CYP1A2 rs2069514 polymorphism and lung cancer susceptibility: a meta-analysis

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Abstract: Many studies have examined the association between the *CYP1A2* rs2069514 polymorphism gene polymorphisms and lung cancer risk in various populations, but their results have been inconsistent. The PubMed was searched for case-control studies published up to Sep 01, 2014. Data were extracted and pooled odds ratios (ORs) with 95% confidence intervals (CI) were calculated. In this meta-analysis, we asse published studies involving comprising 1,168 cases and 1,598 controls of the association between *CYP1A2* 20695 polymorphism and lung cancer risk. For the homozygote A/A and A allele carriers (G/A + A/A), the pooled were 1.47 (95% CI, 1.15-1.99; P=0.007 for heterogeneity) and 1.43 (95% CI, 1.07-1.90; P=0.00 eterogeneity), when compared with the homozygous wild-type genotype (G/G). In the stratified anal y ethn the significantly risks were found among non-Asians for both the A allele carriers and homozy te A/A owever, no significant associations were found in Asian population all genetic models. These results om the meta-analysis suggest that *CYP1A2* rs2069514 polymorphism contributes to risk of lung cancer among non ian p ulation.

Keywords: *CYP1A2*; polymorphism; lung cancer; s cep lity; meta-analysis

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Introduction

Lung cancer remains the deadli cancer worldwide despite improvements in diagnostic and therapeutic techniques (1). Its incidence has yet to peak in many parts of world, particularly in China, which has become a major public health challenge (2). The mechanism of lung carcinogenesis is still not fully understood. Besides smoking status established as the most important single factor in causing lung cancer, host factors, including genetic polymorphisms, have been some growing interest in the study of the tumorigenesis of lung cancer (3). Many environmental carcinogens require metabolic activation by various drug-metabolizing enzymes.

The cytochromes P450 (CYPs) are involved in the metabolic transformation of numerous endogenous and exogenous compounds including carcinogens, and they play important roles in the development of various cancers (4,5). *CYP1A2* is an important enzyme involved in the activation of tobacco-specific nitrosamines (5,6). A number of single-nucleotide polymorphisms have been identified in the *CYP1A2* gene, and these polymorphisms may be modulating factors in the host's susceptibility to lung cancer (7). The predominant homozygous allele, the heterozygous allele and the homozygous rare allele of the *CYP1A2* rs2069514 polymorphism are named the homozygous wild-type genotype (G/G), A allele carriers (G/A) and the rare homozygote (A/A), respectively.

Many studies have investigated associations between *CYP1A2* rs2069514 gene polymorphism and lung cancer risk, but there is the perception that the findings have been inconsistent. A single study may be too underpowered to detect a possible small effect of the polymorphisms on lung cancer, especially when the sample size is relatively small. Different types of study populations may also

contribute the disparate findings. Hence, we performed a meta-analysis of all eligible studies to derive a more precise estimation of the associations of *CYP1A2* rs2069514 polymorphism with lung cancer.

Materials and methods

Publication search

The electronic databases PubMed were searched for studies to include in the present meta-analysis, using the terms: "*CYP1A2*" or "Cytochrome P450 1A2", "rs2069514", "polymorphism" and "lung cancer". An upper date limit of Sep 01, 2014 was applied; no lower date limit was used. The search was performed without any restrictions on language and was focused on studies that had been conducted in humans. Concurrently, the reference lists of reviews and retrieved articles were searched manually. Only full-text articles were included. When the same patient population appeared in several publications, only the most recent or complete study was included in this meta-analysis.

Inclusion criteria

The included studies have to meet the following criteria: (I) evaluating the *CYP1A2* rs2069514 polymorphism and lung cancer risk; (II) case-control studies; and (III) supply the number of individual genotypes for *CYP1A2* rs2069514 genotype in lung cancer cases and controls respectively.

Data extraction

Information was carefully extracted from all eligible publications independently by two authors according to the inclusion criteria listed above. Disagreement was resolved by discussion between the two authors.

The following data were collected from each study: first author's surname, year of publication, ethnicity, total numbers of cases and controls, and numbers of cases and controls with the GG, GA and AA genotypes, respectively. If data from any of the above categories were not reported in the primary study, items were treated as "not applicable". We did not contact the author of the primary study to request the information. Different ethnicity descents were categorized as Asian, and non-Asian. We did not require a minimum number of patients for a study to be included in our meta-analysis.

Statistical analysis

Odds ratio (OR) with 95% confidence interval (CI) was used to assess the strength of association between the *CYP1A2* rs2069514 polymorphism and lung cancer risk. The pooled ORs for the risk associated with the genotypes of homozygote G/G and A allele carriers (G/A + A/A) with the G/G genotype were calculated. Subgroup analyses were done by ethnicity. Heterogeneity assumption was checked by the chi-square-based Q-test (8). A P value greater than 0.10 for the Q-test indicates a lack of heterogeneity among studies, so the pooled OR estimate of the each study was calculated by the fixed-effects model (the Mantel-Haenszel method) (9). Otherwise, the random-effects model (the DerSimonian and Laird method) was used (10). One-way sensitivity analysis was performed to assess the stability of the results, namely, a single study in the meta-analysis was deleted each time to reflect the influence of the individual data-set to the pooled OR (11). 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 assessed by the method of Egger's linear regression test, a linear regression approach to measure the funnel plot asymmetry on the natural logarithm scale of the OR. 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) (12). All of the calculations were performed using STATA version 11.0 (STATA Corporation, College Station, TX, USA).

Results

Study characteristics

A total of six publications involving 1,168 lung cancer cases and 1,598 controls met the inclusion criteria and were ultimately analyzed (13-18). *Table 1* presents the main characteristics of these studies. Among the six publications, all were published in English. The sample sizes ranged from 291 to 1,200. Almost all of the cases were histologically confirmed. Controls were mainly healthy populations. There were two groups of Asians, four groups of non-Asian population.

Meta-analysis results

Table 2 listed the main results of this meta-analysis. Overall,

Table 1 Distribution of *CYP1A2* rs2069514 among lung cancer cases and controls included in this meta-analysis

First author-year	Ethnicity (country of origin)	Total sample (case/control)	Lung cancer			Controls		
			GG	GA	AA	GG	GA	AA
Gervasini 2012 (13)	Caucasian (Spain)	95/196	90	5	0	192	4	0
Pavanello 2012 (14)	Caucasian (Italy)	423/777	417	6	0	764	13	0
Singh 2010 (15)	Asian (India)	200/200	171	29	0	175	25	0
Zienolddiny 2008 (17)	Caucasian (Norway)	243/214	237	6	0	206	8	0
B'chir 2009 (16)	African (Tunisia)	101/98	51	50		86	14	
Osawa 2007 (18)	Asian (Japan)	106/113	65	36	5	63	42	8

GG indicates wild-type; GA indicates heterozygote; AA indicates variant homozygote; #, the number of the combined GA and AA genotypes.

Table 2 Summary ORs for various contrasts of *CYP1A2* rs2069514 polymorphisms in this meta-analysis

Types	No. of studies	(G/A + A/A) *vs.* G/G		A/A *vs.* G/G	
		OR (95% CI)	P (Q-test)	OR (95%CI)	P (Q-test)
Total	6	1.43 (1.07-1.90)	0.000	1.47 (1.15-1.99)	0.007
Asian	2	0.96 (0.65-1.42)	0.318	0.90 (0.58-1.33)	0.003
Non-Asian	4	2.32 (1.51-3.56)	0.001	2.44 (1.63-3.74)	0.006

P (Q-test), P value of Q-test for heterogeneity test; OR, odds ratio; CI, confidence interval.

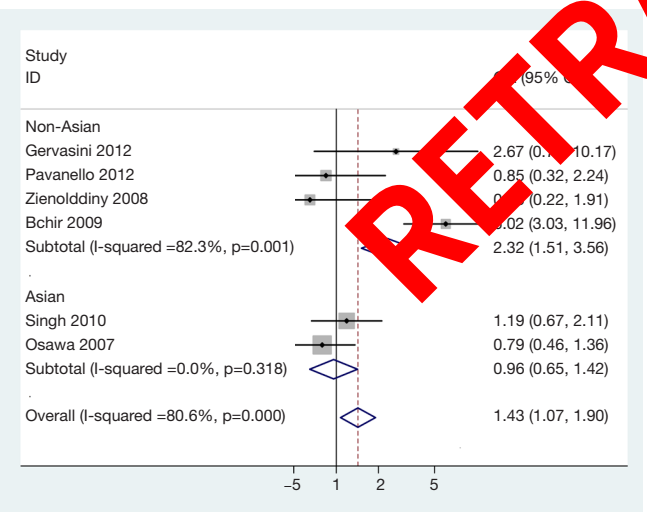

Figure 1 Forest plot (random-effects model) of lung cancer risk associated with *CYP1A2* rs2069514 polymorphism for (G/A + A/A) versus G/G. Each box represents the OR point estimate, and its area is proportional to the weight of the study. The diamond (and broken line) represents the overall summary estimate, with CI represented by its width. The unbroken vertical line is set at the null value (OR =1.0). OR, odds ratio; CI, confidence intervals.

for the homozygote A/A and A allele carriers (G/A + A/A), the pooled ORs for all studies combined 1,168 cases and 1,598 controls were 1.47 (95% CI, 1.15-1.99; P=0.007 for heterogeneity) and 1.43 (95% CI, 1.07-1.90; P=0.000 for heterogeneity) (*Figure 1*), when compared with the homozygous wild-type genotype (G/G).

In the stratified analysis by ethnicity, significantly risks were found among non-Asian for both the A allele carriers (OR =2.32; 95% CI, 1.51-3.56; P=0.001 for heterogeneity) and homozygote A/A (OR =2.44; 95% CI, 1.63-3.74; P=0.006 for heterogeneity). Among Asian populations, no significant association was found in A/A *vs.* G/G (OR =0.90; 95% CI, 0.58-1.33; P=0.003 for heterogeneity), or A allele carriers *vs.* G/G (OR =0.96; 95% CI, 0.65-1.42; P=0.318 for heterogeneity).

Sensitivity analyses

A single study involved in the meta-analysis was deleted each time to reflect the influence of the individual data set to the pooled ORs, and the corresponding pooled ORs were not materially altered (data not shown).

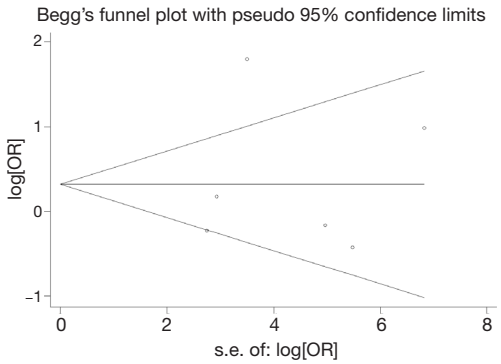

Figure 2 Begg's funnel plot of *CYP1A2* rs2069514 polymorphism and lung cancer risk for (G/A + A/A) *vs.* G/G. OR, odds ratio.

Publication bias

Begg's funnel plot and Egger's test were performed to access the publication bias of literatures. Evaluation of publication bias for G/A + A/A *vs.* GG showed that the Egger test was not significant (P=0.869). The funnel plots for publication bias (*Figure 2*) also did not show some asymmetry. These results did not indicate a potential for publication bias.

Discussion

CYP1A2 is a key factor in the metabolic activation of carcinogenic aromatic and heterocyclic amines, the inhibition activity of this enzyme may represent a logical strategy for preventing the development of human cancers induced by the aromatic and heterocyclic amines (19). Thus, genetic mutations in the *CYP1A2* gene are considered to be associated with increased *CYP1A2* activity and may be linked to the carcinogenic process (20).

Recently, genetic variants of the *CYP1A2* rs2069514 gene in the etiology of several cancers have drawn increasing attention. To we knowledge, this meta-analysis is firstly available for comprehensively evaluating the associations between *CYP1A2* rs2069514 polymorphism and lung cancer risk. This meta-analysis summarizes all the available data on the association between *CYP1A2* rs2069514 polymorphism and lung cancer risk, including a total of 1,168 cases and 1,598 controls. Our results indicated that *CYP1A2* rs2069514 polymorphism contributes to risk of lung cancer among non-Asian population, but for Asian population.

When stratified according to ethnicity, non-Asians with the A allele carriers and the homozygote A/A showed an increased risk of lung cancer compared with those with the G/G genotype. However, among Asian population, no significant associations were found for all genetic models. These findings indicate that polymorphism of *CYP1A2* rs2069514 may be important in specific ethnicity of lung cancer patients and the effect of A allele on the risk of lung cancer may differ by ethnicity. Population stratification is an area of concern, and can lead to spurious evidence for the association between the marker and disease, suggesting a possible role of ethnic differences in genetic backgrounds and the environment they lived in (21). In addition, it also likely that the observed ethnic differences may be due to the chance because studies with small sample size may have insufficient statistical power to detect a slight effect or may have generated a fluctuated assessment.

Some limitations of this meta-analysis should be acknowledged. Firstly, heterogeneity is a potential problem when interpreting all the results of meta-analyses. Although we minimized the likelihood by performing a careful search for published studies, using the explicit criteria for study inclusion, performing data extraction and data analysis strictly, the significant between-study heterogeneity still existed in almost each comparison. The presence of heterogeneity can result from differences in the selection of controls, age distribution, the lifestyle factors, and so on. Although most of the controls were selected from healthy populations, some studies had selected controls among friends or family of lung cancer patients or patients with other diseases. Secondly, only published studies were included in this meta-analysis. The presence of publication bias indicates that non-significant or negative findings may be unpublished. Lastly, our results were based on unadjusted estimates, while a more precise analysis should be conducted if individual data were available, which would allow for the adjustment by other covariates including age, ethnicity, family history, environmental factors and lifestyle.

In conclusion, this meta-analysis suggests that the *CYP1A2* rs2069514 polymorphism is associated with lung cancer risk among non-Asian population, but not among Asian population. In addition, it is necessary to conduct large trials using standardized unbiased methods, homogeneous lung cancer patients and well matched controls, with the assessors blinded to the data.

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