RESEARCH ARTICLE

Four Polymorphisms in the Cytochrome P450 1A2 (CYP1A2) Gene and Lung Cancer Risk: a Meta-analysis

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Abstract

Background: Previous published data on the association between CYP1A2 rs762551, rs2069514, rs2069526, and rs2470890 polymorphisms and lung cancer risk have not allowed a definite conclusion. The present meta-analysis of the literature was performed to derive a more precise estimation of the relationship. Materials and Methods: 8 publications covering 23 studies were selected for this meta-analysis, including 1,665 cases and 2,383 controls for CYP1A2 rs762551 (from 8 studies), 1,456 cases and 1,792 controls for CYP1A2 rs2069514 (from 7 studies), 657 cases and 984 controls for CYP1A2 rs2069526 (from 5 studies) and 691 cases and 968 controls for CYP1A2 rs2470890 (from 3 studies). Results: When all the eligible studies were pooled into the meta-analysis for the CYP1A2 rs762551 polymorphism, significantly increased lung cancer risk was observed in the dominant model (OR=1.21, 95 % CI=1.00-1.46). In the subgroup analysis by ethnicity, significantly increased risk of lung cancer was observed in Caucasians (dominant model: OR=1.29, 95%CI=1.11-1.51; recessive model: OR=1.33, 95%CI=1.01-1.75; additive model: OR=1.49, 95%CI=1.12-1.98). There was no evidence of significant association between lung cancer risk and CYP1A2 rs2069514, s2470890, and rs2069526 polymorphisms. Conclusions: In summary, this meta-analysis indicates that the CYP1A2 rs762551 polymorphism is linked to an increased lung cancer risk in Caucasians. Moreover, our work also points out the importance of new studies for rs2069514 associations in lung cancer, where at least some of the covariates responsible for heterogeneity could be controlled, to obtain a more conclusive understanding about the function of the rs2069514 polymorphism in lung cancer development.

Keywords: CYP1A2 - polymorphism - lung cancer - susceptibility - meta-analysis

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Introduction

Lung cancer is a major cause of cancer-related death in the worldwide and the overall survival rate has still an extremely poor (Jemal et al., 2011). The exact mechanism of lung cancer is still under investigation. Epidemiological studies have demonstrated tobacco smoking as well as environmental tobacco smoke in non-tobacco users as the major risk factor in the development of lung cancer (Zhong et al., 2000; Parkin et al., 2001). However, only 10-15% of lifelong smokers develop lung cancer indicating that genetic factors may play an important role in determining the susceptibility to lung cancer (Hecht et al., 1999; Strange et al., 1999; Schneider et al., 2004).

Various Polymorphisms have been studied to elucidate the association with the risk of lung cancer (Liu et al., 2013; Zhu et al., 2013; Bayram, 2014). CYP1A2 is located on chromosome 15q in opposite orientation and separated by 23.3 kb, it is a major drug-metabolizing enzyme, with a wide range of substrates (Eaton et al., 1995). Its role in the metabolism of polycyclic aromatic hydrocarbons (PAHs) and heterocyclic amines (HAs) underlines its possible significance in carcinogenesis. Since both PAHs and Has are present in food, the activity of the CYP1A2 enzyme may affect the formation of their activated forms after absorption from the large bowel, and thus influence on the risk of cancer. An approximately 15- to 60-fold inter-individual variation in CYP1A2 mRNA, protein expression and enzyme activity has been reported in human liver (Shimada et al., 1994). Further, interethnic differences in CYP1A2 activity have also been reported (Relling et al., 1992; Bartoli et al., 1996). CYP1A2 is an important gene in catalyzing 2- and 4-hydroxylations of estrogens (Yamazaki et al., 1998; Tsuchiya et al., 2005; Nebert et al., 2006) and metabolism of carcinogens (Eaton et al., 1995; Nebert et al., 1996; Nebert et al., 2004). In humans, CYP1A2 is highly polymorphic and several single nucleotide polymorphisms (SNPs) including four common SNPs represented as CYP1A2 *p*.N516N (rs2470890; 1545T>C), CYP1A2*1C (rs2060514; -3858G>A), and CYP1A2*1F (rs762551; -163C>A) alleles have been identified in different ethnic population worldwide(Chida., 1999; Aklilllu et al., 2003; Ghotbi et al., 2007). CYP1A2*1C, located in the 5'-non-coding promoter region of CYP1A2, was reported to be associated with decreased enzyme inducibility in

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Japanese smokers but seems to be very rare (Nakajima et al., 1999). Likewise, CYP1A2*1F, located in intron 1, has been associated with decreased caffeine metabolism in Caucasian smokers (Sachse et al., 1999).

To date, a number of molecular epidemiological studies have been done to evaluate the association between CYP1A2 rs762551, rs2069514, and rs2470890 polymorphisms and lung cancer risk in diverse populations (Gemignani et al., 2007; Osawa et al., 2007; Zienolddiny et al., 2008; Bchir et al., 2009; Aldrich et al., 2009; Singh et al., 2010; Gervasini et al., 2012; Pavanello et al., 2012). However, the results were inconsistent or even contradictory. Therefore, we performed a comprehensive meta-analysis by including the most recent and relevant articles to identify statistical evidence of the association between CYP1A2 rs762551, rs2069514, and rs2470890 polymorphisms and risk of lung cancer that have been investigated. Meta-analysis is a powerful tool for summarizing the different studies. It can not only overcome the problem of small size and inadequate statistical power of genetic studies of complex traits, but also provide more reliable results than a single case-control study.

Materials and Methods

Identification and eligibility of relevant studies

A comprehensive literature search was performed using the PubMed and EMBASE database for relevant articles published (the last search update was Apr. 15, 2014) with the following key words "CYP1A2", "cytochrome P-450 1A2", "cytochrome P450 1A2", "polymorphism", "Variant", or "Mutation", and "Lung". In addition, studies were identified by a manual search of the reference lists of reviews and retrieved studies. We included all the case-control studies and cohort studies that investigated the association between CYP1A2 rs762551, rs2069514, rs2069526, and rs2470890 polymorphisms and lung cancer risk with genotyping data. All eligible studies were retrieved, and their bibliographies were checked for other relevant publications. When the same sample was used in several publications, only the most complete study was included following careful examination.

Inclusion criteria

The included studies have to meet the following criteria: (1) only the case-control studies or cohort studies were considered; (2) evaluated the CYP1A2 rs762551, rs2069514, rs2069526, and rs2470890 polymorphisms and the risk of lung cancer; (3) the genotype distribution of the polymorphism in cases and controls were described in details and the results were expressed as odds ratio (OR) and corresponding 95% confidence interval (95%CI). Major reasons for exclusion of studies were as follows: (1) not for cancer research; (2) only case population; and (3) duplicate of previous publication.

Data extraction

Information was carefully extracted from all eligible studies independently by two investigators according to the inclusion criteria listed above. The following data were collected from each study: first author's name, year of publication, country of origin, ethnicity, source of controls (population-based controls and hospital-based controls), sample size, and numbers of cases and controls in the CYP1A2 rs762551, rs2069514, rs2069526, and rs2470890 genotypes whenever possible. Ethnicity was categorized as "Caucasian", "Asian", "Latinos", and "African". When one study did not state which ethnic groups was included or if it was impossible to separate participants according to phenotype, the sample was termed as "mixed population". We did not define any minimum number of patients to include in this meta-analysis. Articles that reported different ethnic groups and different countries or locations, we considered them different study samples for each category cited above.

Statistical analysis

Crude odds ratios (ORs) together with their corresponding 95%CIs were used to assess the strength of association between the CYP1A2 rs762551, rs2069514, rs2069526, and rs2470890 polymorphisms and the risk of lung cancer. Following published recommendations for quality assessment in meta-analyses of genetic associations, we examined: choice of genetic models (we adopted three genetic models, avoiding assuming only one "wrong" genetic model). The pooled ORs were performed for dominant model (AA+AG versus GG), recessive model (AG+GG versus AA), and additive model (AA versus GG), respectively. Between-study heterogeneity was assessed by calculating Q-statistic (Heterogeneity was considered statistically significant if $p<0.10$) (Davey et al., 1997) and quantified using the I^2 value, a value that describes the percentage of variation across studies that are due to heterogeneity rather than chance, where $I^2=0\%$ indicates no observed heterogeneity, with 25% regarded as low, 50% as moderate, and 75% as high (Higgins et al., 1997). If results were not heterogeneous, the pooled ORs were calculated by the fixed-effect model (we used the Q-statistic, which represents the magnitude of heterogeneity between-studies) (Mantel et al., 1959). Otherwise, a random-effect model was used (when the heterogeneity between-studies were significant) (Dersimonian et al., 1986). Moreover, sensitivity analysis was performed by excluding a single study each time. We also ranked studies according to sample size, and then repeated this meta-analysis. Sample size was classified according to a minimum of 200 participants and those with fewer than 200 participants. The cite criteria were previously described (Klug et al., 2009). Last, sensitivity analysis was also performed, excluding studies whose allele frequencies in controls exhibited significant deviation from the Hardy-Weinberg equilibrium (HWE), given that the deviation may denote bias. Deviation of HWE may reflect methodological problems such as genotyping errors, population stratification or selection bias. Begg's funnel plots (Begg et al., 1994), and Egger's linear regression test (Egger et al., 1997), were used to assess publication bias. A meta-regression analysis was carried out to identify the major sources of between-studies variation in the results, using the log of the ORs from each study as dependent variables, and ethnicity, source of

controls, HWE, and sample size as the possible sources of heterogeneity. All of the calculations were performed using STATA version 10.0 (STATA Corporation, College Station, TX).

Results

Literature search and meta-analysis databases

Relevant publications were retrieved and preliminarily screened. As shown in Figure 1, 52 publications were identified, among which 17 irrelevant papers were excluded. Thus, 35 publications were eligible. Among these publications, 26 articles were excluded because they were review articles, case reports, and other polymorphisms of CYP1A2. In addition, 1 article (Pavanello et al., 2007). was excluded because of this population overlapped with another included study (Pavanello et al., 2012). As summarized in Table 1, 8 articles with 23 studies were selected for this meta-analysis, including 1,665 cases and 2,383 controls for CYP1A2 rs762551 (from 8 studies), 1,456 cases and 1,792 controls for CYP1A2 rs2069514 (from 7 studies), 657 cases and 984 controls for CYP1A2 rs2069526 (from 5 studies) and 691 cases and 968 controls for CYP1A2 rs2470890 (from 3 studies). Tables 1 list all essential information such as the publication year, first author, Country, ethnicity, source of controls, matching, and the numbers of cases and controls for CYP1A2 rs762551, rs2069514, rs2069526 and rs2470890 respectively. Genotype frequencies for lung cancers and controls by ethnicity were listed in Table 2.

Meta-analysis results

Table 2 lists the main results of the meta-analysis of CYP1A2 rs762551 polymorphism and lung cancer risk. When all the eligible studies were pooled into the meta-analysis of CYP1A2 rs762551 polymorphism, significantly increased lung cancer risk was observed in dominant model (OR=1.21, 95%CI=1.00-1.46, *p* value of heterogeneity test [P_h]=0.083, I^2=44.4 %). In the subgroup analysis by ethnicity, significantly increased risk of lung cancer was observed in the Caucasians (dominant model: OR=1.29, 95%CI=1.11-1.51, P_h= 0.948, I^2=0.0%; recessive model: OR=1.33, 95%CI=1.01-1.75, P_h= 0.181, I^2=41.4%; additive model: OR=1.49, 95%CI=1.12-1.98, P_h=0.358, I^2=2.7%).

Table 2 also lists the main results of the meta-analysis of CYP1A2 rs2069514 and CYP1A2 rs247890 polymorphism and lung cancer risk. When all the eligible studies were pooled into the meta-analysis of CYP1A2 rs2069514 and CYP1A2 rs247890 polymorphisms, there was no evidence of significant association between lung cancer risk and CYP1A2 rs2069514 and CYP1A2 rs247890 polymorphisms. And in subgroup analysis by

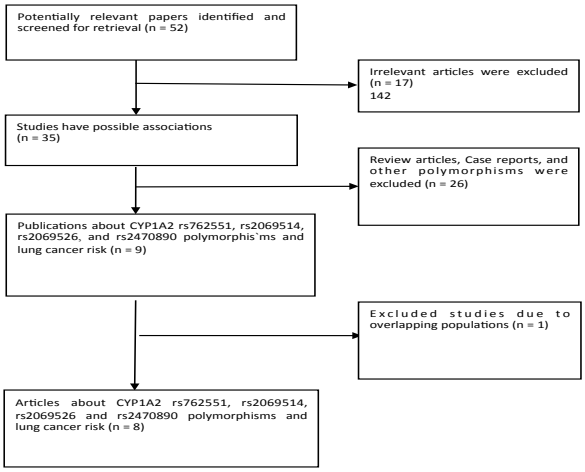

Figure 1. Study Flow Chart Explaining the Selection of the 8 Eligible Case-control Studies Included in the Meta-Analysis

Table 1. Main Characteristics of all Studies Included in the Meta-Analysis

First author/year	Country	Ethnicity	SNP	Case-control	SC	HWE
Gervasini 2012	Spain	Caucasian	CYP1A2 rs762551	95-196	HB	0.787
Pavanello 2012	Italy	Caucasian	CYP1A2 rs762551	421-776	PB	0.859
Singh 2010-2011	India	Asian	CYP1A2 rs762551	200-200	HB	0.227
Zienolddiny 2008	Norway	Caucasian	CYP1A2 rs762551	335-393	PB	0.956
Bchir 2009	Tunisia	African	CYP1A2 rs762551	101-98	HB	0.018
Aldrich 2009	USA	Latinos	CYP1A2 rs762551	113-299	HB	0.76
Osawa 2007	Japan	Asian	CYP1A2 rs762551	103-111	HB	0.833
Gemignani 2007	Multiple	Caucasian	CYP1A2 rs762551	297-310	HB	0.945
Gervasini 2012	Spain	Caucasian	CYP1A2 rs2069514	95-196	HB	0.787
Pavanello 2012	Italy	Caucasian	CYP1A2 rs2069514	423-777	PB	0.859
Singh 2010-2011	India	Asian	CYP1A2 rs2069514	200-200	HB	0.227
Zienolddiny 2008	Norway	Caucasian	CYP1A2 rs2069514	243-214	PB	0.956
Bchir 2009	Tunisia	African	CYP1A2 rs2069514	101-98	HB	0.018
Osawa 2007	Japan	Asian	CYP1A2 rs2069514	106-113	HB	0.833
Gemignani 2007	European	Caucasian	CYP1A2 rs2069514	288-194	HB	0.945
Gervasini 2012	Spain	Caucasian	CYP1A2 rs2069526	95-196	HB	0.787
Singh 2010-2011	India	Asian	CYP1A2 rs2069526	200-200	HB	0.227
Zienolddiny 2008	Norway	Caucasian	CYP1A2 rs2069526	194-239	PB	0.956
Bchir 2009	Tunisia	African	CYP1A2 rs2069526	101-98	HB	0.018
Gemignani 2007	European	Caucasian	CYP1A2 rs2069526	247-251	HB	0.945
Zienolddiny 2008	Norway	Caucasian	CYP1A2 rs2470890	295-371	PB	0.956
Aldrich 2009	USA	Latinos	CYP1A2 rs2470890	113-299	HB	0.76
Gemignani 2007	European	Caucasian	CYP1A2 rs2470890	283-298	HB	0.945

*PB Population-based study, HB Hospital-based study, SC Source of controls, HWE Hardy-Weinberg equilibrium

Table 2. Stratified Analysis of CYP1A2 Polymorphisms on Lung Cancer Risk

Genetic contrasts	Analysis	N	Sample size		Test of association		Test of heterogeneity	
			Case	Control	OR	95%CI	*P*	I^2
CYP1A2 rs762551								
Dominant model	Overall	8	1665	2383	1.21	1.00-1.46*	0.083	44.40%
	Caucasian	4	1148	1675	1.29	1.11-1.51	0.948	0.00%
Recessive model	Overall	7	1570	2187	1.39	0.92-2.11*	0.001	73.90%
	Caucasian	3	1053	1479	1.33	1.01-1.75	0.181	41.40%
Additive model	Overall	7	867	1274	1.45	0.93-2.26*	0.001	73.40%
	Caucasian	3	579	879	1.49	1.12-1.98	0.358	2.70%
CYP1A2 rs2069514								
Dominant model	Overall	7	1446	1692	-	-	<0.001	79.50%
	Caucasian	4	1039	1481	0.86	0.50-1.50	0.301	17.90%
Recessive model	Overall	7	1203	1678	-	-	0.003	88.60%
	Caucasian	4	796	1267	-	-	-	-
Additive model	Overall	7	1092	1568	-	-	0.001	90.60%
	Caucasian	4	781	1251	-	-	-	-
CYP1A2 rs2470890								
Dominant model	Overall	3	691	968	1.04	0.74-1.45*	0.073	61.70%
Recessive model	Overall	3	691	968	0.95	0.74-1.45	0.749	0.00%
Additive model	Overall	3	362	532	1.02	0.75-1.37	0.749	0.00%
CYP1A2 rs2069526								
Dominant model	Overall	5	837	984	1.16	0.56-2.42*	0.002	77.10%
Recessive model	Overall	4	643	745	4.51	1.85-10.96	-	-
Additive model	Overall	4	643	745	5.08	2.06-12.52	-	-

*N, Number of study, *Random-effect model was used when *P* value of heterogeneity test (P_h) < 0.10; otherwise, fixed-effect model was used, the bold values indicate that the results have statistic significan

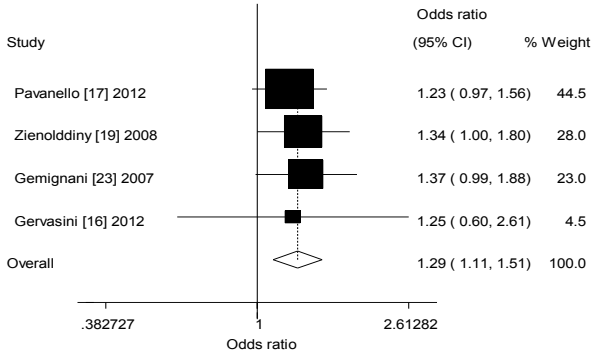

Figure 2. Forest Plot of CYP1A2 rs762551polymorphism and Lung Cancer Risk in Caucasians (Dominant Model)

ethnicity, no significant association was found in any genetic model.

We also examined the association of the CYP1A2 rs2069526 polymorphism and lung cancer risk (Table 2). Significantly increased lung cancer risk was observed in recessive model (OR=4.51, 95%CI=1.85-10.96) and in additive model (OR=5.08, 95%CI=2.06-12.52).

Test of heterogeneity and sensitivity

We tested the inclusion criteria of this meta-analysis by a sensitivity analysis. Sensitivity analysis was conducted to determine whether modification of the inclusion criteria of this meta-analysis affected the results. A single study involved in the meta-analysis was deleted each time to reflect the influence of individual data set to the pooled Ors, and the corresponding pooled ORs were not essentially altered for CYP1A2 rs2069514 and CYP1A2 rs2470890 polymorphism and lung cancer risk (data not shown). After the study of Bchir et al (B'chir et al., 2009). was deleted, the results of CYP1A2 rs762551 were changed (dominant model: OR=1.15, 95%CI= 0.83-1.57, P_h=0.000, I^2= 79.7%) in overall analysis. In addition, when the study of Bchir et al(B'chir et al., 2009) was deleted, the results of CYP1A2 rs2069526 were also changed (data not shown).

Publication bias

Both Begg's funnel plot and Egger's test were performed to assess the publication bias of literatures. Begg's funnel plots did not reveal any evidence of obvious asymmetry in these genetic polymorphisms (Figure not shown). The Egger's test results suggested no evidence of publication bias in the meta-analysis of CYP1A2 rs762551, rs2069514, rs2069526 and rs2470890 (data not shown), indicating that our results were statistically robust.

Discussion

CYP1A2 is an important member of the cytochrome P450 super-family in the metabolic activity 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 (Miranda et al., 2000). Thus, genetic mutations in the CYP1A2 gene are considered to be associated with increased CYP1A2 activity and may be linked to the carcinogenic process (Bozina et al., 2009). CYP1A2 have been reported to be associated with different kinds of cancer risk such as Cholangiocarcinoma, lung cancer (Kukongviriyapan., 2012; Deng et al., 2013). A number of epidemiologic studies have reported the association of CYP1A2 with lung cancer risk. However, the results remained controversial. Some original studies thought that CYP1A2 rs762551, rs2069514, rs2069526 and rs2470890 polymorphisms

were associated with lung cancer risk, but others had different opinions (Deng et al., 2013; Tian et al., 2013; Ma et al., 2014). Genetic alterations in the regulatory region of CYP1A2, given its prominent role in the activation of certain procarcinogens may be associated with lung cancer risk in a high-incidence area. Available data on the effect of CYP1A2 polymorphisms in lung cancer are scarce, especially in comparison with the bulk of studies on other genes involved in carcinogen activation/ detoxification (Cui et al., 2012). In order to resolve this conflict, a Meta -analysis was conducted to explore the association between CYP1A2 rs762551, rs2069514, rs2069526 and rs2470890 polymorphisms and lung cancer risk.

When all the eligible studies were pooled into the meta-analysis of CYP1A2 polymorphisms, there was significant association between lung cancer risk and CYP1A2 rs762551. However, significant between-study heterogeneity was detected in any genetic model. Hence, we performed subgroup analysis by ethnicity. In the stratified analysis by ethnicity for CYP1A2 rs762551, significantly increased lung cancer risk was found among Caucasians (dominant model: OR=1.29, 95%CI=1.11-1.51; recessive model: OR=1.33, 95%CI=1.01-1.75; additive model: OR=1.49, 95%CI=1.12-1.98), but not other populations. After the study of Bchir et al (B'chir et al., 2009) was deleted, the results of CYP1A2 rs762551 were changed (dominant model: OR=1.15, 95%CI= 0.83-1.57) in overall analysis. It should be considered that the apparent inconsistency of these results may underlie differences in ethnicity, lifestyle and disease prevalence as well as possible limitations due to the relatively small sample size. The current knowledge of carcinogenesis indicates a multi-factorial and multistep process that involves various genetic alterations and several biological pathways. Thus, it is unlikely that risk factors of cancer work in isolation from each other. And the same polymorphisms may play different roles in cancer susceptibility, because cancer is a complicated multi-genetic disease, and different genetic backgrounds may contribute to the discrepancy (Hirschhorn et al., 2002). And even more importantly, the low penetrance genetic effects of single polymorphism may largely depend on interaction with other polymorphisms and/or a particular environmental exposure. These findings indicate that CYP1A2 rs762551 polymorphism may be important in specific ethnicity of lung cancer risk, especially in Caucasians, but not in all populations for lung cancer, suggesting a possible role of ethnic difference in genetic background and the environment they lived in.

We noticed that 2 meta-analysis had been reported on the cancer risk with CYP1A2 polymorphism. We have read with great interest the recent meta-analysis by Tian et al (Tian et al., 2009). This meta-analysis indicated that CYP1A2 rs762551 polymorphism might be not association with lung cancer risk. We have also read the recent meta-analysis by Li et al (Zhenzhen et al., 2013). Li et al (Zhenzhen et al., 2013). had 7 studies for CYP1A2 rs762551 polymorphism in lung cancer. Their meta-analysis suggested that no significant associations with the risk of lung cancer in any model. Having analyzed an almost twofold larger number of studies than the previous meta-analysis (Tian et al., 2009; Deng et al., 2013; Zhenzhen et al., 2013). our results seem to confirm and establish the trend in the meta-analysis of CYP1A2 rs762551 polymorphism that the data by the previous meta-analysis (Tian et al., 2009; Zhenzhen et al., 2013; Deng et al., 2013) had indicated. However, the results of the present meta-analysis are not in accordance with those reported the previous meta-analysis (Tian et al., 2009; Zhenzhen et al., 2013). Our meta-analysis indicates that CYP1A2 rs762551 polymorphism may be associated with increased lung cancer risk in Caucasians, which is according with Deng's meta-analysis (Deng et al., 2013).

In this meta-analysis, there was no evidence of significant association between lung cancer risk and CYP1A2 rs2069514, s2470890, and rs2069526 polymorphisms. However, at any case, the association between CYP1A2 rs2069514, s2470890, and rs2069526 polymorphisms and lung cancer risk essentially remains an open field, as the number of studies (n=7 for rs2069514, n=3 for rs2470890, and n=5 for 2069526) is considerably smaller than that needed for the achievement of robust conclusions (Higgins et al., 2008).

In the present meta-analysis, highly between-studies heterogeneity was observed for rs2069514. The reason may be that the hospital-based studies have some biases because such controls may contain certain benign diseases which are prone to develop malignancy and may not be very representative of the general population. Thus, the use of a proper and representative cancer-free control subjects is very important in reducing biases in such genotype association studies. Possible sources of heterogeneity, such as controls source and ethnicity did not demonstrate the evidence of any significant variation by meta-regression. It is possible that other limitations of recruited studies may partially contribute to the observed heterogeneity. And this indicates that it may be not appropriate to use an overall estimation of the relationship between CYP1A2 rs2069514 polymorphism and risk of lung cancer. Hence, new studies are important for rs2069514 association with lung cancer risk.

There are several limitations in this meta-analysis. First, the controls were not uniformly defined. Although all the controls were healthy populations, most of them were common populations, some controls were population-based; other controls were hospital-based. Hence, non-differential misclassification bias is possible. Second, in the subgroup analysis may have had insufficient statistical power to check an association. Third, we were also unable to examine the interactions among gene-environment, lacking of the original data of the included studies limited our further evaluation of potential interactions, which may be an important component of the association between CYP1A2 rs762551, rs2069514, rs2069526 and rs2470890 polymorphisms and environment and lung cancer risk. Fourth, it was much difficult to get the all articles published in various languages. We only included the studies published in English and Chinese. Last, our results were based on unadjusted published estimates. Because of data limitations, we were unable to adjust them such as age, smoking, alcohol consumption etc.

In summary, this meta-analysis indicates that CYP1A2

rs762551 polymorphism showed an increased lung cancer risk in Caucasians and rs2069526 and rs2470890 polymorphisms may be not associated with lung cancer risk. Moreover, our work also points out the importance of new studies for rs2069514 association in lung cancer, where at least some of the covariates responsible for heterogeneity could be controlled, to obtain a more conclusive understanding about the function of the rs2069514 polymorphism in lung cancer development

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