EJGO European Journal of Gynaecological Oncology

CYP1A1 polymorphisms and cervical cancer risk: a meta-analysis

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Summary

Objective: Cytochrome P4501A1(CYP1A1) may contribute to the development of cervical cancer through affecting the metabolism of estrogen and carcinogens. The current data of connection between the CYP1A1 polymorphisms and cervical cancer risk is not thoroughly acceptable. We conduct a meta-analysis to evaluate whether there is certain correlation between polymorphisms of CYP1A1 and cervical cancer. *Materials and Methods:* Some eligible case-control studies are expected to be identified from Embase, PubMed and other databases. Pooled odds ratios (ORs) and 95% CIs are calculated in a fixed-effects or random effects model as appropriate. *Results:* There were 13 case-control studies, including 2374 cases and 2436 controls.. Overall, the pooled results showed that there was a strong connection between cervical cancer and CYP1A1 MspI polymorphism in all models: allele contrast(C *vs*. T) , OR=1.43,95% CI = 1.11–1.83; homozygote comparison(CC *vs*. TT), OR=2.09, 95% CI=1.26–3.48; heterozygote comparison(CT *vs*. TT), OR=1.48, 95% CI=1.12–1.95; dominant model (CC+CT *vs*. TT), OR=1.53, 95% CI=1.11–2.10; recessive model(CC *vs*. CT+TT), OR=1.64, 95% CI= 1.13–2.39). There were also strong associations between cervical cancer and CYP1A1 Ile462Val polymorphism in all models except for the recessive model. *Conclusion:* Present meta-analyses reveal that both MspI and Ile462Val polymorphisms may be correlated with cervical cancer.

Key words: Cytochrome P4501A1(CYP1A1), cervical cancer, polymorphism, meta-analysis.

Introduction

Today cervical cancer is one of the most frequent and devastating cancers among females. Data shows that it causes 250,000 deaths annually and a majority of cases are in developing geographic areas [1]. Molecular biological and epidemiological data established an etiological link between cervical cancer and high-risk human papillomavirus (HR-HPV) infection [2, 3]. Fortunately, for most HPV infected cases, the immune system in the body helps to remove the virus. Only a minority of HPV infected females suffer from cervical cancer. Therefore, HPV is not the only reason for cervical cancer. It indicates that other factors, such as genes or lifestyles, may jointly contribute to the durability of HPV infection, as well as the lethal transformation of cervical epithelial cells [4, 5].

Tobacco smoke is known as a risk factor of cervical cancer and contributes to various carcinogens including polycyclic aromatic hydrocarbons and nitrosamines [6]. Cytochrome P4501A1 (CYP1A1), a member of CYP1 family, is involved in the metabolism of endogenous molecules and xenobiotics, and plays an important role in the activation of carcinogens in tobacco smoke [7, 8]. CYP1A1 also was reported to participate in the conversion and metabolism of estrogen [9]. Two single nucleotide polymorphisms of CYP1A1, MspI, and Ile462Val, were reported as risk factors of cervical cancer. MspI polymorphism is a T-to-C transition located in the 3'- flanking region. Ile462Val is located at codon462in the heme-binding region of exon 7 and alters the protein structure by the replacement of isoleucine (Ile) by valine (Val) [10, 11].

In the past two decades, much research has been done to explore the potential association between the CYP1A1 polymorphisms and cervical cancer risk in different ethnicities; however, the results are inconclusive and inconsistent [12-17]. Because a single study may not be sufficient to find the overall effects, the present authors carried out a meta-analysis to evaluate the associations between CYP1A1 polymorphisms (MspI and Ile462Val) with the risk of cervical cancer.

Materials and Methods

Embase, PubMed, China National Knowledge Infrastructure (CNKI), and Chinese Biomedicine databases were searched for all articles on the relationship between cervical cancer and CYP1A1 polymorphism (last search update July 10, 2015). The following keywords were used: ''CYP1A1''or "MspI" or "Ile462Val" and ''variant'' or ''polymorphism'' and ''cervical cancer''.

All studies, no matter what the sample size was, were taken into consideration if they conformed to these points: (i) assessment of the relationship between one or two polymorphisms (MspI and Ile462Val) and cervical cancer risk, (ii) case–control studies and (iii) adequate data to get an odds ratio (OR) by 95% confidence interval (95% CI). The authors excluded those studies if they fell in the following: (i) abstract, comment, review or editorial, (ii) studies focusing on assessing the connections between CYP1A1 poly-

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Revised manuscript accepted for publication January 18, 2016

morphisms and cervical cancer with chemotherapy or (iii) without adequate data.

Two reviewers (H. Chen and K. Yi) extracted information from all qualified publications independently based on the inclusion criteria listed above. Disagreements were resolved by in consultation with an arbitrator (J. Chen).

The following information was collected from all qualified publications: first author's surname, year of publication, country of participants, sample size of cases and controls, source of control groups (population-based or hospital-based controls), ethnicity, distribution of genotypes, genotyping methods, Hardy-Weinberg equilibrium (HWE), and minor allele frequency (MAF). Hospital-based case-control study (HCC) was based on data of patients in hospitals, and population-based case-control study (PCC) was of healthy people. Ethnicities were divided into Asian, Caucasian or mixed.

The Fisher's exact test was used to assess HWE of the control group in each research and a p value < 0.05 indicated significant dis-equilibrium. The OR and corresponding 95 % CI was used to evaluate the strength of the association between the CYP1A1 polymorphisms and cervical cancer risk. Taken the CYP1A1 MspI (T6235C) polymorphism as an instance, the authors obtained five results of ORs: (i) allele contrast (C *vs.* T), (ii) homozygous comparison (CC *vs.* TT), (iii) heterozygous comparison (CT *vs.* TT), (iv) dominant model (CC+CT *vs.* TT), and (v) recessive model (CC *vs.* CT+TT). The authors also conducted layered analysis based on source of control groups, ethnicity and HWE.

The Cochran Q statistic and the I^2 were used to verify and confirm the heterogeneity analysis. A p value > 0.10 for the Q statistic indicated a lack of heterogeneity across studies. The authors chose the fixed-effects model (the Mantel-Haenszel method) to calculate the ORs [18] and the random-effects model (the DerSimonian and Laird method) to pool the OR [19]. Sensitivity analysis and cumulative meta-analyses were conducted to check on the final results.

The Egger's weighted regression method and the Begg's rank correlation method were used to explore the publication bias by visual inspection of the funnel plot (p value < 0.05 was considered statistically significant) [20, 21]. The authors used the STATA software, version 13.0 to process the statistical analyses.

Results

After performing a careful literature search, the authors finally narrowed the scope to 26 articles that may have warranted an in-depth confirmation. When they looked into the titles and abstracts of these articles, they further excluded eight articles. Then, they retrieved for full texts of 18 articles and proceeded to remove another five articles, because three focused on literature review [22-24], and two were about cervical intraepithelial neoplasia (CIN) [25, 26]. Finally they collected 13 case controlled studies in ten publications [12-17, 27-33], including 11 studies on MspI and nine studies on Ile462Val polymorphisms, based on meta-analysis of observational studies in epidemiology (MOOSE) guidelines [34]. The literature search and study selection procedures are displayed in Figure 1.

The characteristics of selected studies are exhibited in Table 1 [12-17, 27-33]. There were six studies of subjects of Caucasian descent, six studies of subjects of Asian descent, and one study of subjects with mixed descent. Research had been conducted in China, Korea, Japan, India, Mexico, Turkey, Germany, Israel, and Poland. The case definitions used in the individual studies were pathologically or histologically diagnosed with cervical cancer. Controls were chiefly based on healthy populations and matched for age and/or geographical area, of which ten studies were population-based and three studies were hospital-based. Of these, two studies for MspI polymorphism were out of HWE [13, 16], and four studies for Ile462Val polymorphism were deviated from HWE [15, 16, 29, 30].

Connection between the MspI polymorphism and cervical cancer susceptibility was assessed. Eleven case controlled studies with 1,833 cases and 1,739 controls for CYP1A1MspI were included [13-17, 27-29, 31-33]. The meta-analysis results are presented in Table 2. The forest plot assessing connections between MspI polymorphism and cervical cancer risk are presented in Figure 2A.

Overall, the authors found that there was a significant correlation between CYP1A1 MspI polymorphism and cervical cancer in these models: allele contrast (C *vs*. T), OR= 1.43, 95% CI=1.11–1.83; homozygote comparison (CC *vs*. TT), OR=2.09, 95% CI = 1.26–3.48; heterozygote comparison (CT *vs*. TT), OR=1.48, 95% CI=1.12–1.95; dominant model (CC+CT *vs*. TT), OR=1.53, 95% CI=1.11–2.10; recessive model (CC *vs*. CT+TT), OR=1.64, 95% CI=1.13–2.39).

To evaluate the actual impacts of connections between MspI polymorphism and cervical cancer risk, analyses of stratification were conducted by source of controls, ethnicity and HWE. When stratified according to the source of controls, a significant association was found in these studies of HCC in all models. In the ethnicity-based stratified analysis, the authors observed a significant correlation in mixed descent in all models. When stratified by HWE, the authors found a significant correlation among studies conforming to HWE in all models (Table 2)

Connection between the CYP1A1 Ile462Val polymorphism and cervical cancer susceptibility was assessed. The authors eventually achieved nine case controlled studies including 1,509 cases and 1,646 controls for CYP1A1 Ile462Val [12, 13, 15-17, 29-31, 33]. The assessment of the connection between CYP1A1 Ile462Val polymorphism and cervical cancer is shown in Table 3 and Figure 2B. The authors found that there was a significant correlation between CYP1A1 Ile462Val polymorphism and cervical cancer risk in four models: allele contrast (Val *vs*. Ile), OR=1.60, 95% CI=1.17–2.20; homozygote comparison (Val/Val *vs*. Ile/Ile), OR=2.26, 95% CI=1.09–4.66; heterozygote comparison (Val/Ile *vs*. Ile/Ile), OR=2.01, 95% CI=1.42–2.85; dominant model (Val/Val +Val/Ile *vs*. Ile/Ile), OR=1.94, 95% CI=1.37–2.76.

In the ethnicity-based stratified analysis, the authors observed a significant association among Asian descent in dominant model and heterozygote comparison, as well as in mixed population in homozygote comparison, heterozygote

Table 1. — *Characteristics of studies included in this meta-analysis.*

Author	Year	Country	Ethnicity	SNPs studied	Source of controls	Genotyping methods	Simple size (case/control)	MAF in Controls	HWE
Kim	2000	Korea	Asian	MspI	PCC	PCR-RFLP	181/181	0.37	0.05
Sugawara	2003	Japan	Asian	MspI, Ile462Val	PCC	PCR	72/31	0.16,0.27	0.23,0.28
Joseph	2005	India	Mixed	MspI, Ile462Val	HCC	PCR-RFLP	147/165	0.10,0.09	0.24,0.20
Taskiran	2006	Turkey	Caucasian	Ile462Val	HCC	PCR-RFLP	85/202	0.13	<0.01
Zhang	2006	China	Asian	MspI, Ile462Val	HCC	PCR-RFLP	50/30	0.35,0.31	0.29,0.01
Juarez-Cedillo	2007	Mexico	Mixed	MspI	HCC	PCR-RFLP	155/155	0.21	0.64
Nishino	2008	Japan	Asian	MspI	PCC	PCR-RFLP	124/117	0.37	0.63
Gutman	2009	Israel	Caucasian	MspI, Ile462Val	HCC	PCR-RFLP	43/123	0.13,0.17	0.38,0.32
Ding	2011	China	Asian	MspI, Ile462Val	PCC	PCR-RFLP	280/280	0.37,0.47	0.04,<0.01
Von Keyerling	2011	Germany	Caucasian	MspI	HCC	PCR-RFLP	405/337	0.10	0.18
Shi	2011	China	Asian	MspI, Ile462Val	PCC	PCR-RFLP	176/112	0.21,0.38	0.87,<0.01
Abbas	2014	India	Mixed	MspI, Ile462Val	HCC	PCR-RFLP	200/208	0.28,0.17	0.04,0.06
Roszak	2014	Poland	Caucasian	Ile462Val	PCC	PCR-RFLP	456/495	0.03	0.50

Abbreviations: SNPs, single nucleotide polymorphisms; HCC, hospital-based case-control; PCC, population-based case-control; PCR-RFLP, polymerase chain reaction-restriction fragment length polymorphism; MAF, minor allele frequency; HWE, Hardy–Weinberg equilibrium.

Table 2. — *Quantitative analyses of the CYP1A1 MspI polymorphism on the cervical cancer.*

Genetic model			Allele contrast		Homozygote		Heterozygote		Dominant model		Recessive model	
Variables	Sample size		C *vs*. T		CC *vs*. TT		CT *vs*. TT		CC+CT *vs*. TT		CC *vs*. CT+TT	
	N[a]	Case/control	OR(95%CI)	p_{value}[b]	OR(95%CI)	p_{value}[b]	OR(95%CI)	p_{value}[b]	OR(95%CI)	p_{value}[b]	OR(95%CI)	p_{value}[b]
Total	11	1833/1739	1.43(1.11,1.83)	0.000	2.09(1.26,3.48)	0.002	1.48(1.12,1.95)	0.000	1.53(1.11,2.10)	0.000	1.64(1.13,2.39)	0.057
Ethnicity												
Asian	6	883/751	1.11(0.96,1.28)	0.557	1.17(0.85,1.61)	0.816	1.12(0.89,1.41)	0.350	1.14(0.93,1.40)	0.395	1.14(0.85,1.54)	0.891
Caucasian	2	448/460	1.14(0.70,1.86)	0.055	3.87(0.44,34.2)	0.234	1.06(0.76,1.48)	0.466	1.14(0.81,1.62)	0.308	2.88(1.30,6.34)	0.248
Mixed	3	502/528	2.41(1.69,3.43)	0.202	4.57(1.91,10.9)	0.057	2.71(2.05,3.59)	0.401	2.98(2.08,4.28)	0.162	3.97(0.49,32.3)	0.076
Source of controls												
PCC[c]	5	833/721	1.11(0.95,1.29)	0.418	1.18(0.85,1.65)	0.715	1.12(0.86,1.46)	0.246	1.15(0.90,1.47)	0.272	1.17(0.86,1.58)	0.847
HCC[c]	6	1000/1018	1.70(1.17,2.45)	0.000	3.46(1.61,7.42)	0.045	1.79(1.31,2.82)	0.001	1.88(1.17,3.05)	0.000	2.44(1.24,4.82)	0.079
HWE[d] in controls												
Yes	9	1353/1251	1.45(1.08,1.95)	0.000	2.37(1.24,4.53)	0.009	1.47(1.07,2.02)	0.004	1.55(1.09,2.20)	0.000	1.89(1.12,3.19)	0.062
No	2	480/488	1.32(0.70,2.49)	0.001	1.55(0.63,3.82)	0.020	1.43(0.51,4.05)	0.000	1.47(0.54,3.99)	0.000	1.26(0.86,1.84)	0.280

[a]Number of comparisons. [b]p value of Q-test for heterogeneity test. Random-effects model was used when p value for heterogeneity test < 0.05, otherwise, fixed-effects model was used. [c]HCC, hospital-based case-control; PCC, population-based case-control. [d]HWE, Hardy–Weinberg equilibrium.

Table 3. Quantitative analyses of the CYP1A1 Ile462Val polymorphism on the endmetriosis.

Genetic model			Allele contrast		Homozygote		Heterozygote		Dominant model		Recessive model	
Variables	Sample size		Val *vs*. Ile		Val / Val *vs*. Ile/ Ile		Val/ Ile *vs*. Ile/ Ile		Val/Val +Val/Ile *vs*. Ile/ Ile		Val/Val *vs*. Val/ Ile + Ile/ Ile	
	N[a]	Case/control	OR(95%CI)	p_{value}[b]	OR(95%CI)	p_{value}[b]	OR(95%CI)	p_{value}[b]	OR(95%CI)	p_{value}[b]	OR(95%CI)	p_{value}[b]
Total	9	1509/1646	1.60(1.17,2.20)	0.000	2.26(1.09,4.66)	0.013	2.01(1.42,2.85)	0.001	1.94(1.37,2.76)	0.000	1.55(0.78,3.08)	0.012
Ethnicity												
Asian	4	578/453	1.23(0.90,1.67)	0.112	1.19(0.66,5.39)	0.023	1.62(1.11,2.36)	0.255	1.51(1.04,2.19)	0.229	1.27(0.49,3.29)	0.024
Caucasian	3	584/820	1.78(0.86,3.72)	0.002	4.77(1.73,13.2)	0.130	2.41(0.90,6.47)	0.000	2.21(0.85,5.74)	0.000	0.96(0.25,3.74)	0.272
Mixed	2	347/373	2.05(0.86,3.72)	0.060	1.21(0.13,11.6)	0.738	1.99(1.29,3.06)	0.203	2.17(1.31,3.59)	0.124	3.86(1.41,10.6)	0.765
Source of controls												
PCC[c]	4	984/918	1.21(0.92,1.60)	0.129	1.96(0.39,9.96)	0.009	1.49(1.14,1.93)	0.955	1.39(1.08,1.78)	0.724	1.51(0.32,7.22)	0.006
HCC[c]	5	525/728	1.99(1.31,3.03)	0.006	2.79(1.48,5.25)	0.409	2.70(1.49,4.87)	0.001	2.55(1.48,4.38)	0.002	1.69(0.81,3.50)	0.254
HWE[d] in controls												
Yes	5	918/1022	1.59(1.14,2.22)	0.079	2.84(0.71,11.4)	0.166	1.71(1.33,2.18)	0.496	1.73(1.28,2.34)	0.222	2.42(0.65,9.00)	0.195
No	4	591/624	1.68(0.94,3.00)	0.000	2.00(0.87,4.58)	0.028	2.70(1.24,5.89)	0.000	2.42(1.13,5.18)	0.000	1.25(0.61,2.55)	0.046

[a]Number of comparisons. [b]p value of Q-test for heterogeneity test. Random-effects model was used when p value for heterogeneity test < 0.05, otherwise, fixed-effects model was used. [c]HCC, hospital-based case-control; PCC, population-based case-control. [d]HWE, Hardy–Weinberg equilibrium.

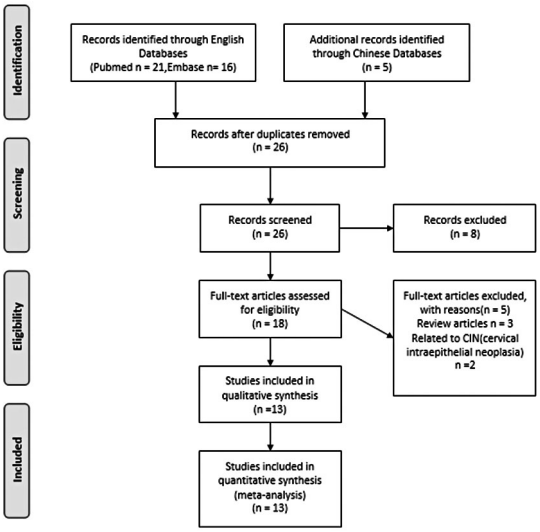

Figure 1. — Literature search and study selection procedures used for a meta-analysis of CYP1A1 genetic polymorphisms and cervical cancer.

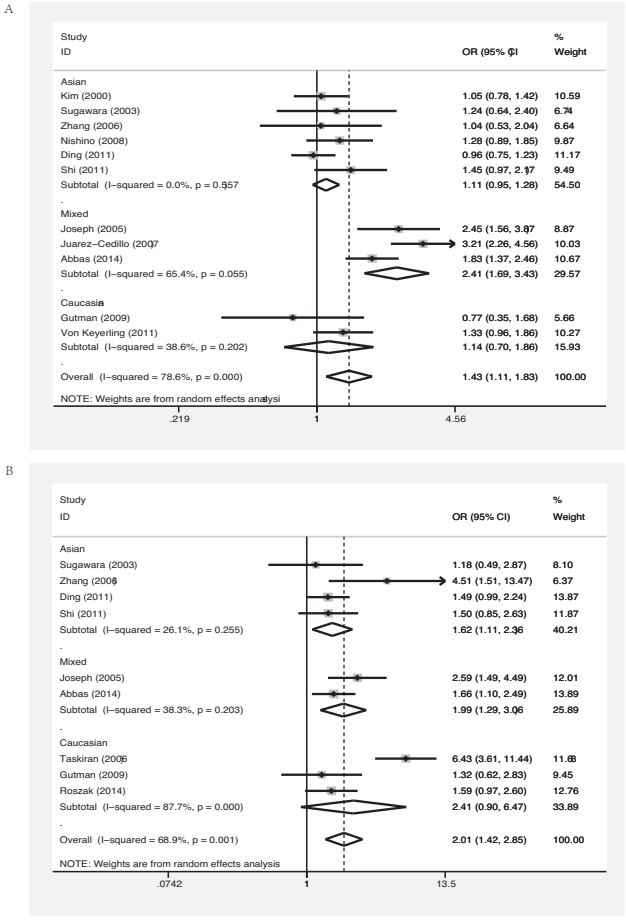

Figure 2. — A) Forest plots of ORs with 95% CIs for CYP1A1 MspI polymorphism and risk for cervical cancer. B) Forest plots of ORs with 95% CIs for CYP1A1 Ile462Val polymorphism and risk for cervical cancer.

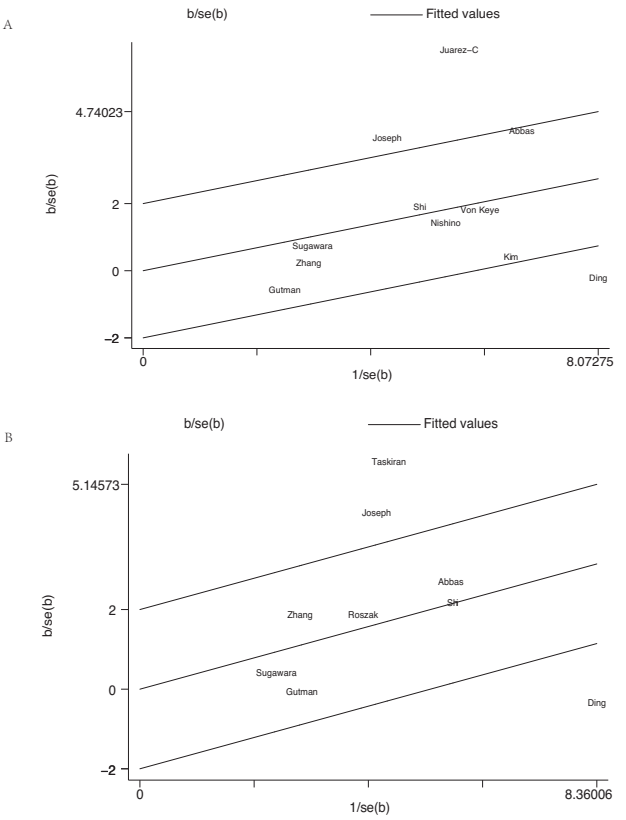

Figure 3. — A) Galbraith plots for heterogeneity test of CYP1A1 MspI polymorphism. B) Galbraith plots for heterogeneity test of CYP1A1 Ile462Val polymorphism.

comparison, and dominant model. When stratified according to the source of controls, the authors observed a significant association among studies of PCC in dominant model and heterozygote comparison and among studies of HCC in allele contrast, homozygote comparison, heterozygote comparison, and dominant model. When stratified by HWE, a significant association was detected among studies conforming to HWE in allele contrast, dominant model, and heterozygote comparison (Table 3).

For CYP1A1 MspI polymorphism, a substantial heterogeneity was detected among studies in overall comparisons: allele contrast (C *vs*. T), $p_{\text{heterogeneity}} < 0.001$; homozygote comparison (CC *vs*. TT), $p_{\text{heterogeneity}} = 0.002$; heterozygote comparison (CT *vs*. TT), $p_{\text{heterogeneity}} < 0.001$; dominant model (CC+CT *vs*. TT), $p_{\text{heterogeneity}} < 0.001$; recessive model (CC *vs*. CT+TT), $p_{\text{heterogeneity}} = 0.057$.

Galbraith plot analyses were used to probe into sources of heterogeneity across studies. The authors noticed that there were three studies contributing to the heterogeneity for allele contrast of CYP1A1 MspI polymorphism (Figure 3A) [16, 28, 31]. The heterogeneity dropped sharply when removing three outlier studies (C *vs*. T: $p_{\text{heterogeneity}} = 0.205$). Then authors also noticed that there were two stud-

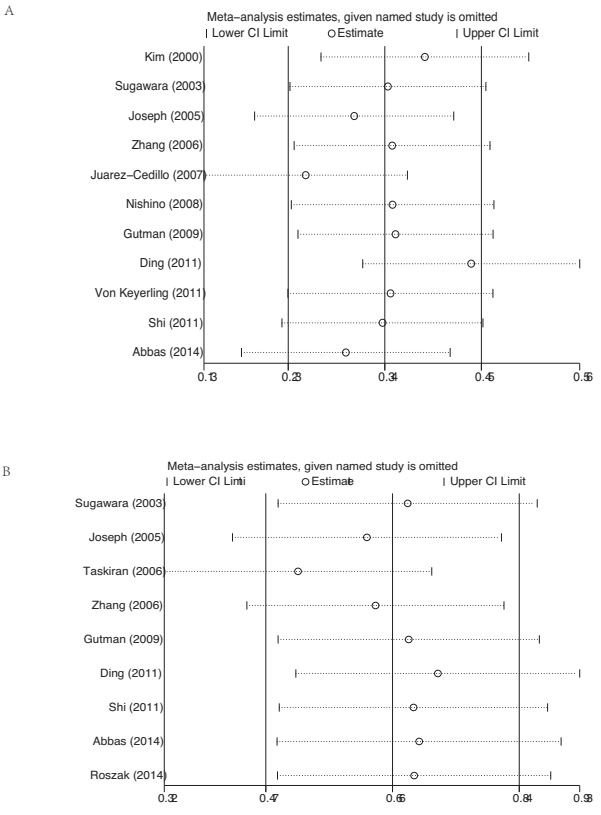

Figure 4. — A) Sensitivity analysis of associations between CYP1A1 MspI polymorphism and cervical cancer. B) Sensitivity analysis of associations between CYP1A1 Ile462Val polymorphism and cervical cancer.

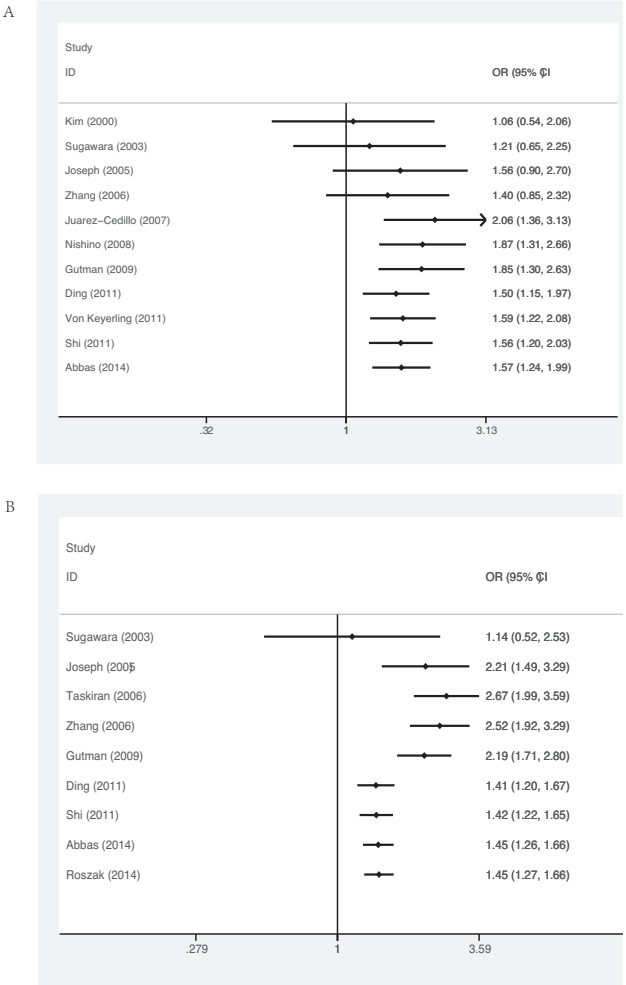

Figure 5. — A) Cumulative meta-analysis of the CYP1A1 MspI polymorphism on the cervical cancer. B) Cumulative meta-analysis of the CYP1A1 Ile462Val polymorphism on the cervical cancer.

ies contributing to the heterogeneity for heterozygote comparison of MspI polymorphism [16, 28]. The heterogeneity also dropped sharply when removing two outlier studies (CC *vs*. TT: $p_{\text{heterogeneity}} = 0.348$). They also noticed that there were three studies contributing to the heterogeneity for heterozygote comparison of MspI polymorphism [13, 16, 28]. The heterogeneity dropped when removing three outlier studies (CT *vs*. TT: $p_{\text{heterogeneity}} = 0.295$). There were four studies contributing to the heterogeneity for dominant model of MspI polymorphism [13, 16, 28, 31]. The heterogeneity dropped sharply when removing four outlier studies (CC+CT *vs*. TT: $p_{\text{heterogeneity}} = 0.753$). The authors also noticed that there was one study contributing to the heterogeneity for recessive model of MspI polymorphism [28]. The heterogeneity dropped when removing outlier study (CC *vs*. CT+TT: $p_{\text{heterogeneity}} = 0.437$).

For CYP1A1 Ile462Val polymorphism, heterogeneity was also observed in all models: allele contrast (Val *vs*. Ile), $p_{\text{heterogeneity}} < 0.001$, homozygote comparison (Val/Val *vs*. Ile/Ile), $p_{\text{heterogeneity}} = 0.013$, heterozygote comparison (Val/Ile *vs*. Ile/Ile) $p_{\text{heterogeneity}} = 0.001$; dominant model (Val/Val+Val/Ile *vs*. Ile/Ile), $p_{\text{heterogeneity}} < 0.001$; recessive model (Val/Val vs. Val/ Ile + Ile/ Ile), $p_{\text{heterogeneity}} = 0.012$.

The authors applied the Galbraith plot analysis to assess sources of heterogeneity among these studies. They confirmed that there were three studies contributing to the heterogeneity for allele contrast of CYP1A1 Ile462Val polymorphism [16, 28, 30](Figure 3B). The heterogeneity dropped sharply when removing three outlier studies (Val *vs*. Ile: $p_{\text{heterogeneity}} = 0.744$). The authors confirmed that there were two studies contributing to the heterogeneity for heterozygote comparison of Ile462Val polymorphism [15, 16]. The heterogeneity dropped sharply when removing two outlier studies (Val/Val vs. Ile/ Ile): $p_{\text{heterogeneity}} = 0.409$). They also confirmed that there was only one study contributing to the heterogeneity for heterozygote comparison of Ile462Val polymorphism [30]. The heterogeneity dropped sharply when removing outlier study (Val/Ile *vs*.

Ile/ Ile: $p_{heterogeneity} = 0.426$). The authors confirmed that there were two studies contributing to the heterogeneity for dominant model of Ile462Val polymorphism [16, 30]. The heterogeneity dropped when removing two outlier studies (Val/Val +Val/Ile vs. Ile/Ile: $p_{heterogeneity} = 0.279$). They confirmed that there were two studies contributing to the heterogeneity for recessive model of Ile462Val polymorphism [15, 31]. The heterogeneity dropped when removing two outlier studies (Val/Val vs. Val/ Ile + Ile/ Ile: $p_{heterogeneity} = 0.338$)

The authors adopted a sensitivity analysis to assess the impacts of every study on general pooled OR and they found two most influential studies on the pooled OR for the connection between CYP1A1 MspI and cervical cancer risk (Figure 4)[16, 28]. However, the significant associations remained after the removal of the two studies. Regarding the connection of the CYP1A1 Ile462Val with cervical cancer risk, the research of Taskrian *et al.* was taken as the most influential one on the pooled OR [30]. The sensitivity analysis result held when removing the study.

Based on the publication time, the authors conducted a cumulative meta-analysis of the connections by categorizing all the qualified studies. The cumulative meta-analysis of the connection between CYP1A1 MspI and Ile462Val and cervical cancer risk proved that there were strong connections with the increase of data gradually, although there were no connection confirmed at the very beginning (Figure 5).

The authors used Begg's and Egger's tests to examine whether there was a publication bias of the literatures. The curves of the Begg's funnel plots showed no tendency of any asymmetry. The statistical results also indicated no publication bias [(i) CYP1A1 MspI, C vs. T: Begg's test $p = 0.94$, Egger's test $p = 0.84$; CC *vs*. TT: Begg's test $p = 0.28$, Egger's test $p = 0.20$; CT *vs*. TT: Begg's test $p = 0.53$, Egger's test $p = 0.84$; CC+CT *vs*. TT: Begg's test $p = 0.87$, Egger's test $p = 0.88$; CC *vs*. CT+TT: Begg's test $p = 0.15$, Egger's test $p = 0.13$; (ii) CYP1A1 Ile462Val, Val *vs*. Ile: Begg's test $p = 0.84$, Egger's test $p = 0.29$; Val/Val *vs*. Ile/Ile: Begg's test $p = 0.45$, Egger's test $p = 0.34$; Val/Ile *vs*. Ile/Ile: Begg's test $p = 0.92$, Egger's test $p = 0.54$; Val/Val +Val/Ile *vs*. Ile/Ile: Begg's test $p = 0.60$, Egger's test $p = 0.57$; Val/Val *vs*. Val/ Ile + Ile/ Ile: Begg's test $p = 0.71$, Egger's test $p = 0.57$].

Discussion

On the basis of 13 case controlled studies, this meta-analysis demonstrates that there are significant connections implicating CYP1A1 polymorphisms and cervical cancer. It seems that both polymorphisms of CYP1A1 MspI and Ile462Val may cause increased risks for cervical cancer. The authors found that there were significant associations between CYP1A1 MspI polymorphism and cervical cancer risk in all examined models. They also conducted subgroup analysis based on source of controls, ethnicity, and HWE, and found that there were significant associations among studies of mixed descent, trials of HCC, and studies conforming to HWE.

Interestingly, the authors found significant associations between MspI and cervical cancer in studies within HWE but not in studies deviated from HWE. Violation of HWE may be attributed to methodological reasons including non-random mating, selection bias, and population stratification, as well as technical reasons including genotyping errors and assay non-specificity [35, 36]. Deviation from HWE may indicate that allele-based evaluation of genetic effects is biased and the results of genetic association researches might be counterfeit [37]. The power of pooled analysis based on studies rejected by HWE conformity may be limited to evaluate the association. So the stratified analysis excluding studies deviated from HWE were modified to generate the results of improved quality and explore the real associations statistically.

As for CYP1A1 Ile462Val polymorphism, significant associations were found in four models (allele contrast, heterozygote comparison, homozygote comparison, and dominant model).When stratified for source of controls, significant associations in the four aforementioned models were also observed among studies of HCC. However, the associations among studies of PCC were only detected in heterozygote comparison and dominant model. The reason for this discrepancy remains unknown, but selection biases of HCC study may be a possible factor. The control group of subjects based on the hospital may be disease-related groups, and may not be the representative of the general population, particularly when the studied genotype and disease status of hospital based control may be relevant. Although the control of the hospital is more convenient and is easier to recruit, the control subjects based on population may be better to reduce the bias in these genetic association studies. Different control sources should be considered as a possible confounding factor on the conclusion of current meta-analysis.

The results implicating CYP1A1 MspI polymorphism are partially consistent with an early study. Xia *et al.* performed a meta-analysis based on ten studies and found significant associations between MspI and cervical cancer in allele contrast, homozygote comparison, dominant model, and recessive model [22]. Another meta-analysis including six studies for MspI polymorphism and four studies for Ile462Val polymorphism was conducted and the results revealed that significant associations of MspI polymorphism were found in heterozygote comparison and recessive model, and significant associations of Ile462Val polymorphism were found in heterozygote comparison, homozygote comparison, and dominant model [24]. The difference of ethnic composition that might lead to the diversity of results: diversified meta-analyses covered various initial trials, which were studied in various ethnic units, and the

ethnic composition in different meta-analyses could be quite different. In addition, the use of different research approaches, for example, standards for inclusion or exclusion of studies, size of samples, quality of previous researches, and bias of choice, might serve as a contributor to the diversified results. Another possible reason is that the early study was based on a small sample size, which may cause the inaccurate estimation of risks.

Regarding the meta-analysis, a critical problem is the heterogeneity degree because non-homogeneous researches might produce misguided results. In the meta-analysis, the authors used I^2 statistics and Q-test to assess the significance of heterogeneity and confirmed that there was an apparent heterogeneity in these included studies in all models of CYP1A1 MspI and Ile462Val polymorphisms. They drew a Galbraith plot in order to identify the origins of heterogeneity, and confirmed that there were several studies chiefly contributing to the heterogeneity. The heterogeneity decreased significantly and the conclusion maintained unchanged after removing of the outlier studies. Another major concern in the meta-analysis is publication bias caused by the potential selective publication of reports. In the current meta-analysis, the authors adopted Egger's test and Begg's funnel plot to evaluate the publication bias, and found that there was no publication bias according to the statistical results and curves of funnel plots. They noticed that the results held as they conducted a sensitivity analysis. It indicates that the results are reliable and robust. Meanwhile, they conducted the cumulative meta-analysis by categorizing the included studies based on publication time. The results revealed that there was a stable trend of pooled OR and they found significant associations emerging with accumulation of data over time, although there was no connection at all at the very beginning.

There were some defects in this study: (i) due to the limited quantity of samples in these researches, as well as the limited quantity of researches covered by meta-analysis, the results would be insufficient to examine the actual connections statistically; (ii) this study was on the basis of unadjusted OR estimates because not all included trials provided adjusted ORs. Even if they did, the ORs might have been adjusted by different factors, such as race, age or smoking status; (iii) there was apparent heterogeneity among studies of MspI polymorphism in these models, and the genotype distribution of the included studies in control group was inconsistent with HWE; (iv) lack of the united data of the two-SNP restricted an in-depth pooled analysis of possible connections between two single-SNPs.

In conclusion, the present meta-analysis suggests that the polymorphisms of CYP1A1 MspI and Ile462Val may be associated with cervical cancer risk. Considering the relatively small number of included subjects and limited ethnicities populations in present meta-analysis, well-designed and larger multicenter case controlled studies are necessary to validate the connection and further enrich the present findings.

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