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*CYP2E1 Pst*I polymorphism increases cervical neoplasia risk: a meta-analysis

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ABSTRACT. Cytochrome P4502E1 (*CYP2E1*) is a key enzyme in the metabolic activation of many carcinogens, but the roles of *CYP2E1* polymorphisms in cervical neoplasia (CN) are inconclusive. Published case-control cohort studies from the Pubmed, Embase, and China National Knowledge Infrastructure databases were retrieved. Data were extracted and pooled odds ratios with 95% confidence intervals were calculated. Seven studies examining 1097 cases and 1117 controls were included in this meta-analysis. The pooled effect size showed no association between *CYP2E1 Rsa*I and *Dra*I polymorphisms and CN risk in a codominant model. However, using a recessive model, an association between the *Pst*I polymorphism and CN risk was observed (odds ratio: 2.10, 95% confidence interval: 0.96-4.62, P = 0.06), indicating that individuals with the homozygous rare genotype have a higher risk of developing CN compared to those with homozygous wild-type and heterozygous genotypes. When stratified by ethnicity, the *Pst*I polymorphism was significantly correlated with CN susceptibility in non-Asians (odds ratio: 3.74, 95% confidence interval: 1.13-12.43, P =

0.03). This meta-analysis suggests that the *CYP2E1* PstI polymorphism increases the risk of CN in non-Asians.

Key words: Cervical neoplasia; Cytochrome P450; Polymorphism

INTRODUCTION

Cytochrome P4502E1 (CYP2E1) is a member of the cytochrome P450 superfamily and a key enzyme in the metabolic activation of many carcinogens. The *Dra*I, *Pst*I, and *Rsa*I restriction fragment length polymorphism patterns of the *CYP2E1* gene are associated with a predisposition to cancer in humans (Agundez, 2004).

Cervical cancer is the second most common type of cancer among women worldwide. In addition to other risk factors (human papilloma virus infections, chemical reagents exposure, etc.), genetic background independently plays an important role in this process (Au et al., 2003). Over the past decade, several studies have focused on the relationship between *CYP2E1* gene polymorphisms and cervical neoplasia (CN), including high-grade squamous intraepithelial lesion, cervical intraepithelial neoplasia, carcinoma *in situ*, and invasive cervical cancer (Kim et al., 2000; Ferreira et al., 2006; Sierra-Torres et al., 2003, 2006; Nishino et al., 2008; Liu et al., 2009; von Keyserling et al., 2011). However, the results were not conclusive. In this study, we performed a meta-analysis to determine the relationship between *CYP2E1* gene polymorphisms and CN risk.

MATERIAL AND METHODS

Search strategy

A literature search was conducted using the Pubmed, Embase, and China National Knowledge Infrastructure (www.cnki.net) databases. The following search terms were utilized: cytochrome P4502E1 or *CYP2E1*, and gene polymorphism or polymorphism or variant, and cervical squamous intraepithelial lesion or cervical intraepithelial neoplasia or cervical neoplasia or cervical carcinoma or cervical cancer.

Data extraction

Two independent reviewers collected the data according to inclusion and exclusion criteria. For inclusion in the meta-analysis, retrieved articles had to state the number of cases and controls and number of individual genotypes in cases and controls. Exclusion criteria in the meta-analysis were: 1) not a genetic study, 2) duplicated report, and 3) no useful data reported. Unpublished data were not considered. Disagreement was resolved by discussion before reaching a consensus.

Statistical analyses

Categorical variables were presented as the odds ratio (OR) with 95% confidence interval (CI). For *CYP2E1 Dra*I, *Pst*I, and *Rsa*I polymorphisms, the 3 different genotypes were referred to as the homozygous wild-type genotype (c1c1), heterozygous genotype (c1c2), and

homozygous rare genotype (c2c2), respectively. OR1, OR2, and OR3 were calculated as follows: 1) c2c2 *vs* c1c1; 2) c1c2 *vs* c1c1; 3) c2c2 *vs* c1c2. Pairwise differences (OR1, OR2, and OR3) were used to identify the most appropriate genetic model as previously described (Chen et al., 2013). Pooled ORs with 95%CIs were calculated and $P < 0.05$ was considered to be statistically significant. Heterogeneity was evaluated using the Q test. Meta-analysis was conducted using the fixed-effect model when there was no heterogeneity ($P \geq 0.1$). Otherwise, the random-effect model was used. Subgroup analysis was performed by ethnicity. The Begg rank correlation test and the Egger linear regression test were used to identify potential publication bias. All analyses were conducted using Revman 5.0 (Cochrane Collaboration, Oxford, UK) and Stata 11.0 (StataCorp, College Station, TX, USA).

RESULTS

Studies included in the meta-analysis

Forty-two studies were relevant to the search terms. After reviewing the titles, abstracts, and articles, 35 studies were excluded, and 7 studies examining 1097 cases and 1117 controls matched the inclusion criteria (Figure 1). Of the 7 included studies, 6 were published in English and 1 was published in Chinese. These studies were carried out in China, Japan, Korea, USA, Portugal, Colombia, and Germany. Although the ethnicity was not indicated by Sierra-Torres et al. (2006), a non-Asian mixed population in Colombia was assumed. The main features of the included studies are presented in Table 1.

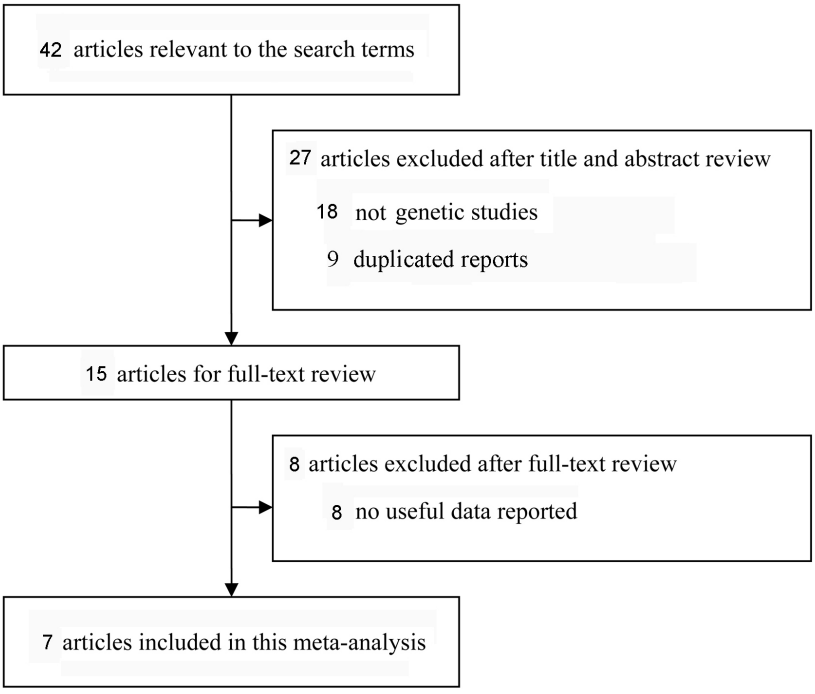

Figure 1. Flow diagram of search process.

Table 1. Main characteristics of included studies.

Reference	Country	Race	Source of case	Genotype	Polymorphisms	Case (N)				Control (N)				HWE (P)
						Total	c1c1	c1c2	c2c2	Total	c1c1	c1c2	c2c2	
Kim 2000	Korea	Asian	CC	PCR+RFLP	*Pst*I	181	116	58	7	181	122	53	6	0.996
					*Dra*1	181	9	67	105	181	16	67	98	0.654
Torres 2003	USA	Caucasian, Hispanic, African American	CIN, CC	PCR+RFLP	*Pst*I	69	58	9	2	72	61	10	1	0.742
Ferreira 2006	Portugal	Caucasian	CIN, CC	PCR+RFLP	*Rsa*I	181	170	11	0	273	259	13	1	0.198
					*Dra*1	181	148	29	4	273	199	66	8	0.682
Torres 2006	Colombia	ND (non-Asian)	HSIL, CIS	PCR+RFLP	*Pst*I	91	73	9	9	92	75	15	2	0.517
Nishino 2008	Japan	Asian	CIN, CC	PCR+RFLP	*Rsa*I	124	74	44	6	117	68	42	7	0.988
					*Dra*1	124	43	70	11	117	49	56	12	0.789
Liu 2009	China	Asian	CIN, CC	PCR+RFLP	*Rsa*I	62	46	15	1	45	32	12	1	0.994
Keyserling 2011	Germany	Caucasian	HSIL CIN, CC	LDR+PCR	*Pst*I	389	367	21	1	337	311	26	0	0.762

HWE: Hardy-Weinberg equilibrium; PCR: polymerase chain reaction; RFLP: restriction fragment length polymorphism; HSIL: high-grade squamous intraepithelial lesion; CIN: cervical intraepithelial neoplasia; CIS: carcinoma *in situ*; CC: cervical cancer; ND: not described; LDR: ligation-detection reaction; c1c1: homozygous wild-type genotype; c1c2: heterozygous genotype; c2c2: homozygous rare genotype

Quantitative synthesis

After calculating OR1, OR2, and OR3, the most appropriate genetic models for the *Pst*I, *Rsa*I, and *Dra*I polymorphisms were the recessive model, codominant model, and co-dominant model, respectively. In the codominant model, no association was observed between the *Rsa*I and *Dra*I polymorphisms and CN risk (data not shown). However, using the recessive model, the pooled effect size showed an association between the *Pst*I polymorphism and CN risk (c2c2 *vs* c1c1+c1c2, OR: 2.10, 95%CI: 0.96-4.62, P = 0.06, Figure 2), indicating that individuals with the homozygous rare genotype had a higher, but not significant, risk of CN compared to those with the homozygous wild-type genotype and heterozygous genotype. In subgroup analysis by ethnicity, the results indicated that the PstI polymorphism was significantly correlated with CN susceptibility in non-Asians (c2c2 *vs* c1c1+c1c2, OR: 3.74, 95%CI: 1.13-12.43, P = 0.03, Figure 2).

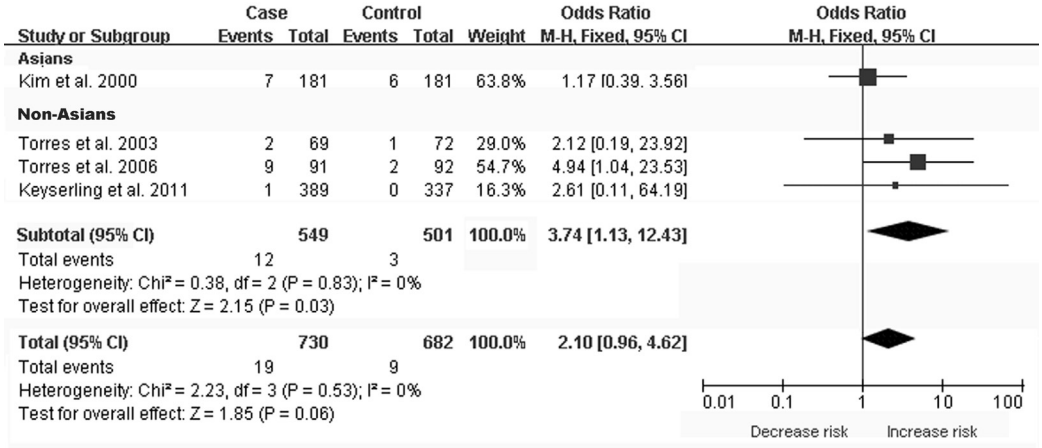

Figure 2. Forest plots of OR with 95%CI for the association between *CYP2E1 Pst*I polymorphism and cervical neoplasia risk (c2c2 *vs* c1c1+c1c2).

Analyses of heterogeneity, sensitivity, and publication bias

Significant heterogeneity was not observed between all studies in c2c2 *vs* c1c1+c1c2 for the *Pst*I polymorphism. When stratified by ethnicity, no heterogeneity was observed in non-Asians. After exclusion of each study, the pattern of the pooled effect size was still significant for the *Pst*I polymorphism. Publication bias was not observed based on the Begg rank correlation test (P = 0.734) and the Egger linear regression test (P = 0.547).

DISCUSSION

CYP2E1, a key enzyme in the metabolic activation of several carcinogens, contributes to the development of CN. Recently, the association between *CYP2E1* polymorphisms and CN risk has received increasing attention because of its potential in transcriptional regulation of gene expression (Agundez, 2004). However, in this meta-analysis, the *CYP2E1 Rsa*I and *Dra*I polymorphisms were not found to be correlated with CN risk in a codominant model (the most

appropriate), which is consistent with the results of previous studies (Kim et al., 2000; Ferreira et al., 2006; Liu et al., 2009).

Notably, the *Pst*I restriction site polymorphism in the 5' flanking region of the *CYP2E1* gene has been shown to affect the transcriptional regulation of gene expression for several carcinogens (Carriere et al., 1996), which is associated with cancer development (El-Zein et al., 1997; Hildesheim et al., 1997). Sierra-Torres et al. (2006) indicated that the *Pst*I homozygous variant (c2/c2) conferred an overall greater than 6-fold increase in the risk for high-grade squamous intraepithelial lesion in a non-Asian population, even after adjusting for wood smoke exposure and human papillomavirus-infection; however, no significant effect of the c2/c2 genotype on the overall risk for CC was reported in a Korean population by Kim et al. (2000), suggesting the role of *Pst*I in CN susceptibility may depend on ethnicities.

In this meta-analysis, we observed an association between the *Pst*I polymorphism and CN risk in a recessive model (the most appropriate) with no heterogeneity, indicating that individuals with the homozygous rare genotype (c2/c2) had a higher risk of CN than those with the homozygous wild-type genotype (c1/c1) and heterozygous genotype (c1/c2), although statistical significance was not reached. Further results confirmed that the *Pst*I polymorphism was significantly correlated with CN susceptibility in non-Asians. Moreover, after excluding each study, the pattern of the pooled effect size remained significant. Publication bias was not suggested in the present study, possibly because of the deliberate search strategy and data extraction methods used.

However, there were some limitations to this meta-analysis. First, the sample size was small. Second, the pooled estimates were not adjusted for confounding factors. Third, lack of the original data in the studies limited further analysis.

In conclusion, although the pooled estimates should be interpreted with caution, our meta-analysis results suggest that the *CYP2E1 Pst*I polymorphism is associated with CN risk in non-Asians. However, large sample size studies in different populations, as well as more detailed data regarding individual differences and environmental factors, are warranted.

Conflicts of interest

The authors declare no conflict of interest.

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