Association between CYP1A1 gene polymorphisms and cervical cancer susceptibility: a meta-analysis

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Abstract

Introduction: The aim of this study is to systemically analyze the association of CYP1A1 gene MspI and Ile462Val polymorphisms with cervical cancer susceptibility.
Material and methods: The publications about the associations between CYP1A1 polymorphism and cervical cancer were retrieved through PubMed, Embase, Chinese Biomedical Literature Database, Wanfang Data, Database of Chinese Scientific and Technical Periodicals (VIP) and China Knowledge Network. The Hardy-Weinberg equilibrium test was used to evaluate the quality of the included studies, and the data in the studies selected were analyzed by Stata 12.0 software. Potential publication bias was assessed with funnel plots and a modified Egger's linear regression test.
Results: A total of 17 studies were enrolled in this analysis. There were 14 articles on the MspI polymorphism, including 2448 cases and 2520 controls. We found a significant association between MspI polymorphism and cervical cancer susceptibility (C vs. T, OR = 1.333, 95% CI: 1.214–1.464, $p \leq 0.001$; CC vs. TT, OR = 1.962, 95% CI: 1.571–2.450, $p \leq 0.001$; CC/CT vs.TT, OR = 1.591, 95% CI: 1.406–1.800, $p \leq 0.001$; CC vs.TT/CT, OR = 1.429, 95% CI: 1.177–1.736, $p \leq 0.001$). In total, 11 articles, including 2137 cases and 2116 controls, analyzed the Ile462Val polymorphism and the risk of cervical cancer. The results showed a significant association between Ile462Val polymorphism and cervical cancer susceptibility (Val vs. Ile, OR = 1.338, 95% CI: 1.199–1.493, $p \leq 0.001$; ValVal vs. IleIle, OR = 1.576, 95% CI: 1.188–2.090, $p = 0.002$; ValVal/ValIle vs. IleIle, OR = 1.498; 95% CI: 1.299–1.728, $p \leq 0.001$).
Conclusions: Both MspI and Ile462Val polymorphisms of the CYP1A1 gene are associated with the risk of cervical cancer.

Key words: cervical cancer, CYP1A1, MspI polymorphism, Ile462Val polymorphism, meta-analysis.

Introduction

Cervical cancer is one of the most common gynecological malignancies. High-risk HPV infection is a risk factor for cervical cancer [1, 2]. In a cost-effectiveness study of different cervical screening approaches in developing countries, screening females once in a lifetime, at the age of 35 years, with a one- or two-visit screening strategy involving VIA or HPV testing reduced lifetime risk of cancer by approximately 25–36% [3]. However, less than 1% of HPV-infected patients suffer from cervical cancer, suggesting that early sexual activity, multiple partners, and frequent change of partners are also related to cervical cancer and that high-risk

HPV infection is a necessary but insufficient factor for cervical cancer [4–6]. Despite evidence showing the protective effect of HPV vaccine against cervical cancer, it is still a dilemma whether to introduce this vaccine as a routine in several other countries such as India, Sweden and Japan [7]. Smoking, drinking, long-term usage of oral contraceptives and other risk factors may also lead to the occurrence of cervical cancer [8, 9]. The identification of risk factors is critical for the treatment of cervical cancer and in-depth understanding of the disease.

The cytochrome P450 1A1 (CYP1A1) gene is a key member of the CYP1 family and is involved in the metabolism of endogenous and exogenous compounds *in vivo*. For example, benzopyrene becomes an active and carcinogenic intermediate following CYP1A1 metabolism [10]. In addition, phenylphosphatol estrogen is formed after catalysis by CYP1A1, which further leads to the formation of ROS and DNA adducts and the occurrence of mutations during DNA replication [11–14]. Studies have shown that genomic instability caused by gene mutation and chromosome rearrangement is one of the most important factors for tumorigenesis [15–17]. It is reported that two polymorphisms of CYP1A1, MspI (T3801C, rs4646903) and Ile462Val (A4889G, rs1048943), are closely related with cervical cancer [18–22]. The Rs4646903 polymorphism is located in the 3' untranslated region, while the rs1048943 polymorphism is located on exon 7, whose mutation results in the substitution of an amino acid at position 462 [23, 24]. Point mutations at rs4646903 and rs1048943 can lead to dysregulated CYP1A1 mRNA expression [17]. A number of studies have reported the association between the two polymorphisms and the occurrence of cervical cancer in different ethnic groups, but the conclusions of different studies are still inconsistent [20, 21].

In this study, meta-analysis was used to evaluate the association of CYP1A1 rs4646903 and rs1048943 polymorphisms with cervical cancer. Our data may provide a basis for further study on the role of genetic factors in the pathogenesis of cervical cancer.

Material and methods

Literature retrieval

Literature reporting the association of CYP1A1 polymorphism and cervical cancer was retrieved through PubMed, Embase, Chinese Biomedical Literature Database, Wanfang Data, Database of Chinese Scientific and Technical Periodicals (VIP) and China Knowledge Network. The keywords for retrieval were 'cytochrome P4501A1' or 'CYP1A1' or 'Ile462Val' or 'A4889G' or 'rs1048943' or 'MspI' or 'T3801C' or 'rs4646903' and 'cervical carcinoma' or 'cervical cancer' or 'cervix cancer'. At the same time, the reference list of the retrieved literature was manually entered into the above mentioned databases to screen more suitable literature.

Eligibility criteria

Studies were included in the meta-analysis if they met the following criteria: 1) they appeared online or in a peer-reviewed journal published in English or Chinese before 31 March 2017; 2) they were case-control studies; 3) the control group comprised healthy individuals; 4) the full text could be retrieved; 5) the distribution frequency of the CYP1A1 gene polymorphisms or the corresponding OR value is provided and the data are clearly expressed.

The exclusion criteria were as follows: 1) articles with incomplete data; 2) articles with cervical intraepithelial neoplasia or non-cervical cancer patients as research subjects; 3) the studies only researched the correlation between progression, severity, phenotypic modification, sensitivity to response to treatment, or survival with gene polymorphism; 4) articles with family relevance analysis; 5) repetitive reports or articles with poor quality or limited information.

The outcome indicator of this study is the incidence of cervical carcinoma.

Data extraction

Data were extracted by two authors independently. Disagreements were resolved by discussion or a third person. The following data were extracted from each study: year of publication, first author, the country where the study was performed, the ethnicity of participants, genotyping methods, genes and genotype data. We classified case selection as population-based if the study included data from different ethnicities, including Caucasians, Asians and others. The Hardy-Weinberg equilibrium (HWE) test was used to evaluate the quality of the enrolled studies.

Statistical analysis

Statistical analysis was performed with STATA version 12.0 (Stata Corporation, College Station, TX, USA). The Hardy-Weinberg equilibrium (HWE) in the controls was tested by the chi-square test for goodness of fit. For the genetic variants, allelic, homozygous, dominant and recessive models were computed. Estimates of association between CYP1A1 polymorphism and cervical cancer were evaluated by odds ratios (ORs) and corresponding 95% confidence intervals (CIs). Heterogeneity between studies was assessed by the Cochran Q statistic and I^2 statistic. Generally, $p > 0.1$ and

I^2 < 25% correspond to heterogeneity; and p < 0.1 and I^2 > 50% correspond to large heterogeneity. If the data were heterogeneous, a random effects model was adopted; if the data were homogeneous, a fixed effects model was applied. Potential publication bias was assessed with funnel plots and a modified Egger's linear regression test was used to identify significant asymmetry. For all data, two-tailed tests were used throughout and P < 0.05 was considered significant.

Results

Basic information of included studies

A total of 130 articles were identified according to the keywords (Figure 1). After being screened by title and abstract, 109 articles including 47 irrelevant articles, 41 articles with overlapping data, 4 reviews and 17 articles on animals or cells were excluded. The remaining publications underwent screening of the full text, identifying a total of 17 eligible articles that included 14 articles on the MspI polymorphism [19–22, 25–34] and 11 on the Ile462Val polymorphism [20, 25–28, 31–33, 35–37] of the CYP1A1 gene. All articles included in the meta-analysis are shown in Table I.

Meta-analysis results for MspI

For the 14 articles on the MspI polymorphism, 2248 patients and 2520 healthy controls were enrolled. As shown in Figure 2, we found that the MspI polymorphism of the CYP1A1 gene was significantly associated with susceptibility to cervical cancer (Figure 2 A, C vs. T, OR = 1.333, 95% CI: 1.214–1.464, $p \leq 0.001$) (Figure 2 B, CC vs. TT, OR = 1.962, 95% CI: 1.571–2.450, $p \leq 0.001$) (Figure 2 C, CC/CT vs.TT, OR = 1.591, 95% CI: 1.406–1.800, $p \leq 0.001$) (Figure 2 D, CC vs. TT/CT, OR = 1.429, 95% CI: 1.177–1.736, $p \leq 0.001$).

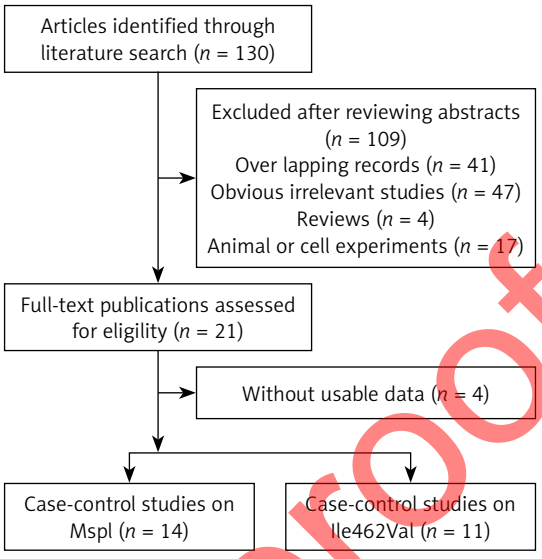

Figure 1. Study flow chart explaining the selection of the seventeen eligible case control articles enrolled in the meta-analysis

Table I. Quality scores of studies included in the meta-analysis

Author (year)	Ethnicity	Study design	Polymorphisms studied	Genotyping method	HWE in controls
Kim (2000)	Asians	HCS	MspI	PCR-RFLP	0.05
Sugawara (2003)	Asians	HCS	MspI, Ile462Val	PCR-RFLP	0.23/0.28
Taskiran (2006)	Caucasian	HCS	Ile462Val	PCR-RFLP	0.15
Joseph (2006)	Caucasian	HCS	MspI, Ile462Val	PCR-RFLP	0.24/0.20
Juarez-Cedillo (2007)	others	HCS	MspI	PCR-RFLP	0.64
Li (2009)	Asians	HCS	MspI, Ile462Val	PCR-RFLP	0.56/0.36
Gutman (2009)	Caucasian	HCS	MspI, Ile462Val	PCR-RFLP	0.39/0.30
Geng (2010)	Asians	HCS	Ile462Val	PCR-RFLP	0.01
Shi (2011)	Asians	HCS	MspI, Ile462Val	PCR-RFLP	0.87/0.25
Ding (2011)	Asians	HCS	MspI, Ile462Val	PCR-RFLP	0.04/0.003
Von (2011)	Caucasian		MspI	PCR-RFLP	0.18
Abbas (2014)	Caucasian	HCS	MspI, Ile462Val	PCR-RFLP	0.36/0.30
Roszak (2014)	Caucasian	HCS	Ile462Val	PCR-RFLP	1.00
Kleine (2015)	Caucasian	HCS	MspI	PCR-RFLP	0.23
Tan (2016)	Mixed	HCS	MspI	PCR-RFLP	0.94
Matos (2016)	Caucasian	HCS	MspI	PCR-RFLP	0.81
Li (2016)	Asians	HCS	MspI, Ile462Val	Taqman	0.79/0.84

HWE – Hardy-Weinberg equilibrium.

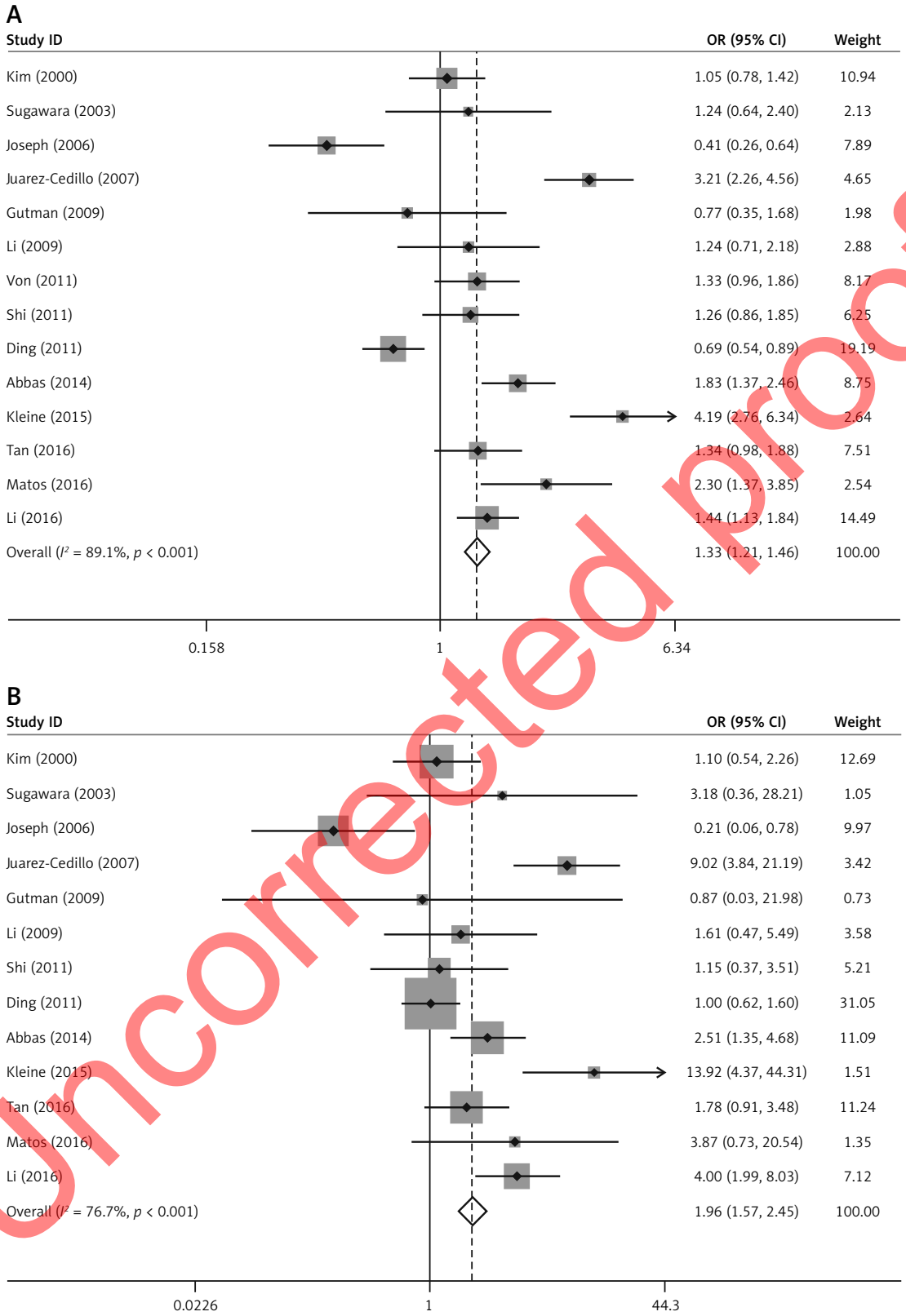

Figure 2. Significant association between CYP1A1 MspI polymorphism and the risk of cervical cancer as determined by (**A**) allele model (C vs. T, p = 0.000); (**B**) homozygote model (CC vs. TT, p = 0.000)

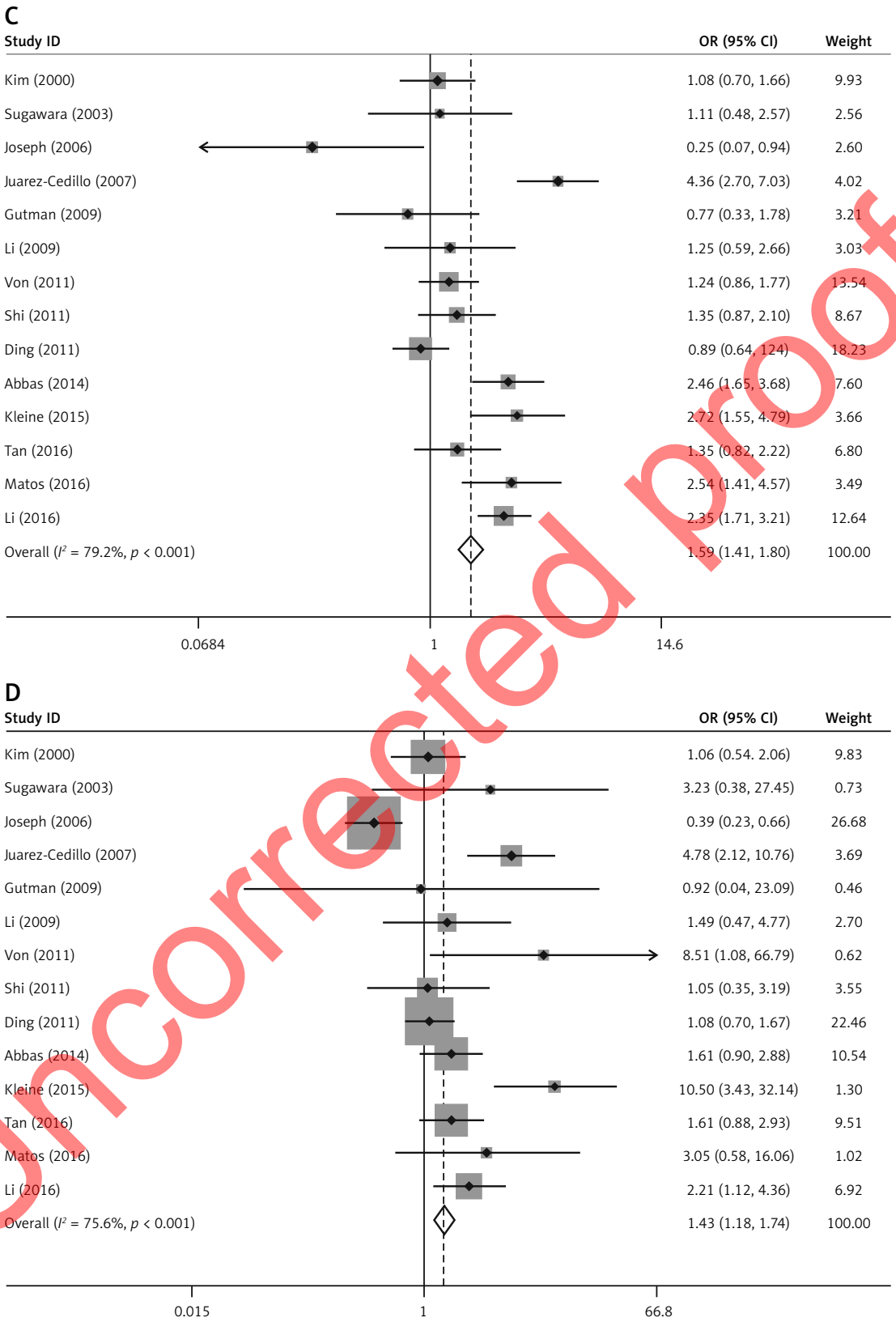

Figure 2. Cont. (**C**) dominant model (CC/CT vs. TT, p = 0.000) and (**D**) recessive model (CC vs. TT/CT, p = 0.000)

In the meta-analysis stratified by ethnicity, the MspI polymorphism was associated with cervical cancer among Caucasian women in allelic, homozygous and dominant models (C vs. T, OR = 1.470, 95% CI: 1.257–1.719, $p \leq 0.001$; CC vs. TT, OR = 2.241, 95% CI: 1.506–3.333, $p \leq 0.001$; CC/CT vs.TT, OR = 1.650, 95% CI: 1.344–2.025, $p \leq 0.001$). In homozygous, dominant and recessive models, the MspI polymorphisms was associated with cervical cancer among Asian women (CC vs. TT, OR = 1.603, 95% CI: 1.194–2.153, $p = 0.002$; CC/CT vs. TT, OR = 1.450, 95% CI: 1.224–1.717, $p \leq 0.001$; CC vs. TT/CT, OR = 1.321, 95% CI: 1.005–1.737, $p = 0.046$) (Table II).

Meta-analysis results for Ile462Val

There were 11 studies that analyzed the Ile-462Val polymorphism, including 2137 patients and 2116 healthy controls. As shown in Figure 3, the Ile462Val polymorphism of the CYP1A1 gene was significantly associated with the risk of cervical cancer (Figure 3 A, Val vs. Ile, OR = 1.338, 95% CI: 1.199–1.493, $p \leq 0.001$) (Figure 3 B, ValVal vs. IleIle, OR = 1.576, 95% CI: 1.188–2.090, $p = 0.002$) (Figue 3 C, ValVal/ValIle vs. IleIle, OR = 1.498; 95% CI: 1.299–1.728, $p \leq 0.001$). However, no correlation was found in the recessive model (Figure 3 D, ValVal vs. IleIle/ValIle, OR = 1.262, 95% CI: 0.995–1.600, $p = 0.055$).

Subgroup analysis by ethnicity found that the Ile462Val polymorphism had an association with the risk of cervical cancer among Caucasian women in allelic and dominant models (Val vs. Ile, OR = 1.701, 95% CI: 1.392–2.077, $p \leq 0.001$; ValVal/ValIle vs. IleIle, OR = 1.405, 95% CI: 1.247–1.583, $p \leq 0.001$). In allelic, homozygous and dominant models, the Ile462Val polymorphism had associations with the risk of cervical cancer among Asian women (Val vs. Ile, OR = 1.210, 95% CI: 1.062–1.379, $p = 0.004$; ValVal vs. IleIle, OR = 1.575, 95% CI: 1.156–2.146, $p = 0.004$; ValVal/ValIle vs. IleIle, OR = 1.313, 95% CI: 1.101–1.565, $p = 0.002$) (Table III).

Publication bias analysis

Publication bias was assessed by funnel plots and modified Egger's test, and no possible publication bias was found. The results of Egger's test of MspI genotypes were C vs. T, $p = 0.219$; CC vs. TT, $p = 0.127$; CC/CT vs.TT, $p = 0.331$; CC vs. TT/CT, $p = 0.631$ (Figure 4). The results of Egger's test of Ile462Val genotypes were Val vs. Ile, $p = 0.891$; ValVal vs. IleIle, $p = 0.233$; ValVal/ValIle vs. IleIle, $p = 0.825$; ValVal vs. IleIle/ValIle, $p = 0.279$ (Figure 5). Similar results were obtained by funnel plots (Figures 6 and 7).

Discussion

Cervical cancer is still the most important gynecological malignancy in developing countries, with the incidence increasing year by year [38]. Cytochrome P450 1A1 mainly participates in the occurrence of cancer by regulating the metabolism of proteins, DNA, lipids and estrogens [39, 40]. A number of studies have reported the association between CYP1A1 gene polymorphism and

Table II. Meta-analysis of the association between CYP1A1 gene MspI polymorphism and cervical cancer risk

Contrast model	Number of studies	Subjects (cases/controls)	OR (95% CI)	*P*-value	I^2 (%)
Total studies:					
C vs. T	14	2448/2520	1.333 (1.214–1.464)	≤ 0.001	89.1
CC vs. TT	14	2448/2520	1.962 (1.571–2.450)	≤ 0.001	76.7
CC/CT vs. TT	14	2448/2520	1.591 (1.406–1.800)	≤ 0.001	79.2
CC vs. TT/CT	14	2448/2520	1.429 (1.177–1.736)	≤ 0.001	75.6
Subgroup analysis:					
Caucasians:					
C vs. T	7	999/1137	1.470 (1.257–1.719)	≤ 0.001	91.0
CC vs. TT	7	999/1137	2.241 (1.506–3.333)	≤ 0.001	79.1
CC/CT vs. TT	7	999/1137	1.650 (1.344–2.025)	≤ 0.001	74.4
CC vs. TT/CT	7	999/1137	1.225 (0.905–1.658)	0.190	84.2
Asians:					
C vs. T	7	1240/1163	1.088 (0.957–1.238)	0.199	70.6
CC vs. TT	7	1240/1163	1.603 (1.194–2.153)	0.002	61.6
CC/CT vs. TT	7	1240/1163	1.450 (1.224–1.171)	≤ 0.001	77.2
CC vs. TT/CT	7	1240/1163	1.321 (1.005–1.737)	0.046	0.0

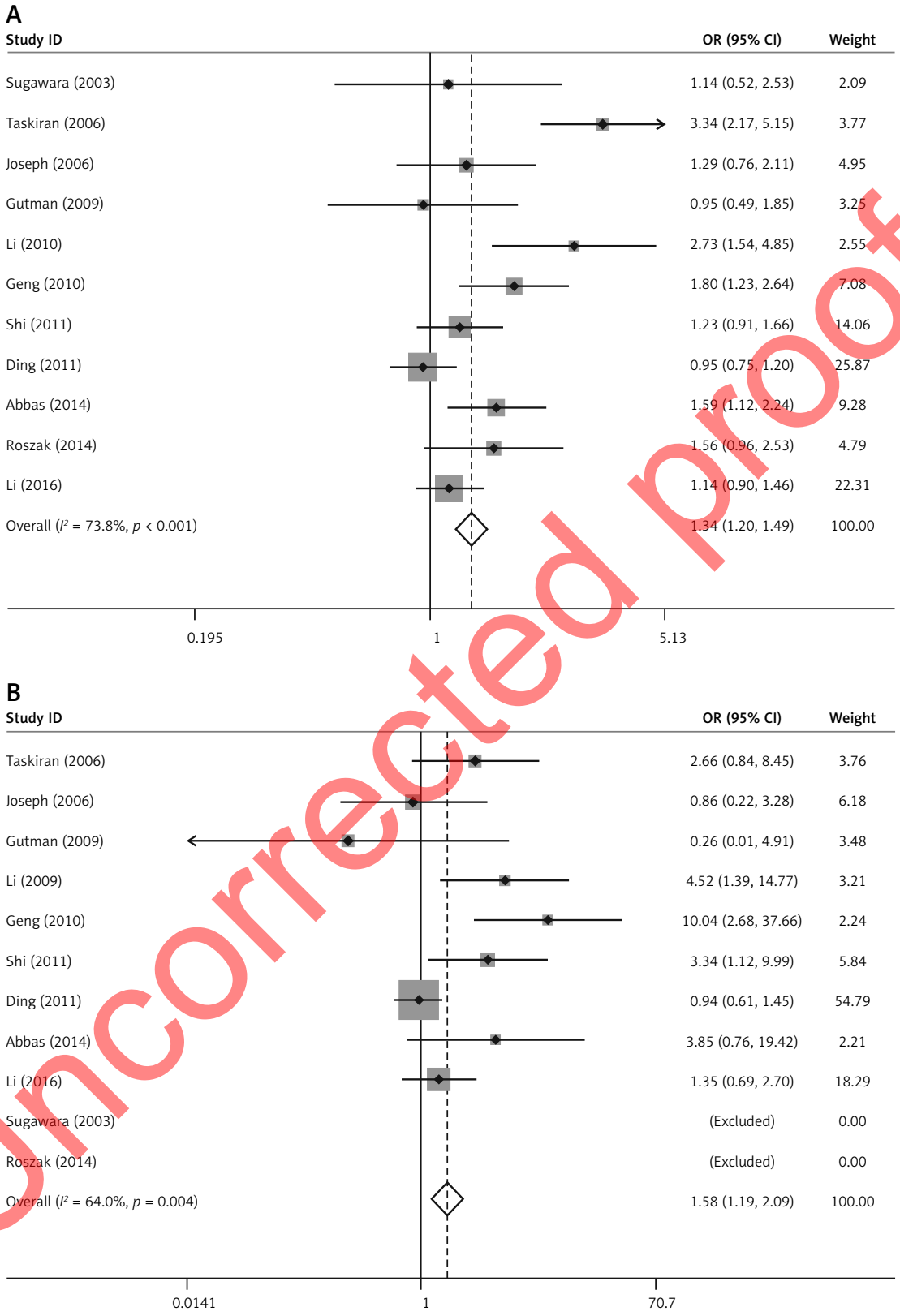

Figure 3. Significant association between CYP1A1 Ile462Val polymorphism and the risk of cervical cancer as determined by (**A**) allele model (Val vs. Ile, p = 0.000), (**B**) homozygote model (ValVal vs. IleIle, p = 0.009)

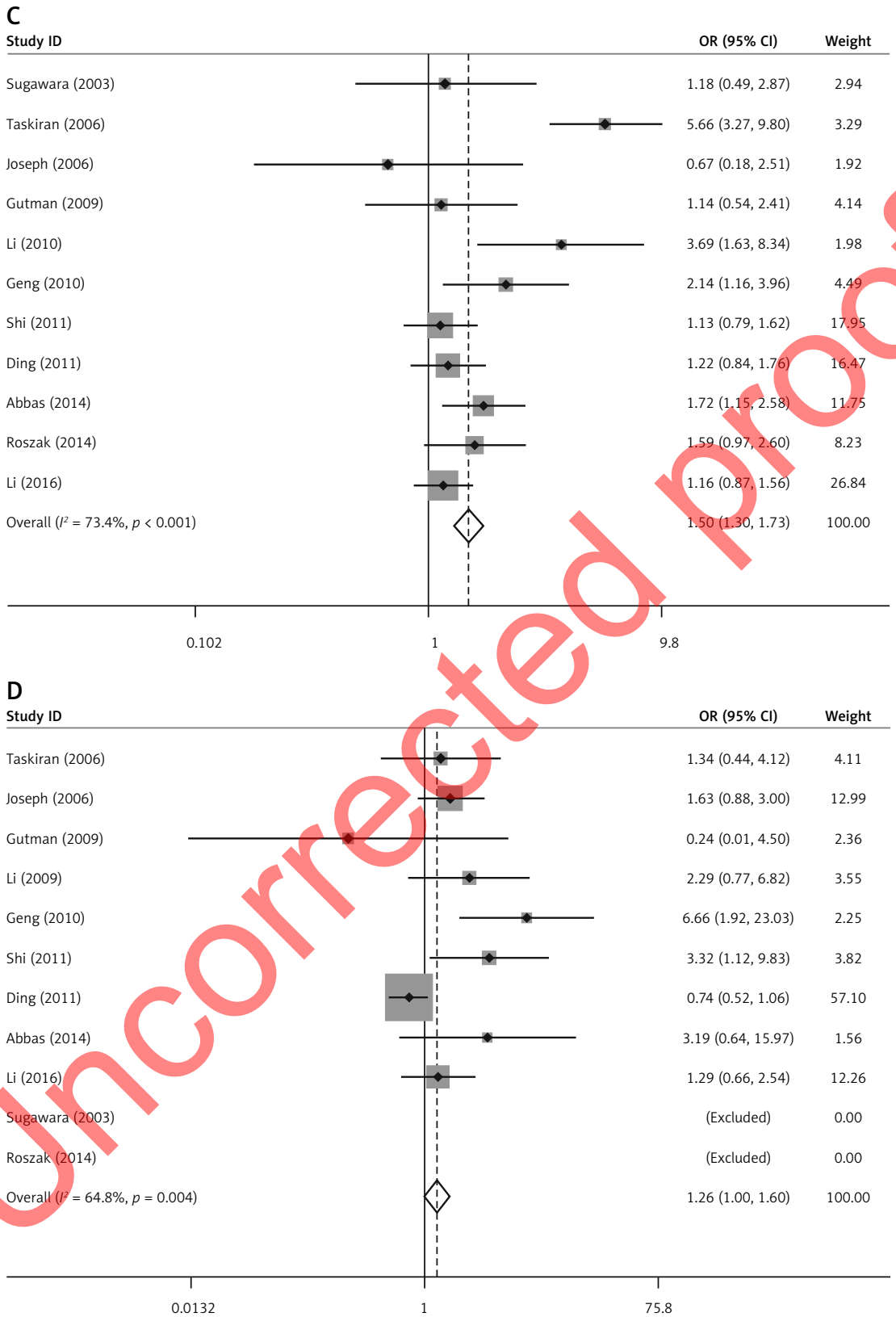

Figure 3. Cont. (**C**) dominant model (ValVal/Vallle vs. Ilelle, p = 0.000) and (**D**) recessive model (ValVal vs. Ilelle/Vallle, p = 0.055)

Table III. Meta-analysis of the association between CYP1A1 gene Ile462Val polymorphism and cervical cancer risk

Contrast model	Number of studies	Subjects (cases/controls)	OR (95% CI)	*P*-value	I^2 (%)
Total studies:					
Val vs. Ile	11	2137/2116	1.338 (1.199–1.493)	≤ 0.001	73.8
ValVal vs. IleIle	11	2137/2116	1.576 (1.188–2.090)	0.002	64.0
ValVal/ValIle vs. IleIle	11	2137/2116	1.498 (1.299–1.728)	≤ 0.001	73.4
ValVal vs. IleIle/ValIle	11	2137/2116	1.262 (0.995–1.600)	0.055	64.8
Subgroup analysis:					
Caucasians:					
Val vs. Ile	5	931/1084	1.701 (1.392–2.077)	≤ 0.001	71.2
ValVal vs. IleIle	5	931/1084	1.580 (0.794–3.145)	0.193	28.2
ValVal/ValIle vs. IleIle	5	931/1084	1.405 (1.247–1.583)	≤ 0.001	96.3
ValVal vs. IleIle/ValIle	5	931/1084	1.530 (0.940–2.489)	0.087	0.0
Asians:					
Val vs. Ile	6	1206/1032	1.210 (1.062–1.379)	0.004	69.0
ValVal vs. IleIle	6	1206/1032	1.575 (1.156–2.146)	0.004	77.8
ValVal/ValIle vs. IleIle	6	1206/1032	1.313 (1.101–1.565)	0.002	58.7
ValVal vs. IleIle/ValIle	6	1206/1032	1.190 (0.907–1.561)	0.208	78.9

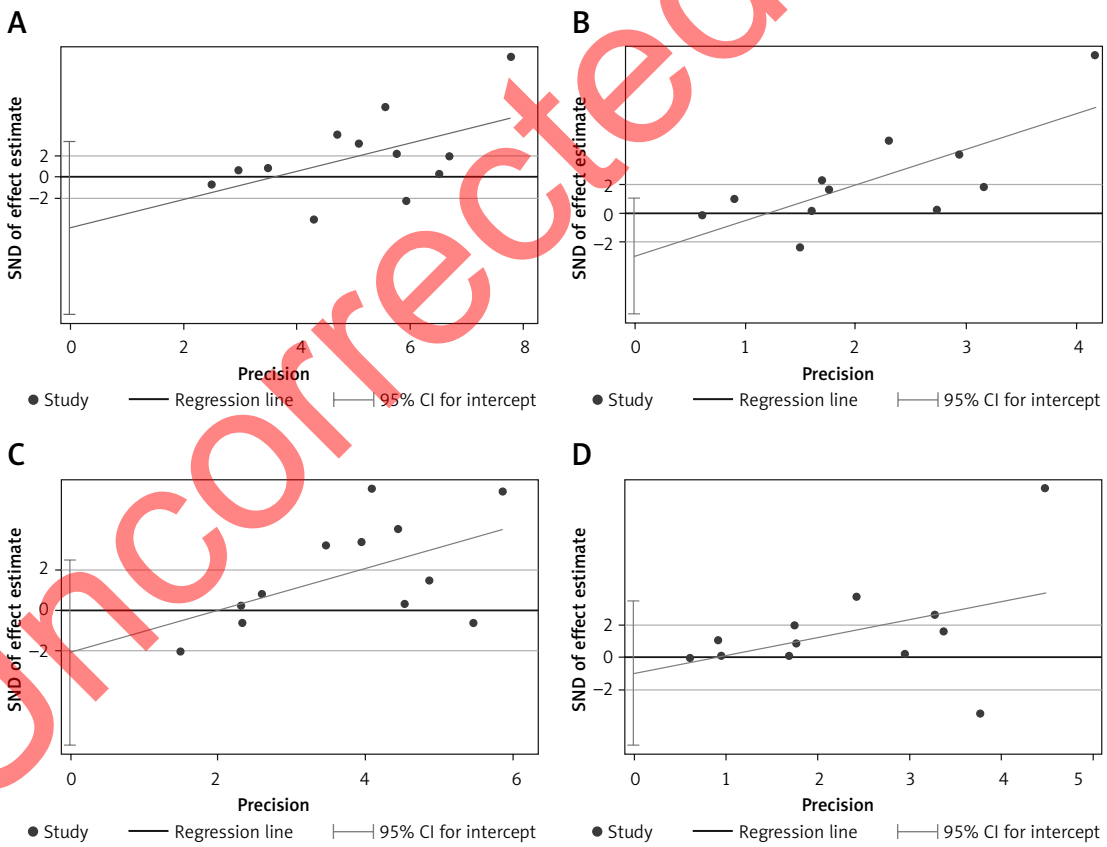

Figure 4. Egger's test on MspI polymorphism did not show any obvious evidence of publication bias in all genetic models. **A** – allele model (C vs. T, $p = 0.219$); **B** – homozygote model (CC vs. TT, $p = 0.127$); **C** – dominant model (CC/CT vs. TT, $p = 0.331$); **D** – recessive model (CC vs. TT/CT, $p = 0.631$)

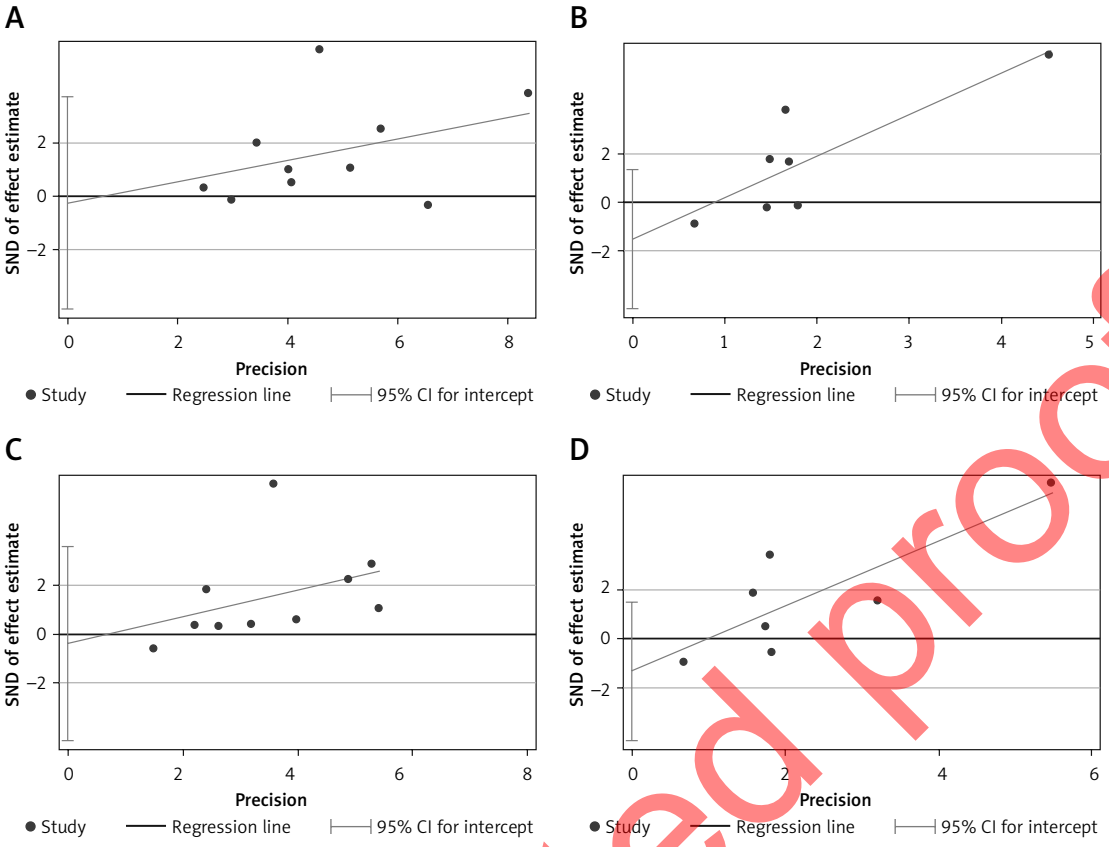

Figure 5. Egger's test on Ile462Val polymorphism did not show any obvious evidence of publication bias in all genetic models. **A** – allele model (Val vs. Ile, p = 0.891), **B** – homozygote model (ValVal vs. IleIle, p = 0.233), **C** – dominant model (ValVal/ValIle vs. IleIle, p = 0.825); **D** – recessive model (ValVal vs. IleIle/ValIle, p = 0.279)

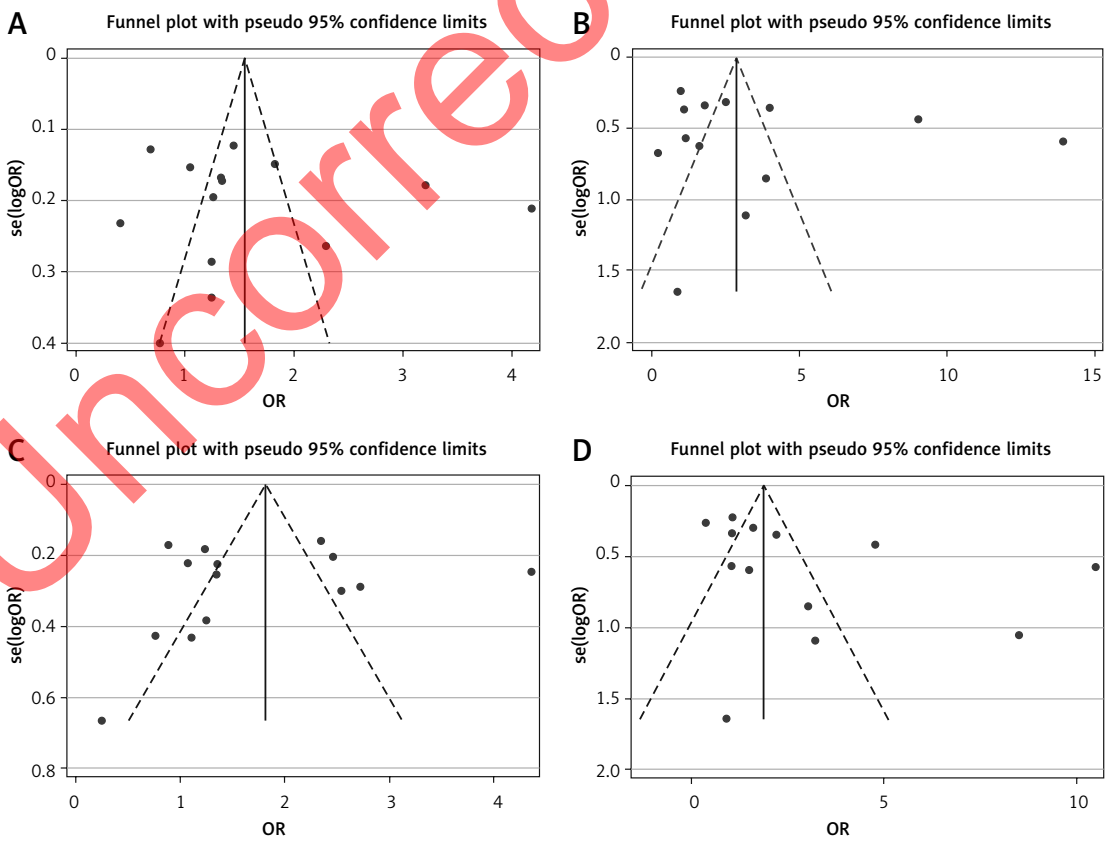

Figure 6. Funnel plots of MspI polymorphism did not show any obvious evidence of publication bias in all genetic models. **A** – allele model (C vs. T); **B** – homozygote model (CC vs. TT); **C** – dominant model (CC/CT vs. TT); **D** – recessive model (CC vs. TT/CT)

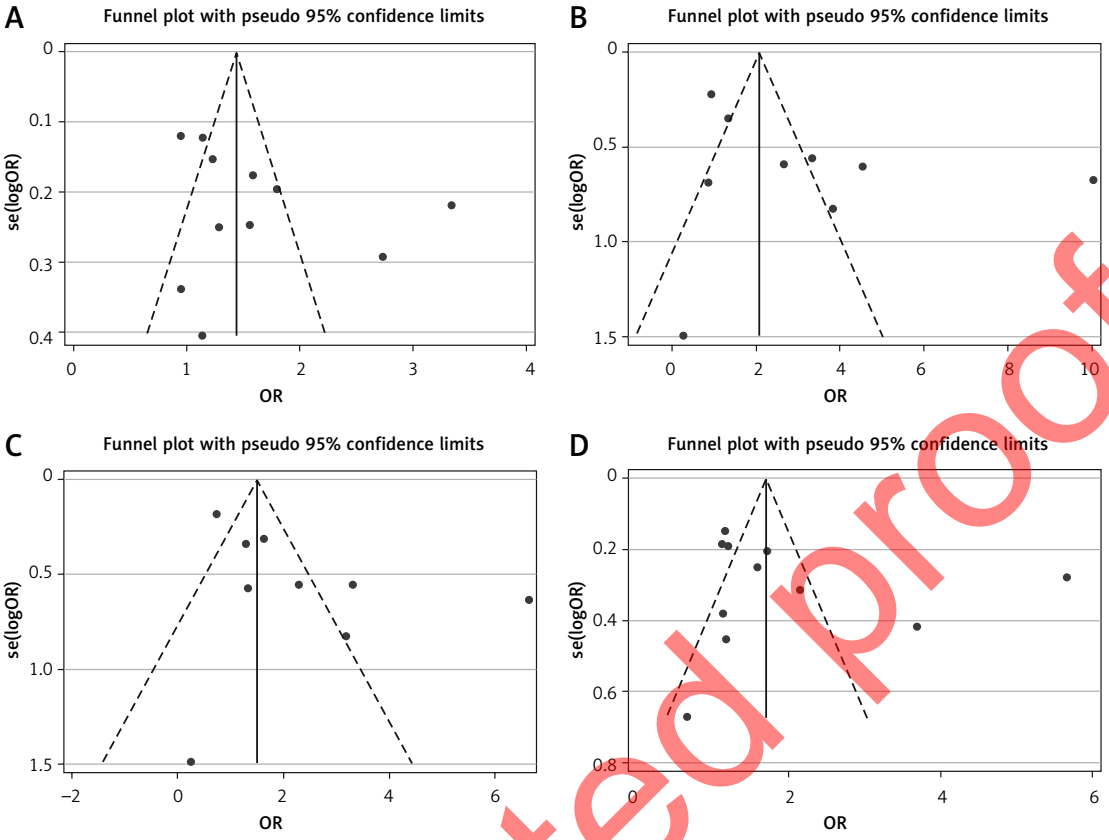

Figure 7. Funnel plots of Ile462Val polymorphism did not show any obvious evidence of publication bias in all genetic models. **A** – allele model (Val vs. Ile); **B** – homozygote model (ValVal vs. IleIle); **C** – dominant model (ValVal/VallIe vs. IleIle); **D** – recessive model (ValVal vs. IleIle/VallIe)

the susceptibility to cervical cancer, but the conclusion is controversial due to the differences in the study design, the study population, the detection method and the sample size [19–22]. Therefore, the current study investigated the correlation between CYP1A1 gene polymorphism and cervical cancer susceptibility through a meta-analysis on 17 studies.

A total of 14 articles on the MspI polymorphism were enrolled in our study, which included 2448 patients and 2520 healthy controls. Analysis results of allelic, homozygous, dominant and recessive models all indicate that the MspI polymorphism of the CYP1A1 gene is closely associated with the risk of cervical cancer. This result is in accordance with a meta-analysis on the relationship between MspI polymorphism and cervical cancer by Xia *et al.* [41]. Additionally, analysis stratified by ethnicity showed the association of MspI polymorphism and the risk of cervical cancer in Caucasian women and Asian women in multiple genetic variants. However, a study by Sergentanis *et al.* failed to identify any association between MspI polymorphism and cervical cancer susceptibility among Asian women, in which only 3 articles on an Asian population were included [42]. We suppose that the results of our study are more accurate because the small number of studies on Asian women in their study may increase the inaccuracy of the meta-analysis conclusions.

For meta-analysis of Ile462Val polymorphism, 11 articles including 2137 cervical cancer patients and 2116 healthy controls were enrolled. We found that the Ile462Val polymorphism of the CYP1A1 gene was significantly associated with the risk of cervical cancer. Subgroup analysis by ethnicity showed that the Ile462Val polymorphism was associated with the risk of cervical cancer among Caucasian women in allelic and dominant models, and among Asian women in allelic, homozygous and dominant models. Generally our results are similar to those of Yang *et al.* and Sergentanis *et al.* [42, 43]. However, their studies did not report the association between Ile462Val polymorphism and cervical cancer susceptibility in the Asian population. We speculate that the difference in results may due to differences in the number of selected articles as well as the number of cases [42, 43]. Further meta-analysis with larger samples is still needed to obtain a more accurate conclusion for the association between Ile462Val polymorphism and cervical cancer susceptibility in Asian women.

Previous studies have reported differences in the association between CYP1A1 gene MspI polymorphism and susceptibility to different cancers [42, 44, 45]. In addition, the Ile462Val polymor-

phism is closely related to the risk of ovarian cancer, lung cancer and liver cancer, but is not related to the risk of gastric cancer or breast cancer [44–48]. Here, in the current meta-analysis, we found that both MspI and Ile462Val polymorphisms were associated with the risk of cervical cancer, indicating that these polymorphisms may have distinctive roles in different kinds of cancer. This may be caused by the specific CYP1A1 functions in different tissues or cells.

The present study had some limitations. First, data on the family history, smoking, drinking, age and other environmental exposure factors were lacking for the enrolled articles. Thus, non-adjusted ORs were obtained. Second, due to the lack of adequate pathological data, stratified analysis could not be done based on pathological types. Third, there was heterogeneity among the included studies. Fourth, this study did not analyze the interactions between genes or between genes and the environment and their impact on the association between gene polymorphisms and cancer.

In summary, this meta-analysis demonstrates that the MspI and Ile462Val polymorphisms of the CYP1A1 gene are involved in the development of cervical cancer. To further verify such associations, studies with a larger number of samples, accurate sample information and reasonable study designs are warranted.

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest.

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