RESEARCH COMMUNICATION

Lack of Association of the Cyclooxygenase 8473 T>C Polymorphism with Lung Cancer: Evidence from 9841 Subjects

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Abstract

Objective: Epidemiological studies on the association between T8473C polymorphism of cyclooxygenase 2 (COX 2) and lung cancer risk have provided ambiguous data. To derive a more precise estimation of the association, we conducted a meta-analysis. Methods: Systemic searches of the PubMed and MEDLINE databases were performed, with the last report up to May 2011. The meta-analysis was conducted with a fixed/random effect model. Results: A total of 7 studies including 4,373 lung cancer patients and 5,468 controls were covered. Crude odds ratios (ORs) with 95% confidence intervals (CIs) were used to assess the strength of association. No obvious associations were found for all genetic models when all studies were pooled into the meta-analysis (for C vs. T: OR = 0.948, 95% CI = 0.709-1.268; for TC vs. TT: OR = 0.970, 95% CI = 0.823-1.143; for CC vs. TT: OR = 1.141, 95% CI = 0.666-1.956; for CC/TC vs. TT: OR = 1.102, 95% CI = 0.818-1.251; for CC vs. TT/TC: OR = 1.090, 95% CI = 0.716-1.660). In the subgroup analyses by ethnicity (Asian and Caucasian) and source of controls (population based and hospital based), also no significant associations were found for all genetic models. Conclusions: Taken together, this meta-analysis suggests that the COX 2 T8473C polymorphism is not associated with lung cancer risk

Keywords: COX 2 - polymorphism - lung cancer - meta-analysis

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Introduction

Lung cancer is the leading cause of cancer-related mortality worldwide, with nearly 1.6 million new cases diagnosed and 1.4 million deaths each year (Jemal et al., 2010a; 2010b). Although smoking accounts for 80% of the worldwide lung cancer, less than 20% of smokers develop lung cancer, suggesting that genetic susceptibility involves in the pathogenesis of lung cancer (Hecht., 1999; Peto et al., 2000). With the development of high-throughput genotyping, genetic association studies have been extremely successful in recent years, identifying susceptibility several loci associated with lung cancer (Reyes-Gibby et al., 2009; Bi et al., 2010). An important one is the cyclooxygenases 2 (COX 2) gene, mapped to chromosome 1q25.2-q25.3 in human, is 8.3 kb in size, contains 10 exons and produces an mRNA of 4.6 kb (Khuri et al., 2001; Hedelin et al., 2007). Studies have observed a relatively high expression of COX 2 in human lung epithelial cells and fibroblasts after exposure to tobacco smoke (Shishodia et al., 2003; Martey et al., 2004). Accumulative evidences support that COX 2 plays a key role in lung cancer and can serve as a potential marker of poor prognosis (Han et al., 2006; Ulivi et al., 2008).

A common single nucleotide polymorphism (T8473C) locates at nt427 downstream from the stop condon, and the locus is within a functional region, which could alter gene expression through both messager stability and translational efficiency in vitro (Cok et al., 2001). To date, a number of case-control studies were conducted to evaluate the association between COX 2 T8473C polymorphism and susceptibility to lung cancer (Campa et al., 2004; 2005; Hu et al., 2005; Park et al., 2006; Vogel et al., 2008; Liu et al., 2010; Lim et al., 2011). However, the results were conflicting rather than conclusive. There are several factors that may influence the discordance, including sample size, ethnic background, uncorrected multiple hypothesis testing and publication bias (Zou et al., 2011). In an attempt to address a more precise estimation of relationship, we performed this meta-analysis including 7 eligible studies.

Materials and Methods

Publication search

Exhaustive searches of the PubMed and MEDLINE databases (last search was updated on May 20, 2011) were performed using the following search term "COX-2" or "COX2" or "COX 2" or "cyclooxygenase-2" or "PTGS2" or "PTGS-2" or "prostaglandin endoperoxide

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synthase 2" and "polymorphism" or "polymorphisms" or "polymorphism, genetic" or "polymorphism, single nucleotide" or "genetic variant" and "lung cancer" or "carcinoma of lung". Additional eligible literature was collected from review articles and bibliographies of other relevant studies simultaneously. No restrictions were placed on language. Only published studies with full text papers were recruited, and meeting or conference abstracts were not considered. When more than one of the same or overlapping population was included in several publications, only the study with larger sample size was used in this meta-analysis.

Inclusion criteria

The included studies must meet the following criteria: (1)evaluation of T8473C polymorphism of COX 2 and lung cancer risk; (2)it was a case-control study; (3) presenting sufficient data to estimate an odds ratio (OR) with 95% confidence interval (CI).

Data extraction

Information was carefully extracted from all eligible publications independently according to the meta-analysis of observational studies in epidemiology (MOOSE) guidelines (Stroup et al., 2000) by two investigators (Pan F and Tian J) and the result was reviewed by a third investigator (Zhang Y). Disagreement was resolved by discussion with our research team. From each study, we collected the first author's name, publication date, ethnicity, country of origin, source of controls, total number of cases and controls, genotype frequencies of cases and controls and genotyping method.

Statistical methods

The goodness-of-fit Chi-square test was used to estimate the Hardy-Weinberg equilibrium (HWE) among the control subjects to compare the observed genotype frequencies with the expected ones. Statistical power analyses were done using G*Power 3.1 at the level 0.05 level of significance, assuming an OR of 1.5 (small effect size) (Faul et al., 2009).

Crude ORs with 95% CIs were used to measure the association strength between COX 2 T8473C polymorphism and lung cancer risk. We examined the following pooled ORs: (1) minor allele versus major allele (additive model); (2) heterozygous versus common homozygous carriers and rare homozygous versus common homozygous carriers (codominant model); (3) rare allele carriers versus common homozygous carriers (dominant model); (4) rare homozygous carriers versus common allele carriers (recessive model). Heterogeneity assumption was checked by the Chi-square test based Q-statistic (Cochran., 1954). The fixed-effects model or the random-effects model was used to calculate pooled ORs, depending on the absence (P>0.1 and I^2≤50%) or presence (P≤0.1 or I^2>50%) of Q-statistic (DerSimonian et al., 1986; Mantel et al., 1959). Heterogeneity among studies was also assessed by another measure, I^2 =100%×(Q-df)/Q (Higgins et al., 2002), interpreted as the proportion of total variation contributed by variation between studies rather than by chance. Significance of the pooled ORs was determined by the Z test, and 95% CIs were calculated. Subgroup analyses were derived by ethnicity and source of controls. Sensitivity analysis was performed by limiting the meta-analysis to studies conforming to HWE to assess the stability of the results (Zintzaras et al., 2010). An estimate of potential publication bias was carried out by the funnel plot, in which the standard error of log (OR) of each study was plotted against its log (OR). An asymmetric plot suggests a possible publication bias. Funnel plot asymmetry was further assessed by the method of Egger's linear regression test. The significance of the intercept was determined by the t-test suggested by Egger (P < 0.05 was considered representative of statistically significant publication bias) (Egger et al., 1997). Analyses were performed using STATA version 7.0 (Stata Corporation, College Station, TX).

Results

Characteristics of eligible studies

Seven studies (Campa et al., 2004; 2005; Hu et al., 2005; Park et al., 2006; Vogel et al., 2008; Liu et al., 2010; Lim et al., 2011) met the inclusion criteria after our systemic review. Characteristics are summarized in Table 1. Two of the eligible studies from the same population contained overlapping data (Vogel et al., 2008; Sørensen et al., 2005), and we selected the study with larger sample size (Vogel et al., 2008). A total of 4373 lung cancer patients and 5468 controls were included in the present study. Four were conducted in Asians and three s in Caucasians. There were five hospital-based studies and two population-based studies. The results of the HWE test for the genotypes distribution in controls were also listed in Table 1. Only one study did not abide by HWE (Liu et

Table 1. Characteristics of Studies Investigating the Association between the COX 2 T8473C Polymorphism and Lung Cancer Risk

Author/Year	Ethnicity (country)	Sample size		Genotypes (cases/controls)			Method	P^{HWE}	Power[1]
		cases	controls	T/T	T/C	C/C		(control)	
Campa 2004	Caucasian (Norway)	250(HB)	214(PB)	31/65	107/99	112/50	Taqman	0.304	57.7
Campa 2005	Caucasian (six in Europe)	2135(HB)	2115(HB)	855/805	886/904	224/228	Taqman	0.285	100.0
Hu 2005	Asian (China)	322(HB)	323(PB)	234/209	83/107	5/7	PCR-PIRA	0.113	71.9
Park 2006	Asian (Korea)	582(HB)	582(PB)	352/330	205/220	25/32	PCR-PIRA	0.552	92.7
Vogel 2008	Caucasian (Denmark)	428(PB)	800(PB)	182/310	183/341	38/93	Taqman	0.959	93.9
Liu 2010	Asian (China, Taiwan)	358(HB)	716(PB)	239/468	119/248	0/0	PCR-RFLP	2.09e-08	90.6
Lim 2011	Asian (Singapore, China)	298(HB)	718(HB)	182/462	100/228	15/28	Taqman	0.984	89.0

[1](a=0.05,OR=1.5); HWE, Hardy-Weinberg equilibrium; HB, Hospital-based study; PB, population-based study; OR, odds ratio

Table 2. Meta-analysis of the COX 2 T8473C Polymorphism and Lung Cancer Risk

Study groups(n)	Comparison	Test of association			Test of heterogeneity			Model
		OR (95%CI)	Z	*P*	$\chi 2$	*P*	I^2	
Total (7)	C vs. T	0.948 (0.709-1.268)	0.36	0.720	98.79	0.000	93.9	R
	TC vs. TT	0.970 (0.823-1.143)	0.36	0.719	16.37	0.012	63.3	R
	CC vs. TT	1.141 (0.666-1.956)	0.48	0.631	37.31	0.000	86.6	R
	CC/TC vs. TT	1.102 (0.818-1.251)	0.11	0.916	30.17	0.000	80.1	R
	CC vs. TT/TC	1.090 (0.716-1.660)	0.40	0.688	26.57	0.000	81.2	R
Ethnicity								
Asian (4)	C vs. T	0.786 (0.521-1.187)	1.14	0.252	38.03	0.000	92.1	R
	TC vs. TT	0.906 (0.788-1.042)	1.38	0.166	4.45	0.217	32.5	F
	CC vs. TT	0.897 (0.604-1.330)	0.54	0.588	2.44	0.296	17.9	F
	CC/TC vs. TT	0.905 (0.790-1.037)	1.44	0.151	5.47	0.141	45.1	F
	CC vs. TT/TC	0.922 (0.624-1.361)	0.41	0.682	1.77	0.413	0.0	F
Caucasian (3)	C vs. T	1.208 (0.778-1.874)	0.84	0.400	39.66	0.000	95.0	R
	TC vs. TT	1.138 (0.787-1.644)	0.69	0.493	11.47	0.003	82.6	R
	CC vs. TT	1.408 (0.571-3.473)	0.74	0.457	34.44	0.000	94.2	R
	CC/TC vs. TT	1.270 (0.769-2.096)	0.93	0.350	24.07	0.000	91.7	R
	CC vs. TT/TC	1.222 (0.633-2.359)	0.60	0.551	24.28	0.000	91.8	R
Source								
Population (5)	C vs. T	0.918 (0.571-1.476)	0.35	0.723	90.71	0.000	95.6	R
	TC vs. TT	0.978 (0.752-1.272)	0.16	0.869	14.95	0.005	73.2	R
	CC vs. TT	1.143 (0.418-3.125)	0.26	0.795	35.00	0.000	91.4	R
	CC/TC vs. TT	1.037 (0.732-1.469)	0.20	0.839	28.25	0.000	85.8	R
	CC vs. TT/TC	1.058 (0.495-2.260)	0.15	0.885	24.42	0.000	87.7	R
Hospital (2)	C vs. T	0.973 (0.892-1.062)	0.61	0.541	1.95	0.163	48.7	F
	TC vs. TT	0.953 (0.844-1.076)	0.77	0.440	1.32	0.250	24.3	F
	CC vs. TT	0.957 (0.785-1.168)	0.43	0.667	1.22	0.268	18.3	F
	CC/TC vs. TT	0.957 (0.853-1.074)	0.74	0.458	1.82	0.177	45.2	F
	CC vs. TT/TC	0.989 (0.820-1.193)	0.12	0.908	0.80	0.370	0.0	F

OR odds ratio, CI confidence interval, R random effects model, F fixed effects model.

al., 2010). The genotype distribution in overall controls was consistent with HWE ($P = 0.920$). Additionally, most of studies had more than 80% statistical power (Table 1).

Meta-analysis

Table 2 lists the main results of the meta-analysis and the heterogeneity test. Totally, no obvious associations were found for all genetic models when all studies were pooled into the meta-analysis (for C vs. T: OR = 0.948, 95% CI = 0.709-1.268, $P = 0.000$ and $I^2 = 93.9$ for heterogeneity; for TC vs. TT: OR = 0.970, 95% CI = 0.823-1.143, $P = 0.012$ and $I^2 = 63.3$ for heterogeneity; for CC vs. TT: OR = 1.141, 95% CI = 0.666-1.956, $P = 0.000$ and $I^2 = 86.6$ for heterogeneity; for CC/TC vs. TT: OR = 1.102, 95% CI = 0.818-1.251, $P = 0.000$ and $I^2 = 80.1$ for heterogeneity; for CC vs. TT/TC: OR = 1.090, 95% CI = 0.716-1.660, $P = 0.000$ and $I^2 = 81.2$ for heterogeneity). In the subgroup analyses by ethnicity (Asian and Caucasian) and source of controls (population based and hospital based), also no significant associations were found for all genetic models (Table 2).

Sensitivity analysis

Sensitivity analysis was performed by limiting the meta-analysis to studies conforming to HWE to assess the stability of the results. The corresponding ORs were not materially altered (data not shown), indicating that our results were statistically robust.

Publication bias

Begg's funnel plot and Egger's test were performed to evaluate the publication bias of literature. The shape of the funnel plots did not reveal obvious asymmetry (figures not shown), and the Egger's test also did not demonstrate any evidence of publication bias (for C vs. T: $P = 0.785$; for TC vs. TT: $P = 0.354$; for CC vs. TT: $P = 0.657$; for CC/TC vs. TT: $P = 0.330$; for CC vs. TT/TC: $P = 0.872$).

Discussion

Strong evidence suggests that COX 2 plays an important role in the etiology of lung carcinogenesis. Employment of selective COX 2 inhibitors can reduce lung tumor formation in carcinogen-treated animal models (Rioux et al., 1998; Yao et al., 2000) and reduce the risk of human lung cancer both in vitro and in vivo (Hida et al., 2002; Qadri et al., 2005; Harris et al., 2007). In contrast, COX 2 expression is abundant in the normal tumor-progenitor cells of lung-cancer-sensitive mice (Wardlaw et al., 2000). More recently, overexpression of COX 2 has been found in non-small cell lung cancer (NSCLC) (Wu et al., 2010; Petkova et al., 2004). Furthermore, high levels of COX 2 mRNA and protein expression have been detected in different histologic types of lung cancer and in approximately one third of premalignant lesions (Wolff et al., 1998).

The specific function of COX 2 makes it a strong candidate gene for susceptibility to lung cancer. Several studies have been conducted on the association between COX 2 mutation and lung cancer, but the results were conflicting. Some studies demonstrated an association, whereas others failed to replicate the result. Such

discrepancies may be partially due to the relatively small sample size.

Liu et al. (Liu et al., 2010) performed a meta-analysis about the association of the COX 2 T8473C polymorphism with lung cancer. Their results suggested that the COX 2 gene is a factor for suffering from lung cancer, especially of small cell type among Asians. However, the authors have several concerns related to the article. In the inclusion criteria, they stated that "(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)". Actually, the genotype distributions of controls in one selected eligible study were not in agreement with HWE (Liu et al., 2010). Thus, the study should be excluded. Moreover, Campa et al. (Campa et al., 2004; 2005) conducted two studies about the COX 2 T8473C polymorphism with risk of lung cancer in 2004 and 2005, respectively. One study included 464 subject of Caucasian origin from the Norwegian population, the subjects of the other study were from six countries in central and Eastern Europe (Romania, Hungary, Poland, Russia, Slovakia and Czech Republic). They were not the same population with different sample size and both of them should be recruited in the meta-analysis. To reach a precise conclusion, we present a more systematic review to further investigate the association of COX 2 T8473C polymorphism and lung cancer risk.

In the present meta-analysis, no obvious associations were found for all genetic models in the overall studies population. These findings were consistent with a case-control study nested within a prospective cohort of 57,053 individuals with no previous cancer diagnosis (Vogel et al., 2008). It has been suggested that the role of COX 2 T8473C mutation in lung cancer is not only determined by the functional mechanism of this mutation but also mediated by ethnic background and the source of controls (Hu et al., 2005; Lim et al., 2011). However, when we conducted subgroup analyses according to racial ancestry and the source of controls, no significant associations were found in any subgroup of population. It's worth noting that owing to limited number of studies, our results concerning subgroup analysis should be interpreted with caution.

Heterogeneity is a potential problem that may affect the interpretation of the results. Although some diversity in the studies about designs, inclusion criteria, ethnic background and genotyping assays, there was no statistically significant heterogeneity in overall comparison. Additionally, sensitivity analysis also excluded "winner's curve phenomenon", so we have sufficient evidence to support the meta-analysis result of no significant association between T8473C polymorphism and lung cancer risk in the overall studies population.

Some limitations of this study should be acknowledged. Firstly, the total number of studies and the number of individuals with the variant CC genotype is relatively limited. More studies based on larger sample size and case-control design are still needed. Secondly, some controls were selected from hospital populations. Such subjects may not always be truly representative of the general population. Thirdly, our results are based on unadjusted estimates and a more precise analysis should be performed if more detailed data were available, including age, sex, body mass index (BMI), smoking status, and other lifestyle factors. Last, but not the least, meta-analysis essentially remains retrospective research, which was subject to the methodological deficiencies.

In spite of limitations mentioned above, our meta-analysis also had some advantages. First, substantial number of cases and controls were pooled together and increased statistical power of the analysis. Second, the results of subgroup analyses and sensitivity analyses were not materially altered and did not draw different conclusions, indicating that the whole pooled results were robust. Third, no publication bias were found, indicating that our results may be unbiased.

In summary, our meta-analysis suggests that COX 2 T8473C polymorphism is not associated with lung cancer risk. Further case-control studies based on larger sample size and well-matched controls are still needed to reach a definitive conclusion.

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