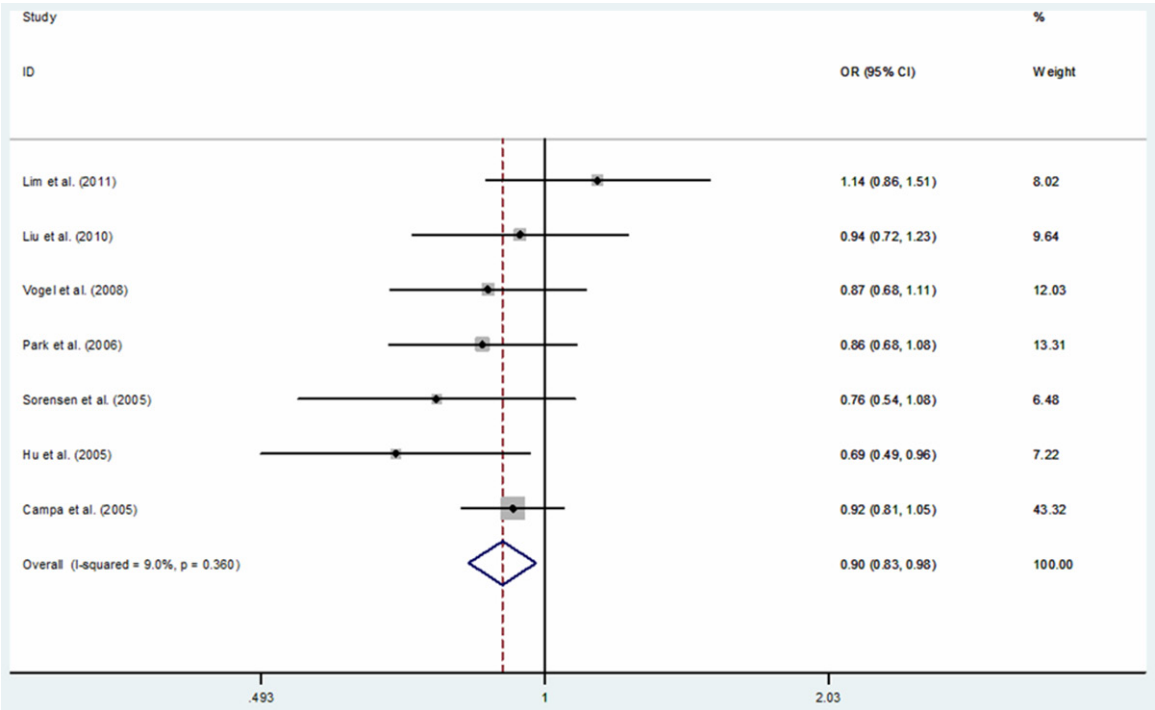

Figure 3. Meta-analysis with a fixed-effects model for the association between *COX-2* rs5275T>C polymorphism and mixed histology LC risk (CC+TC *vs.* TT compare genetic model).

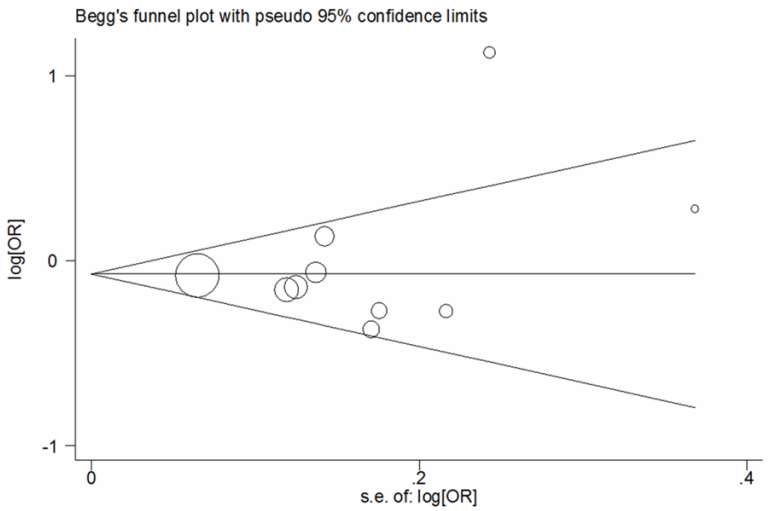

Figure 4. Begg's funnel plot of meta-analysis of between the *COX-2* rs5275T>C polymorphism and the risk of overall LC in the dominant model.

Discussion

Large sample sizes with an adequate methodological quality and unbiased epidemiological investigations of predisposition SNPs could provide insight into the in vivo correlation of candidate genes with malignancy. The involvement of COX-2 enzyme in the process of synthetic PGs might underlie the vital mechanism responsible for the correlation between *COX-2* variants and LC. So far, a number of investigations have been performed on association of *COX-2* rs5275T>C polymorphism with LC, but the findings of them remain sconflicting. Our study is the most comprehensive pooled-analysis considered a functional SNP of *COX-2* and the correlation to the risk of LC. In total, the current analysis involved ten publications for LC which provided 5,023 cases and 6,659 controls.

In the current analysis, the combined evidence indicated that *COX-2* rs5275T>C variants did not contribute to the development of over all LC. However, LC is a complex disease with high heterogeneity, and the type of histology may involve in the development of LC. In a stratified analysis by the histology of LC, a significant decrease in mixed histology LC risk was found in allele genetic model ($P = 0.012$) and dominant genetic model ($P = 0.013$), but not NSCLC (**Table 3**).

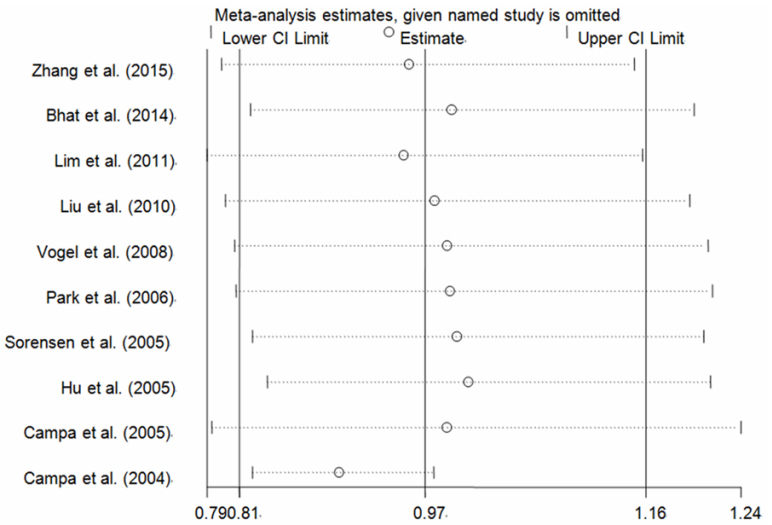

Figure 5. Sensitivity analysis of the influence of CC+TC *vs*. TT compare genetic model in overall LC meta-analysis (random-effects estimates).

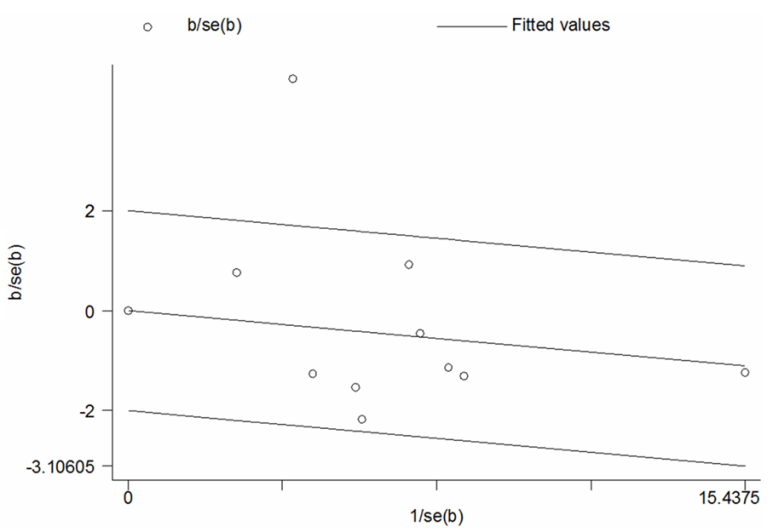

Figure 6. Galbraith radial plot of meta-analysis (CC+TC *vs*. TT compare genetic model).

In a stratified analysis by different ethnicity, the CC and TC genotype were correlated with a borderline statistically decreased susceptibility of LC among Asians in the dominant model (OR, 0.90, 95% CI, 0.79-1.02, $P = 0.112$).

Some possible reasons may response for the inconsistent results. Firstly, since the distributions of the *COX-2* rs5275T>C variants were different between different populations, race differences might lead to these outcomes. For example, in Asians subgroup, the corresponding OR and 95% CI were 0.90 and 0.79-1.02 in the dominant genetic model, while in Caucasians, they were 1.11 and 0.76-1.63, respectively. On the other hand, study design with small sample sizes or some confounding factors may also influence the findings. Most of these included publications did not consider these important factors, such as the histology of LC and the use of nonsteroidal anti-inflammatory drug (NSAID). NSAID is one of the popular medicines, which used worldwide for the treatment and/or prevention of various diseases, such as coronary artery disease, ankylosis spondylitis and rheumatoid arthritis et al. Recently, some epidemiological studies have demonstrated that NSAID use is associatedwith a decreased risk of developing cancer [27, 28]. NSAID users homozygous (TT) in *COX-2* rs5275T>C variants indicated significantly decreased cancer susceptibility compared with non-NSAID users and among the USA population [27]. In the included ten publications, seldom study has focused on these important environmental factors, which may lead to bias. It is possible that the different type of histology may modest effects on LC and cover the effects of *COX-2* rs5275T>C variants. Different histology, like NSCLC and small cell LC (SCLC), has different biological behavior. In the current study, there were seven case-control studies which had performed on mixed type of histology. These unconsidered factors mixed together may also mask the role of *COX-2* rs5275T>C variants. Thus, even if *COX-2* rs5275T>C variants has a causal effect on different type of LC, it may take a long time to be identified.

In the current study, significant heterogeneity was observed (**Table 3**). In general, the major

sources of heterogeneity among LC involved ethnicity and the type of histology. Stratified analyses were conducted according to these important factors. Heterogeneity was reduced in some subgroups, suggesting the different influences of these important variables, even in the same SNP (**Table 3**). The analysis of a subset of NSCLC and Caucasians suggested a correlation with more noteworthy heterogeneity. According to the Galbraith radial plot (**Figure 6**) and the forest plot (**Figure 2**), one major outlier was identified [20]. Reviewing this included paper, it involved some deficiencies, such as small sample sizes, mixed histology of LC and hospital-based study design et al.

In our study, two case-control studies deviated from the HWE in controls, which showed the presence of population stratification and/or genotyping errors [18, 22]. When we discarded them, the relationship between *COX-2* rs5275T>C variants and the risk of LC was not changed, attesting the robustness of our findings.

Although considerable efforts were done to analyze the possible relationship between *COX-2* rs5275T>C variants and the susceptibility of LC, some limitations should be addressed. Large heterogeneity was observed in four genetic models, which indicated these results inherited from the current study should be interpreted with caution. Additionally, only ten published literatures were included in our work; therefore, certain unpublished epidemiological studies, if any, might ineluctably be discarded and lead to bias. Finally, we only focused on rs5275T>C variants in *COX-2* gene, and did not dwell on other susceptibility genes or SNPs.

In summary, this meta-analysis highlighted that *COX-2* rs5275C allele modestly modified the risk of mixed histology LC. However, due to insufficient environmental factors involved, a more detailed analysis of the relationship of the rs5275T>C variants with the susceptibility of LC could not be done, but the present pooled-analysis may help us to understand the effect of the *COX-2* rs5275 C on LC. Nevertheless, for practical reasons, further evidences from more large-scale and well-designed epidemiological studies across different populations incorporating with different type of histology are needed to provide a characterization of the involvement of *COX-2* rs5275C allele in the genetic risk to developing LC.

Acknowledgements

This study was supported in part by Jiangsu University Clinical Medicine Science and Technology Development Fund (JLY20140012).

Disclosure of conflict of interest

None.

Abbreviations

CI, confidence interval; OR, odds ratio; HWE, Hardy-Weinberg equilibrium; *COX-2*, *Cyclooxygenase-2.*

Address correspondence to: Weifeng Tang, Department of Cardiothoracic Surgery, Affiliated People's Hospital of Jiangsu University, Zhenjiang 212000, China. E-mail: twf001001@126.com

References

[1] Torre LA, Bray F, Siegel RL, Ferlay J, Lortet-Tieulent J and Jemal A. Global cancer statistics, 2012. CA Cancer J Clin 2015; 65: 87-108.

[2] Yang P. Two classic lyrics joined by a contemporary tune-environmental pro-carcinogen exposure and genetic susceptibility in lung cancer risk. J Thorac Oncol 2014; 9: 1063-1065.

[3] Fathy M, Hamed M, Youssif O, Fawzy N and Ashour W. Association between environmental tobacco smoke exposure and lung cancer susceptibility: modification by antioxidant enzyme genetic polymorphisms. Mol Diagn Ther 2014; 18: 55-62.

[4] Kiyohara C, Yoshimasu K, Shirakawa T and Hopkin JM. Genetic polymorphisms and environmental risk of lung cancer: a review. Rev Environ Health 2004; 19: 15-38.

[5] Koyi H, Branden E, Gnarpe J, Gnarpe H and Steen B. An association between chronic infection with Chlamydia pneumoniae and lung cancer. A prospective 2-year study. APMIS 2001; 109: 572-580.

[6] Scrimini S, Pons J, Agusti A, Clemente A, Sallan MC, Bauca JM, Soriano JB, Cosio BG, Lopez M, Crespi C and Sauleda J. Expansion of myeloid-derived suppressor cells in chronic obstructive pulmonary disease and lung cancer: potential link between inflammation and cancer. Cancer Immunol Immunother 2015; 64: 1261-1270.

[7] Bozinovski S, Vlahos R, Anthony D, McQualter J, Anderson G, Irving L and Steinfort D. COPD and squamous cell lung cancer: aberrant inflammation and immunity is the common link. Br J Pharmacol 2016; 173: 635-48.

[8] Coffey RJ, Hawkey CJ, Damstrup L, Graves-Deal R, Daniel VC, Dempsey PJ, Chinery R, Kirkland SC, DuBois RN, Jetton TL and Morrow JD. Epidermal growth factor receptor activation

induces nuclear targeting of cyclooxygenase-2, basolateral release of prostaglandins, and mitogenesis in polarizing colon cancer cells. Proc Natl Acad Sci U S A 1997; 94: 657-662.

[9] Tan W, Wu J, Zhang X, Guo Y, Liu J, Sun T, Zhang B, Zhao D, Yang M, Yu D and Lin D. Associations of functional polymorphisms in cyclooxygenase-2 and platelet 12-lipoxygenase with risk of occurrence and advanced disease status of colorectal cancer. Carcinogenesis 2007; 28: 1197-1201.

[10] Hedelin M, Chang ET, Wiklund F, Bellocco R, Klint A, Adolfsson J, Shahedi K, Xu J, Adami HO, Gronberg H and Balter KA. Association of frequent consumption of fatty fish with prostate cancer risk is modified by COX-2 polymorphism. Int J Cancer 2007; 120: 398-405.

[11] Zweifel BS, Davis TW, Ornberg RL and Masferrer JL. Direct evidence for a role of cyclooxygenase 2-derived prostaglandin E2 in human head and neck xenograft tumors. Cancer Res 2002; 62: 6706-6711.

[12] Hu Z, Miao X, Ma H, Wang X, Tan W, Wei Q, Lin D and Shen H. A common polymorphism in the 3'UTR of cyclooxygenase 2/prostaglandin synthase 2 gene and risk of lung cancer in a Chinese population. Lung Cancer 2005; 48: 11-17.

[13] Higgins JP, Thompson SG, Deeks JJ and Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557-560.

[14] DerSimonian R and Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7: 177-188.

[15] Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959; 22: 719-748.

[16] Begg CB and Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994; 50: 1088-1101.

[17] Egger M, Davey Smith G, Schneider M and Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997; 315: 629-634.

[18] Zhang T, Li J, Xia T, Zhang N, Zhang Y and Zhao J. Association between COX-2 polymorphisms and non-small cell lung cancer susceptibility. Int J Clin Exp Pathol 2015; 8: 3168-3173.

[19] Bhat IA, Rasool R, Qasim I, Masoodi KZ, Paul SA, Bhat BA, Ganaie FA, Aziz SA and Shah ZA. COX-2 overexpression and -8473 T/C polymorphism in 3' UTR in non-small cell lung cancer. Tumour Biol 2014; 35: 11209-11218.

[20] Campa D, Zienolddiny S, Maggini V, Skaug V, Haugen A and Canzian F. Association of a common polymorphism in the cyclooxygenase 2 gene with risk of non-small cell lung cancer. Carcinogenesis 2004; 25: 229-235.

[21] Lim WY, Chen Y, Ali SM, Chuah KL, Eng P, Leong SS, Lim E, Lim TK, Ng AW, Poh WT, Tee A, Teh M, Salim A and Seow A. Polymorphisms in inflammatory pathway genes, host factors and lung cancer risk in Chinese female never-smokers. Carcinogenesis 2011; 32: 522-529.

[22] Liu CJ, Hsia TC, Wang RF, Tsai CW, Chu CC, Hang LW, Wang CH, Lee HZ, Tsai RY and Bau DT. Interaction of cyclooxygenase 2 genotype and smoking habit in Taiwanese lung cancer patients. Anticancer Res 2010; 30: 1195-1199.

[23] Vogel U, Christensen J, Wallin H, Friis S, Nexo BA, Raaschou-Nielsen O, Overvad K and Tjonneland A. Polymorphisms in genes involved in the inflammatory response and interaction with NSAID use or smoking in relation to lung cancer risk in a prospective study. Mutat Res 2008; 639: 89-100.

[24] Park JM, Choi JE, Chae MH, Lee WK, Cha SI, Son JW, Kim CH, Kam S, Kang YM, Jung TH and Park JY. Relationship between cyclooxygenase 8473T>C polymorphism and the risk of lung cancer: a case-control study. BMC Cancer 2006; 6: 70.

[25] Sorensen M, Autrup H, Tjonneland A, Overvad K and Raaschou-Nielsen O. A genetic polymorphism in prostaglandin synthase 2 (8473, T->C) and the risk of lung cancer. Cancer Lett 2005; 226: 49-54.

[26] Campa D, Hung RJ, Mates D, Zaridze D, Szeszenia-Dabrowska N, Rudnai P, Lissowska J, Fabianova E, Bencko V, Foretova L, Janout V, Boffetta P, Brennan P and Canzian F. Lack of association between polymorphisms in inflammatory genes and lung cancer risk. Cancer Epidemiol Biomarkers Prev 2005; 14: 538-539.

[27] Nagao M, Sato Y and Yamauchi A. A meta-analysis of PTGS1 and PTGS2 polymorphisms and NSAID intake on the risk of developing cancer. PLoS One 2013; 8: e71126.

[28] Nagao M, Sato Y and Yamauchi A. A meta-analysis of the association of PPARgamma rs1801282 polymorphism and NSAID usage with the risk of developing cancer. Biol Pharm Bull 2014; 37: 1062-1067.