Cytochrome P450 1A1 gene polymorphisms and cervical cancer risk

A systematic review and meta-analysis

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Abstract

Objective: This meta-analysis aims to examine whether the MspI and Ile462Val polymorphisms of cytochrome P450 1A1 (CYP1A1) are associated with cervical cancer risk.

Methods: Eligible case–control studies were identified dated until July 2017. Pooled odds ratios (ORs) were used to assess the strength of the association between the two variants and cervical cancer risk.

Results: Thirteen studies were eligible (2148 cases and 2252 controls) concerning MspI polymorphism and 8 studies were eligible (1466 cases and 1690 controls) for Ile462Val polymorphism. MspI polymorphism seemed to result in cervical cancer risk in any genetic model (C allele vs T allele: OR = 1.44, 95% confidence interval [CI] = 1.16–1.79; heterozygous model: OR = 1.40, 95% CI = 1.08–1.82; homozygous model: OR = 2.22, 95% CI = 1.48–3.33, dominant model: OR = 1.50, 95% CI = 1.14–1.98 and recessive model: OR = 1.80, 95% CI = 1.35–2.41); similar significantly increased risk was found among Caucasians and Asians. Ile462Val polymorphism was associated with elevated cervical cancer risk (Val allele vs Ile allele: OR = 1.85, 95% CI = 1.27–2.67; heterozygous model: OR = 1.42, 95% CI = 1.28–1.61; homozygous model: OR = 2.94, 95% CI = 1.15–7.54; dominant model: OR = 2.00, 95% CI = 1.33–3.00); this finding was replicated upon Caucasian population.

Conclusion: This meta-analysis demonstrated that polymorphisms in MspI and Ile462Val of CYP1A1 were risk factors for developing cervical cancer.

Abbreviations: CYP1A1 = Cytochrome P450 1A1, HPV = human papillomavirus.

Keywords: cervical cancer, CYP1A1, meta-analysis, polymorphism

1. Introduction

Cervical cancer is the fourth most frequent female malignancy worldwide, causing an approximate 266,000 deaths per year in global area. In the recent years, the incidence of cervical cancer is gradually increasing with the trend of patients being young.[1] It is well known that human papillomavirus (HPV) infection is a prerequisite for cervical cancer. Moreover, some other HPV cofactors such as genetic susceptibility, premature sexuality, parity, and tobacco use may also contribute to cervical cancer pathogenesis.[2–4]

Cytochrome P450 1A1 (CYP1A1) is a key enzyme of CYP1 family related with the metabolism of many endogenous substrates and environmental procarcinogens. CYP1A1 may contribute to the formation of highly reactive intermediate metabolites, and these metabolites can form DNA adducts, which, if obstructed, would initiate or promote oncogenesis.[5,6]

Several single-nucleotide polymorphisms have been identified in the *CYP1A1* gene, all of which were localized on chromosome 15q22.[7] Such polymorphisms were considered playing an important role in determining individual susceptibility to many cancers, involving cervical cancer. Among these polymorphisms, the most commonly studied is the MspI polymorphism (2A, m1, T3801C, or rs4646903), which is located in the 3′′ noncoding region of the *CYP1A1* gene. Another commonly studied polymorphism is Ile462Val (2C, m2, or rs1048943), which gives rise to an amino acid transition in exon 7. The underlying biochemical hypothesis explaining the effect of the 2 variants is that both of them may influence mRNA expression or mRNA stability of the gene, resulting in a highly inducible activity of the enzyme.[8,9]

To date, a plenty of studies have reported the association between CYP1A1 MspI and Ile462Val polymorphisms and cervical cancer risk.[10–20] However, the relationship remains controversial. Although a meta-analysis conducted by Sergentanis et al investigated the association between CYP1A1 polymorphisms and cervical cancer,[21] we found some newly published and eligible studies that warrant the analysis to derive a more precise estimation of the relation and better evaluate the possible risk factor of cervical cancer.

2. Methods

2.1. Publication search

The PubMed and EMBASE databases were searched using the following keywords: "CYP1A1" or "cytochrome P450 1A1"

and "cervical cancer" (last search was updated on July 15, 2017). All published papers with English language and available full text matching the eligible criteria were retrieved. Additional studies were identified by manual search of the references of original studies. Of the studies with overlapping data published by the same investigators, only the most complete study was included in this meta-analysis.

2.2. Inclusion and exclusion criteria

The studies were identified according to the following inclusion criteria: case–control cervical cancer studies on CYP1A1 MspI or Ile462Val polymorphism with sufficient genotype distribution data, containing information about available genotype frequency that can help infer the results in the studies, pathologically confirmed cervical cancer cases and cancer-free controls, and published studies with full-text articles. The major reasons for exclusion of studies were no usable data reported, no control population, and duplicates or overlapping populations.

2.3. Data extraction

All of the data were extracted from all eligible publications independently by 2 of the authors according to the prelisted inclusion criteria. An agreement was reached through discussion and consultation between the 2 reviewers (BD and WS). For each study, the following characteristics were collected: the first author's last name, publication year, country of origin, ethnicity, genotyping methods, and tumor histologic type. Different ethnic descents were categorized as Caucasian and Asian. All analyses were based on studies which have been previous published, thus no ethical approval and patient consent are required.

2.4. Statistical analysis

The strength of the association between CYP1A1 MspI or Ile462Val polymorphism and cervical cancer risk was measured by odds ratios (ORs) with 95% confidence intervals (CIs). The significance of the summary ORs was determined with a Z test. The codominant model (heterozygous carriers vs "wild type" and homozygous carriers vs "wild type"), dominant model (heterozygous and homozygous carriers grouped together vs "wild type"), and recessive model (homozygous carriers vs "wild type" and heterozygous carriers grouped together) were estimated.

Heterogeneity assumption was checked by χ^2-based Q test. A P-value more than 0.10 for the Q test indicated lack of heterogeneity among the studies, and the summary OR estimate of each study was calculated by the fixed-effects model (the Mantel–Haenszel method).[22] Otherwise, the random-effects model (DerSimonian and Laird method) was used.[23] To explore the reasons of heterogeneity, subgroup analyses such as ethnicity study were performed. Galbraith plots were used to show the impact of individual study on the overall homogeneity. In the absence of individual heterogeneity, all the points were expected to lie within the confidence bounds.[24,25]

An estimate of publication bias was carried out by funnel plot,[26] using the standard error of log (OR). An asymmetric plot suggests the possibility of publication bias. Funnel plot asymmetry was evaluated by Egger's linear regression test,[27] a linear regression approach to assess funnel plot asymmetry on the natural logarithm scale of the OR.[28] Statistical significance for the interpretation of the Egger's test was defined as $P < .05$.
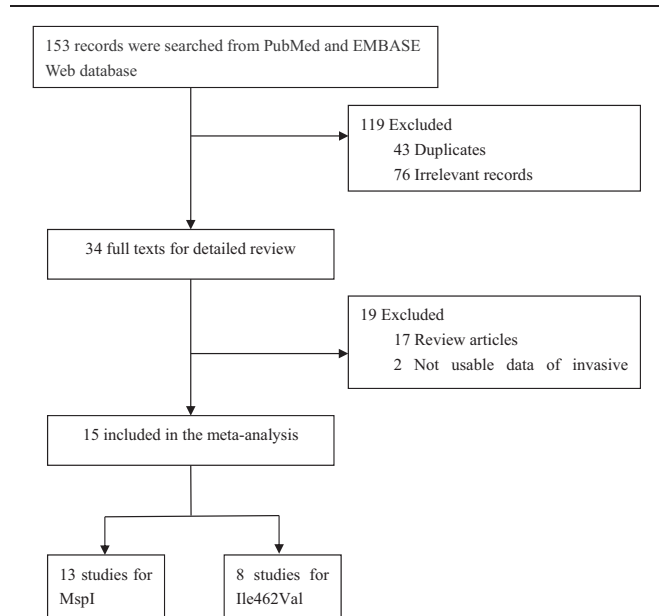

Figure 1. Studies identified with criteria for inclusion and exclusion.

Sensitivity analysis was performed by excluding a single study at a time. Studies were ranked based on sample size before the meta-analysis was repeated. Sample size was classified according to greater than 200 participants and those with less than or equal to 200 participants. Hardy–Weinberg equilibrium (HWE) was calculated by using the goodness-of-fit test, and significant deviation was considered when $P < .05$.

All statistical analyses were performed with the Stata software (version 10; StataCorp LP, College Station, TX), using 2-sided P-values.

3. Results

3.1. Eligible studies

Total searches yielded 153 entries. First, carefully screening the titles and abstracts, 119 of these articles were excluded (43 were duplicates and 76 were not cervical cancer research). Second, full texts were reviewed from 34 articles, 19 articles were excluded for the following reasons: 2 case–control studies[29,30] were excluded because no usable data of invasive cervical cancer, 17 were reviews instead of case–control studies. As a result, 15 case–control researches were included in the current meta-analysis. A flow diagram of the search process is shown in Figure 1.

The main characteristics of studies included in the meta-analysis are shown in Table 1. With respect to MspI polymorphism, 13 studies[10–13,15–18,20,31–34] (2148 cases and 2252 controls) were eligible. What needs illustration is that the study of Tan et al was performed on mixed ethnicity population, after careful assessment and discussion, we classified the Indians as Caucasians and categorized Malay and Chinese as Asian population while performing subgroup analyses.[34] Therefore, 9 studies[10,15–18,20,32–34] (1323 cases and 1401 controls) were performed on Caucasians, and 5 studies[11–13,31] (825 cases and 851 controls) were performed on Asian population. Concerning Ile462Val polymorphism, 8 studies[10,12,14,16,18,19,31,32] (1466 cases and 1690 controls) were eligible. Regarding race, 6 studies[10,14,16,18,19,32] (1031 cases and 1291 controls) were

Table 1

Main characteristics of studies included in the meta-analysis.

References	Country	Ethnicity	Tumor histologic type	Genotyping method	Polymorphisms	Cases/Controls	Cases			Controls			P-HWE controls
							XX	Xx	xx	XX	Xx	xx	
Kim et al[13]	Korea	Asian	HPV-16 or HPV-18 positive women, 100% squamous or adenocervical carcinoma	PCR-RFLP	MspI	181/181	62	99	20	65	97	19	.050
Sugawara et al[12]	Japan	Asian	NA	PCR	MspI	72/31	33	32	7	15	15	1	.230
					Ile462Val	75/31	48	27	0	21	10	0	.284
Taskiran et al[14]	Turkey	Caucasian	83.5% squamous, 16.5% adenocervical carcinoma	PCR	Ile462Val	85/202	33	47	5	158	35	9	<.05
Joseph et al[16]	India	Caucasian	Invasive cervical cancer or H-SILs	PCR-RFLP	MspI	147/165	94	43	10	135	27	3	.243
					Ile462Val	147/165	91	45	11	136	26	3	.197
Juarez-Cedillo et al[15]	Mexico	Caucasian	Invasive cervical cancer and positive HPV-16 infection	PCR-RFLP	MspI	155/155	43	80	32	97	50	8	.641
Nishino et al[11]	Japan	Asian	Squamous cervical carcinoma or CIN 3 lesions	PCR-RFLP	MspI	124/117	42	58	24	48	52	17	.634
Gutman et al[10]	Israel	Caucasian	NA	PCR-RFLP	MspI	43/123	34	9	0	90	30	1	.377
					Ile462Val	43/121	29	14	0	85	31	5	.324
von Keyserling et al[17]	Germany	Caucasian	CIN II-III or invasive squamous carcinoma and adenocarcinoma	TaqMan	MspI	405/337	314	81	10	273	63	1	.182
Roszak et al[19]	Polish	Caucasian	NA	PCR-RFLP	Ile462Val	456/495	415	41	0	466	29	0	.502
Abbas et al[18]	India	Caucasian	Cervical cancer	PCR-RFLP	MspI	200/208	66	102	32	114	72	22	.040
					Ile462Val	200/208	110	84	6	141	65	2	.062
Matos et al[20]	Portugal	Caucasian	Preneoplastic lesions and cancer	PCR-RFLP	MspI	124/105	64	36	5	99	23	2	.624
Tan et al[34]	Malaysia	Mixed	Squamous cell carcinoma/adenocarcinoma/ adenosquamous carcinoma	PCR-RFLP	MspI	106/195	35	47	24	78	87	30	.484
Li et al[31]	China	Asian	Cervical cancer	TaqMan	MspI	360/368	188	145	27	227	128	13	.327
					Ile462Val	360/368	199	141	20	217	135	16	.381
Satinder et al[33]	India	Caucasian	Cervical cancer	PCR-RFLP	MspI	150/150	61	75	14	67	73	10	.092
Jain et al[32]	India	Caucasian	Cervical cancer with stages I-IV	PCR-RFLP	MspI	100/100	43	48	9	29	61	10	<.05
					Ile462Val	100/100	50	30	20	77	23	0	.193

X/x for T/C of Msp T>C, Ile/Val of Ile462Val.

CIN=cervical intraepithelial neoplasia, HB=hospital based, HPV=human papillomavirus, HWE=Hardy–Weinberg equilibrium, PB=population based, PCR=polymerase chain reaction, RFLP=restriction fragment length polymorphism.

P value for HWE in control group.

Table 2

Results of meta-analysis for cytochrome P450 1A1 (CYP1A1) MspI polymorphism and cervical cancer risk.

	C allele vs T allele		Heterozygous (TC vs TT)		Homozygous (CC vs TT)		Dominant model (CC and TC vs TT)		Recessive model (CC vs TT and TC)	
	OR (95% CI)	P*	OR (95% CI)	P*	OR (95% CI)	P*	OR (95% CI)	P*	OR (95% CI)	P*
Overall (n=13)	1.44 (1.16–1.79)[†]	<.001	1.40 (1.08–1.82)[†]	<.001	2.22 (1.48–3.33)[†]	.010	1.50 (1.14–1.98)[†]	<.001	1.80 (1.35–2.41)[*,†]	.190
Caucasian (n=9)	1.45 (1.03–2.05)[†]	<.001	1.52 (1.02–2.29)[†]	<.001	2.33 (1.13–4.81)[†]	.002	1.57 (1.02–2.41)[†]	<.001	1.94 (1.10–3.40)[†]	.035
Asian (n=5)	1.32 (1.14–1.53)[*,†]	.441	1.24 (1.00–1.52)[*,†]	.884	1.89 (1.32–2.69)[*,†]	.423	1.34 (1.10–1.64)[*,†]	.787	1.71 (1.23–2.37)[*,†]	.391

95% CI=95% confidence interval, ORs=Odds ratios.

[*] P value of Q test for heterogeneity test, only fixed effects model was used in this meta-analysis because the P values for heterogeneity test were all higher than .1.

[†] Statistically significant results.

performed on Caucasians, 2 studies[12,31] (435 cases and 399 controls) were performed on Asian population.

3.2. Quantitative data synthesis

The pooled ORs along with their 95% CIs are presented in detail in Tables 2 and 3.

MspI polymorphism seemed to confer elevated cervical cancer risk concerning C allele vs T allele (pooled OR=1.44, 95% CI=1.16–1.79; Fig. 2), heterozygous carriers (pooled OR=1.40, 95% CI=1.08–1.82), homozygous carriers (pooled OR=2.22, 95% CI=1.48–3.33), and at the dominant model (pooled OR=1.50, 95% CI=1.14–1.98), as well as at the recessive model (pooled OR=1.80, 95% CI=1.35–2.41). Further subgroup analysis by ethnicity suggested that the variant was associated with cervical risk in Caucasian population (C allele vs T allele: OR=1.45, 95% CI=1.03–2.05; heterozygous model: OR=1.52, 95% CI=1.02–2.29; homozygous model: OR=2.33, 95% CI=1.33–4.81; dominant model: OR=1.57, 95% CI=1.02–2.41 and recessive model: OR=1.94, 95% CI=1.10–3.40); and MspI CC genotype was related with high risk of cervical cancer in Asian population under all 5 genetic models (for C allele vs T allele: OR=1.32, 95% CI=1.14–1.53; heterozygous model: OR=1.24, 95% CI=1.00–1.52; homozygous model: OR=1.89, 95% CI=1.32–2.69; dominant model: OR=1.34, 95% CI=1.10–1.64 and recessive model: OR=1.71, 95% CI=1.23–2.37) (Table 2).

With respect to Ile462Val polymorphism, significantly increased cervical cancer risk was found for Val allele vs Ile allele (pooled OR=1.85, 95% CI=1.27–2.67; Fig. 3), heterozygous genotype (pooled OR=1.42, 95% CI=1.28–1.61), homozygous genotype (pooled OR=2.94, 95% CI=1.15–7.54) and dominant model (pooled OR=2.00, 95% CI=1.33–3.00); these findings were replicated upon Caucasians (Val allele vs Ile allele: OR=2.16, 95% CI=1.45–3.21; heterozygous model: OR=1.73, 95% CI=1.48–2.02; homozygous model: OR=3.91, 95% CI=1.28–11.82 and

dominant model: OR=2.38, 95% CI=1.53–3.69). However, no significant association was found in Asian population (for C allele vs T allele: OR=1.14, 95% CI=0.91–1.44; for heterozygous model: OR=1.14, 95% CI=0.86–1.53 and for dominant model: OR=1.17, 95% CI=0.88–1.54) (Table 3).

3.3. Test of heterogeneity

There was significant between–study heterogeneity for most of models of MspI and Ile462Val polymorphisms. Hence, we assessed the source of heterogeneity for allele comparison (CC and TC vs TT for MspI; Val/Val and Ile/Val vs Ile/Ile for Ile462Val) by ethnicity, genotyping method, and sample size. As a result, sample size was found to contribute to substantial heterogeneity for MspI polymorphism (P=.042); no significant heterogeneity was found for any of the considered stratification variables for Ile462Val polymorphism (P>.05).

Galbraith plots showed that estimates in 4 studies for Ile462Val[10,13,15,17] were potential sources of heterogeneity (Fig. 4). When these studies were excluded, heterogeneity disappeared and the results of the combined analyses after excluding these studies still showed significant association (Val allele vs Ile allele of Ile462Val: OR=1.43, 95% CI 1.12–1.82; P for heterogeneity=.528) between CYP1A1 Ile462Val polymorphism and cervical cancer risk.

3.4. Publication bias

Concerning MspI polymorphism, publication bias was not detected at any comparison (P=.279 for the analysis on C allele vs T allele, P=0.322 for the analysis on heterozygous carriers, P=.354 for the analysis on homozygous carriers, P=0.241 for the dominant model, P=.610 for the recessive model). Regarding Ile462Val polymorphism, publication bias was not detected at any comparison (P=.893 for the analysis on Val allele vs Ile allele, P=.943 for the analysis on heterozygous carriers, P=.993 for the analysis on homozygous carriers, P=.996 for the

Table 3

Results of meta-analysis for cytochrome P450 1A1 (CYP1A1) Ile462Val polymorphism and cervical cancer risk.

	Val allele vs Ile allele		Heterozygous (Ile/Val vs Ile/Ile)		Homozygous (Val/Val vs Ile/Ile)		Dominant model (Val/Val and Ile/Val vs Ile/Ile)		Recessive model (Val/Val vs Ile/Ile and Ile/Val)	
	OR (95% CI)	P*	OR (95% CI)	P*	OR (95% CI)	P*	OR (95% CI)	P*	OR (95% CI)	P*
Overall (n=8)	1.85 (1.27–2.67)[†]	<.001	1.42 (1.28–1.61)[†]	<.001	2.94 (1.15–7.54)[†]	.027	2.00 (1.33–3.00)[†]	<.001	2.24 (0.92–5.50)	.038
Caucasian (n=6)	2.16 (1.45–3.21)[†]	.001	1.73 (1.48–2.02)[†]	.003	3.91 (1.28–11.82)[*,†]	.085	2.38 (1.53–3.69)[†]	.001	2.82 (0.85–9.42)	.047
Asian (n=2)	1.14 (0.91–1.44)[*]	.996	1.14 (0.86–1.53)[*]	.939	–	–	1.17 (0.88–1.54)[*]	.974	–	–

95% CI=95% confidence interval, OR=Odds ratios.

[*] P value of Q test for heterogeneity test, only fixed effects model was used in this meta-analysis because the P values for heterogeneity test were all higher than .1.
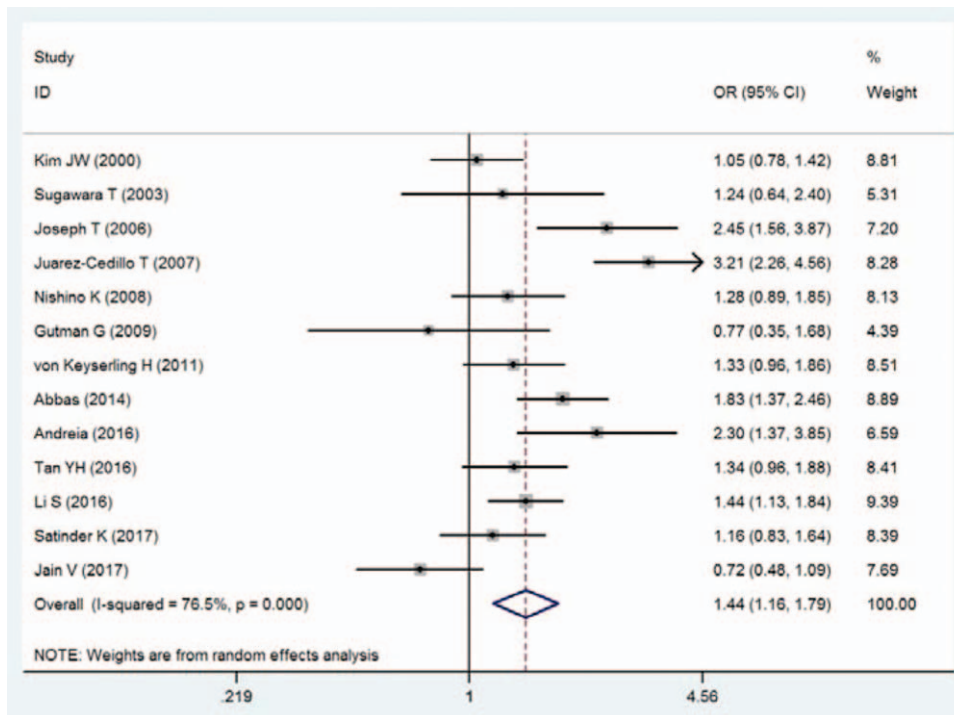
[†] Statistically significant results.

Figure 2. Forest plot of cervical cancer risk associated with cytochrome P450 1A1 (CYP1A1) MspI C allele vs T allele. The squares and horizontal lines correspond to the study-specific odds ratio (OR) and 95% confidence of interval (CI). The area of the squares reflects the study-specific weight (inverse of the variance). The diamond represents the summary OR and 95% CI.

dominant model, and $P = .910$ for the recessive model). In addition, the shapes of the funnel plots did not reveal any evidence of obvious asymmetry in all genetic models (Figs. 5 and 6).

3.5. Sensitivity analysis

After examining the genotype frequencies in controls, we detected significant deviations from HWE in 4 studies,[13,14,18,32] after the exclusion of the 3 studies, the summary ORs were not effectively
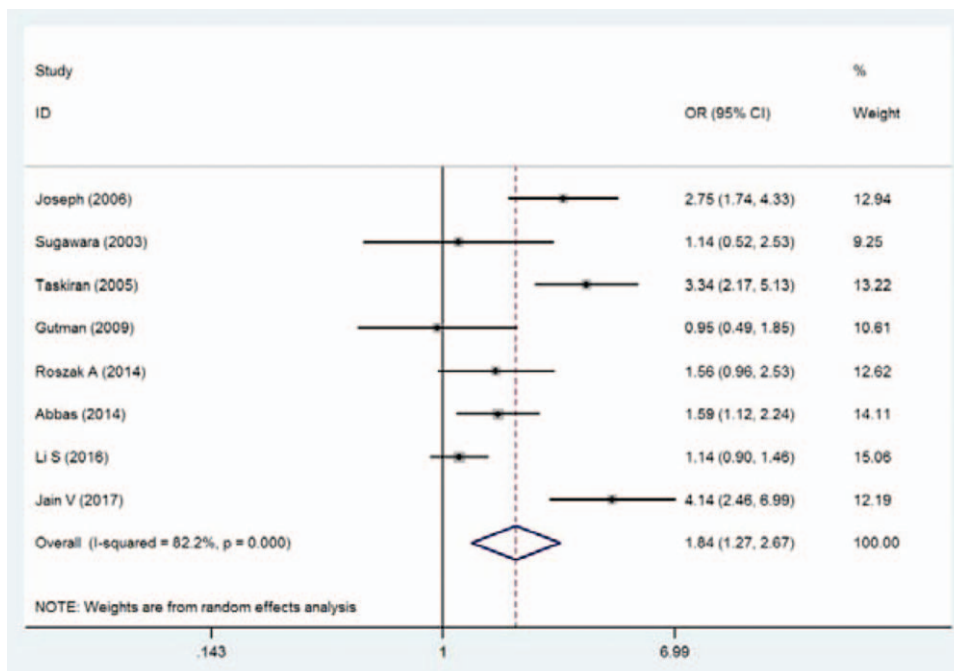

Figure 3. Forest plot of cervical cancer risk associated with cytochrome P450 1A1 (CYP1A1) Ile462Val Val allele vs Ile allele. The squares and horizontal lines correspond to the study-specific odds ratio (OR) and 95% confidence of interval (CI). The area of the squares reflects the study-specific weight (inverse of the variance). The diamond represents the summary OR and 95% CI.
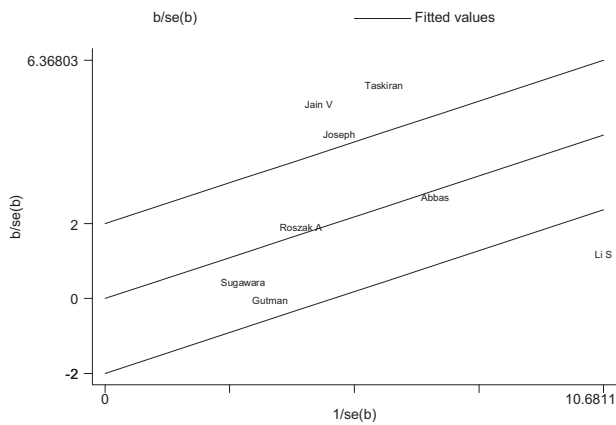
Figure 4. Identification of studies acting as sources of heterogeneity by the Galbraith plot under the cytochrome P450 1A1 (CYP1A1) Ile462Val dominant model (Val/Val and Ile/Val vs Ile/Ile). Each name represents a separate study for the indicated association. The random effects model was used.
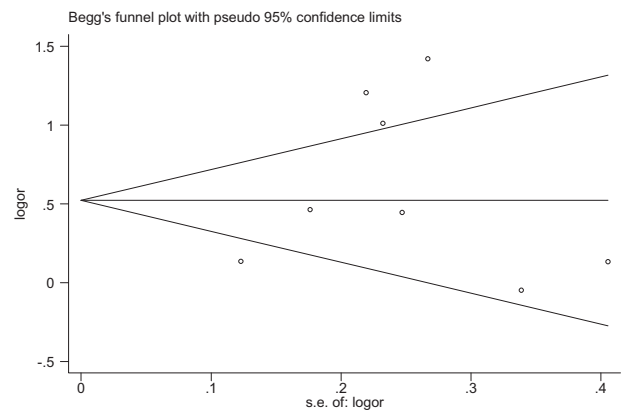

Figure 6. Begg's funnel plot for publication bias test (Ile462Val Val allele vs Ile allele). Each point represents a separate study for the indicated association. Log[or], natural logarithm of odds ratio. Horizontal line, means effect size.

influenced without including the studies (C allele vs T allele of MspI: OR = 1.56, 95% CI 1.24–1.98; Val allele vs Ile allele of Ile462Val: OR = 1.69, 95% CI 1.17–2.44). Although the sample size for cases and controls in all eligible studies ranged from 103 to 951, the corresponding pooled ORs were not qualitatively altered with or without the study of small sample. Moreover, no other single study modified the overall results qualitatively as indicated by sensitivity analyses, suggesting that the results were convincing.

4. Discussion

Numbers of researches have revealed the possible relation between CYP1A1 polymorphisms and cervical cancer risk, yet studies have produced inconsistent conclusion. These inconsistent results prompted our meta-analysis. Meta-analysis is recognized as a useful means of analyzing inconsistent results because it increases sample size and statistical power.[35]

Our results indicated that either MspI or Ile462Val polymorphism of CYP1A1 increased cervical cancer risk, people with C

allele for MspI or Val allele for Ile462Val might be under more cervical cancer risk. Further stratification by ethnicity revealed that the 2 polymorphisms were related with cervical cancer risk in European population, which is consistent with the previous findings made by Sergentanis et al.[21] Unlike the previous research, our study firstly revealed that CYP1A1 MspI variant increased cervical cancer risk in Asian population, yet no significant correlation for Asians was observed for Ile462Val polymorphism.

Moreover, in contrast with the previous Sergentanis et al's study, there are some advantages in our analysis. First, the previous meta-analysis was time limited, for some recent case–control studies were conducted after its publication, especially in the past 2 years.[20,31–34] In total, our study included a total of 2148 cases and 2252 controls for MspI and 1466 cases and 1690 controls for Ile462Val; in contrast, the previous study by Sergentanis et al included 722 cases and 770 controls for MspI, 350 cases and 519 controls for Ile462Val, respectively. The sample size of our study is almost triple as large as theirs, giving a greater power to evaluate the relation. Second, we explored the source of heterogeneity by subgroup analysis or Galbraith plots yet the previous study did not do, the extent of heterogeneity of the previous study might influence the conclusion of the meta-analysis.[36]

Interestingly, our subgroup analysis based on ethnicity indicated that the CYP1A1 Ile462Val polymorphism played different roles in Asian and Caucasian population. In the Caucasian population, people with Ile462Val Val allele might have higher risk of cervical cancer, whereas in Asian, no significant correlation had been found. Different genetic backgrounds might be the cause of the conflicting results in these populations, subsequently resulting in different genetic susceptibility to the same disease. In addition, only 2 studies[12,31] were included for Ile462Val polymorphism in Asian population, the interpretation of results should be done cautiously and further studies were needed to validate the results.

In the meta-analysis, obvious heterogeneity was observed throughout the studies, hence stratified analyses and Galbraith plots were used to discover the sources of heterogeneity. Sample size was found to contribute to substantial heterogeneity for MspI polymorphism. Further Galbraith plots investigation
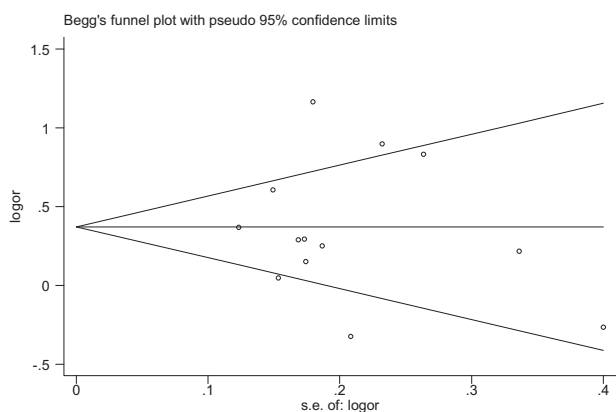

Figure 5. Begg's funnel plot for publication bias test (MspI C allele vs T allele). Each point represents a separate study for the indicated association. Log[or], natural logarithm of odds ratio. Horizontal line, means effect size.

revealed that 4 studies[10,13,15,17] might cause heterogeneity for Ile462Val analysis. After excluding the 4 studies, the pooled ORs with 95% CIs had no significant changes without the heterogeneity. Furthermore, there were 4 studies which the genotype frequencies in the controls significantly deviated from the HWE,[13,14,18,32] our study included the above-mentioned studies but excluded them in the sensitivity analysis. The exclusion of the 4 studies had no effect in our results, which demonstrated the reliability and robustness of the study. Publication bias is another significant problem which has negative effect on the results. In the present study, funnel plots and Begg's and Egger's tests were applied to assess the publication bias. Neither the shape of funnel plot nor Egger's and Begg's tests showed obvious publication bias, indicating that the results of our study were stable and credible.

There were several limitations of this meta-analysis that should be addressed. First, data remained relatively scarce regarding some populations in our study. Second, this meta-analysis was based on unadjusted estimates, while more precise estimates could be included if individual data were available, allowing for adjusted estimates by age, menstrual status, etc. Third, a further evaluation of potential interactions was restricted due to lack of the original data of the reviewed studies, because cervical cancer might be modulated by the interactions between gene and HPV infection as well as environment. In spite of these limitations, our meta-analysis also possessed some advantages. First, a systematic review of the association of CYP1A1 polymorphisms with cervical cancer risk was statistically more effective than any single study. Second, compared to previous meta-analysis the sample size was triple and the latest studies were retrieved. Third, the quality of case–control studies in current meta-analysis was satisfactory and met our inclusion criteria.

In the future, several factors must be considered in designing reliable case–control studies. One of the most important elements is large sample size with adequate power. The control population selection is also crucial due to the possible various genetic backgrounds or different exposure to environmental toxicants. Lastly, to further clarify the relation between the CYP1A1 polymorphisms and cervical cancer risk, more studies including information on the data of HPV infection are demanded.

The results based on the large sample size strongly give the conclusion that the C allele of MspI and Val allele of Ile462Val are risk factors for developing cervical cancer. In the future-ethnicity-specific studies with expanded sample size are required to further estimate the effect size of the association.

Author contributions

Data curation: B. Ding.
Formal analysis: B. Ding.
Funding acquisition: B. Ding.
Investigation: B. Ding.
Methodology: B. Ding.
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Software: W. Sun, Y. Shen.
Supervision: Y. Shen, Y. Cai.
Validation: Y. Shen, M. Ren.
Visualization: W. Sun, M. Ren.
Writing – original draft: B. Ding.
Writing – review & editing: B. Ding, Yunlang Cai, M. Ren, S. Han.

References

[1] World Cancer Report 2014. World Health Organization. 2014. Chapter 5.12.
[2] Scheurer ME, Tortolero-Luna G, Adler-Storthz K. Human papillomavirus infection: biology, epidemiology, and prevention. Int J Gynecol Cancer 2005;15:727–46.
[3] Castellsague X, Munoz N. Chapter 3: Cofactors in human papillomavirus carcinogenesis – role of parity, oral contraceptives, and tobacco smoking. J Natl Cancer Inst Monogr 2003;20–8.
[4] Magnusson PK, Lichtenstein P, Gyllensten UB. Heritability of cervical tumours. Int J Cancer 2000;88:698–701.
[5] Crofts F, Taioli E, Trachman J, et al. Functional significance of different human CYP1A1 genotypes. Carcinogenesis 1994;15:2961–3.
[6] Nebert DW, McKinnon RA, Puga A. Human drug-metabolizing enzyme polymorphisms: effects on risk of toxicity and cancer. DNA Cell Biol 1996;15:273–80.
[7] Crofts F, Cosma GN, Currie D, et al. A novel CYP1A1 gene polymorphism in African-Americans. Carcinogenesis 1993;14:1729–31.
[8] Shah PP, Saurabh K, Pant MC, et al. Evidence for increased cytochrome P450 1A1 expression in blood lymphocytes of lung cancer patients. Mutat Res 2009;670:74–8.
[9] Agundez JA. Cytochrome P450 gene polymorphism and cancer. Curr Drug Metab 2004;5:211–24.
[10] Gutman G, Morad T, Peleg B, et al. CYP1A1 and CYP2D6 gene polymorphisms in Israeli Jewish women with cervical cancer. Int J Gynecol Cancer 2009;19:1300–2.
[11] Nishino K, Sekine M, Kodama S, et al. Cigarette smoking and glutathione S-transferase M1 polymorphism associated with risk for uterine cervical cancer. J Obstet Gynaecol Res 2008;34:994–1001.
[12] Sugawara T, Nomura E, Sagawa T, et al. CYP1A1 polymorphism and risk of gynecological malignancy in Japan. Int J Gynecol Cancer 2003;13:785–90.
[13] Kim JW, Lee CG, Park YG, et al. Combined analysis of germline polymorphisms of p53, GSTM1, GSTT1, CYP1A1, and CYP2E1: relation to the incidence rate of cervical carcinoma. Cancer 2000;88:2082–91.
[14] Taskiran C, Aktas D, Yigit-Celik N, et al. CYP1A1 gene polymorphism as a risk factor for cervical intraepithelial neoplasia and invasive cervical cancer. Gynecol Oncol 2006;101:503–6.
[15] Juarez-Cedillo T, Vallejo M, Fragoso JM, et al. The risk of developing cervical cancer in Mexican women is associated to CYP1A1 MspI polymorphism. Eur J Cancer 2007;43:1590–5.
[16] Joseph T, Chacko P, Wesley R, et al. Germline genetic polymorphisms of CYP1A1, GSTM1 and GSTT1 genes in Indian cervical cancer: associations with tumor progression, age and human papillomavirus infection. Gynecol Oncol 2006;101:411–7.
[17] von Keyserling H, Bergmann T, Schuetz M, et al. Analysis of 4 single-nucleotide polymorphisms in relation to cervical dysplasia and cancer development using a high-throughput ligation-detection reaction procedure. Int J Gynecol Cancer 2011;21:1664–71.
[18] Abbas M, Srivastava K, Imran M, et al. Association of CYP1A1 gene variants rs4646903 (T > C) and rs1048943 (A > G) with cervical cancer in a North Indian population. Eur J Obstet Gynecol Reprod Biol 2014;176:68–74.
[19] Roszak A, Lianeri M, Sowińska A, et al. CYP1A1 Ile462Val polymorphism as a risk factor in cervical cancer development in the Polish population. Mol Diagn Ther 2014;18:445–50.
[20] Matos A, Cindy Castelão C, Pereira da Silva A, et al. Epistatic interaction of CYP1A1 and COMT polymorphisms in cervical cancer. Oxid Med Cell Longev 2016;2016:1–7.
[21] Sergentanis TN, Economopoulos KP, Choussein S, et al. Cytochrome P450 1A1 (CYP1A1) gene polymorphisms and cervical cancer risk: a meta-analysis. Mol Biol Rep 2012;39:6647–54.
[22] Thakkinstian A, McElduff P, DEste C, et al. A method for meta-analysis of molecular association studies. Stat Med 2005;24:1291–306.
[23] Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst 1959;22:719–48.
[24] DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177–88.
[25] Bax L, Ikeda N, Fukui N, et al. More than numbers: the power of graphs in meta analysis. Am J Epidemiol 2009;169:249–55.
[26] Munafo MR, Clark TG, Flint J. Assessing publication bias in genetic association studies: evidence from a recent meta-analysis. Psychiatry Res 2004;129:39–44.
[27] Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629–34.

[28] Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. Biometrics 1994;50:1088–101.

[29] Goodman MT, McDuffie K, Hernandez B, et al. CYP1A1, GSTM1, and GSTT1 polymorphisms and the risk of cervical squamous intraepithelial lesions in a multiethnic population. Gynecol Oncol 2001;81:263–9.

[30] Agorastos T, Papadopoulos N, Lambropoulos AF, et al. Glutathione-S-transferase M1 and T1 and cytochrome P1A1 genetic polymorphisms and susceptibility to cervical intraepithelial neoplasia in Greek women. Eur J Cancer Prev 2007;16:498–504.

[31] Li S, Li G, Kong F, et al. The association of CYP1A1 gene with cervical cancer and additional SNP-SNP interaction in Chinese women. J Clin Lab Anal 2016;30:1220–5.

[32] Jain V, Ratre YK, Amle D, et al. Polymorphism of CYP1A1 gene variants rs4646903 and rs1048943 relation to the incidence of cervical cancer in Chhattisgarh. Environ Toxicol Pharmacol 2017;52:188–92.

[33] Satinder K, Sobti RC, Pushpinder K. Impact of single nucleotide polymorphism in chemical metabolizing genes and exposure to wood smoke on risk of cervical cancer in North-Indian women. Exp Oncol 2017;39:69–74.

[34] Tan YH, Sidik SM, Syed Husain SN, et al. CYP1A1 MspI polymorphism and cervical carcinoma risk in the multi-ethnic population of Malaysia: a case-control study. Asian Pac J Cancer Prev 2016;17:57–64.

[35] Yach D. Meta-analysis in epidemiology. S Afr Med J 1990;78:94–7.

[36] Higgins JP1, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539–58.