Genetics and Molecular Research

Meta-analysis of correlation between the *CYP1A2* -3860 G > A polymorphism and lung cancer risk

J. Ren, B.Z. He, T.S. Zhang, S.P. Lu and T. Yan

Jinan Seventh People's Hospital, Shandong Province, China

Corresponding author: S.P. Lu
E-mail: lushiping05@126.com

Genet. Mol. Res. 15 (2): gmr.15028353
Received December 28, 2015
Accepted February 11, 2016
Published June 17, 2016
DOI http://dx.doi.org/10.4238/gmr.15028353

ABSTRACT. The aim of this meta-analysis was to assess the association between a polymorphism (-3860 G > A) in the cytochrome P450 1A2 (*CYP1A2*) gene and lung cancer susceptibility. Relevant studies were retrieved from the PubMed and EMBase databases, and additionally evaluated for conformance with the inclusion criteria. The odds ratios (ORs) and their 95% confidence intervals (95%CIs) in all selected studies were used to assess the relationship between the *CYP1A2* -3860 G > A polymorphism and lung cancer risk. The data was pooled using Stata v.11. Six studies, comprising 1168 lung cancer patients and 1598 controls, were included in this meta-analysis. We found no correlation between the *CYP1A2* -3860 G > A polymorphism and lung cancer risk in any of the models (AA *vs* GG: OR = 4.79, 95%CI = 0.03-702.67; GA *vs* GG: OR = 1.33, 95%CI = 0.74-2.39; dominant model: OR = 1.41, 95%CI = 0.69-2.90; recessive model: OR = 4.07, 95%CI = 0.04-368.35). Moreover, we observed no statistically significant association between *CYP1A2* -3860 G > A and lung cancer susceptibility when stratified by the ethnicity of the sample populations, sample size, and study quality, except in a low-quality study. Our findings indicated that

the -3860 G > A polymorphism in *CYP1A2* might not be a risk factor for lung cancer.

Key words: Lung cancer; Meta-analysis; Cytochrome P450; Polymorphism; Risk

INTRODUCTION

Lung cancer was the most commonly diagnosed type of cancer and the leading cause of cancer-related deaths in males worldwide in 2008; it was also the fourth most-common type of cancer and the second leading cause of cancer-related deaths among females in the same year (Jemal et al., 2011). The mechanism of lung carcinogenesis remains marginally understood. Lung cancer is believed to be solely influenced by environmental factors, such as exposure to cigarette smoke and asbestos. However, a very small proportion of people exposed to these risk factors ultimately develop lung cancer, which suggests that genetic factors may also play a role in the development of lung cancer (Brennan et al., 2011; Marshall and Christiani, 2013).

The cytochrome P450 family is involved in the metabolic transformation of numerous endogenous and exogenous compounds, including carcinogens, which play important roles in the development of various types of cancer (Nebert and Dalton, 2006). Cytochrome P450 1A2 (CYP1A2) belonging to the cytochrome P450 family, is an enzyme that plays a key role in the activation of major classes of indirect carcinogens (Boobis et al., 1994). The *CYP1A2* gene is mapped to chromosome 15q24.1, a highly polymorphic region according to the National Center for Biotechnology Information single nucleotide polymorphism (NCBI dbSNP; http://www.ncbi.nlm.nih.gov) and SNP500Cancer (http://variatgps.nci.nih.gov) databases (Zhou et al., 2009).

Previous studies have proposed that the *CYP1A2* -3860G > A (rs2069514) polymorphism may be associated with increased risk of lung cancer by influencing the function of CYP1A2. However, the results of these studies are controversial, which could be attributed to the possible minor effect of the polymorphism on cancer risk, or the relatively small sample size in each of the published studies. Meta-analysis is a powerful tool used to summarize and draw inferences from the results of different studies. This analysis overcomes problems of individual studies, such as a small sample size and inadequate statistical power of genetic studies of complex traits, and produces results that are more reliable than those of a single case-control study (Yi et al., 2013). Therefore, we performed a meta-analysis of all eligible published case-control studies, and evaluated the effect of the *CYP1A2* -3860 G > A polymorphism on lung cancer risk.

MATERIAL AND METHODS

Literature search strategy

Scientific literature databases, including PubMed and EMBase, were searched for all possible studies analyzing the effect of the *CYP1A2* -3860 G > A polymorphism on lung cancer risk, using the following keyword combinations: (Cytochrome P450 1A2 or *CYP1A2* or -3860 G > A) and (lung cancer or tumor). All related studies published in English were included. The reference lists of retrieved articles were manually searched. In case of more

than one scientific article with the same data, only the study with the largest sample size was included. The literature search was updated on November 1, 2015.

Inclusion criteria and data extraction

The studies were selected carefully based on the following criteria: 1) studies evaluating the association between the *CYP1A2* -3860 G > A variant and lung cancer; 2) studies with a case-control or cohort design; and 3) those providing sufficient data for calculation of odds ratio (ORs) with 95% confidence intervals (CIs). The following information was extracted from each study: 1) name of the first author, 2) year of publication, 3) country, 4) ethnicity of the included population, 5) sample size of cases and controls, 6) genotype distribution in cases and controls, and 7) P-value for the Hardy-Weinberg equilibrium test in controls. All published studies deemed suitable were retrieved and reviewed independently by two reviewers. Disagreements were resolved by a discussion.

Quality assessment

The quality of the included studies was also evaluated by the same two independent investigators, according to predefined quality assessment rules (Table 1) (Jiang et al., 2010). The criteria cover the representativeness of cases, source of controls, ascertainment of lung cancer, total sample size, quality control of genotyping methods, and conformance of the control population with the Hardy-Weinberg equilibrium (HWE). Disagreements were resolved by a consensus. The total score ranged from 0 (worst) to 15 (best). Studies scored < 10 were classified as "low quality" studies and those scored ≥ 10 were believed to be of "high quality."

Table 1. Scale for quality assessment.

Criteria	Score
Source of cases	
Selected from population or cancer registry	3
Selected from hospital	2
Selected from pathological archives, but without a description	1
Not described	0
Source of controls	
Population-based	3
Blood donors or volunteers	2
Hospital-based (cancer-free patients)	1
Not described	0
Specimens obtained from patients to determine genotypes	
White blood cells or normal tissues	3
Tumor tissues or exfoliated cells of tissue	0
Hardy-Weinberg equilibrium in controls	
Hardy-Weinberg equilibrium	3
Hardy-Weinberg disequilibrium	0
Total sample size	
≥1000	3
≥500 but <1000	2
≥200 but <500	1
->0 but <200	0

Statistical analysis

The strength of association between the *CYP1A2* -3860 G > A polymorphism and

lung cancer risk was measured between groups using pooled ORs with their 95% Cis, using a homozygote comparison (AA *vs* GG), a heterozygote comparison (GA *vs* GG), a dominant model (AA+GA *vs* GG), and a recessive model (AA v*s* GA+GG). Between-study heterogeneity was estimated using the I^2 test (Higgins et al., 2003). I^2 represents the variability that can be attributed to heterogeneity rather than chance. I^2 values of 25, 50, and 75% were defined as low, moderate, and high estimates, respectively. A significant $I^2 > 50\%$ indicated heterogeneity across studies, and the random effects model was used for meta-analysis; in other cases, the fixed effects model was used. Additionally, we performed sub-group analyses by stratifying the cases and controls based on their ethnicity. Sensitivity analysis was performed by comparing the values of a random effects model against those of the fixed effects model. Begger's funnel plot and the Egger tests were used to evaluate possible publication bias (Egger et al., 1997). All data was analyzed using Stata v.11.0 (Stata Corporation, College Station, TX, USA).

RESULTS

Study characteristics

A systematic database search and manual review of the reference lists in eligible studies yielded a total of 119 publications; these were rigorously analyzed by the reviewers for conformance with the inclusion criteria, leading to the selection of six articles, comprising 1168 lung cancer patients and 1598 controls, for this meta-analysis (Osawa et al., 2007; Zienolddiny et al., 2008; B'chir et al., 2009; Singh et al., 2010-2011; Pavanello et al., 2012; Gervasini et al., 2013). The year of publication of these studies ranged from 2007 to 2013. Detailed information regarding the included studies and the selection method are presented in Table 2 and in Figure 1. Of these, three studies were performed in Caucasians, 2 in Asians, and one in people of African descent. All included reports were written in English. The genetic distributions of control groups in all studies conformed to the HWE.

Table 2. Characteristics of studies included in the meta-analysis.

Name of first author	Year	Area	Race	Cases/controls	Genotypes for cases			Genotypes for controls			HWE test	Quality scores
					GG	GA	AA	GG	GA	AA		
Osawa	2007	Japan	Asians	106/113	65	36	5	63	42	8	0.78	13
Zienolddiny	2008	Norway	Caucasians	243/214	237	6	0	206	8	0	0.78	11
B'chir	2009	Tunisia	Africans	101/98	51	35	15	84	14	0	0.45	9
Singh	2010	India	Asians	200/200	171	29	0	175	25	0	0.35	11
Pavanello	2012	Italy	Caucasians	423/777	417	6	0	764	13	0	0.81	15
Gervasini	2012	Spain	Caucasians	95/196	90	5	0	192	4	0	0.89	13

Overall and subgroup analyses

The results of this meta-analysis, analyzing the correlation between the *CYP1A2* -3860 G > A polymorphism and lung cancer risk, are summarized in Table 3. We found no evidence of a significant association between the *CYP1A2* -3860 G > A polymorphism and lung cancer risk when the ORs and 95% Cis of all eligible studies were pooled and analyzed (AA *vs* GG: OR = 4.79, 95%CI = 0.03-702.67; GA *vs* GG: OR = 1.33, 95%CI = 0.74-2.39; Dominant model: OR = 1.41, 95%CI = 0.69-2.90; Recessive model: OR = 4.07, 95%CI = 0.04-368.35). Stratification of the patients and controls based on ethnicity, sample size, and study quality

also revealed the lack of a statistically significant association between the polymorphism and cancer risk, except in a low-quality study (B'chir et al., 2009).

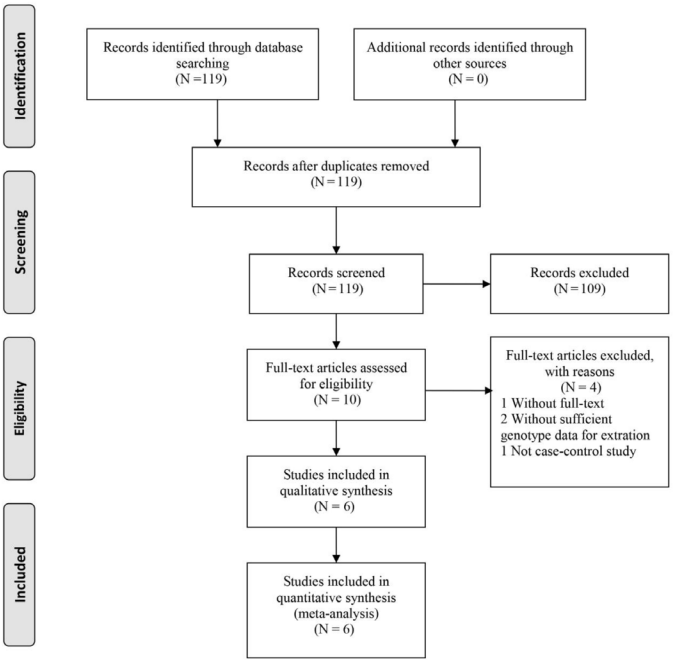

Figure 1. Flow chart depicting the study selection procedure.

Table 3. Summary odds ratios and 95% confidence intervals of the correlation between the *CYP1A2* -3860 G > A polymorphism and lung cancer risk.

Variables	N [a]	AA *vs* GG		GA *vs* GG		Dominant model		Recessive model	
		OR (95%CI)	I^2	OR (95%CI)	I^2	OR (95%CI)	I^2	OR (95%CI)	I^2
Total	6	4.79 (0.03-702.67)	90.6%	1.33 (0.74-2.39)	68.9%	1.41 (0.69-2.90)	80.2%	4.07 (0.04-368.35)	88.6%
Ethnicity									
Asian	2	0.61 (0.19-1.95)	-	0.99 (0.66-1.48)	0.0%	0.96 (0.65-1.42)	0.0%	0.65 (0.21-2.05)	
Caucasian	3	-		0.99 (0.53-1.85)	28.2%	0.99 (0.53-1.85)	28.2%	-	
Sample size									
>500	1	-		0.85 (0.32-2.24)	-	0.85 (0.32-2.24)	-	-	
≤500	5	4.79 (0.03-702.67)	90.6%	1.44 (0.73-2.84)	73.8%	1.56 (0.68-3.58)	83.4%	4.07 (0.05-368.35)	88.6%
Quality									
High-quality	5	0.61 (0.19-1.95)	-	0.99 (0.71-1.39)	0.0%	0.97 (0.69-1.36)	0.0%	0.65 (0.21-2.05)	-
Low-quality	1	50.86 (2.98-868.3)	-	4.12 (2.02-8.38)	-	5.88 (2.96-11.70)	-	35.30 (2.08-598.74)	-

[a]Number of comparisons; OR = odds ratio; 95%CI = 95% confidence interval.

Publication bias

The Begger's funnel plot was constructed and the Egger's test was performed to assess the publication bias of the included studies for *CYP1A2* -3860 G > A polymorphism. The shape of the funnel plot did not reveal any evidence of obvious asymmetry. The Egger test was subsequently used to provide statistical evidence of funnel plot symmetry. The results still did not suggest any evidence of publication bias for the *CYP1A2* -3860 G > A polymorphism.

DISCUSSION

Global cancer statistics identify lung cancer as one of the most prevalent and deadliest among human cancers. A previous study estimated approximately 228,190 people to be diagnosed with lung cancer, as well as 159,480 lung cancer-related deaths to occur, in 2013 in the United States alone (Gervasini et al., 2013). Lung cancer is a fatal disease with a complex carcinogenesis. Tobacco smoking and air pollution have been previously deemed as key risk factors of lung cancer. However, relevant genetic variations must be identified and assessed to understand the potential mechanisms involved in lung carcinogenesis. Over the past decade, several epidemiological studies have reported an association between the *CYP1A2* -3860 G > A polymorphism and lung cancer risk. However, the results of these studies are far from conclusive. The interpretation of these studies has been further complicated by the analysis of multiple ethnic populations in the same study, insufficient power of the study, and minimal effect of the polymorphism on lung cancer risk. The increased number of studies over the past few years compounds the need for data reconciliation.

This meta-analysis was performed in six studies, comprising 1168 lung cancer patients and 1598 controls. As the data can be confounded by the differences between subgroups, we stratified the studies by ethnicity, sample size, and study quality. The pooled data indicated that the *CYP1A2* -3860 G > A polymorphism was not a risk factor of lung cancer in humans, in all genetic models. When stratified based on the ethnicity and sample size, we observed that the *CYP1A2* -3860 G > A polymorphism was not correlated with lung cancer risk. However, when stratified according to the study quality, we found a correlation between this polymorphism and increased lung cancer risk in a low-quality study; this was considered as a misestimate of the inclusion criteria bias.

Several limitations should be acknowledged when interpreting the results of this meta-analysis. Our results were based on unadjusted estimates; a more precise analysis must be conducted using the individual raw data from all studies, if available, which would allow for adjustment by other co-variants, including age, sex, cigarette smoking status, and other lifestyle-related factors. Secondly, a meta-analysis is a retrospective study; therefore, there might be a recall and selection bias. Finally, only articles written in English were included; therefore, some potential articles may have been inadvertently excluded.

In conclusion, the *CYP1A2* -3860 G > A polymorphism might not contribute to increased risk of lung cancer in humans. Future studies are recommended to identify the possible gene-gene and gene-environment interactions affecting this association.

Conflicts of interest

The authors declare no conflict of interest.

REFERENCES

B'chir F, Pavanello S, Knani J, Boughattas S, et al. (2009). CYP1A2 genetic polymorphisms and adenocarcinoma lung cancer risk in the Tunisian population. *Life Sci.* 84: 779-784. http://dx.doi.org/10.1016/j.lfs.2009.03.008

Boobis AR, Lynch AM, Murray S, de la Torre R, et al. (1994). CYP1A2-catalyzed conversion of dietary heterocyclic amines to their proximate carcinogens is their major route of metabolism in humans. *Cancer Res.* 54: 89-94.

Brennan P, Hainaut P and Boffetta P (2011). Genetics of lung-cancer susceptibility. *Lancet Oncol.* 12: 399-408. http://

dx.doi.org/10.1016/S1470-2045(10)70126-1
Egger M, Davey Smith G, Schneider M and Minder C (1997). Bias in meta-analysis detected by a simple, graphical test. *BMJ* 315: 629-634. http://dx.doi.org/10.1136/bmj.315.7109.629
Gervasini G, Ghotbi R, Aklillu E, San Jose C, et al. (2013). Haplotypes in the 5¢-untranslated region of the CYP1A2 gene are inversely associated with lung cancer risk but do not correlate with caffeine metabolism. *Environ. Mol. Mutagen.* 54: 124-132. http://dx.doi.org/10.1002/em.21747
Higgins JP, Thompson SG, Deeks JJ and Altman DG (2003). Measuring inconsistency in meta-analyses. *BMJ* 327: 557-560. http://dx.doi.org/10.1136/bmj.327.7414.557
Jemal A, Bray F, Center MM, Ferlay J, et al. (2011). Global cancer statistics. *CA Cancer J. Clin.* 61: 69-90. http://dx.doi.org/10.3322/caac.20107
Jiang DK, Ren WH, Yao L, Wang WZ, et al. (2010). Meta-analysis of association between TP53 Arg72Pro polymorphism and bladder cancer risk. *Urology* 76: 765.e1-765.e7. http://dx.doi.org/10.1016/j.urology.2010.04.044
Marshall AL and Christiani DC (2013). Genetic susceptibility to lung cancer - light at the end of the tunnel? *Carcinogenesis* 34: 487-502. http://dx.doi.org/10.1093/carcin/bgt016
Nebert DW and Dalton TP (2006). The role of cytochrome P450 enzymes in endogenous signalling pathways and environmental carcinogenesis. *Nat. Rev. Cancer* 6: 947-960. http://dx.doi.org/10.1038/nrc2015
Osawa Y, Osawa KK, Miyaishi A, Higuchi M, et al. (2007). NAT2 and CYP1A2 polymorphisms and lung cancer risk in relation to smoking status. *Asian Pac. J. Cancer Prev.* 8: 103-108.
Pavanello S, Fedeli U, Mastrangelo G, Rota F, et al. (2012). Role of CYP1A2 polymorphisms on lung cancer risk in a prospective study. *Cancer Genet.* 205: 278-284. http://dx.doi.org/10.1016/j.cancergen.2012.02.004
Singh AP, Pant MC, Ruwali M, Shah PP, et al. (2010-2011). Polymorphism in cytochrome P450 1A2 and their interaction with risk factors in determining risk of squamous cell lung carcinoma in men. *Cancer Biomark.* 8: 351-359.
Yi L, Xiao-Feng H, Yun-Tao L, Hao L, et al. (2013). Association between the XRCC1 Arg399Gln polymorphism and risk of cancer: evidence from 297 case-control studies. *PLoS One* 29;8:e78071.
Zhou SF, Chan E, Zhou ZW, Xue CC, et al. (2009). Insights into the structure, function, and regulation of human cytochrome P450 1A2. *Curr. Drug Metab.* 10: 713-729. http://dx.doi.org/10.2174/138920009789895552
Zienolddiny S, Campa D, Lind H, Ryberg D, et al. (2008). A comprehensive analysis of phase I and phase II metabolism gene polymorphisms and risk of non-small cell lung cancer in smokers. *Carcinogenesis* 29: 1164-1169. http://dx.doi.org/10.1093/carcin/bgn020