Association between cytochrome P450 1A1 (CYP1A1) gene polymorphisms and the risk of renal cell carcinoma: a meta-analysis

Fan-dong Meng, Ping Ma, Cheng-guang Sui, Xin Tian & You-hong Jiang

Molecular Oncology Department of Cancer Research Institution, The First Hospital of China Medical University, Shenyang 110001, China.

Cytochrome P450 1A1 (CYP1A1) usually metabolizes carcinogens to their inactive derivatives but occasionally converts the chemicals to more potent carcinogens. To date, many studies have evaluated the association between the CYP1A1 MspI and Ile462Val polymorphisms and renal cell carcinoma (RCC) risk, but the results have been conflicting. To more precisely evaluate the potential association, we carried out a meta-analysis of seven published case-control studies. The meta-analysis indicated that the MspI polymorphism was associated with an increased RCC risk (allele model: OR = 1.49, 95%CI 1.03–2.16; homozygous model: OR = 1.64, 95%CI 1.13–2.40; dominant model: OR = 1.72, 95%CI 1.07–2.76). No significant associations were found for the Ile462Val polymorphism for all genetic models. When stratified by smoking status, smokers carrying the variant Vt and Val allele were more susceptible to RCC (Vt allele: OR = 3.37, 95%CI = 2.24–5.06; Val allele: OR = 2.07, 95%CI = 1.34–3.19). These data indicate that the CYP1A1 MspI polymorphism significantly increased RCC risk, while the Ile462Val polymorphism was not associated with RCC. Among smokers, individuals with the CYP1A1 Vt allele and Val allele showed a significantly increased risk of RCC. More well-designed studies with larger samples are warranted to show the underlying mechanisms of CYP1A1 in the development of RCC.

In 2014, an estimated 63,920 people in the United States will be diagnosed with cancers of the kidney and renal pelvis, the vast majority of which are renal cell carcinoma (RCC), with an estimated 13,860 deaths. Over the past two decades, the incidence of these cancers has increased by approximately 2% per year. Smoking, obesity, and germline mutations in specific genes are established risk factors for RCC. Multiple studies indicated the gene-environment interactions in relation to RCC are linked to genes involved in metabolism enzymes. Polymorphisms in genes encoding carcinogen metabolizing enzymes that alter their expression and function may increase or decrease carcinogen activation and/or deactivation. Among the cytochrome P450s (CYPs) involved in pro-carcinogen activation, cytochrome P450 1A1 (CYP1A1) has been the most widely studied. CYP1A1 is a member of the CYP1 family and plays a key role in the metabolism of drugs and environmental chemicals. The human CYP1A1 enzyme is the most active among the CYPs in metabolizing pro-carcinogens, particularly the polycyclic aromatic hydrocarbons, into highly reactive intermediates. When these compounds bind to DNA and form adducts, they may contribute to carcinogenesis. Two functional nonsynonymous polymorphisms in the CYP1A1 gene have been recently studied: a thymine (T) to cytosine (C) transition in the noncoding 3'-flanking region (MspI, rs4646903), and an adenine (A) to guanine (G) substitution at codon 462 in exon 7 (Ile462Val, rs1048943). These variations could alter CYP1A1 expression and function, potentially influencing the balance between metabolic activation and detoxification of toxicants, and ultimately leading to individual susceptibilities to cancer.

To date, a number of meta-analyses have been performed to explore the association between the MspI and Ile462Val polymorphisms of CYP1A1 and various cancers, including prostate, esophageal, lung, cervical, head and neck cancers. However, a meta-analysis to investigate the association between CYP1A1 MspI and Ile462Val polymorphisms and RCC risk has not been performed. Here we performed a meta-analysis of all currently available publications to examine whether the genotype status of the two polymorphisms in CYP1A1 is associated with RCC risk.
Results

Characteristics of included studies. After a literature search, five publications were eligible for the meta-analysis. Fig. 1 illustrates the trial flow chart. The studies by Chen et al. and Wang et al. were related to CYP1A1 MspI and Ile462Val polymorphisms, so they were regarded as two independent studies. Seven case-control studies were eligible according to the inclusion criteria, among which three studies (531 cases and 739 controls) examined the CYP1A1 MspI polymorphism and four studies (742 cases and 975 controls) examined the CYP1A1 Ile462Val polymorphism. Of the five publications, three were published in English and two were written in Chinese, and four were conducted in China and one was based in India. A list of details from the studies included in the meta-analysis is provided in Table 1.

Meta-analysis results. The summary of meta-analysis for CYP1A1 MspI and Ile462Val polymorphisms with RCC is shown in Table 2 and Table 3.

Analysis for CYP1A1 MspI polymorphism. Overall, MspI polymorphism was significantly associated with the increased risk of RCC under three genetic comparison models (allele model: OR =

Table 1 | Characteristics of publications identified for the meta-analysis

| Study    | Year | Country | Ethnicity | Source of Control | HWE  | Sample Size [Case/Control] | Genotype Distribution [Case/Control] | Genotyping Method |
|----------|------|---------|-----------|-------------------|------|--------------------------|-------------------------------------|------------------|
| Wang [19] | 2008 | China   | Asian     | PB                | <0.001 | 143/153                  | MspI [rs4646903]                      | PCR-RFLP         |
| Chen [21] | 2011 | China   | Asian     | PB                | 0.022  | 181/350                  |                                      | PCR-RFLP         |
| Wang [22] | 2012 | China   | Asian     | PB                | 0.053  | 207/236                  |                                      | PCR-RFLP         |
| Wang [20] | 2008 | China   | Asian     | PB                | 0.001  | 158/139                  |                                      | PCR-RFLP         |
| Chen [21] | 2011 | China   | Asian     | PB                | <0.001 | 181/350                  |                                      | PCR-RFLP         |
| Wang [22] | 2012 | China   | Asian     | PB                | 0.064  | 207/236                  |                                      | PCR-RFLP         |
| Ahmad [23] | 2013 | India   | Asian     | PB                | 0.382  | 196/250                  |                                      | PCR-ASO          |

HWE = Hardy-Weinberg equilibrium, PCR-RFLP = polymerase chain reaction - restriction fragment length polymorphism, PCR-ASO = allele specific oligonucleotide.
### Table 2 | Meta-analysis of the association between CYP1A1 MspI polymorphism and renal cell carcinoma risk

|                  | OR (95%CI) | P_Or  | P_h  | OR (95%CI) | P_Or  | P_h  | OR (95%CI) | P_Or  | P_h  |
|------------------|------------|-------|------|------------|-------|------|------------|-------|------|
|                  |            |       |      |            |       |      |            |       |      |
| Overall          | 1.49(1.03–2.16) | 0.035 | 0.010 | 1.64(1.13–2.40)* | 0.010* | 0.190 | 1.35(0.94–1.93)* | 0.105* | 0.459 |
|                  | 1.72(1.07–2.76) | 0.026 | 0.013 |            |       |      |            |       |      |
| HWE test         |            |       |      |            |       |      |            |       |      |
| HWE              | 1   | 1.15(0.87–1.52) | 0.324 | - | 1.23(0.70–2.17) | 0.474 | - | 1.12(0.66–1.91) | 0.670 | - |
|                  | 1.22(0.84–1.77) | 0.303 | - |            |       |      |            |       |      |
| Non-HWE          | 2   | 1.71(1.11–2.62) | 0.014 | 0.014 | 2.10(1.26–3.49)* | 0.004* | 0.251 | 1.57(0.97–2.57)* | 0.069* | 0.405 |
|                  | 2.12(1.60–2.81)* | <0.001* | 0.068 |            |       |      |            |       |      |

OR: odds ratio, 95% CI: 95% confidence interval, P_Or: P value for the pooled ORs, P_h: P value for heterogeneity analysis.
*Estimates for fixed-effects model.

### Table 3 | Meta-analysis of the association between CYP1A1 Ile462Val polymorphism and renal cell carcinoma risk

|                  | OR (95%CI) | P_Or  | P_h  | OR (95%CI) | P_Or  | P_h  | OR (95%CI) | P_Or  | P_h  |
|------------------|------------|-------|------|------------|-------|------|------------|-------|------|
|                  |            |       |      |            |       |      |            |       |      |
| Overall          | 1.14(0.78–1.67) | 0.503 | <0.001 | 1.22(0.58–2.55) | 0.598 | <0.001 | 1.08(0.59–2.01) | 0.796 | 0.001 |
|                  | 1.24(0.83–1.87) | 0.293 | 0.006 |            |       |      |            |       |      |
| HWE test         |            |       |      |            |       |      |            |       |      |
| HWE              | 2   | 1.06(0.90–1.25) | 0.469 | <0.001 | 1.30(0.87–1.95) | 0.205 | <0.001 | 1.31(0.89–1.94) | 0.172 | <0.001 |
|                  | 1.20(0.85–1.59) | 0.969 | <0.001 |            |       |      |            |       |      |
| Non-HWE          | 2   | 1.09(0.31–3.84) | 0.899 | 0.001 | 0.84(0.35–2.01) | 0.693* | 0.130 | 0.90(0.37–2.17) | 0.812* | 0.178 |
|                  | 1.06(0.28–3.99) | 0.935 | 0.002 |            |       |      |            |       |      |
| Country          |            |       |      |            |       |      |            |       |      |
| China            | 3   | 1.06(0.90–1.25) | 0.469 | <0.001 | 1.30(0.87–1.95) | 0.205 | <0.001 | 1.31(0.89–1.94) | 0.172 | <0.001 |
|                  | 1.00(0.85–1.51) | 0.969 | <0.001 |            |       |      |            |       |      |
| India            | 1   | 1.09(0.31–3.84) | 0.899 | 0.001 | 0.84(0.35–2.01) | 0.693* | 0.130 | 0.90(0.37–2.17) | 0.812* | 0.178 |
|                  | 1.06(0.28–3.99) | 0.935 | 0.002 |            |       |      |            |       |      |

OR: odds ratio, 95% CI: 95% confidence interval, P_Or: P value for the pooled ORs, P_h: P value for heterogeneity analysis.
*Estimates for fixed-effects model.
1.49, 95%CI 1.03–2.16; homozygous model: OR = 1.64, 95%CI 1.13–2.40; dominant model: OR = 1.72, 95%CI 1.07–2.76) (Fig. 2). When stratified by HWE test, we found significant associations between the MspI polymorphism and increased risk of RCC in non-HWE studies. Obvious heterogeneity was observed in allele model and dominant model. Further studies are needed to confirm the roles of study design with regard to heterogeneity.

**Analysis for CYP1A1 Ile462Val polymorphism.** No significant association was found between the Ile462Val polymorphism and RCC risk for all genetic models (allele model: OR = 1.14, 95%CI 0.78–1.67; homozygous model: OR = 1.22, 95%CI 0.58–2.55; recessive model: OR = 1.08, 95%CI 0.59–2.01; dominant model: OR = 1.24, 95%CI 0.83–1.87). When stratified by HWE test and country, the polymorphism was not significantly associated with RCC risk. Obvious heterogeneity was observed in all genetic models. Neither the HWE test or country could explain the heterogeneity, which could have been caused by the limited number of included studies.

**CYP1A1 polymorphisms and smoking in RCC.** The impact of the combination of CYP1A1 polymorphisms and smoking on RCC is shown in Table 4. Among the smokers, individuals with the CYP1A1 Vt allele and Val allele showed a significantly increased risk of RCC (Vt allele: OR = 3.37, 95%CI = 2.24–5.06; Val allele: OR = 2.07, 95%CI = 1.34–3.19). However, no significant interaction was found between smoking and the CYP1A1 Vt allele or Val allele (P = 0.08 and P = 0.07, respectively).

**Publication bias and sensitivity analysis.** Begg’s funnel plot and Egger’s test were performed to assess the publication bias of included studies. As shown in Fig. 3, the Begg’s funnel plot was symmetrical in the allele model. The Egger’s test results found no significant evidence of publication bias (P = 0.405 for allele model). The leave-one-out sensitivity analysis indicated that no single study qualitatively changed the pooled ORs (data not shown). The results of sensitivity analyses indicated that the data of our meta-analysis are relatively stable and credible.

**Discussion**

CYP1A1 is a member of the CYP1 family and participates in the metabolism of a vast number of xenobiotics, as well as endogenous substrates. CYP1A1 plays a key role in phase I metabolism of polycyclic aromatic hydrocarbons and in estrogen metabolism. The dysfunction of CYP1A1 can cause damage to DNA, lipids, and proteins, which further results in carcinogenesis. Polymorphisms of the CYP1A1 enzymes may contribute to the variable susceptibility to carcinogenesis by altering the level of gene expression or messenger RNA stability, resulting in highly inducible activity of the enzyme.

To the best of our knowledge, this is the first meta-analysis to assess the association between the CYP1A1 MspI and Ile462Val polymorphisms and RCC risk. Our results suggested an important role of the CYP1A1 MspI polymorphism in the risk of developing RCC. The overall pooled ORs suggested that individuals carrying the variant C allele and the homozygous genotype CC were significantly more susceptible to RCC compared with those carrying the wild-type TT genotype (allele model: OR = 1.49, 95%CI 1.03–2.16; homozygous model: OR = 1.64, 95%CI 1.13–2.40). However, our results showed that the CYP1A1 Ile462Val polymorphism was not associated with RCC. Several studies have suggested the CYP1A1 polymorphisms were associated with elevated risks of prostate cancer, esophageal cancer, and head and neck cancer. However, no significant associations between the CYP1A1 polymorphisms and risks for gastric cancer and colorectal cancer were found in other stud-
These contradictory findings indicate that polymorphisms of CYP1A1 might exert different effects in different types of cancers.

Epidemiological studies have shown that cigarette smoking is an important risk factor for RCC. In the subgroup analysis based on smoking status, we evaluated the interaction between CYP1A1 genotypes and smoking in patients with RCC. In our meta-analysis, we found that individuals with the CYP1A1 Vt allele and Val allele showed a significantly increased risk of RCC among smokers. This implied that polymorphisms in metabolic genes might greatly increase susceptibility carcinogens to RCC in smokers.

Several limitations should be taken into consideration when analyzing the results of our meta-analysis. First, only seven independent case-control studies with 885 cases and 1,128 controls were included in our study. More studies with larger samples are needed to take further power of meta-analysis and obtain more reliable results. Second, all seven studies were performed in Asians, and there was no study involving Caucasians or Africans. Therefore, further studies are needed to investigate the association between CYP1A1 polymorphisms and RCC risk, especially in Caucasians and Africans. Third, several studies departed from the HWE, which may have led to a bias for the overall estimates of the meta-analysis. Finally, the gene-gene and gene-environment interplay plays crucial roles in the development of RCC. Previous research implicated a variety of risk factors in RCC development, including obesity, smoking, hypertension, renal disease and viral hepatitis. More studies with enough statistical power are needed for further evaluation.

In conclusion, our meta-analysis suggests that the CYP1A1 MspI polymorphism significantly increased RCC risk, while the Ile462Val polymorphism was not associated with RCC. Among smokers, individuals with the CYP1A1 Vt allele and Val allele showed a significant highly increased risk of RCC. Considering the limited sample size and ethnicities included in the meta-analysis, further larger scale studies are necessary to enrich the present findings, especially in Caucasians and Africans.

**Methods**

**Identification of eligible studies.** We performed a literature search of the PubMed, Embase, China National Knowledge Infrastructure (CNKI) and Web of Science databases to identify individual studies on the association between the CYP1A1 MspI and Ile462Val polymorphisms and RCC risk up to July 20, 2014. We used the following keywords and subject terms: “polymorphism” or “SNP” or “gene mutation” or “gene variants”, and “renal cell cancer” or “renal cell tumor” or “renal cell carcinoma”, and “Cytochrome P450 1A1” or “CYP1A1” or “MspI” or “Ile462Val”. References of all primary studies and review articles were reviewed to obtain additional references. When multiple publications reported on the same or overlapping data, the largest or most complete study was chosen.

**Inclusion/exclusion criteria.** Publications were selected if they satisfied the following inclusion criteria: (1) a case-control study; (2) an evaluation of the association between the CYP1A1 MspI and Ile462Val polymorphisms and RCC risk; and (3) sufficient information to estimate the odds ratio (OR) and a 95% confidence interval (CI). Articles were excluded based on the following: (1) an irrelevant study; (2) a duplicate publication; (3) based on incomplete data; or (4) case-only studies, letters and reviews.

**Data extraction.** Based on the inclusion criteria, two investigators (Meng and Tian) independently reviewed and extracted data from all eligible studies. The following items were extracted: first author, year of publication, ethnicity, country of origin, source of controls (population-based, hospital-based, sample size, genotyping method, p-values for Hardy-Weinberg equilibrium (HWE), and genotype distribution in cases and controls.

**Statistical methods.** The pooled ORs with corresponding 95% CIs were calculated to assess the association between the CYP1A1 gene polymorphisms and the risk of RCC under four genetic models: the allele model (A vs. G), homozygous model (AA vs. GG), recessive model (AA + GA vs. GG), and dominant model (AA + GA vs. GG). We tested whether genotype frequencies of controls were in HWE using the $x^2$ test. The heterogeneity between the studies was evaluated with the $I^2$-based test (Cochran’s Q test) and F statistic tests. Heterogeneity between studies was considered to be significant when $P < 0.05$ for Q-tests or when $I^2$ was more than 75%. The fixed effect model (Mantel-Haenszel method) was conducted if between-study heterogeneity was not significant. Otherwise, the random effect model (DerSimonian and Laird method) was used. Beggar’s funnel plot and Egger’s test were carried out to assess the publication bias risk. We performed sensitivity analysis by deleting each single study from the meta-analysis in turn to assess the stability of the final results. All analyses were performed using STATA version 12.0 software (STATA Corporation, College Station, TX, USA).

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![Figure 3](image-url)
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**Author contributions**

Designed the study: J.Y. and M.F. Searched databases and collected full-text papers: M.P., S.C. and T.X. Extracted and analyzed the data: J.Y., M.F. and T.X. Statistical analyses: J.Y. and M.F. Wrote the main manuscript text: J.Y., M.F. and M.P. All authors reviewed the manuscript.

**Additional information**

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