

Original Article

CYP1A1 genetic polymorphisms and uterine leiomyoma risk: a meta-analysis

Fen Wang, Jiyong Chen, Lin Wang, Yulan Ma, Niyazi Mayinuer

Department of Gynecology, The Peoples' Hospital of Xinjiang, Urumqi 830001, China

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Abstract: Background: Some studies assessed the association between CYP1A1 MspI and Ile462Val polymorphisms and uterine leiomyoma (UL) risk. However, the results were controversial. We did this meta-analysis to determine the association between CYP1A1 MspI and Ile462Val polymorphisms and UL risk. Materials and methods: We searched databases containing PubMed, Springer Link, EMBASE, Chinese National Knowledge Infrastructure (CNKI) up to 11 October 2014. Pooled ORs and 95% CIs were used to assess the strength of the associations. Results: In total, 9 case-control studies with 2157 UL cases and 2197 healthy controls were included in this meta-analysis. CYP1A1 Ile462Val polymorphism was significantly associated with UL risk (OR = 2.29, 95% CI 1.75-2.99, $P < 0.00001$). In the subgroup analysis by race, significantly increased risks were found in the Asians (OR = 2.76, 95% CI 1.86-4.09, $P < 0.00001$) and Caucasians (OR = 1.87, 95% CI 1.30-2.68, $P = 0.0007$). However, MspI polymorphism was not significantly associated with UL risk (OR = 1.15, 95% CI 0.90-1.47, $P = 0.27$). In the subgroup analysis by race, no significant association was found in the Asians (OR = 1.15, 95% CI 0.86-1.54, $P = 0.35$). Conclusion: In summary, the results of the meta-analysis suggested that CYP1A1 Ile462Val polymorphism was significantly associated with UL risk.

Keywords: Meta-analysis, CYP1A1, polymorphism, uterine leiomyoma

Introduction

Uterine leiomyoma (UL) is the commonest benign uterine tumors. During women's reproductive years, the estimated incidence of UL is 20%-40% [1]. Race, age, caffeine intake, parity, and pregnancy are considered to be associated with UL risk [2]. However, the molecular pathogenesis of UL is still largely unknown. Cumulative evidence suggested that genetics may play an important role in the UL pathogenesis [3].

The P450 cytochrome system (CYP450) was a group of enzymes which involves in steroid hormone biosynthesis and in metabolic activation of carcinogens [4]. CYP1A1 is one of CYP450 enzymes involved in estrogen catabolism. CYP1A1 had a critical role in the estrone to 2-hydroxy catechol metabolites and 2-hydroxylation of estradiol for O-methylation to 2-methoxy intermediates [5]. It was possible that certain polymorphisms affecting the CYP1A1 activity might lead to UL.

The CYP1A1 gene was located on chromosome 15q22-q24. CYP1A1 gene was 5,987 base pairs long, which encoded a 512-amino acid protein. Until now, 19 polymorphisms of CYP1A1 gene have been found [6]. Some studies have been investigated the association between CYP1A1 MspI and Ile462Val polymorphisms and UL risk [7-15]. However, the results were controversial. We did this meta-analysis to determine the association between CYP1A1 MspI and Ile462Val polymorphisms and UL risk.

Materials and methods

Materials

We searched databases containing PubMed, Springer Link, EMBASE, Chinese National Knowledge Infrastructure (CNKI) up to 11 October 2014, using the following terms: ("uterine leiomyoma") and ("CYP1A1" or "cytochrome p-450 cyp1a1"). We limited the languages to English and Chinese. Besides, the references from retrieved articles were also searched.

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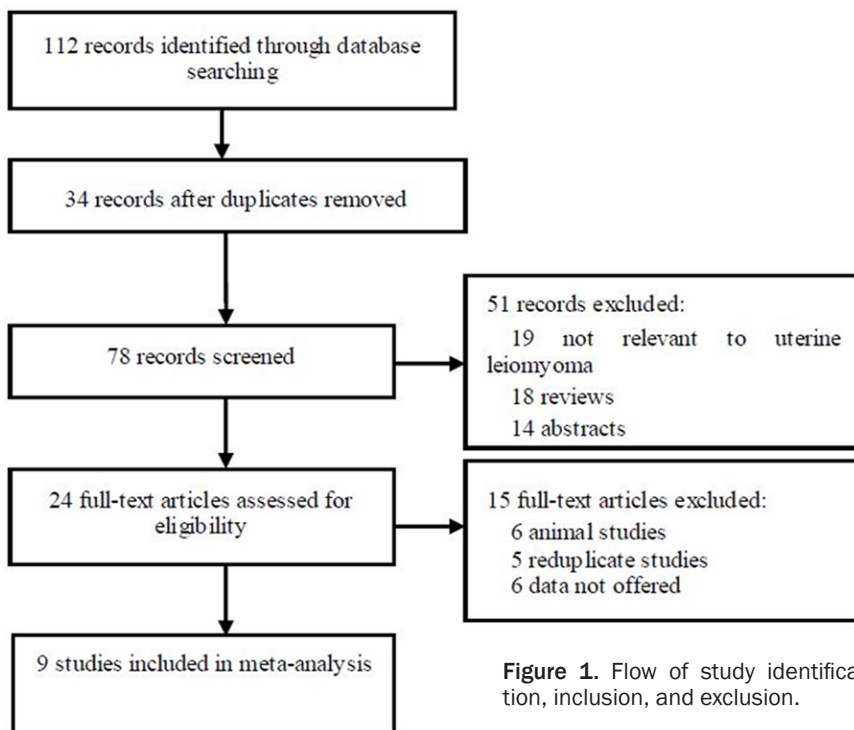


Figure 1. Flow of study identification, inclusion, and exclusion.

Table 1. Characteristics of the included studies

Study	Year	Race	Age	Case (n)	Control (n)	Genotyping method	Polymorphisms
Herr	2006	Caucasian	40.3	118	222	PCR-RFLP	Ile462Val
Ye	2008	Asian	46.9	100	110	PCR-RFLP	MspI, Ile462Val
Jin	2008	Asian	42.3	156	170	PCR-RFLP	MspI
Barao	2010	Caucasian	50	124	215	PCR-RFLP	MspI
El-Shennawy	2011	Caucasian	45.8	160	100	PCR-RFLP	Ile462Val
Zhou	2011	Asian	44.1	123	123	PCR-RFLP	MspI
Mortezaei	2014	Caucasian	44	276	157	PCR-RFLP	Ile462Val
Shen Y	2014	Asian	30-50	800	800	PCR-RFLP	Ile462Val
Shen	2014	Asian	40	300	300	PCR-RFLP	Ile462Val

PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism method.

Inclusion/exclusion criteria

Studies had to meet the following criteria: (1) case-control study or cohort study evaluating on association between CYP1A1 MspI and Ile462Val polymorphisms and UL risk; (2) all patients with the diagnosis of UL confirmed by histological examination; (3) all studies provided odds ratios (ORs), and their 95% confidence intervals (CIs); (4) the distribution of the genotypes in control groups was in the Hardy-Weinberg equilibrium (HWE). Studies were excluded when they were: (1) duplicate papers; (2) study with incomplete data; (3) meta-analysis,

letters, reviews, or editorial articles.

Data extraction

Data were extracted by two authors independently. Discrepancies, if any, were resolved by discussion. The following data was collected from every study: author, year of publication, race, age, genotyping method, numbers of cases and controls, polymorphisms.

Statistical analysis

Statistical analysis was carried out by using STATA statistical package (version 11, STATA, College Station, TX). The distributions of genotypes in controls were tested by HWE using the Chi-square test. The association of CYP1A1 MspI and Ile462Val polymorphisms and UL risk was estimated by ORs with 95% CIs. The heterogeneity was tested by the Q-statistics with P -values < 0.1 .

The random effect model (DerSimonian and Laird) was selected to summarize the combined OR and their 95% CI. The significance of the pooled OR was determined by the Z test. Publication bias was investigated by the method of Egger's test. All the P values were two sided. P value less than 0.05 was considered statistically significant.

Results

Eligible studies

The flow chart of **Figure 1** summarizes the literature review process. According to the inclu-

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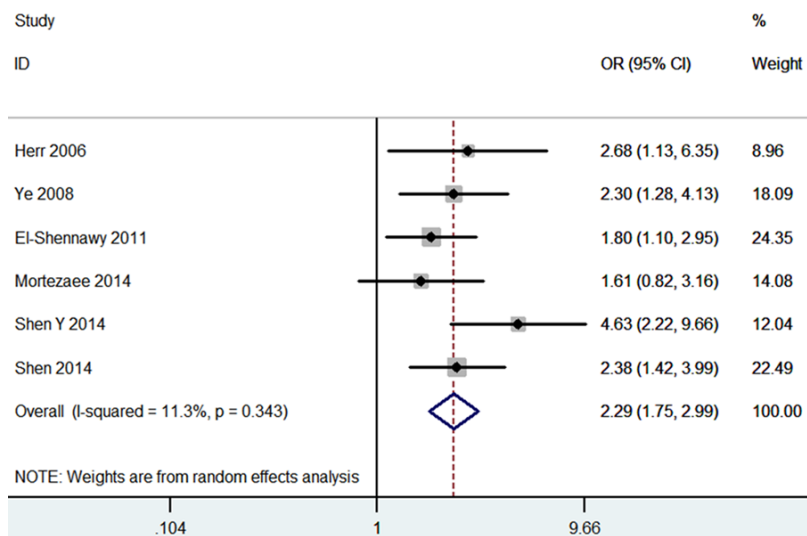


Figure 2. Forest plot for the association between CYP1A1 Ile462Val polymorphism and UL risk.

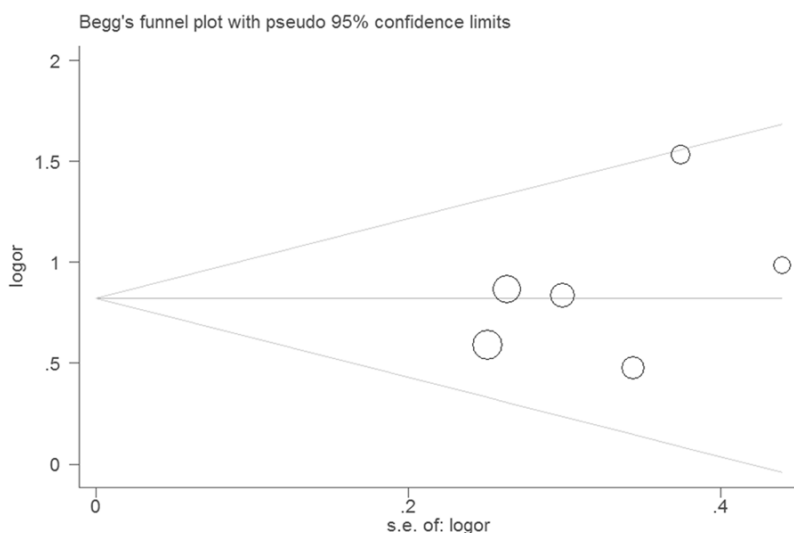


Figure 3. Funnel plot for the association between CYP1A1 Ile462Val polymorphism and UL risk.

sion and exclusion criteria, 9 case-control studies were included. The publication year of involved studies ranged from 2006 to 2014. In total, 2157 UL cases and 2197 healthy controls were included in this meta-analysis. Four studies were conducted in Caucasians, while five studies conducted in Asians. Six studies assessed the association between CYP1A1 Ile462Val polymorphism and UL risk, while four studies estimated the association of CYP1A1 MspI polymorphism and UL risk. The characteristics of the included studies are summarized in **Table 1**.

Quantitative synthesis

CYP1A1 Ile462Val polymorphism and UL risk: Six studies with 1754 cases and 1689 controls assessed the association between CYP1A1 Ile462Val polymorphism and UL risk. In this meta-analysis, CYP1A1 Ile462Val polymorphism was significantly associated with UL risk (OR = 2.29, 95% CI 1.75-2.99, $P < 0.00001$; **Figure 2**). In the subgroup analysis by race, significantly increased risks were found in the Asians (OR = 2.76, 95% CI 1.86-4.09, $P < 0.00001$) and Caucasians (OR = 1.87, 95% CI 1.30-2.68, $P = 0.0007$). There was no significant publication bias ($P = 0.136$; **Figure 3**).

CYP1A1 MspI polymorphism and UL risk: Four studies with 503 cases and 618 controls assessed the association between CYP1A1 MspI polymorphism and UL risk. CYP1A1 MspI polymorphism was not significantly associated with UL risk (OR = 1.15, 95% CI 0.90-1.47, $P = 0.27$; **Figure 4**). In the subgroup analysis by race, no significant association was found in the Asians (OR = 1.15, 95% CI 0.86-1.54, $P = 0.35$). There was also no significant publication bias ($P = 0.795$; **Figure 5**).

Discussion

To our knowledge, this was the first meta-analysis which estimated the association between CYP1A1 polymorphisms and UL risk. Results from this meta-analysis indicated that CYP1A1 Ile462Val polymorphism might contribute to the risk of UL. However, CYP1A1 MspI polymorphism might have no role in the development of

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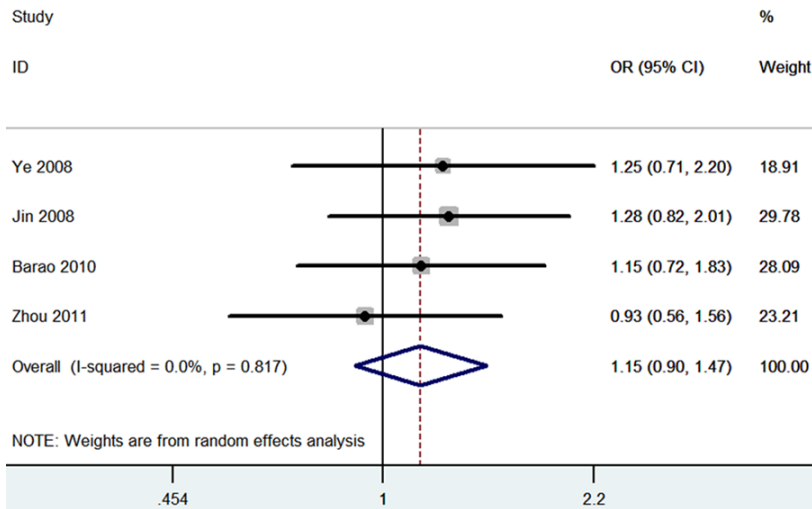


Figure 4. Forest plot for the association between CYP1A1 MspI polymorphism and UL risk.

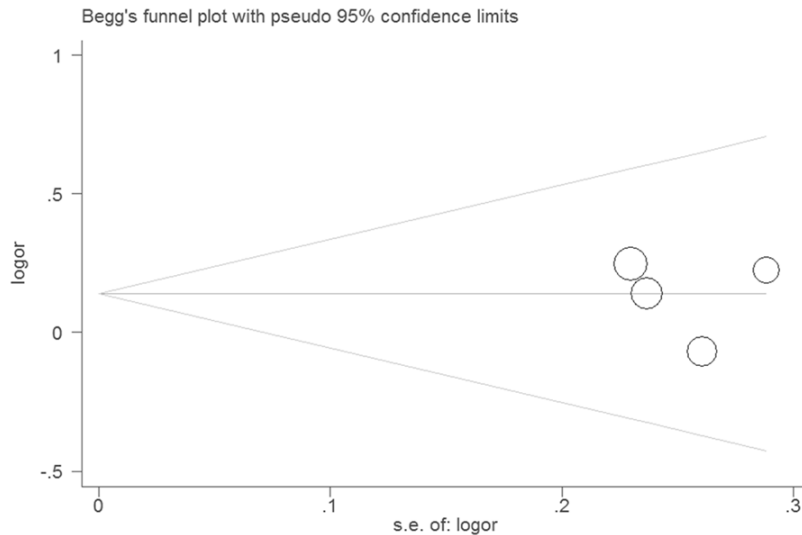


Figure 5. Funnel plot for the association between CYP1A1 MspI polymorphism and UL risk.

UL. In the subgroup based on race, we found that Asians and Caucasians with CYP1A1 Ile462Val polymorphism showed increased UL risk, respectively. These results suggested that the doctors should pay more attention to the women carrying CYP1A1 Ile462Val polymorphism. There were only four studies investigating CYP1A1 MspI polymorphism. Although no significant association between CYP1A1 MspI polymorphism and UL was detected, more studies are still needed to be conducted.

Recently, CYP1A1 Ile462Val polymorphism has been reported to contribute to endometrial cancer, cervical cancer, ovarian cancer, and bre-

ast cancer risks [16-19]. CYP1A1 mainly participated in the first phase of xenobiotic metabolism. Many environmental carcinogens, such as alkaloids or heterocyclic aromatic amines, were the main substrates of CYP1A1. Estrone and testosterone were also metabolized during first phase via CYP1A1 [20]. The polymorphisms of CYP1A1 gene might influence the effectiveness of the metabolism of environmental carcinogens. The Ile462Val polymorphism lead to a substitution of isoleucine to valine. Consequently, the effectiveness of CYP1A1 enzyme increased and higher levels of carcinogenic active molecules might be involved in UL development.

Our meta-analysis had some strengths. First, it was the first meta-analysis which reported the association between CYP1A1 polymorphisms and UL risk. Second, we followed the inclusion and exclusion criteria strictly to reduce possible selection bias. Third, no significant heterogeneity was

found and Egger's test detected no obvious publication bias. However, several limitations of this meta-analysis should be addressed. First, only nine studies were included in this meta-analysis. The number was small. Second, only studies in Chinese and English were included in the meta-analysis. Therefore, selection bias might exist. Third, subgroup analyses regarding other factors could not be conducted due to insufficient data could be available.

In summary, the results of the meta-analysis suggested that CYP1A1 Ile462Val polymorphism was significantly associated with UL risk.

Disclosure of conflict of interest

None.

Address correspondence to: Fen Wang, Department of Gynecology, The Peoples' Hospital of Xinjiang, Ti-anchi Road No. 91, Urumqi 830001, China. Tel: +86-0991-8562222; E-mail: wangfenxinjiang@sina.cn

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