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Original Article

Association between CYP1A1 polymorphisms and cervical cancer risk: a meta-analysis in the Chinese population

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Abstract: Background: Although various individual studies have evaluated the correlation between cytochrome P450 1A1 (CYP1A1) polymorphisms and cervical cancer susceptibility, the results remain inconclusive. Therefore, we performed a meta-analysis in the Chinese population to provide comprehensive data on the association between CYP1A1 polymorphisms and cervical cancer. Methods: Eligible studies were identified via databases such as PubMed, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure (CNKI), and Chinese Biology Medicine (CBM), throughout December 2015. Pooled odds ratios (ORs) and 95% confidence intervals (CIs) were used to assess the strengths of these associations. Results: Six studies documenting a total of 1239 cases and 1144 controls were included in this meta-analysis. Overall, no significant association was found between CYP1A1 polymorphisms and cervical cancer risk in the Chinese population. However, in the stratified analysis by geographical areas, a significantly elevated risk of cervical cancer was associated with CYP1A1 Ile462Val variants in Northern China (G vs. A: OR = 1.77, 95% CI = 1.17-2.67; GG vs. AA: OR = 4.13, 95% CI = 1.97-8.67; GG vs. GA+AA: OR = 2.71, 95% CI = 1.37-5.37; GG +GA vs. AA: OR = 2.18, 95% CI = 1.44-3.30). Conclusions: This meta-analysis showed that the CYP1A1 Ile462Val polymorphism may contribute to cervical cancer development in Northern China, and further studies in other ethic groups are required for definite conclusions.

Keywords: Meta-analysis, cytochrome P450 1A1, polymorphism, cervical cancer

Introduction

Cervical cancer is the third most commonly diagnosed cancer and the fourth leading cause of cancer death in females worldwide, accounting for 9% (529,800) of the total new cancer cases and 8% (275,100) of the total cancer deaths among females in 2008 [1]. More than 85% of these cases and deaths occur in developing countries [1]. Squamous cell carcinoma (SCC), adenocarcinoma (ADC), and adenosquamous cell carcinoma (ADSC) are the three most common histological subtypes of cervical cancer. The mechanisms of cervical cancer have not been fully illustrated. Various evidence has shown that certain types of the oncogenic virus human papillomavirus (HPV) are closely related to the occurrence of cervical cancer [2] and its precursor lesion cervical intraepithelial neoplasia (CIN) [3]. However, only a small portion of women go on to develop cervical cancer following infection with HPV [4], and this suggests that other factors, including genetic susceptibility, may also contribute to cervical cancer. In recent years, many common low-penetrance genes have been identified as potential cervical cancer susceptibility genes. Of these genes, an important one is cytochrome P450 1A1 (CYP1A1), which plays an essential role in the metabolic activation of major classes of tobacco procarcinogen such as aromatic amines and polycyclic aromatic hydrocarbons (PAHs) [5]. So it may affect the metabolism of the environmental carcinogens and alter susceptibility to cervical cancer [6-8]. Two functional polymorphisms have been most investigated in recent

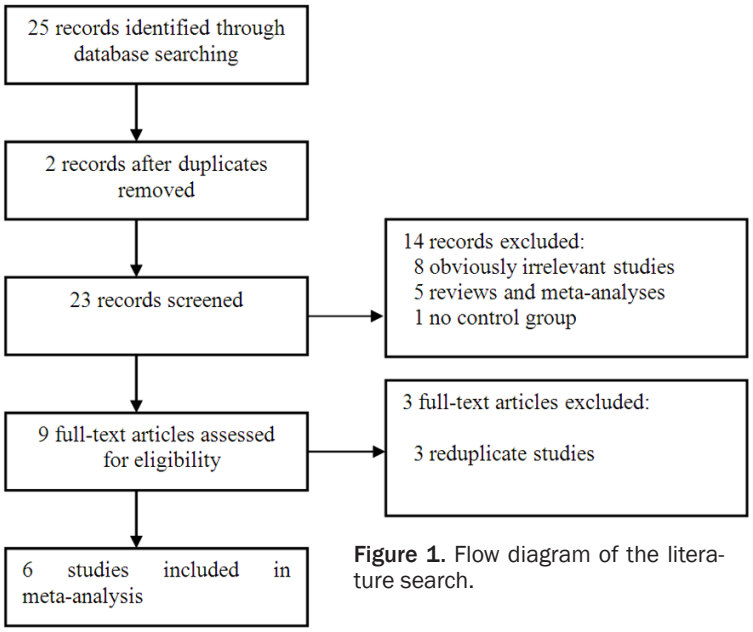

Figure 1. Flow diagram of the literature search.

years. One is the 3801T>C substitution (MspI) in the 3'non-coding region and the other is the 2455A>G (Ile462Val) located in exon 7 [9]. MspI and Ile462Val polymorphisms have three genotypes respectively: wild type (TT, AA), heterozygous type (TC, AG) and homozygous type (CC, GG).

Some studies have attempted to clarify this relationship between CYP1A1 polymorphisms and cervical cancer, but there has been no definite consensus to date. Differences in study results may be due to ethnic and geographical heterogeneity of the patients studied, as well as the limited number of patients included in each study. For addressing the association between CYP1A1 polymorphisms and cervical cancer risk better, we performed a meta-analysis of all eligible studies conducted in the Chinese population.

Materials and methods

Search strategy and selection criteria

We performed a search for studies that examined associations between CYP1A1 polymorphisms and cervical cancer through December 2015. The databases included PubMed, Springer Link, Ovid, Chinese Wanfang Data Knowledge Service Platform, Chinese National Knowledge Infrastructure (CNKI), and Chinese Biology Medicine (CBM). No restriction was imposed on search language. Combinations of keywords, such as, 'P450 1A1', 'CYP1A1', 'cervical cancer', 'Chinese', 'China' and 'Taiwan' were entered as Medical Subject Headings (MeSH) or text words. References in identified studies were also investigated to identify additional studies not indexed by the electronic databases.

Inclusion criteria: (1) they were case-control or cohort studies describing the association between CYP1A1 polymorphisms and cervical cancer, (2) they provided the genetypes in cases and controls, (3) participants were Chinese population. Exclusion criteria: (1) duplicate publications, (2) incomplete data, (3) no control, (4) meta-analyses, letters, reviews, meeting abstract, or editorial articles.

Data extraction

We conducted a systematic review and meta-analysis in accordance with the guidelines provided by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement. Two investigators independently extracted data from all included publications and discrepancy was resolved by consensus or a third reviewer. Titles and abstracts of all identified studies were screened firstly. Full articles were scrutinized if the title and abstract were ambiguous. We extracted study characteristics from each included study. The following information was extracted from each report: first author's surname, year of publication, geographic areas, source of controls (population-based [PB] and hospital-based [HB]), sample size, numbers of cases and controls for the MspI and Ile462Val genotypes. Hardy-Weinberg equilibrium (HWE) in controls was calculated from corresponding genotype distributions.

Statistical analysis

The odd ratios (ORs) together with the 95% confidence intervals (CIs) were used to asse-

Table 1. Characteristics of studies included in the meta-analysis

References	Source of controls	Areas	Polymorphism	Cases number	Controls number	Cases			Controls			HWE	
						Homozygous type	Heterozygous type	Wild type	Homozygous type	Heterozygous type	Wild type	X^2	*P*
Huang 2006	HB	Taiwan	Ile/Val	99	110	36	62	1	14	95	1	62.16	0.000
Li 2009	PB	Shandong	Ile/Val	50	61	14	26	10	38	17	6	3.25	0.071
Li 2009	PB	Shandong	MspI	50	61	21	22	7	29	26	6	0.00	0.961
Geng 2010	PB	Anhui	MspI	176	112	89	78	9	71	36	5	0.03	0.873
Geng 2010	PB	Anhui	Ile/Val	176	112	34	121	21	32	76	4	22.44	0.000
Ding 2011	PB	Jiangsu, Shanghai	Ile/Val	280	280	72	129	79	83	100	97	22.57	0.000
Ding 2011	PB	Jiangsu, Shanghai	MspI	280	280	126	104	50	118	115	47	4.18	0.041
Zhang 2011	HB	Shanxi	Ile/Val	30	30	10	15	5	14	13	3	0.00	0.994
Shen 2013	PB	Xinjiang	MspI	98	98	44	49	5	34	60	4	12.08	0.001

Table 2. Association of the CYP1A1 Ile/Val polymorphism on cervical cancer susceptibility

Analysis model		n	OR_r (95% CI)	OR_f (95% CI)	P_h
G vs. A	Total analysis	5	1.23 (0.80-1.89)	1.08 (0.92-1.27)	0.000
	HB	2	0.91 (0.37-2.27)	0.75 (0.53-1.06)	0.031
	PB	3	1.23 (0.80-1.89)	1.20 (1.00-1.43)	0.002
	South China	2	0.78 (0.50-1.21)	0.85 (0.69-1.04)	0.272
	North China	3	1.77 (1.17-2.67)	1.68 (1.28-2.21)	0.006
GG vs. AA	Total analysis	5	2.06 (0.80-5.33)	1.38 (0.97-1.98)	0.013
	HB	2	1.41 (0.69-6.84)	1.51 (0.37-6.09)	0.285
	PB	3	2.51 (0.71-8.89)	1.38 (0.95-1.99)	0.003
	South China	2	0.92 (0.60-1.41)	0.92 (0.60-1.41)	0.548
	North China	3	4.09 (1.95-8.61)	4.13 (1.97-8.67)	0.750
GG vs. (AA+GA)	Total analysis	5	1.59 (0.71-3.57)	1.01 (0.75-1.38)	0.028
	HB	2	1.61 (0.42-6.16)	1.67 (0.42-6.13)	0.767
	PB	3	1.67 (0.56-4.99)	0.99 (0.72-1.35)	0.006
	South China	2	0.75 (0.52-1.06)	0.75 (0.52-1.06)	0.777
	North China	3	2.63 (1.32-5.24)	2.71 (1.37-5.37)	0.722
(GG+GA) vs. AA	Total analysis	5	1.28 (0.59-2.80)	1.19 (0.93-1.53)	0.000
	HB	2	0.64 (0.10-4.22)	0.46 (0.27-0.80)	0.003
	PB	3	1.88 (1.00-3.54)	1.56 (1.18-2.08)	0.021
	South China	2	0.57 (0.12-2.65)	0.84 (0.61-1.15)	0.000
	North China	3	2.27 (1.24-4.18)	2.18 (1.44-3.30)	0.158

ORr: Odd ratio for random-effect model; ORf: Odd ratio for fixed-effect model; P_h: *P* value for heterogeneity test; North China included Shandong, Anhui, Shanxi; South China included Taiwan, Shanghai, Jiangsu.

ss the strengths of association between CYP1A1 polymorphisms and cervical cancer risk. The presence of between-study heterogeneity was investigated using the chi-square-based Cochran's Q statistic test with *P*-values <0.10. When *P* value of the heterogeneity test was ≥0.10, the fixed-effects model based on the Mantel-Haenszel method was selected to summarize the combined OR and their 95% CI. Otherwise, the random-effects model based on the DerSimonian and Laird method was used. We compared the results of fixed-effects model and random-effects model, to evaluate the sensitivity of our analysis. For the purpose of exploring sources of heterogeneity, stratified analyses according to geographic areas and source of controls were also performed. All statistical analyses were conducted using the Stata 10.0 software (StataCorp, College Station, TX).

Results

Description of included studies

Figure 1 graphically illustrates the trial flow chart. A total of 23 articles that examined the association between CYP1A1 polymorphisms and cervical cancer risk were identified after document duplication removed in different databases. After screening the titles and abstracts, 14 articles were excluded because they were review articles, no control group and irrelevant to the current study. Of the 9 potentially relevant articles [10-17] identified for full study retrieval, three [10-12] were excluded due to duplicate studies. Finally, 6 studies [13-18] met the inclusion criteria. The publication year of involved studies ranged from 2006 to 2013. In total, 1239 cases and 1144 controls were involved in this meta-analysis, which evaluated the relationship between CYP1A1 polymorphisms and cervical cancer in Chinese. The characteristics of the included studies are summarized in **Table 1**.

Meta-analysis results

Concerning CYP1A1 Ile462Val polymorphism, no significant association was found in the total analyses and stratified analysis according to source of controls. However, when we performed a stratified analysis by geographical areas, a significantly elevated risk of cervical cancer was associated with the variants of Ile462Val genotype in the population from North China (for G vs. A: OR = 1.77, 95% CI = 1.17-2.67; for GG vs. AA: OR = 4.13, 95% CI = 1.97-8.67; for GG vs. GA+AA: OR = 2.71, 95% CI = 1.37-5.37; for GG +GA vs. AA: OR = 2.18, 95% CI = 1.44-3.30) (**Table 2**, **Figure 2**). With respect to CYP1A1 MspI polymorphism, it did not reach significance in overall and subgroup analyses (**Table 3**).

Sensitive analysis

In order to compare the difference and evaluate the sensitivity of the meta-analyses, we

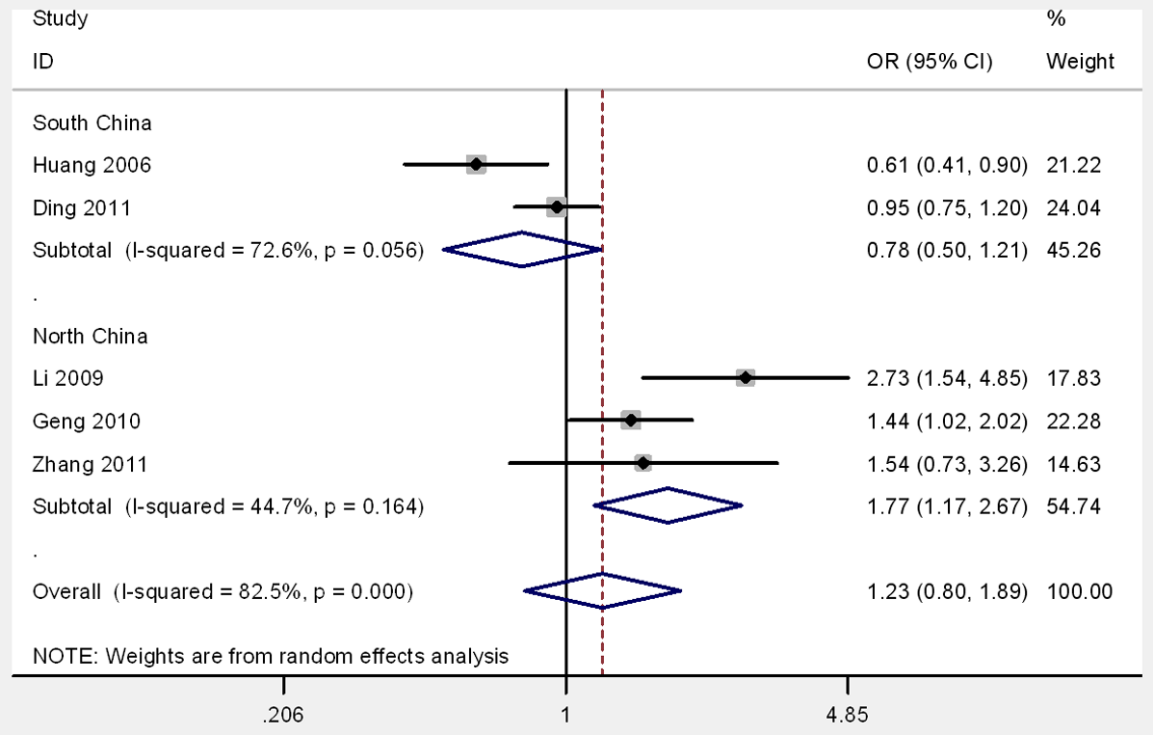

Figure 2. The forest plot of subgroup analysis by geographical areas (CYP1A1 Ile/Val, G vs. A).

Table 3. Association of the CYP1A1 MspI polymorphism on cervical cancer susceptibility

Analysis model		n	OR_r (95% CI)	OR_f (95% CI)	P_h
C vs. T	Total analysis	4	1.06 (0.83-1.35)	1.04 (0.87-1.24)	0.189
	North China	3	1.13 (0.78-1.64)	1.13 (0.88-1.46)	0.515
CC vs. TT	Total analysis	4	1.09 (0.74-1.62)	1.09 (0.74-1.62)	0.853
	North China	3	1.34 (0.66-2.75)	1.34 (0.66-2.75)	0.855
CC vs. (TT+TC)	Total analysis	4	1.14 (0.78-1.64)	1.14 (0.78-1.64)	0.961
	North China	3	1.29 (0.65-2.58)	1.29 (0.65-2.59)	0.951
(CC+TC) vs. TT	Total analysis	4	1.04 (0.70-1.56)	1.02 (0.81-1.29)	0.059
	North China	3	1.12 (0.61-2.06)	1.16 (0.84-1.61)	0.045

ORr: Odd ratio for random-effect model; ORf: Odd ratio for fixed-effect model; P_h: *P* value for heterogeneity test; North China included Shandong, Anhui, Shanxi; South China included Taiwan, Shanghai, Jiangsu.

used both models (the fixed-effects model and random-effects model) to evaluate the stability of the meta-analysis. All the significant results were not materially altered (**Table 2**). Hence, results of the sensitivity analysis suggest that the data in this meta-analysis are relatively stable and credible.

Discussion

Convincing evidence has emerged that individual susceptibility to cervical cancer is partially determined by a number of genetic variations. The relationship between CYP1A1 polymorphisms and cervical cancer risk attracted the attention of both doctors and researchers. To date, a number of studies have reported the association between CYP1A1 polymorphisms and cervical cancer risk, but the results were inconclusive. Recently, there are several published meta-analyses regarding CYP1A1 polymorphisms and cervical cancer risk [19-24]. Of these, two meta-analyses [23-24] found the CYP1A1 polymorphisms showed a positive association with cervical cancer in Caucasians not in Asians, while Xia et al. [22] found significant results in both Caucasians and Asians. Regional and racial difference is one likely reason for the conflict results. Therefore, we conducted this meta-analysis to provide a more precise estimate of the association between CYP1A1 polymorphisms and susceptibility to cervical cancer in the Chinese population, in order to lessen the

impact of regional and racial differences. This is the first meta-analysis demonstrating a variety of associations implicating CYP1A1 polymorphisms and cervical cancer risk in Chinese people.

A total of 5 studies with 1239 cases and 1144 controls were included to systematically explore the association between CYP1A1 polymorphisms and the risk of cervical cancer in this meta-analysis. From the combined statistical results, we did not find a significant association between CYP1A1 polymorphisms and the risk of cervical cancer in the overall analysis. To further explain environmental factors can modulate the risk, a subgroup analysis stratified by geographical areas was performed. We found that G allele, GG genotype carries might have a higher risk of cervical carcinoma in North China, but not in South China. This result suggested that differences in genetic backgrounds as well as in the environment may influence the association between CYP1A1 Ile462Val polymorphism and cervical cancer risk.

Compared to the previous meta-analysis [19-24], the current study included more researches which were conducted in the Chinese population. The effects of gene-environment interactions with respect to cervical cancer risk were also determined by subgroup analyses. Sensitivity analyses confirmed the reliability and stability of the meta-analysis. Therefore, our results indicated a significant association between CYP1A1 Ile462Val polymorphism and cervical cancer in individuals from Northern China.

There were some limitations to this meta-analysis. First, the meta-analysis has been obligatorily based on a rather limited number of studies; nevertheless, it seems that the underlying associations were sizeable enough to reach statistical significance despite the context of relatively low statistical power. Second, this ethnic-specific meta-analysis only included data from Chinese patients with cervical cancer, and thus, our results are only applicable to this ethnic group. Third, since this meta-analysis was based primarily on unadjusted effect estimates and CIs, confounding factors were not controlled. Finally, due to the limitations of funnel plotting, which requires a range of studies, we did not evaluate publication bias in this meta-analysis.

In conclusion, this meta-analysis demonstrates that CYP1A1 Ile462Val polymorphism might contribute to individual susceptibility to cervical cancer in Northern China. Further studies are needed to determine if the CYP1A1 polymorphism confer cervical cancer risk in other ethnic groups. Cervical cancer is a multifactorial disease caused by not only genetic factors but also environmental factors, and studies analyzing gene-gene and gene-environment interactions are required to confirm our results.

Disclosure of conflict of interest

None.

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