CYP1A1 MspI and exon7 gene polymorphisms and lung cancer risk: An updated meta-analysis and review

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Abstract

Background: Many studies have examined the association between the CYP1A1 MspI and exon 7 gene polymorphisms and lung cancer risk in various populations, but their results have been inconsistent.

Methods: To assess this relationship more precisely, a meta-analysis and review were performed. The PubMed, Embase, Web of Science, and CNKI database was searched for case-control studies published up to June 2010. Data were extracted and pooled odds ratios (OR) with 95% confidence intervals (CI) were calculated.

Results: Ultimately, 64 studies, comprising 18,397 subjects from 49 case-control studies of the MspI genotype and 18,518 patients from 40 case-control studies of the exon 7 genotype, were included. A significantly elevated lung cancer risk was associated with 2 MspI genotype variants (for type C vs Type A: OR = 1.26, 95% CI = 1.12-1.42; for types B and C combined vs Type A: OR = 1.20, 95% CI = 1.13-1.28) in overall population. In the stratified analysis, a significant association was found in Asians, Caucasians, lung SCC, lung AC and Male population, not in mixed population, lung SCLC and Female population. However, inconsistent results were observed for CYP1A1 exon7 in our meta-analysis, two variants of the exon 7 polymorphism were associated with a significantly higher risk for lung cancer (for Val/Val vs Ile/Ile: OR = 1.24, 95% CI = 1.09-1.42; for (Ile/Val + Val/Val) vs Ile/Ile: OR = 1.15, 95% CI = 1.07-1.24) in overall population. In the stratified analysis, a significant association was found in Asians, Caucasians, lung SCC and Female population, not in mixed population, lung AD, lung SCLC and Male population. Additionally, a significant association was found in smoker population and not found in non-smoker populations for CYP1A1 MspI and exon7 gene.

Conclusions: This meta-analysis suggests that the MspI and exon 7 polymorphisms of CYP1A1 correlate with increased lung cancer susceptibility and there is an interaction between two genotypes of CYP1A1 polymorphism and smoking, but these associations vary in different ethnic populations, histological types of lung cancer and gender of case and control population.

Keywords: CYP1A1, Polymorphism, Lung cancer, Susceptibility, Meta-analysis

1. Introduction

Lung cancer remains the most lethal cancer worldwide, despite improvements in diagnostic and therapeutic techniques [1]. Its incidence has not peaked in many parts of the 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 MspI site in the 3’-untranslated region (rs4646903;3801T.C) [8]. The MspI restriction site polymorphism resulted in three genotypes: a predominant homozygous m1 allele without the MspI site (genotype A), the heterozygote (genotype B), and a homozygous rare m2 allele with the MspI site (genotype C). The exon 7 restriction site 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 (Febs Lett 1990;263:131-133)[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 MspI polymorphism and lung cancer risk in 2000, in a meta-analysis performed by Le Marchand L et al. [11] included only 11 studies, the exon 7 polymorphism did not correlate with lung cancer risk. Shi × [12], however, noted a greater risk of lung cancer for CYP1A1 MspI and exon 7 polymorphism carriers in a meta-analysis that included only Chinese population.

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 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, gender and smoking status of case and control population.

2. Materials and methods
2.1 Publication search
We searched for studies in the PubMed, Embase, Web of Science, and CNKI (China National Knowledge Infrastructure) electronic databases to include in this meta-analysis, using the terms “CYP1A1,” “Cytochrome P450 1A1,” “polymorphism,” and “lung cancer.” An upper date limit of June, 2010 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. We also reviewed the Cochrane Library for relevant articles. Concurrently, the reference lists of reviews and retrieved articles were searched manually. When the same patient population appeared in several publications, only the most recent or complete study was included in this meta-analysis.

2.2 Inclusion criteria
For inclusion, the studies must have met the following criteria: they (1) evaluated CYP1A1 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 MspI and 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.

2.3 Data extraction
Information was extracted carefully from all eligible publications independently by 2 authors, based on the inclusion criteria above. Disagreements were resolved through a discussion between the 2 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 MspI and exon 7 genotypes, respectively. If data from any category were not reported in the primary study, the items were designated “not applicable.” 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. Cigarette types were classified as filtered or unfiltered commercial products and local traditional hand-made khii yo and yamuan, both unfiltered. 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 require a minimum number of patients for a study to be included in our meta-analysis.
2.4 Statistical analysis

OR (odds ratios) with 95% CIs were used to determine the strength of association between the CYP1A1 MspI and exon7 polymorphisms and lung cancer risk. We evaluated this risk with regard to combinations of variants (i.e., type B and type C for MspI and Ile/Val and Val/Val for exon 7) versus the wild-type homozygotes (type A for MspI and Ile/Ile for exon 7).

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 studies, so that the pooled OR estimate of each study was calculated by the fixed-effects model (the Mantel-Haenszel method) [14]. Otherwise, the random-effects model (the DerSimonian and Laird method) was used [15]. In addition, subgroup analysis stratified by ethnicity, gender and histological types of lung cancer was also performed.

One-way sensitivity analyses were performed to determine the stability of the results–each individual study in the meta-analysis was omitted to reflect the influence of the individual dataset on the pooled OR [16].

Potential publication biases were estimated by funnel plot, in which the standard error of log (OR) of each study was plotted against its log (OR). An asymmetrical plot suggests a publication bias. Funnel plot asymmetry was assessed by Egger’s linear regression test, a linear regression approach that measures the funnel plot asymmetry on a natural logarithm scale of the OR. The significance of the intercept was determined by t-test, as suggested by Egger (P < 0.05 was considered a statistically significant publication bias) [17].

All calculations were performed using STATA, version 10.0 (Stata Corporation, College Station, TX).

3. Results

3.1 Study characteristics

Two hundred and fifty-seven potentially relevant citations were reviewed, and 64 publications met the inclusion criteria and included in our meta-analysis [9,18-80]. Study search process was shown in Figure 1. Table 1 presents the principal characteristics of these studies. For the MspI genotype, 49 studies of 7658 lung cancer cases and 11839 controls were ultimately analyzed. Raimondi’s study [58] sorted the data for Caucasians and Asians; therefore, each group in the study was considered separately in the pooled subgroup analyses. For the exon7 polymorphism, 40 studies of 6067 lung cancer cases and 12451 controls were analyzed.

Of the 64 publications, 50 were published in English and 14 were written in Chinese. The sample sizes ranged from 104 to 1824. All cases were histologically confirmed. The controls were primarily healthy populations and matched for age, ethnicity, and smoking status.

There were 26 groups of Asians, 11 groups of Caucasians, and 12 mixed populations for MspI; for exon7, there were 22 groups of Asians, 10 groups of Caucasians, and 8 mixed populations. All polymorphisms in the control subjects were in Hardy-Weinberg equilibrium.

3.2 Meta-analysis results

3.2.1 Association of CYP1A1 MspI variant with lung cancer risk

Table 2 lists the primary results. Overall, a significantly elevated risk of lung cancer was associated with 2 variants of CYP1A1 MspI (for Type C vs Type A: OR = 1.26, 95% CI = 1.12-1.42, P = 0.003 for heterogeneity; for types B and C combined vs Type A: OR = 1.20, 95% CI = 1.13-1.28, P = 0.000 for heterogeneity) (Figure 2).

In the stratified analysis by ethnicity, significantly increased risks were observed among Asians for both type C vs Type A (OR = 1.24, 95% CI = 1.12-1.43; P = 0.004 for heterogeneity), types B and C combined vs Type A (OR = 1.30, 95% CI = 1.17-1.44; P = 0.002 for heterogeneity). In Caucasians, there was also significant association in Type C vs Type A (OR = 1.25; 95% CI = 1.09-1.36; P = 0.052 for heterogeneity), types B and C combined vs Type A (OR = 1.35; 95% CI = 1.18-1.54; P = 0.046 for heterogeneity). However, in mixed populations, no significant associations were observed (Table 2).

Fourteen [9,19,22,24,26,29,31,32,40,47,53,58,64,78] out of 64 studies examined the association of CYP1A1 MspI genotype and the risk of different histological types of lung cancer including SCC, AC and SCLC. Among lung SCC and lung AC, significantly increased risks were observed for both type C vs Type A, types B and C combined vs Type A. However, among lung SCLC, no significant associations were observed for both type C vs Type A (OR = 0.96; 95% CI = 0.70-1.26; P = 0.864 for heterogeneity) or types B and C combined vs Type A (OR = 1.06; 95% CI = 0.77-1.45; P = 0.976 for heterogeneity) (Figure 3).

Seven [45,56,61,64,74-76] out of 64 studies included the association of CYP1A1 MspI genotype and lung cancer risk stratified by gender (Male and Female). For Male population (3 studies), significantly increased risks were observed for both type C vs Type A (OR = 1.39; 95% CI = 1.23-1.79; P = 0.210 for heterogeneity), types B and C combined vs Type A (OR = 1.46; 95% CI = 1.07-1.98; P = 0.380 for heterogeneity). However, for Female population (7 studies), no significant associations were observed for both type C vs Type A (OR = 0.92; 95% CI = 0.84-1.16; P = 0.003 for heterogeneity) or types B and C combined vs Type A (OR = 0.85; 95% CI = 0.71-1.02; P = 0.000 for heterogeneity) (Figure 4).
Thirteen [24,31,47,56,59-61,64,72,75,78] out of 64 studies included the association of CYP1A1 MspI genotype and lung cancer risk stratified by smoking status (non-smokers or never smokers and smokers). For smokers, significantly increased risks were observed for both type C vs Type A (OR = 1.62; 95% CI = 1.33-1.96; \(P = 0.000\) for heterogeneity), types B and C combined vs Type A (OR = 1.75; 95% CI = 1.44-2.13; \(P = 0.003\) for heterogeneity). However, for non-smokers, no significant associations were observed for both type C vs Type A (OR = 1.18; 95% CI = 0.96-1.186; \(P = 0.086\) for heterogeneity) or types B and C combined vs Type A (OR = 1.09; 95% CI = 0.90-1.33; \(P = 0.114\) for heterogeneity) (Figure 5).

### 3.2.2 Association of CYP1A1 exon7 variant with lung cancer risk

For all studies in the meta-analysis, the genotype, an increased risk for lung cancer was associated with 2 exon7 variants (for Val/Val vs Ile/Ile: OR = 1.24, 95% CI = 1.09-1.42, \(P = 0.004\) for heterogeneity; for Ile/Val and Val/Val combined vs Ile/Ile: OR = 1.15, 95% CI = 1.07-1.24, \(P = 0.000\) for heterogeneity) (Figure 6).

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), Ile/Val and Val/Val combined vs Ile/Ile (OR = 1.21, 95% CI = 1.09-1.34; \(P = 0.000\) for heterogeneity). A significant association
Table 1 Distribution of CYP1A1 MspI and exon7 genotypes among lung cancer cases and controls included in this meta-analysis

| First author-year | Ethnicity(country of origin) | Total sample size (case/control) | Lung cancer cases of MspI genotype | Controls of MspI genotype | Lung cancer cases of exon7 genotype | Controls of exon7 genotype |
|-------------------|-------------------------------|----------------------------------|-----------------------------------|---------------------------|-----------------------------------|---------------------------|
|                   |                               |                                  | Type B | Type C | Type A | Type B | Type C | Type A | Ile/Val | Val/Val | Ile/Val | Val/Val | Ile/Val | Val/Val |
| Kawajiri K-1990    | Asia(Japan)                   | 68/104                           | 28     | 16     | 24     | 42     | 11     | 51     | NA      | NA      | NA      | NA      | NA      | NA      |
| Tefre T-1991       | Caucasian(Norway)             | 221/212                          | 47     | 2      | 172    | 43     | 2      | 167    | NA      | NA      | NA      | NA      | NA      | NA      |
| Hirvonen A-1992    | Caucasian(Finnish)            | 87/121                           | 22     | 0      | 65     | 24     | 2      | 95     | NA      | NA      | NA      | NA      | NA      | NA      |
| Shields PG-1993    | Mixed populations             | 56/48                            | 11     | 2      | 43     | 12     | 3      | 33     | NA      | NA      | NA      | NA      | NA      | NA      |
| Nakachi K-1993     | Asia(Japan)                   | 31/127                           | 7      | 13     | 11     | 55     | 11     | 61     | 11      | 6       | 14      | 4       | 4       | 79      |
| Alexandre AK-1994  | Caucasian(Sweden)             | 296/329                          | 44     | 4      | 248    | 52     | 2      | 276    | 16      | 0       | 280     | 23      | 0       | 306     |
| Kelsey KT-1994     | Mixed(African Americans)      | 72/97                            | 11     | 1      | 60     | 21     | 2      | 74     | NA      | NA      | NA      | NA      | NA      | NA      |
| Cantlay AM-1995    | Caucasian(Edinburgh)          | 129/281                          | NA     | NA     | NA     | NA     | NA     | NA     | 21      | 2       | 106     | 33      | 3       | 245     |
| Kihara M-1995      | Asia(Japan)                   | 97/258                           | 45     | 16     | 36     | 105    | 41     | 112    | 31      | 5       | 59      | 98      | 14      | 143     |
| Xu XP-1996         | Caucasian(USA)                | 207/238                          | 35     | 2      | 170    | 48     | 2      | 233    | NA      | NA      | NA      | NA      | NA      | NA      |
| Garcia-ClosaM-1997 | Mixed populations             | 416/446                          | 75     | 4      | 337    | 73     | 4      | 369    | NA      | NA      | NA      | NA      | NA      | NA      |
| Ishibe N-1997      | Mixed(Mexican and African)    | 171/295                          | 68     | 12     | 91     | 106    | 35     | 154    | 31      | 7       | 132     | 70      | 20      | 204     |
| Hong YS-1998       | Asia(Korean)                  | 85/63                            | 45     | 6      | 34     | 31     | 3      | 29     | 68      | 1       | 16      | 60      | 1       | 2       |
| Taioli E-1998      | Mixed populations             | 105/507                          | 30     | 9      | 59     | 101    | 18     | 170    | 8       | 1       | 94      | 18      | 0       | 272     |
| Sugimura H-1998    | Asia(Japan)                   | 247/185                          | NA     | NA     | NA     | NA     | NA     | NA     | 94      | 28      | 125     | 84      | 7       | 94      |
| Le Marchand L-1998 | Mixed populations             | 341/456                          | 121    | 35     | 183    | 160    | 44     | 250    | 68      | 6       | 263     | 105     | 13      | 335     |
| Xue KX-1999        | Asia(china)                   | 103/131                          | NA     | NA     | NA     | NA     | NA     | NA     | NA      | NA      | NA      | NA      | NA      | NA      |
| Hu YL-1999         | Asia(china)                   | 59/132                           | 22     | 15     | 22     | 76     | 22     | 34     | 33      | 7       | 19      | 102     | 9       | 21      |
| London SJ-2000     | Asia(China)                   | 214/669                          | NA     | NA     | NA     | NA     | NA     | NA     | 39      | 8       | 167     | 130     | 27      | 512     |
| Dresler CM-2000    | Caucasian(USA)                | 158/149                          | 37     | 121    | 17*    | 132    | 31     | 182    | NA      | NA      | NA      | NA      | NA      | NA      |
| Song N-2001        | Asia(China)                   | 217/404                          | 129    | 28     | 60     | 175    | 56     | 173    | 130     | 9       | 78      | 181     | 13      | 210     |
| Ratnasinghe D-2001 | Caucasian(USA)                | 282/324                          | NA     | NA     | NA     | NA     | NA     | NA     | 36      | 3       | 243     | 48      | 3       | 273     |
| Quinones L-2001    | Caucasians(Chile)             | 60/174                           | 29     | 10     | 16     | 38     | 16     | 86     | 35      | 10      | 15      | 52      | 14      | 54      |
| Chen S-2001        | Asia(china)                   | 106/106                          | NA     | NA     | NA     | NA     | NA     | NA     | 38      | 10      | 58      | 33      | 3       | 70      |
| Xue KX-2001        | Asia(china)                   | 106/106                          | NA     | NA     | NA     | NA     | NA     | NA     | 38      | 10      | 58      | 33      | 3       | 70      |
| Yin LH-2002        | Asia(china)                   | 84/84                            | 34     | 13     | 37     | 38     | 18     | 28     | NA      | NA      | NA      | NA      | NA      | NA      |
| Zhou XW-2002       | Asia(china)                   | 92/98                            | 43     | 15     | 34     | 34     | 13     | 51     | 66      | 11      | 15      | 65      | 6       | 65      |
| Cai XL-2003        | Asia(china)                   | 91/138                           | 23     | 36     | 32     | 46     | 39     | 53     | NA      | NA      | NA      | NA      | NA      | NA      |
| Kiyohara C-2003    | Asia(Japan)                   | 158/259                          | 64     | 17     | 77     | 115    | 28     | 116    | NA      | NA      | NA      | NA      | NA      | NA      |
| Taioli E-2003      | Mixed populations             | 109/424                          | 20     | 5      | 84     | 75     | 4      | 345    | 16      | 1       | 93      | 70      | 2       | 635     |
| Wang J-2003        | Asia(china)                   | 162/181                          | 76     | 22     | 64     | 78     | 38     | 65     | NA      | NA      | NA      | NA      | NA      | NA      |
| Dialyna IA-2003    | Caucasians(Greek)             | 122/178                          | 28     | 5      | 89     | 45     | 3      | 130    | NA      | NA      | NA      | NA      | NA      | NA      |
| Dong CT-2004       | Asia(china)                   | 82/91                            | NA     | NA     | NA     | NA     | NA     | NA     | NA      | NA      | NA      | NA      | NA      | NA      |
| Gu YF-2004         | Asia(china)                   | 180/224                          | 129    | 51     | 138*   | 86     | NA     | NA      | NA      | NA      | NA      | NA      | NA      | NA      |
| Liang GY-2004      | Asia(china)                   | 152/152                          | 82     | 20     | 50     | 71     | 11     | 70     | NA      | NA      | NA      | NA      | NA      | NA      |
| Study | Region          | Cases | MspI | Exon7 | TypeB | TypeC | Ile/Val | Val/Val | Combined TypeB and TypeC | Combined Ile/Val and Val/Val |
|-------|----------------|-------|------|-------|-------|-------|---------|---------|--------------------------|-----------------------------|
| Chen  | Asia (China)   | 58/62 | 15   | 23    | 20    | 18    | 24      | NA      | NA          | NA                         |
| Yang  | Asia (China)   | 200/144 | NA   | NA    | NA    | NA    | NA      | 96      | 11          | 90                         |
| Sobri | Asia (India)   | 100/76 | 45   | 6     | 49    | 29    | 5       | 42      | 67          | 29                         |
| Wenzl | Asian (USA)    | 128/181 | 35   | 0     | 93    | 30    | 4       | 116     | 5*          | 12*                        |
| Wrensc | Mixed populations | 371/944 MspI 363/930 Exon7 | 166* | 205 | 472* | 472 | 64* | 302 | 219* | 711 |
| Ng    | Asia (Singapore) | 126/162 | 61   | 22    | 41    | 87    | 19      | 56      | 39          | 13                         |
| Larsen| Caucasians (Australia) | 1050/581 | NA   | NA    | NA    | NA    | NA      | 84      | 8           | 958                        |
| Raimondi | Caucasians | 165/519 MspI 175/723 Exon7 | 43* | 122 | 102* | 417 | 32* | 143 | 67* | 656 |
| Raimondi | Asians | 46/138 MspI 60/212 Exon7 | 28* | 18 | 95* | 43 | 30* | 30 | 96* | 116 |
| Sreeja| Asia (India)   | 146/146 | 53   | 22    | 71    | 45    | 8       | 93      | NA          | NA                         |
| Adonis| Mixed populations | 57/103 | 31   | 11    | 15    | 33    | 26      | 44      | NA          | NA                         |
| Belogu| Caucasians (Russia) | 141/450 | 35   | 2     | 104   | 90    | 3       | 357     | NA          | NA                         |
| Li    | Asia (China)   | 150/152 | NA   | NA    | NA    | NA    | NA      | 104     | 14          | 32                         |
| Pisani| Asia (Thailand) | 211/408 | 87   | 55    | 26    | 155   | 78      | 53      | 79          | 10                         |
| Yang  | Asia (Korea)   | 314/349 | NA   | NA    | NA    | NA    | NA      | 116     | 16          | 182                        |
| Tao   | Asia (China)   | 47/94   | 19   | 4     | 24    | 37    | 14      | 43      | NA          | NA                         |
| Cote  | Mixed populations | 354/440 | 80   | 5     | 269   | 95    | 6       | 339     | 19          | 0                          |
| Xia   | Asia (China)   | 58/116  | 36   | 5     | 17    | 58    | 18      | 40      | NA          | NA                         |
| Qi    | Asia (China)   | 53/72   | 29   | 7     | 17    | 38    | 11      | 23      | NA          | NA                         |
| Yoon  | Asia (Korea)   | 213/213 | NA   | NA    | NA    | NA    | NA      | 76      | 10          | 127                        |
| Gallegos-Arreola | Mixed populations | 222/248 | NA   | NA    | NA    | NA    | NA      | 91      | 40          | 91                         |
| Shah  | Asia (India)   | 200/200 | 94*  | 106   | 63*   | 137   | 67*     | 133     | 44*         | 156                        |
| Kumar | Asia (India)   | 93/253  | NA   | NA    | NA    | NA    | NA      | 17      | 3           | 73                         |
| Cote  | Mixed populations | 502/523 | 109  | 14    | 373   | 110   | 7       | 402     | 38          | 0                          |
| Homna | Mixed populations | 200/264 | 76   | 11    | 113   | 94    | 9       | 161     | NA          | NA                         |
| Klinch | Asia (Thailand) | 85/82   | 66*  | 19    | 66*   | 16    | 47*     | 33      | 42*         | 38                         |
| Timofeeva| Caucasians (Germany) | 619/1264 | NA   | NA    | NA    | NA    | NA      | 248     | 61          | 260                        |
| Shaffi| Asia (India)   | 109/163 | 81*  | 28    | 85*   | 78    | NA      | NA      | NA          | NA                         |
| Jin   | Asia (China)   | 124/154 | 71*  | 79    | 70*   | 80    | NA      | NA      | NA          | NA                         |
| Wright| Caucasians (Australia) | 1040/784 | 219  | 24    | 797   | 128   | 10      | 646     | 103         | 8                          |

NA, not applicable; *, the number of the combined of TypeB and TypeC genotypes; #, the number of the combined Ile/Val and Val/Val genotypes.
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 = 1.28; 95% CI = 1.12-1.45; P = 0.000 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 [22,24,29-32,36,40,53,57,58,70] out of 64 studies examined the association of CYP1A1 exon 7 genotype and the risk of different histological types of lung cancer including SCC, AC and SCLC. 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 = 0.004 for heterogeneity) or Ile/Val and Val/Val combined vs Ile/Ile (OR = 1.38; 95% CI = 1.12-1.66; P = 0.004 for heterogeneity). However, among lung AC and SCLC, no significant associations were observed for both Val/Val vs Ile/Ile (OR = 1.42; 95% CI = 1.18-1.70; P = 0.000 for heterogeneity). However, among lung AC and SCLC, no significant associations were observed for both Val/Val vs Ile/Ile (OR = 1.42; 95% CI = 1.18-1.70; P = 0.000 for heterogeneity). However, among lung AC and SCLC, no significant associations were observed for both Val/Val vs Ile/Ile (OR = 1.42; 95% CI = 1.18-1.70; P = 0.000 for heterogeneity).

Eight [36,54,56,57,70,74,76,77] out of 64 studies included the association of CYP1A1 exon 7 genotype and lung cancer risk stratified by gender (Male and Female). For Female population (3 studies), significantly increased risks were observed for both Val/Val vs Ile/Ile (OR = 1.24; 95% CI = 1.09-1.42; P = 0.004 for heterogeneity), Ile/Val and Val/Val combined vs Ile/Ile (OR = 1.24; 95% CI = 1.18-1.70; P = 0.000 for heterogeneity), Ile/Val and Val/Val combined vs Ile/Ile (OR = 1.24; 95% CI = 1.18-1.70; P = 0.000 for heterogeneity).

Ten [24,31,56,60,70-73] out of 64 studies included the association of CYP1A1 exon 7 genotype and lung cancer risk stratified by smoking status (non-smokers or never smokers and smokers). For smokers, significantly increased risks were observed for both Val/Val vs Ile/Ile (OR = 1.93; 95% CI = 1.71-2.20; P = 0.000 for heterogeneity), Ile/Val and Val/Val combined vs Ile/Ile (OR = 1.93; 95% CI = 1.71-2.20; P = 0.000 for heterogeneity). However, for non-smokers, no significant associations were observed for both Val/Val vs Ile/Ile (OR = 1.15; 95% CI = 0.96-1.39; P = 0.298 for heterogeneity) (Figure 8).

3.3 Sensitivity analyses
On omission of each individual study, the corresponding pooled OR was not altered materially (data not shown).
3.4 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 10 and 11). By Egger’s test—used to provide statistical evidence of funnel plot symmetry—there was no evidence of publication bias (P = 0.558 for publication bias of MspI and P = 0.722 for publication bias of exon 7).

4. 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 MspI and 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 MspI gene polymorphism and lung cancer risk in Asians, Caucasians, lung SCC, lung AC and Male population, no significant association was found in mixed population, lung SCLC.
and Female population. Interestingly, inconsistent results were observed for CYP1A1 exon7 polymorphism in our meta-analysis. For the association between CYP1A1 exon7 gene polymorphism and lung cancer risk, a significant association was found in Asians, Caucasians, lung SCC and Female population, no significant associations were 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 for CYP1A1 MspI and exon7 polymorphisms.

When stratified according to ethnicity, a significantly increased risks were identified among Asians and Caucasians for the 2 MspI genotype variants, however 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 for CYP1A1 MspI and exon7 polymorphisms.

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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 [82]. When sub-group analyses by pathological types were considered, CYPIAl Mspl and exon7 variant alleles were found to be associated with a 1.4-1.9 fold increase in the risk of lung SCC. For lung AC, only CYPIAl Mspl gene polymorphism was significant, however, for lung SCLC, no significant association was found for two genotypes. Our findings were consistent with the Le Marchand L et al study [32] with largest sample sizes of case and control. Le Marchand et al. [32] 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 [83]. Different carcinogenic processes may be involved in the genesis of various tumor types because of the presence of functionally different CYPIAl Mspl and exon7 gene polymorphisms. However, the possible molecular mechanisms to explain these histology-specific differences in the risk of lung cancer remain unresolved.

Recent epidemiological and biochemical studies have suggested increased susceptibility to tobacco carcinogens in women compared to men [84-86]. Moreover, CYPIA1 mRNA expression in the lung has been observed to be more than two-fold higher in female smokers compared with male smokers [87]. Another possibly was due to the effect of circulation estrogens, which have been shown to induce expression of PAH-metabolizing enzymes, such as CYPIA1, thereby increasing metabolic activation of carcinogens [88]. In premenopausal women, a higher expression of estrogen can be expected. Estrogen by itself can be involved in carcinogenesis and additionally, it can stimulate expression of CYPs in the female. In our meta-analysis, we found that the effect of CYPIA1 exon7 genotype was observed only in Females, however, for CYPIA1 Mspl the effect was only observed among Males. Our results, along with the previous studies involved above, suggest the difference roles on the two polymorphisms of

![Forest plot (random-effects model) of lung cancer risk associated with CYP1A1 Mspl for the combined types B and C vs Type A stratified by gender of population.](http://www.jeccr.com/content/30/1/99)
CYP1A1 genotypes in the susceptibility of lung cancer between Females and Males.

As we know, aside from genetic factor, smoking is the major risk factor of lung cancer. Most studies out of 64 studies reported information on smoking habits of cases and controls, however only sixteen eligible publications provided non-smokers information. Our meta-analysis results showed that a significantly increased risk was found to be associated with the CYP1A1 MspI and exon 7 gene polymorphisms and lung cancer risk in smokers, however, no significant association was found among non-smokers neither CYP1A1 MspI or exon 7 genotype. 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 inactive metabolites by the phase II enzymes. Our results should indicate the interaction between CYP1A1 MspI and 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.

Our data were consistent with the primary results of a previous meta-analysis [89] that showed the MspI and Ile-Val polymorphism of CYP1A1 was a risk factor associated with increased lung cancer susceptibility and these associations varied in different ethnic populations. However, that meta-analysis only conducted the stratified analysis according to ethnicity, smoking and histological types and could not analyze the stratified results in-depth. They could not certify the interaction between smoking status, the major risk factor of lung cancer, and the two genotypes of CYP1A1 polymorphism due to the limitation of included studies. We performed more comprehensive stratified analysis by ethnicity, histological types, smoking status and gender and found the different associations in Male and Female population. We concluded
Figure 6 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.

Figure 7 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 by histological types of lung cancer.
Figure 8 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 stratified by gender of population.

Figure 9 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 stratified by smoking status of population.
that MspI and exon 7 polymorphisms of CYP1A1 correlated with increased lung cancer susceptibility and there was an interaction between two genotypes of CYP1A1 polymorphism and smoking, but these associations varied in different ethnic populations, histological types and gender of case and control population.

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 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, different ethnicities were confused with other population, 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 MspI and exon 7 polymorphisms are an important modifying factor in determining susceptibility to lung cancer. The effect of two genotypes of CYP1A1 polymorphism 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 polymorphism 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.

List of abbreviations
CYP1A1: Cytochrome P450 1A1; PAHs: polycyclic aromatic hydrocarbons; CNKI: China National Knowledge Infrastructure; SCC: squamous carcinoma; AC: adenocarcinoma; SCLC: small cell lung cancer; OR: odds ratios; CI: confidence interval

Acknowledgements
This work was supported in part by a grant from the Major Program of Nanjing Medical Science and Technique Development Foundation (Molecular Predictor of Personalized Therapy for Chinese Patients with Non-small Cell Lung Cancer) (Lk-Yu).

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Authors’ contributions
PZ and LKY contributed to the conception and design of the study, the analysis and interpretation of data, the revision of the article as well as final approval of the version to be submitted. SZW and QQ participated in the design of the study, drafted and revised the article. QW participated in the design of the study and helped to revise the article. All authors read and approved the final version of the manuscript.

Competing interests
The authors declare no any conflicts of interest in this work.

Received: 8 September 2011 Accepted: 20 October 2011 Published: 20 October 2011

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Cite this article as: Zhan et al.: CYP1A1 MspI and exon7 gene polymorphisms and lung cancer risk: An updated meta-analysis and review. Journal of Experimental & Clinical Cancer Research 2011 30:99.

doi:10.1186/1756-9966-30-99

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