CYP1A1 Ile462Val Polymorphism Contributes to Lung Cancer Susceptibility among Lung Squamous Carcinoma and Smokers: A Meta-Analysis

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Abstract

Many studies have examined the association between the CYP1A1 Ile462Val gene polymorphisms and lung cancer risk in various populations, but their results have been inconsistent. To assess this relationship more precisely, a meta-analysis was performed. Ultimately, 43 case-control studies, comprising 19,228 subjects were included. A significantly elevated lung cancer risk was associated with 2 Ile462Val genotype variants (for Val/Val vs Ile/Ile: OR = 1.22, 95% CI = 1.08–1.40; for (Ile/Val +Val/Val) vs Ile/Ile: OR = 1.15, 95% CI = 1.07–1.23) in overall population. In the stratified analysis, a significant association was found in Asians, Caucasians and lung SCC, not lung AC and lung SCLC. Additionally, a significant association was found in smoker population and not found in non-smoker populations. This meta-analysis suggests that the Ile462Val polymorphisms of CYP1A1 correlate with increased lung cancer susceptibility in Asian and Caucasian populations and there is an interaction with smoking status, but these associations vary in different histological types of lung cancer.

Introduction

Lung cancer remains the most lethal cancer worldwide, despite improvements in diagnostic and therapeutic techniques [1]. Its incidence has been increasing in many parts of world, particularly in China, which has become a major public health challenge all the world [2]. The mechanism of lung carcinogenesis is not understood. Although cigarette smoking is the major cause of lung cancer, not all smokers develop lung cancer [3], which suggests that other causes such as genetic susceptibility might contribute to the variation in individual lung cancer risk [4,5]. Many environmental carcinogens require metabolic activation by drug-metabolizing enzymes. In recent years, several common low-penetrance genes have been implicated as potential lung cancer susceptibility genes.

Cytochrome P450 1A1 (CYP1A1) metabolizes several suspected procarcinogens, particularly polycyclic aromatic hydrocarbons (PAHs), into highly reactive intermediates [6]. These compounds bind to DNA to form adducts, which, if unrepaired, can initiate or accelerate carcinogenesis. Although PAHs are ubiquitous in the environment, notable sources of exposure that cause the greatest concern include smoking, air pollution, diet, and certain occupations [7]. Two functionally important nonsynonymous polymorphisms have been described for the CYP1A1 gene, a base substitution at codon 462 in exon 7, resulting in substitution of isoleucine with valine (Ile462Val (exon 7)) (National Center for Biotechnology Information single nucleotide polymorphism(SNP) identifier rs1048943; adenine (A) to guanine (G) substitution at nucleotide 2455/2455A.G)) and a point mutation (thymine (T) to cytosine (C)) at the Mspl site in the 3’untranslated region (rs4646903;3801T.C) [8]. The Ile462Val (exon 7) polymorphism resulted in three genotypes: a predominant homozygous (Ile/Ile), the heterozygote (Ile/Val), and the rare homozygous (Val/Val).

An association between CYP1A1 polymorphisms and lung cancer was first reported by Kawajiri and co-workers in 1990 among an Asian study population [9], after which many studies analyzed the influence of CYP1A1 polymorphisms on lung cancer risk; no clear consensus, however, was reached. Moreover, 3 meta-analyses have reported conflicting results. Houlston RS [10] found no statistically significant association between the Mspl polymorphism and lung cancer risk in 15 studies, in a meta-analysis performed by Le Marchand L et al. [11] included only 11 studies, the Ile462Val (exon 7) polymorphism did not correlate with lung cancer risk. Shi X [12], however, noted a greater risk of lung cancer for CYP1A1 Mspl and exon 7 polymorphism carriers in a meta-analysis that included only Chinese population in 15 studies.

A single study might not be powered sufficiently to detect a small effect of the polymorphisms on lung cancer, particularly in relatively small sample sizes. Various types of study populations and study designs might also have contributed to these disparate findings. To clarify the effect of the CYP1A1 Ile462Val (exon 7) polymorphism on the risk for lung cancer, we performed an updated meta-analysis of all eligible case-control studies to date and conducted the subgroup analysis by stratification according to
the ethnicity source, histological types of lung cancer and smoking status of case.

**Materials and Methods**

1. **Publication Search**
   The electronic databases PubMed, Embase, Web of Science, and CNKI (China National Knowledge Infrastructure) were searched for studies to include in this meta-analysis, using the terms “CYP1A1,” “Cytochrome P450 1A1,” “polymorphism,” and “lung cancer.” An upper date limit of March 01, 2012 was applied; we used no lower date limit. The search was performed without any restrictions on language and was focused on studies that had been conducted in humans. We also reviewed the Cochrane Library for relevant articles. The reference lists of reviews and retrieved articles were hand searched simultaneously. When more than one of the same patient population was included in several publications, only the most recent or complete study was used in this meta-analysis.

2. **Inclusion Criteria**
   For inclusion, the studies must have met the following criteria: they (1) evaluated CYP1A1 Ile462Val (exon 7) gene polymorphisms and lung cancer risk; (2) were case-control studies or nested-case control study; (3) supplied the number of individual genotypes for the CYP1A1 Ile462Val (exon 7) polymorphisms in lung cancer cases and controls, respectively; and (4) demonstrated that the distribution of genotypes among controls were in Hardy-Weinberg equilibrium.

3. **Data Extraction**
   Information was carefully extracted from all eligible publications independently by two authors according to the inclusion criteria. Disagreements were resolved through a 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 who harbored the Ile462Val (exon 7) genotypes, respectively. We did not contact the author of the primary study to request the information. Ethnicities were categorized as Asian, Caucasian, and mixed. Histological type of lung cancer was divided to lung squamous carcinoma (SCC), adenocarcinoma (AC) and small cell lung cancer (SCLC) in our meta-analysis. The definition of smoking history is very complicated. The smoking histories covered different periods if changes in the number of cigarettes smoked per day or type of tobacco products occurred. According to the general standards, non-smokers were defined as subjects who had smoked less than 100 cigarettes in their lifetime. Although the precise definition of never-smoking status varied slightly among the studies, the smoking status was classified as non-smokers (or never smoker) and smokers (regardless of the extent of smoking) in our meta-analysis. We did not define any minimum number of patients to include a study in our meta-analysis.

4. **Statistical Analysis**
   OR (odds ratios) with 95% CIs were used to determine the strength of association between the CYP1A1 Ile462Val (exon 7) polymorphisms and lung cancer risk. We evaluated this risk with regard to combinations of variants (Ile/Val and Val/Val) versus the wild-type homozygotes (Ile/Ile).
The pooled ORs for the risk were calculated. Subgroup analyses were performed by ethnicity. Heterogeneity assumptions were assessed by chi-square-based Q-test [13]. A P value greater than 0.10 for the Q-test indicated a lack of heterogeneity among the

| First author-year | Ethnicity(country of origin) | Total sample size (case/control) | Lung cancer cases | Controls |
|-------------------|------------------------------|----------------------------------|------------------|----------|
|                   |                              |                                  | Ile/Val | Val/Val | Ile/Ile | Ile/Val | Val/Val | Ile/Ile |
| Nakachi K-1993    | Asia(Japan)                  | 31/127                           | 11      | 6       | 14      | 44      | 4       | 79      |
| Alexandrie AK-1994| Caucasian(Sweden)            | 296/329                          | 16      | 0       | 280     | 23      | 0       | 306     |
| Cantlay AM-1995   | Caucasian(Edinburgh)         | 129/281                          | 21      | 2       | 106     | 33      | 3       | 245     |
| Kihara M-1995     | Asia(Japan)                  | 97/258                           | 31      | 5       | 59      | 98      | 14      | 143     |
| Ishibe N-1997     | Mixed(Mexican and African)   | 171/295                          | 31      | 7       | 132     | 70      | 20      | 204     |
| Hong YS-1998      | Asia(Korean)                 | 85/63                            | 68      | 1       | 16      | 60      | 1       | 2       |
| Taioli E-1998     | Mixed populations            | 105/307                          | 8       | 1       | 94      | 18      | 0       | 272     |
| Sugimura H-1998   | Asia(Japan)                  | 247/185                          | 94      | 28      | 125     | 84      | 7       | 94      |
| Le Marchand L-1998| Mixed populations            | 341/456                          | 68      | 6       | 263     | 105     | 13      | 335     |
| Xue KX-1999       | Asia(china)                  | 103/131                          | 31      | 18      | 54      | 36      | 11      | 36      |
| Hu YL-1999        | Asia(china)                  | 59/132                           | 33      | 7       | 19      | 102     | 9       | 21      |
| London SJ-2000    | Asia(China)                  | 214/669                          | 39      | 8       | 167     | 130     | 27      | 512     |
| Song N-2001       | Asia(China)                  | 217/404                          | 130     | 9       | 78      | 181     | 13      | 210     |
| Ratnasinghe D-2001| Caucasian(USA)               | 282/324                          | 36      | 3       | 243     | 48      | 3       | 273     |
| Quinones L-2001   | Caucasians(Chile)            | 60/174                           | 35      | 10      | 15      | 52      | 14      | 54      |
| Chen S-2001       | Asia(china)                  | 106/106                          | 38      | 10      | 58      | 33      | 3       | 70      |
| Xue KX-2001       | Asia(china)                  | 106/106                          | 38      | 10      | 58      | 33      | 3       | 33      |
| Zhou XW-2002      | Asia(china)                  | 92/98                            | 66      | 11      | 15      | 65      | 6       | 65      |
| Taioli E-2003     | Mixed populations            | 110/707 exon7                    | 16      | 1       | 93      | 70      | 2       | 635     |
| Dong CT-2004      | Asia(china)                  | 82/91                            | 36      | 18      | 28      | 32      | 10      | 32      |
| Yang XR-2004      | Asia(China)                  | 200/144                          | 96      | 11      | 90      | 39      | 7       | 98      |
| Sobhi RC-2004     | Asia(India)                  | 100/76                           | 67      | 29      | 4       | 53      | 15      | 8       |
| Wenzlaff A5-2005  | Caucasian(USA)               | 128/181                          | 5\(^\#\) | 124  | 14\(^\#\) | 134  |
| Wrensch MR-2005   | Mixed populations            | 363/930 exon7                    | 64\(^\#\) | 302  | 219\(^\#\) | 711  |
| Ng DP-2005        | Asia(Singapore)              | 126/162                          | 39      | 13      | 74      | 63      | 7       | 91      |
| Larsen EJ-2005    | Caucasians(Australia)        | 1050/581                         | 84      | 8       | 958     | 27      | 2       | 552     |
| Raimondi S-2005   | Caucasians                   | 175/723 exon7                    | 32\(^\#\) | 143  | 67\(^\#\) | 656  |
| Raimondi S-2005-2| Asians                       | 60/212 exon7                     | 30\(^\#\) | 30   | 96\(^\#\) | 116  |
| Li DR-2006        | Asia(china)                  | 150/152                          | 104     | 14      | 32      | 105     | 8       | 105     |
| Pisani P-2006     | Asia(Thailand)               | 211/408                          | 79      | 10      | 78      | 129     | 23      | 135     |
| Yang MH-2007      | Asia(Korea)                  | 314/349                          | 116     | 16      | 182     | 111     | 18      | 220     |
| Cote ML-2007      | Mixed populations            | 354/440                          | 19      | 0       | 326     | 34      | 6       | 400     |
| Yoon KA-2008      | Asia(Korea)                  | 213/213                          | 76      | 10      | 127     | 87      | 10      | 116     |
| Gallegos-Arreola-2008| Mixed populations          | 222/248                          | 91      | 40      | 91      | 104     | 11      | 133     |
| Shah PP-2008      | Asia(India)                  | 200/200                          | 67\(^\#\) | 133  | 44\(^\#\) | 156  |
| Kumar M-2009      | Asia(India)                  | 93/253                           | 17      | 3       | 73      | 40      | 3       | 210     |
| Cote ML-2009      | Mixed populations            | 502/523                          | 38      | 0       | 464     | 32      | 2       | 489     |
| Klinchid J-2009   | Asia(Thailand)               | 85/82                            | 47\(^\#\) | 33   | 42\(^\#\) | 38   |
| Timofeeva MN-2009 | Caucasians(German)           | 619/1264                         | 248     | 61      | 260     | 545     | 117     | 585     |
| Wright CM-2010    | Caucasians(Australian)       | 1040/784                         | 103     | 8       | 929     | 40      | 3       | 741     |
| Mota P-2010       | Caucasian(Portugal)          | 175/217                          | 38\(^\#\) | 137  | 49\(^\#\) | 168  |
| Wang Z-2011       | Asia(China)                  | 72/90                            | 9       | 26      | 37      | 25      | 11      | 54      |
| Bai TY-2011       | Asia(China)                  | 106/250                          | 66      | 15      | 25      | 172     | 24      | 54      |

\(^{\#}\)the number of the combined Ile/Val and Val/Val genotypes.
Figure 2. Forest plot (random-effects model) of lung cancer risk associated with CYP1A1 exon7 genotype for the combined Ile/Val and Val/Val vs Ile/Ile. 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).
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1. Study Characteristics

Two hundred and fifty-two potentially relevant citations were reviewed, and 43 publications met the inclusion criteria and included in our meta-analysis [18–59]. The study search process is shown in Figure 1. Table 1 presents the principal characteristics of these studies. Raimondi’s study [43] sorted the data for Caucasians and Asians; therefore, each group in the study was considered separately in the pooled subgroup analyses.

2. Meta-analysis Results

For all studies in the meta-analysis, the genotype, an increased risk for lung cancer was associated with 2 Ile462Val variants (for Val/Val vs Ile/Ile: OR = 1.22, 95% CI = 1.08–1.40, P = 0.004 for heterogeneity; for Ile/Val and Val/Val combined vs Ile/Ile: OR = 1.15, 95% CI = 1.07–1.23, P<0.001 for heterogeneity) (Figure 2).

In the stratified analysis by ethnicity, the risk was higher in Asian carriers of Val/Val vs Ile/Ile (OR = 1.22, 95% CI = 1.16–1.59; P = 0.016 for heterogeneity) and Ile/Val and Val/Val combined vs Ile/Ile (OR = 1.20, 95% CI = 1.09–1.33; P<0.001 for heterogeneity). A significant association was also observed in Caucasian carriers of Val/Val vs Ile/Ile (OR = 1.24; 95% CI = 1.17–1.43; P=0.090 for heterogeneity) and Ile/Val and Val/Val combined vs Ile/Ile (OR = 1.25; 95% CI = 1.11–1.42; P<0.001 for heterogeneity). However, no significant associations were observed in mixed populations for both Val/Val vs Ile/Ile (OR = 0.84; 95% CI = 0.77–1.03; P=0.090 for heterogeneity) or Ile/Val and Val/Val combined vs Ile/Ile (OR = 0.92; 95% CI = 0.79–1.06; P=0.001 for heterogeneity) (Table 2).

Twelve-one out of 43 studies examined the association of CYP1A1 exon 7 genotype and the risk of different histological types of lung cancer including SCC, AC and SCLC (Table 3). Among lung SCC, significantly increased risks were observed for both Val/Val vs Ile/Ile (OR = 1.38; 95% CI = 1.12–1.66; P=0.0001 for heterogeneity). For all studies in the meta-analysis, the genotype, an increased risk for lung cancer was associated with 2 Ile462Val variants (for Val/Val vs Ile/Ile: OR = 1.22, 95% CI = 1.08–1.40, P = 0.004 for heterogeneity; for Ile/Val and Val/Val combined vs Ile/Ile: OR = 1.15, 95% CI = 1.07–1.23, P<0.001 for heterogeneity) (Figure 2).

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Ten out of 40 studies included the association of CYP1A1 exon 7 genotype and lung cancer risk stratified by smoking status (non-smokers or never smokers and smokers) (Table 4). For smokers, significantly increased risks were observed for both Val/Val vs Ile/Ile (OR = 1.60; 95% CI = 1.20–2.09;  

\( P = 0.006 \) for heterogeneity) and Ile/Val and Val/Val combined vs Ile/Ile (OR = 1.62; 95% CI = 1.20–2.09;  

\( P = 0.007 \) for heterogeneity).

\[ P = 0.004 \] for heterogeneity) or Ile/Val and Val/Val combined vs Ile/Ile (OR = 1.42; 95% CI = 1.18–1.70;  

\( P = 0.007 \) for heterogeneity). However, among lung AC and SCLC, no significant associations were observed for both Val/Val vs Ile/Ile or Ile/Val and Val/Val combined vs Ile/Ile (Figure 3).

\[ P = 0.004 \] for heterogeneity).
CI = 1.24–2.11; \( P=0.004 \) for heterogeneity). However, for non-smokers, no significant associations were observed for both Val/Val vs Ile/Ile (OR = 1.02; 95% CI = 0.84–1.39; \( P=0.009 \) for heterogeneity) or Ile/Val and Val/Val combined vs Ile/Ile (OR = 1.07; 95% CI = 0.88–1.31; \( P=0.002 \) for heterogeneity) (Figure 4).

3. 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).

4. Publication Bias
Begg’s funnel plot and Egger’s test were performed to identify any publication bias. The funnel plots did not exhibit any patent asymmetry (Figure 5). By Egger’s test–used to provide statistical evidence of funnel plot symmetry—there was no evidence of publication bias (\( P=0.733 \) for publication bias).

Discussion
CYP genes are large families of endoplasmic and cytosolic enzymes that catalyze the activation and detoxification, respectively, of reactive electrophilic compounds, including many environmental carcinogens (e.g., benzo[a] pyrene). CYP1A1 is a phase I enzyme that regulates the metabolic activation of major classes of tobacco procarcinogens, such as aromatic amines and PAHs [6]. Thus, it might affect the metabolism of environmental carcinogens and alter the susceptibility to lung cancer. This meta-analysis explored the association between the CYP1A1 exon7 gene polymorphisms and lung cancer risk, and performed the subgroup analysis stratified by ethnicity, histological types of lung cancer, gender and smoking status of case and control population. Our results indicated a significant association between CYP1A1 exon7

Table 3. Distribution of CYP1A1 exon7 genotypes among cases and controls stratified by histological types of lung cancer.

| First author-year | Ethnicity (country of origin) | Histology (Scc/Ac/Sclc) | Lung cancer cases | Controls |
|-------------------|-------------------------------|-------------------------|-------------------|---------|
|                   |                               |                         | Ile/Val | Val/Val | Ile/Ile | Ile/Val | Val/Val | Ile/Ile |
| Alexandre AK-1994 | Caucasian(Sweden)             | SCC                     | 9       | 0       | 98      | 23      | 0       | 306     |
|                   |                               | AC                      | 5       | 0       | 79      | 23      | 0       | 306     |
|                   |                               | SCLC                    | 1       | 0       | 57      | 23      | 0       | 306     |
| Kihara M -1995    | Asia(Japan)                   | SCC                     | 23      | 2       | 34      | 98      | 14      | 143     |
|                   |                               | SCLC                    | 8       | 3       | 25      | 98      | 14      | 143     |
| Hong YS-1998      | Asia(Korean)                  | SCC                     | 19      | 1       | 7       | 60      | 1       | 2       |
|                   |                               | AC                      | 24      | 0       | 4       | 60      | 1       | 2       |
|                   |                               | SCLC                    | 12      | 0       | 3       | 60      | 1       | 2       |
| Le Marchand L-1998| Mixed populations             | SCC                     | 21      | 1       | 52      | 105     | 13      | 335     |
|                   |                               | AC                      | 31      | 3       | 126     | 105     | 13      | 335     |
|                   |                               | SCLC                    | 8       | 1       | 42      | 105     | 13      | 335     |
| Sugimura H-1998   | Asia(Japan)                   | SCC                     | 46      | 15      | 61      | 84      | 7       | 94      |
|                   |                               | AC                      | 27      | 8       | 43      | 84      | 7       | 94      |
|                   |                               | SCLC                    | 13      | 5       | 10      | 84      | 7       | 94      |
| Taioli E-1998     | Mixed populations             | SCC                     | 3       | 1       | 33      | 18      | 0       | 272     |
|                   |                               | AC                      | 3       | 1       | 37      | 18      | 0       | 272     |
|                   |                               | SCLC                    | 1       | 0       | 6       | 18      | 0       | 272     |
| London SJ-2000    | Asia(China)                   | SCC                     | 18      | 2       | 54      | 130     | 27      | 512     |
|                   |                               | AC                      | 11      | 0       | 53      | 130     | 27      | 512     |
| Song N-2001       | Asia(China)                   | SCC                     | 81      | 4       | 45      | 181     | 13      | 210     |
|                   |                               | AC                      | 35      | 3       | 26      | 181     | 13      | 210     |
| Sobti RC-2004     | Asia(India)                   | SCC                     | 50      | 17      | 4       | 53      | 15      | 8       |
|                   |                               | SCLC                    | 12      | 12      | 0       | 53      | 15      | 8       |
| Larsen EJ-2005    | Caucasians(Australia)         | SCC                     | 53\(^\circ\) | 426 | 27     | 2      | 552     |
|                   |                               | AC                      | 29\(^\circ\) | 450 | 27     | 2      | 552     |
| Raimondi S-2005   | Caucasians                    | SCC                     | 4\(^\circ\) | 15 | 67\(^\circ\) | 656 |
|                   |                               | AC                      | 15\(^\circ\) | 46 | 67\(^\circ\) | 656 |
| Yoon KA-2008      | Asia(Korea)                   | AC                      | 54      | 7       | 112     | 87      | 10      | 116     |
| Mota P-2010       | Caucasian(Portugal)           | AC                      | 15\(^\circ\) | 42 | 49\(^\circ\) | 168 |
|                   |                               | SCC                     | 9\(^\circ\) | 37 | 49\(^\circ\) | 168 |

\(^\circ\)the number of the combined Ile/Val and Val/Val genotypes.

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gene polymorphism and lung cancer risk Asians, Caucasians, lung SCC and Female population, no significant association was found in mixed population, lung AD, lung SCLC and Male population. Additionally, a significant association was found in smoker population and not in non-smoker populations.

### Table 4. Distribution of CYP1A1 exon7 genotypes among cases and controls stratified by smoking status.

| First author-year | Ethnicity(country of origin) | Smoking status | Lung cancer cases | Controls |
|-------------------|-----------------------------|----------------|------------------|---------|
|                   |                             |                | Ile/Val | Val/Val | Ile/Ile | Ile/Val | Val/Val | Ile/Ile |
| Kihara M-1995     | Asia(Japan)                 | Smokers        | 31      | 5       | 59      | 70      | 11      | 101     |
| Taioli E-2003     | Mixed populations           | Non-smokers    | 4       | 0       | 7       | 35      | 0       | 262     |
|                   |                             | Smokers        | 12      | 1       | 77      | 26      | 1       | 320     |
| Ng DP-2005        | Asia(Singapore)             | Non-smokers    | 39      | 13      | 74      | 63      | 7       | 91      |
| Raimondi S-2005   | Caucasians                  | Non-smokers    | 32      | 143     | 59      | 67      | 656     |
| Raimondi S-2005-2 | Asians                      | Non-smokers    | 30      | 30      | 96      | 96      | 116     |
| Wenzlaff AS-2005  | Caucasian(USA)              | Non-smokers    | 5       | 124     | 14      | 14      | 134     |
| Yoon KA-2008      | Asia(Korea)                 | Non-smokers    | 76      | 10      | 127     | 87      | 10      | 116     |
| Gallegos-Arreola-2008 | Mixed populations       | Non-smokers    | 8       | 8       | 16      | 55      | 11      | 72      |
|                   |                             | Smokers        | 83      | 32      | 75      | 49      | 0       | 61      |
| Shah PP-2008      | Asia(India)                 | Non-smokers    | 16      | 64      | 35      | 35      | 103     |
|                   |                             | Smokers        | 51      | 69      | 9       | 9       | 53      |
| Kumar M-2009      | Asia(India)                 | Non-smokers    | 4       | 1       | 7       | 28      | 2       | 122     |
|                   |                             | Smokers        | 14      | 2       | 66      | 12      | 1       | 88      |

*the number of the combined Ile/Val and Val/Val genotypes.

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When stratified according to ethnicity, a significantly increased risks were identified among Asians and Caucasians for the 2 exon 7 genotype variants, however no significant association was found in mixed population. These findings indicate that polymorphisms of CYP1A1 exon 7 polymorphism may be important in specific ethnicity of lung cancer patients. 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 [60]. In fact, the distribution of the less common Val allele of exon 7 genotype varies extensively between different races, with a prevalence of ~25% among East Asians, ~5% among Caucasians and ~15% among other population. In addition, in our meta-analysis the between-study heterogeneity was existed in overall population, the subgroup of Asian and Caucasian for exon 7 genotypes. The I-squared value of Asian group is 57%, which is lower than the I-squared values for the Caucasians and mixed population studies, suggesting less heterogeneity among the Asian populations. Therefore, additional studies are warranted to further validate ethnic difference in the effect of this functional polymorphism on lung cancer risk.

There are growing biological and epidemiological data to suggest that different lung cancer pathological subtypes, particularly the two most common, are distinct etiological entities that should be analyzed separately [61]. When subgroup analyses by pathological types were considered, CYP1A1 exon7 variant alleles were found to be associated with a 1.4 fold increase in the risk of lung SCC. However, for lung AC and SCLC, no significant association was found. Our findings were consistent with the Le Marchand L et al study [26] with largest sample sizes of case and control. Le Marchand et al. hypothesized that genetic susceptibility to PAHs predominantly caused lung SCC and nitrosamines caused lung AC. With introduction of filter-tipped cigarettes, probably decreased smokers’ exposure to PAHs and increased their exposure to nitrosamines, decreasing trend of SCC, relative to the increase in AC indirectly supports this hypothesis [62]. Different carcinogenic processes may be involved in the genesis of various tumor types because of the presence of functionally different CYP1A1 exon7 gene polymorphisms. However, the possible molecular mechanisms to explain these histology-specific differences in the risk of lung cancer remain unresolved.

As we know, aside from genetic factor, smoking is the major risk factor of lung cancer. Most studies out of 40 studies reported information on smoking habits of cases and controls, however only ten eligible publications provided non-smokers information. Our meta-analysis results showed that a significantly increased risk was found to be associated with the CYP1A1 exon 7 gene polymorphisms and lung cancer risk in smokers, however, no significant association was found among non-smokers. The I-squared value of non-smokers groups is lower than the I-squared values for the smoker population studies, suggesting less heterogeneity among non-smokers populations. Tobacco smoke contains many of carcinogens and procarcinogens, such as benzopyrene and nitrosamine. These compounds are metabolized by the phase I enzymes including CYP family enzymes and converted to inactivemetabolites by the phase II enzymes. Our results should indicate the interaction between CYP1A1 exon 7 gene polymorphisms and smoking in the development of lung carcinoma. However, the association between the extent of smoke exposure and lung cancer risk was not clear, further studies with larger sample size are needed to provide insights into the association.

Some limitations of this meta-analysis should be acknowledged. First, heterogeneity can interfere with the interpretation of the results of a meta-analysis. Although we minimized this likelihood by performing a careful search of published studies, using explicit criteria for a study’s inclusion and performing strict data extraction and analysis, significant interstudy heterogeneity nevertheless existed in nearly every comparison. The presence of heterogeneity

![Begg's funnel plot with pseudo 95% confidence limits](image)

**Figure 5. Begg's funnel plot of CYP1A1 exon7 gene polymorphism and lung cancer risk for the combined Ile/Val and Val/Val vs Ile/Ile.**

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can result from differences in the selection of controls, age distribution, and prevalence of lifestyle factors. Further, only published studies were included in this meta-analysis. The presence of publication bias indicates that non-significant or negative findings might be unpublished. Finally, in the subgroup analyses, differences among populations were confounded with other populations, which may bring in some heterogeneity. As studies among the Indians and Africans are currently limited, further studies including a wider spectrum of subjects should be carried to investigate the role of these variants in different populations.

In conclusion, the results of our meta-analysis have provided the comprehensive and convincing evidence that CYP1A1 exon 7 polymorphisms are an important modifying factor in determining susceptibility to lung cancer. The effect of CYP1A1 exon 7 gene polymorphisms is diverse by the subgroup analysis stratified by ethnicity, histological types of lung cancer and gender of case and control population. More importantly, our study confirms that there is an interaction between two genotypes of CYP1A1 exon 7 gene polymorphisms and smoking. For future studies, strict selection of patients, well-matched controls and larger sample size will be required. Moreover, gene–gene and gene–environment interactions should also be considered.

**Author Contributions**

Conceived and designed the experiments: YJ LS. Performed the experiments: YJ LS. Analyzed the data: YJ. Contributed reagents/materials/analysis tools: QW. Wrote the paper: YJ.

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