RESEARCH COMMUNICATION

Association of the 8473T>C Cyclooxygenase-2 (COX-2) Gene Polymorphism with Lung Cancer Risk in Asians

Fen Liu*, Yan He, Xiaoxia Peng, Wei Wang, Xinghua Yang*

Abstract

Objective: To evaluate the impact of the COX-2 gene 8473T>C polymorphism on lung cancer risk in Asians, we conducted a comprehensive meta-analysis. Methods: A literature search was performed using PubMed and other databases before June 2010. We pooled studies according to the variants of 8473T>C and performed separate analyses according to ethnicity, histological type and smoking status, with attention to study quality and publication bias. Results: A total of five case-control studies including 2,450 cases and 4,302 controls were available. Overall, individuals with the C allele had a reduced lung cancer risk compared with the TT genotype on global analysis (odds ratio [OR] =0.89, 95% confidence interval [CI] =0.81 to 0.97, *P*=0.01, I^2 for heterogeneity =0%). Significant associations were also observed in subgroups of Asian populations (OR=0.84, 95% CI=0.72 to 0.98) when stratified by ethnicity, as well as for small cell lung cancer (OR=0.54, 95% CI=0.31 to 0.95) stratified by pathological type. Conclusions: Our results suggest the COX-2 gene is a factor for suffering from lung cancer, especially of small cell type among Asians.

Keywords: Cyclooxygenase-2 - polymorphism - lung cancer - meta-analysis - molecular epidemiology

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Introduction

Lung cancer is the most common cancer in the world, both in terms of incidence and mortality (Parkin, 2001). Etiological studies of lung cancer indicate that risk factors include smoking, occupation, environmental pollution and hereditary susceptibility. Although smoking is the major risk factor in the development of lung cancer, lung cancer incidence among smokers is only 10%~15%, while 10% ~15% of lung cancer cases occur in non-smokers (Shields, 2002). These observations indicate that there is some hereditary susceptibility to lung cancer.

Inflammation has been recognized as a contributing factor for the pathogenesis of lung cancer. Tobacco smoke may lead to an increased inflammatory response in lung cells (Wright et al.,1988). Prostaglandins, which are important molecules in the inflammatory response, are produced from arachidonic acid through the catalytic activity of cyclooxygenases (COXs), also named prostaglandin endoperoxyde synthases (Herschman, 1996). Nonsteroidal anti-inflammatory drugs (NSAIDs) have received attention as being associated with reduced risk of a variety of cancers including lung cancer (Thun et al., 1991; Harris et al., 2005; Jacobs et al., 2007; Siemes et al., 2008). The inhibition of COX is hypothesized to be one of the mechanisms by which NSAIDs might reduce cancer risk (Thun et al., 2002).

There are at least two isoforms of COX identified: COX-1 is expressed constitutively in most tissues mediating physiologic processes, COX-2 is normally undetectable but can be rapidly induced in response to various inflammatory stimulus or growth factors (Hla et al., 1999). Studies have shown COX-2 is over-expressed in lung cancer, and plays an important role in lung carcinogenesis (Wolff et al., 1998; Castelao et al., 2003).

Due to the possibility that functional polymorphisms in the gene could affect the susceptibility to cancer development, a large number of single-nucleotide polymorphisms (SNPs) affecting coding and noncoding regions of COX-2 have been reported. A common polymorphism 8473T>C (rs5275) in the COX-2 3'-UTR region of the transcript has been described that is associated with several cancers in different ethnic populations (Campa et al., 2004; 2005; Hu et al., 2005; Kang et al. 2005; Sørensena et al., 2005; Langsenlehner et al., 2006; Lee et al., 2006; Park et al., 2006; Sakoda et al., 2006; Shahedi et al., 2006; Lira et al., 2007; Vogel et al., 2008; Pereira et al., 2009; Liu et al., 2010), suggesting that 8473T>C is an important determinant of mRNA stability and thus is associated with the enzyme level (Gou et al., 1998). Carries of the variant C-allele of 8473T>C were found to have both higher basal levels and induced levels of prostaglandin E_2 compared to homozygous carriers of T-allele (Sanak et al., 2005). The variant genotypes may affect the expression or activity of COX-2 enzyme and consequently contribute to variation in individual susceptibility to cancer through aberrant arachidonic acid metabolism. However, the results studies of COX-2

*School of Public Health and Family Medicine, Capital Medical University, Beijing, China. *For correspondence : liufen05@ccmu.edu.cn, xinghuay@263.net*

8473T>C polymorphisms and lung cancer risk remain controversial (Campa et al, 2004; 2005; Hu et al., 2005; Kang et al., 2005; Sørensena et al., 2005; Park et al., 2006; Vogel et al., 2008; Liu et al., 2010).

An inclusive evaluation of the published data on 8473T>C may clarify the relative risk of this genetic polymorphisms with lung cancer risk. Recently, a meta-analyses of the 8473T>C polymorphism of COX-2 and cancer risk was reported, but in our view this study has methodological limitations (Zhu et al., 2010). For example, in this report two overlapping data sets (Sørensen et al., 2005; Vogel et al., 2008) and the same population but with different sample size (Cample et al., 2004; 2005) were included (Zhu et al., 2010). We therefore carried out a more systematic review of all eligible studies on the COX-2 8473T>C polymorphisms and risk of lung cancer following the MOOSE guidelines for meta-analyses of observational studies (Stroup et al., 2000). Our objective was to derive a more definitive estimation of the associations between 8473T>C polymorphism of COX-2 and risk for lung cancer.

Materials and Methods

Search Strategies

PubMed, EMBase, CBMdisc (Chinese BioMedical Literature Database), and CNKI (China National Knowledge Infrastructure) were searched carefully before June 22, 2010 without language limitation. The search strategy was designed by two researchers and included the following keywords (e.g., Mesh terms): 'COX-2' or 'COX2' or 'PTGS2' or 'cyclooxygenase-2', 'polymorphisms' or 'single nucleotide polymorphisms' or 'SNPs' and 'lung cancer'. Furthermore, references in retrieved articles were also screened to trace further relevant studies or by personal contact with the authors if necessary, for example the distribution of the 8473T>C genotypes categorized by the tumor histology or smoking status (Campa et al., 2004; 2005; Park et al., 2006; Vogelet al., 2008; Liu et al., 2010). All of the identified records were examined independently by two reviewers.

Inclusion Criteria

Studies were considered eligible if the publications met all of the following criteria: (1) based on an unrelated case-control design; (2) evaluation of the potential association between lung cancer with genotyping data for the 8473T>C polymorphisms; (3) a genotype distribution of the controls consistent with the Hardy-Weinberg equilibrium (P>0.05). For studies of the same or a subset population, those with the most recent or larger sample size were included (Campa et al., 2004; 2005; Sørensen et al., 2005; Vogel et al., 2008).

Quality Assessment

Quality scoring is controversial in meta-analysis of observational studies. After referring to several quality assessment scales or checklists of observational studies, we followed the recommendations of the "MOOSE guidelines" to come to an overall evaluation of the strength of evidence (Stroup et al., 2000). The study quality was based on the following five criteria, labeled as "yes" or "no": 1) whether either randomly selected or selected to include all in a specific population of cases; 2) whether the response rate for identified cases was higher than 75%; 3) whether controls were drawn from the same population; 4) whether controls were sampled from the general population or from a hospital; 5) whether the response rate for identified controls was higher than 75%. The complete protocol for quality scoring is available on request from XH Yang.

Data Extraction

The following information from each publication was carefully extracted by two investigators independently: the first author's last name, year of publication, country of study and ethnicity, mean age±S.D, variables used for adjustment or matching, control design (hospital or population based, or nested), polymorphisms of COX-2 analyzed, genotyping method and sample size (numbers of case patients and control subjects).

Statistical analysis

First, Hardy-Weinberg equilibrium was tested for the significance of deviation of genotype distribution in the control group for each of the selected case-control data sets, by χ^2 test.

The meta-analysis examined the overall association of the risks (OR, 95% CI) of lung cancer with the COX-2 8473T>C polymorphisms for each study. The pooled ORs for the risk associated with genotype CC and C carriers (CC+TC) compared with TT genotype were calculated respectively for total subjects. A χ^2-based Q test was performed to assess the between-study heterogeneity (Lau et al., 1997). Heterogeneity was considered significant for P<0.10 and the quantity I^2 that represents the percentage of total variation across studies. As a guide, I^2 values of less than 25% is considered "low", values of about 50% considered "moderate", and values of more than 75% considered "high" (Higgins et al., 2003). A random-effect model using the DerSimonian and Laird method and a fixed-effect model using the Mantel-Haenszel method were used to pool the results (Petitti et al., 1994). Random effect is more appropriate when heterogeneity is present. To further explore the origin of heterogeneity, the studies were categorized into different subgroup analyses according to ethnicity, pathological type and smoking status. The significance of the pooled OR was determined by the Z test, a P value of <0.05 was considered significant. Publication bias was investigated by funnel plot and Egger's linear regression test. The significance of the intercept was determined by t-test (Egger et al., 1997). All analyses were done with Review Manager (v4.2; Oxford, England) and Stata statistical software (v.8.0; StataCorp, College Station, TX). All P values were two-sided.

Results

Characteristics of the studies and assessment of quality

A total of nine articles examined the relationship between COX-2 polymorphisms and lung cancer risk (Campa et al., 2004; 2005; Hu et al., 2005; Kang et al.,

2005; Sørensena et al., 2005; Park et al., 2006; Vogel et al., 2008; Liu et al., 2010). Four studies were excluded for the reasons indicated in Figure 1. Among them, one paper was a review article (Zhu et al., 2010). One study evaluated the association of the genotypic polymorphisms in the promoter region of COX-2 gene, instead of the 8473T>C polymorphism in the 3'UTR (Kang et al., 2005). One article investigated a subset population of reported articles (Sørensena et al., 2005) and the other study investigated the population with smaller sample size (Campa et al., 2004). So, the data for our analysis were obtained from five case-control studies (Campa et al, 2005; Hu et al., 2005; Park et al., 2006; Vogel et al., 2008; Liu et al., 2010), including 2450 cancer cases and 4302 controls for 8473T>C polymorphism. Table 1 presents the main characteristics of these studies. All studies reported that genotype distributions in the controls are consistent with Hardy-Weinberg equilibrium.

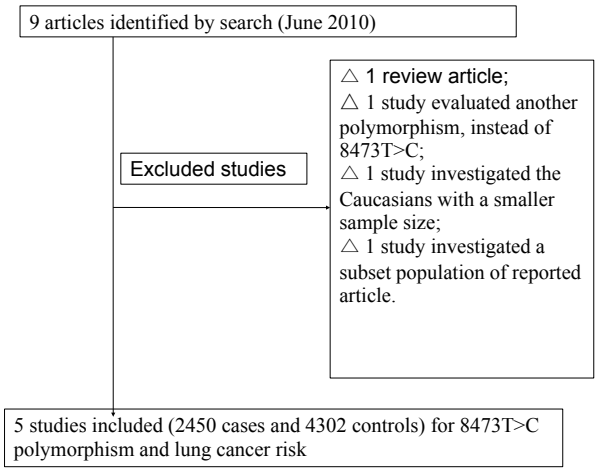

Figure 1. Flow Chart Illustrating Numbers of Studies (Cases and Controls) Included in the Meta-Analyses

Almost all of the case patients were histologically confirmed. Control subjects were mainly drawn from the same population of cases. There are three groups of Asians and two Caucasians. All studies adjusted their data for potential confounders. The quality scores were calculated to each paper as following the criteria of the "MOOSE guidelines". All five studies included were evaluated as high-quality.

Table 1. Main Characterization of Studies Included in This Meta-Analysis when Investigating the Association of COX-2 8473T>C Polymorphisms with Lung Cancer Risk

Reference	Country	Ethnicity	Controls design	Age (Mean±SD)		Gene (polymorphisms)	Sample size		Genotyping methods	Main variables adjustment
				Cases	Controls		Cases	Controls		
Hu, 2005	China	Asian	population-based and cancer-free	56.9±9.9	56.6±6.9	8473C>T (rs5275)	322	323	PCR-PIRA	Frequency-matched, on age (±5 years), sex and ethnicity
Park, 2006	Korea	Asian	healthy volunteers in health-check-up	61.3±9.4	60.2±9.6	8473C>T (rs5275)	582	582	PCR-PIRA	Frequency-matched for age (±5 years) and gender
Vogel, 2008	Denmark	Caucasian	case-cohort study, population-based sub-cohort controls	50 to 64	50 to 64	8473C>T (rs5275), -1195A>G (rs689466)	403	744	PCR-probes	Frequency-matched on sex and age
Campa, 2005	Six countries in Europe (Romania, Hungary, Poland, Russia, Slovakia, Czech Republic)	Caucasian	Most recruited hospital control, Poland is population controls	N/A	N/A	8473C>T (rs5275)	1965	1937	Taqman assay	Frequency-matched for age and gender
Liu, 2010	China, Taiwan	Asian	Non-lung cancer healthy volunteers from health examination cohort of hospital	64.0±6.9	64.8±6.8	-765G>C (rs20417), 8473C>T (rs5275), -1195A>G (rs689466), Intron 1 (rs2745557), Intron 5 (rs16825748), Intron 6 (rs2066826),	716	358	PCR-RFLP	Matching for age, gender and smoking habits

N/A= not available.

Table 2 Summary of Pooled Odds Ratios (ORs) with 95% Confidence Intervals (CIs) and Heterogeneity for Various Genetic Contrasts Performed when Investigating the Association of COX-2 8473T>C Polymorphisms with Lung Cancer Risk

Contrast groups (No. studies)	Pooled OR of CC versus TT of 8473C>T					Pooled OR of (CC+CT) versus TT of 8473C>T				
	No. of CC/TT		OR (95% CI)	*P* value	I^2 *	No. of (CC+CT)/TT		OR (95% CI)	*P* value	I^2*
	Cases	Controls				Cases	Controls			
Total (5)	292/1862	360/2122	0.85 (0.72, 1.01)[a]	0.07	0	1768/1682	2180/2122	0.89 (0.81, 0.97)[C]	0.01	0
Ethnicity										
Asian(3)	30/825	39/1007	0.71 (0.44, 1.17)[b]	0.54	0	437/825	614/1007	0.84 (0.72, 0.98)[C]	0.03	1.4
Caucasian (2)	262/1037	321/1115	0.87 (0.72, 1.05)	0.15	29.5	1331/1037	1566/1115	0.91 (0.81, 1.02)	0.11	0
Histological types										
AC (3)	21/252	132/849	0.70 (0.43, 1.15)	0.16	0	179/252	800/849	0.81 (0.48, 1.36)[d]	0.42	79.9
SCC (3)	19/284	132/849	0.62 (0.37, 1.05)	0.08	0	210/284	800/849	0.93 (0.76, 1.15)	0.52	0
Small cell (3)	14/127	132/849	074 (0.42, 1.33)	0.32	0	69/127	800/849	0.54 (0.31, 0.95)[C]	0.03	62.1
Others (3)	14/103	132/849	0.88 (0.48, 1.62)	0.69	0	81/103	800/849	0.84 (0.61, 1.15)	0.28	0
Smoking status										
Smoking (3)	N/A					1283/1096	1070/793	0.82 (0.64, 1.04)[d]	0.10	57.7
No-smoking (3)	N/A					134/173	601/527	1.01 (0.53, 1.92)[d]	0.97	70.6

*(%) for heterogeneity; [a]Because there is one study with zero sample size of CC genotype both in case and control groups, we only calculated four studies under CC vs. TT; [b] Because there is one study with zero sample size of CC genotype both in case and control groups in Asian subgroup studies, the effects under CC vs. TT contrast were calculated based on the other two studies; [C] Statistically significant, with P<0.05; [d] Random- effects model; AC, adenocarcinomas; SCC, squamous cell carcinomas; N/A= not available

Meta-analysis results

Table 2 summarizes the pooled OR estimates and the corresponding 95% CI of this meta-analysis. The eligible studies included 2450 cancer patients and 4302 control subjects in five data sets. Meta-analysis results show that individuals with the variant CC genotype do not have a modified lung cancer risk (fixed effects pooled OR=0.85, 95% CI=0.72 to 1.01, I^2=0%) contrast with TT genotype in a global analysis (Table 2). After an ethnicity-based sub-analysis, no significant associations with lung cancer risk were found among Asian and Caucasians population (Table 2). However, when C-allele carriers (CC+TC) was contrast with TT genotype, a decreased risk was found (fixed effects pooled OR=0.89, 95% CI=0.81 to 0.97, I^2=0%) in a worldwide population, the same tendency was found among Asians for C-allele carriers (CC+TC) (fixed effects pooled OR=0.84, 95% CI=0.72 to 0.98), no statistically significant associations were observed in Caucasians for C-allele carriers (Table 2).

We further categorized the studies into different subgroup analyses according to pathological type and smoking status, if the data from pathological type and smoking status were not reported in the primary study, we contacted with authors through e-mail to request the information. However, with the exception of Vogel et al.,(2008), we were unable to obtain responses from authors. So we stratified on the available information by histology (Hu et al., 2005; Park et al., 2006; Vogel et al., 2008) and smoking status (Campa et al., 2005; Hu et al., 2005; Vogel et al., 2008) respectively. After stratification by histological type, the pooled OR for the C-allele carriers was 0.54 (95% CI=0.31 to 0.95) for small cell lung cancer. However, no significant associations were found for CC genotype in small cell lung cancer or for all genetic models in lung adenocarnomas, squamous cell as well as other pathological types (Table 2). In the subgroup analysis by smoking status, there were no significant associations among smokers or non-smokers subgroup (Table 2).

We found no evidence of publication bias using the funnel plots and Egger's regression test for CC versus TT genotype (t=0.47, *P*=0.67), and C allele carriers (CC+TC) versus TT genotype (t=-2.39, *P*=0.21) of 8473 T>C polymorphism.

Discussion

This meta-analysis shows that overall, C allele carriers of the 8473T>C polymorphism of COX-2 gene have a reduced risk for lung cancer, especially small cell lung cancer and among Asians. We did not find this association in Caucasians and by histological type. There are several plausible explanations for the lack of an association in the Caucasian population. One reason may be the presence of genetic co-factors in the Caucasian population that mitigate the positive influence of the 8473T>C polymorphism. Indeed, in a study of a Norwegian population reported by Campa et al. in 2004, C allele carriers of 8473T>C polymorphism were reported to have a significant increased risk of lung cancer (Campa et al., 2004). Later the authors repeated the research in six Europe countries with a large sample size (Campa et al., 2005); however, they failed to reproduce any of the associations observed in their previous study (Campa et al., 2004). As the authors mentioned in a later study (Campa et al., 2005), the most likely explanation for the Norwegian study result was that the result was a chance finding.

Zhu and colleagues published a meta-analysis about

COX-2 polymorphisms with cancer risk (Zhu et al., 2010); the authors included all the papers related with cancers. Although they did subgroups analysis according to the cancer types and ethnics, in our view this study has methodological limitations, especially in the subgroup of lung cancer. Following the MOOSE guidelines for meta-analyses of observational studies, the quality of original studies directly influences the reliability of the meta-analysis. If the papers with overlapping data sets (Sørensen et al., 2005; Vogel et al., 2008) or investigated the same population but with different sample size (Campa et al., 2004; 2005), the studies with the most recent or larger sample size were included (Stroup et al., 2000). We therefore carried out a more systematic review of all eligible studies on the COX-2 8473T>C polymorphisms and risk of lung cancer. Also, when stratified according to smoking status, we did not observe any meaningful difference in the magnitude of associations for all genetic models and risk of lung cancer among smokers or non-smokers. Unlike Zhu et al., who found a decreased risk of lung cancer among smokers (Zhu et al., 2009).

Although considerable effort and resources have been put into testing possible associations between 8473T>C polymorphism of COX-2 gene and lung cancer risk, there are still some limitations inherited from the published studies. Firstly, tobacco smoke contains hundreds of chemicals, such as polycyclic aromatic hydrocarbons, aromatic amines, and N-nitroso compounds, which act as carcinogens in laboratory animals (DeBruin and Josephy, 2002). One study suggested a possible interaction between COX-2 and NSAIDs on lung cancer risk (Vogel et al., 2008). Therefore, gene-environment interactions have been of great interest to evaluate the exact roles of genetic polymorphism. However, not all of the reviewed studies analyzed the same environmental factors such as tobacco smoke or the usage of drugs. Thus, these factors limited our further evaluation of potential gene-environment interactions. Secondly, as a meta-analysis of observation studies it may be subject to limitations, such as residual confounding (Takkouche et al., 2008). Thirdly, the quality of the individual studies may largely influence the results of the review. Although, we used the recommendations of the "MOOSE guidelines" (Stroup et al., 2000), it is possible that different criteria would yield other results.

Thus, considering the limited studies and population numbers included in this meta-analysis, our results should be interpreted with caution. For example, the number of individuals with the variant CC genotype is relatively few; and we did not observe any significant association with lung cancer risk in a global analysis as was observed in subgroups analysis. Further, in the histological subgroup analysis, we failed to obtain histological data from authors, thus, the number of different pathological types was relatively small, our results may not have had enough statistical power to explore the real associations.

Despite these limitations, a systematic review of the association of 8473T>C polymorphisms of COX-2 gene with lung cancer risk is statistically more powerful than any single study. The current study supports the view that there is a statistically significant reduced lung cancer risk for C allele carriers among the whole population, especially in Asian and in small cell lung cancer. Moreover, no obvious publication bias was detected in this analysis. These considerations support the reliability of the meta-analysis. Further research should evaluate carefully multiple SNPs that are in linkage disequilibrium and constitute haplotypes, gene-gene and gene-environment interactions on COX-2 polymorphisms, and lung cancer risks are required.

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