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Association of *CYP1A1 Msp*I polymorphism with oral cancer risk in Asian populations: a meta-analysis

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ABSTRACT. Numerous studies regarding the association between the *CYP1A1 Msp*I polymorphism and oral cancer risk in Asian populations have shown controversial results. To get a more precise estimation of this relationship, we conducted a comprehensive meta-analysis. PubMed, the Cochrane Library, Elsevier Science Direct, Web of Knowledge, the Chinese National Knowledge Infrastructure, VIP, and Wan Fang Med Online were searched. Pooled odds ratios (ORs) with 95% confidence intervals (95%CIs) were calculated using fixed-effects or random-effects models. Heterogeneity among studies was assessed using the Cochran Q test and I^2 statistics. Twelve articles including 1925 oral cancer patients and 2335 controls were ultimately included in the meta-analysis. Overall, the meta-analysis showed that the *CYP1A1 Msp*I polymorphism was associated with oral cancer risk in Asians (m1/m1 *vs* m2/m2: OR = 0.46, 95%CI = 0.30-070, P_{OR} = 0.000; m1/m1 *vs* m1/m2+m2/m2: OR = 0.70, 95%CI = 0.51-0.98, P_{OR} = 0.037; m1/m1+m1/m2 *vs* m2/m2: OR = 0.48, 95%CI = 0.35-0.65, P_{OR} = 0.000). Subgroup

analyses showed that the control source (hospital-based or population-based), the genotyping method [polymerase chain reaction (PCR) or PCR-restriction fragment length polymorphism], the country in which the study was conducted, and Hardy-Weinberg equilibrium (Yes or No) were positively related to the association. Sensitivity analysis suggested that the overall results showed no significant change in three genetic models when any one study was removed, and publication bias was undetected by the Egger test. The *CYP1A1 Msp*I polymorphism may be associated with oral cancer risk in Asian populations.

Key words: *CYP1A1*; Polymorphism; Oral cancer; Meta-analysis

INTRODUCTION

Oral cancer, including cancer of the lip, buccal mucosa, tongue, gingival, mouth floor, and hard palate (Wang et al., 2014), is one of the most common head and neck cancers and results in serious damage to a population's oral health, mainly on account of its low survival rate (Rogers et al., 2009) and poor life quality (Nordgren et al., 2008; Infante-Cossio et al., 2009). It has been reported that oral cancer is the eighth most commonly diagnosed cancer worldwide, and is particularly prevalent in Asia. Epidemiologic studies have profiled several important etiologic risk factors including tobacco smoking and chewing, excess alcohol consumption, and betel quid chewing (Warnakulasuriya, 2009). Although considerable effort has been made, the mechanisms that lead to the initiation and progression of oral cancer remain unclear.

Currently, it is generally accepted that genetic factors also participate in the development of oral cancer. Cytochrome P450 1A1 (CYP1A1), a vital phase I xenobiotic metabolizing enzyme, is widely distributed in many epithelial tissues (Totlandsdal et al., 2010; Newland et al., 2011). It is involved in the biotransformation of several tobacco-related pro-carcinogens into reactive electrophilic intermediate metabolites that can damage DNA (Singh et al., 2014). The *CYP1A1 Msp*I polymorphism has been reported to be related to higher risk of tobacco-related lung cancer (Hashibe et al., 2003). The numerous studies on the association between the *CYP1A1 Msp*I polymorphism and oral cancer risk in Asian populations have presented conflicting results. Meta-analysis is a powerful tool for summarizing the results from different studies by producing a single estimate of the major effect with enhanced precision (Long et al., 2012). Therefore, we conducted the present meta-analysis to better quantify the magnitude of the association between the *CYP1A1 Msp*I polymorphism and oral cancer risk.

MATERIAL AND METHODS

Search methods and key words

We searched the electronic databases of PubMed, the Cochrane Library, Elsevier Science Direct, the Web of Knowledge, the Chinese National Knowledge Infrastructure (CNKI), VIP, and Wan Fang Med Online for relevant studies without time or language restrictions. The key words were as follows: (CYP1A1 OR CYP1A1 *Msp*I OR Cytochrome P450 CYP1A1) AND (oral cancer OR oral squamous cell carcinoma OR oral carcinoma OR head and neck). The references of the retrieved articles were searched manually for related publications referring to the association between the *CYP1A1 Msp*I polymorphism and oral cancer risk.

Inclusion and exclusion criteria

For inclusion in the meta-analysis, the studies must have: 1) assessed the association between the *CYP1A1 Msp*I polymorphism and oral cancer risk; 2) had a case-control design; and 3) provided sufficient data to estimate odds ratios (ORs) with their 95% confidence intervals (95%CIs). When the same population was reported by more than one article, only the most recent or complete study was included in the final meta-analysis.

We excluded studies that: 1) were not relevant to cancer research; 2) were review articles; 3) were reports without available data; and 4) duplicated or overlapped with other publications.

Data extraction

Data were extracted independently by two review authors (Ji-Liang Xu and Lei Sun) using a previously prepared data extraction form according to the inclusion criteria mentioned above. The following information was extracted from each study: the first author's surname; the year of publication; the source of the controls; the genotyping method; the country of origin; the ethnicity; the number of genotypes and the frequencies of the *CYP1A1 Msp*I polymorphism in the cases and controls; the total number of cases and controls; and evidence of Hardy-Weinberg equilibrium (HWE). Disagreements between the two review authors were resolved by consensus with a third reviewer (Rong Xia).

Statistical analysis

To evaluate the association between the *CYP1A1 Msp*I polymorphism and oral cancer risk in Asian populations, we calculated ORs with their corresponding 95%CIs. Pooled ORs were obtained for the following three genetic models: m1/m1 *vs* m2/m2, m1/m1 *vs* m1/m2+m2/m2, and m1/m1+m1/m2 *vs* m2/m2. HWE was tested using the chi square (χ^2) statistical method to assess the goodness-of-fit (Lourenço et al., 2011; Zhang et al., 2014). All effect sizes and 95%CIs were calculated on the basis of fixed- or random-effects models. The significance of any discrepancies in the estimates of the effects was assessed by means of the Cochran's Q test for heterogeneity and by a measure of I^2. I^2 values of 25, 50, and 75% were taken as evidence of low, moderate, and high heterogeneity, respectively. If there was no statistical difference with regards to heterogeneity ($P > 0.05$), a fixed-effects (Mantel-Haenszel method) model was used to analyze the data; otherwise, a random-effects model (DerSimonian-Laird method) was applied. To explore the sources of heterogeneity, subgroup analysis was also carried out according to the country source (HB or PB), the genotyping method [polymerase chain reaction (PCR) or PCR-restriction fragment length polymorphism (PCR-RFLP)], the country in which the study was conducted (East Asia or Southeast Asia) and Hardy-Weinberg equilibrium (Yes or No). Publication bias was evaluated using the Egger's linear regression test. An asymmetric funnel plot or $P < 0.05$ by the Egger test was taken to suggest possible publication bias (Fang et al., 2013). All the statistical tests were performed using the STATA program (version 11.0).

RESULTS

Characteristics of included studies

Based on the data collection method and the search strategy, initially 896 articles

were identified through comprehensive database searching. According to the inclusion and exclusion criteria mentioned above, and after screening the type, title, abstract, and full text of each article, 12 relevant articles were ultimately included in the meta-analysis (Sato et al., 1999; Tanimoto et al., 1999; Sreelekha et al., 2001; Kao et al., 2002; Anantharaman et al., 2007; Cha et al., 2007; Sam et al., 2008; Chatterjee et al., 2010; Guo et al., 2012; Shukla et al., 2012; Shukla et al., 2013; Singh et al., 2014). In total, those articles included 1925 oral cancer patients and 2335 controls. A total of 884 articles were excluded for the following reasons: there was publication duplication, the article was irrelevant, the full text was not available, or the article was a review. All cases were histologically confirmed. Among the 12 included studies, 10 were HB, and only 2 were PB. The sample size of the cases ranged from 72 to 446 while the sample size of the controls ranged from 60 to 727. Detailed data for the 12 included studies are listed in Table 1.

Table 1. Characteristics of the included studies (N = 12).

Study	Year	Control source	Genotyping methods	Country	Ethnicity	Cases			Controls			HWE (Control)
						m1/m1	m1/m2	m2/m2	m1/m1	m1/m2	m2/m2	
Tanimoto	1999	HB	PCR-RFLP	Japan	Asian	32	53	15	62	30	8	Yes
Sato	1999	HB	PCR	Japan	Asian	56	55	31	62	65	15	Yes
Streelekha	2001	PB	PCR	Indian	Asian	48	50[a]	NM	50	10 [a]	NM	Yes
Kao	2002	HB	PCR-RFLP	China	Asian	40	52	14	53	79	14	No
Anantharaman	2007	HB	PCR	Indian	Asian	205	195	46	331	345	51	No
Cha	2007	HB	PCR-RFLP	Korea	Asian	20	30	22	49	97	17	No
Sam	2008	HB	PCR-RFLP	Indian	Asian	77	86	24	115	91	14	Yes
Chatterjee	2010	PB	PCR	China	Asian	30	46	26	49	32	19	No
Guo	2012	HB	PCR	China	Asian	NM	185[b]	115	NM	237[b]	63	Yes
Shukla	2012	HB	PCR-RFLP	Indian	Asian	45	60	45	72	72	6	No
Shukla	2013	HB	PCR-RFLP	Indian	Asian	60	30	10	48	46	6	Yes
Singh	2014	HB	PCR-RFLP	Indian	Asian	60	45	17	50	58	19	Yes

HWE = Hardy-Weinberg equilibrium; HB = hospital-based; PB = population-based; PCR = polymerase chain reaction; PCR-RFLP = PCR-restriction fragment length polymorphism; NM not mentioned [a]m1/m2+m2/m2; [b]m1/m1+m1/m2.

Meta-analysis results

Heterogeneity of studies

Prior to conducting the meta-analysis on the association between the *CYP1A1 Msp*I polymorphism and oral cancer risk in Asian populations, we primarily assessed the heterogeneity of the three genetic models: m1/m1 *vs* m2/m2, m1/m1*vs* m1/m2+m2/m2, and m1/m1+m1/m2 *vs* m2/m2. As shown in Table 2, which lists the main results of the meta-analysis, there was marked heterogeneity for all the included studies in the three genetic models: m1/m1 *vs* m2/m2 (I^2 = 67.7%, $P_{Q\text{-test}}$ = 0.001), m1/m1 *vs* m1/m2+m2/m2 (I^2 = 80.9%, $P_{Q\text{-test}}$ = 0.000), and m1/m1+m1/m2 *vs* m2/m2 (I^2 = 60.2%, $P_{Q\text{-test}}$ = 0.005). Therefore, a random-effects model was used to analyze the data.

Overall effects and subgroup analysis

Table 2 presents the main results of the meta-analysis. For all the included studies, a marked association between the *CYP1A1 Msp*I polymorphism and oral cancer risk in Asian populations was seen in m1/m1 *vs* m2/m2 (OR = 0.46, 95%CI = 0.30-070, P_{OR} = 0.000) (Figure 1), m1/m1 *vs* m1/m2+m2/m2 (OR = 0.70, 95%CI = 0.51-0.98, P_{OR} = 0.037) (Figure

2), and m1/m1+m1/m2 *vs* m2/m2 (OR = 0.48, 95%CI = 0.35-0.65, P_{OR} = 0.000) (Figure 3). Subgroup analyses showed that the control source (HB or PB), the genotyping method (PCR or PCR-RFLP), the country in which the study was conducted, and HWE (Yes or No) were positively related to the association.

Table 2. Results of the general population and subgroup analysis in the different models.

CYP1A1	m1/m1 *vs* m2/m2			m1/m1 *vs* (m1/m2+m2/m2)			(m1/m1+m1/m2) *vs* m2/m2		
	OR (95% CI)	P_1[a]	P_2[b]	OR (95% CI)	P_1[a]	P_2[b]	OR (95% CI)	P_1[a]	P_2[b]
Total	0.46 (0.30–0.70)	0.001	0.000	0.70 (0.51–0.98)	0.000	0.037	0.48 (0.35–0.65)	0.005	0.000
Control source									
HB	0.45 (0.28–0.73)	0.001	0.001	0.82 (0.60–1.13)	0.000	**0.228**	0.46 (0.33–0.64)	0.004	0.000
PB	0.45 (0.21–0.94)	-	0.035	0.32 (0.20–0.50)	0.101	0.000	0.69 (0.35–1.34)	-	**0.269**
Genotyping methods									
PCR	0.57 (0.41–0.79)	0.440	0.001	0.56 (0.30–1.05)	0.000	**0.069**	0.52 (0.41–0.65)	0.343	0.000
PCR-RFLP	0.42 (0.22–0.82)	0.000	0.010	0.79 (0.90–1.23)	0.000	**0.300**	0.43 (0.24–0.76)	0.002	0.004
Country									
East Asia	0.43 (0.30–0.61)	0.543	0.000	0.64 (0.40–1.03)	0.005	**0.064**	0.46 (0.36–0.58)	0.416	0.000
Southeast Asia	0.48 (0.22–1.07)	0.000	**0.072**	0.76 (0.47–1.21)	0.000	**0.247**	0.47 (0.23–0.94)	0.001	0.032
HWE									
Yes	0.55 (0.38–0.78)	0.062	0.001	0.67 (0.37–1.20)	0.000	**0.177**	0.50 (0.39–0.64)	0.336	0.000
No	0.38 (0.19–0.76)	0.001	0.006	0.74 (0.50–1.09)	0.006	**0.123**	0.40 (0.21–0.77)	0.001	0.006

OR = odds ratio; 95%CI = 95% confidence interval; HB = hospital-based; PB = population-based; PCR = polymerase chain reaction; PCR-RFLP = PCR-restriction fragment length polymorphism; HWE = Hardy-Weinberg equilibrium [a]P_1 value of the Cochran Q test for heterogeneity [b]P_2 value of test of OR.

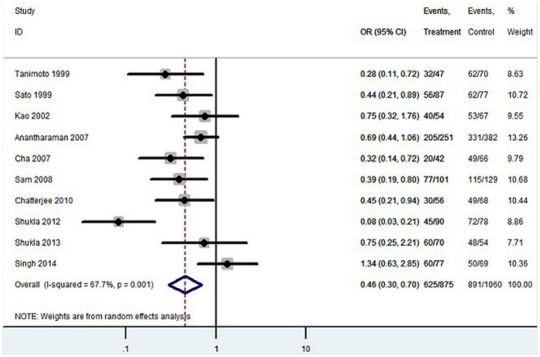

Figure 1. Forest plot of the genetic model m1/m1 *vs* m2/m2.

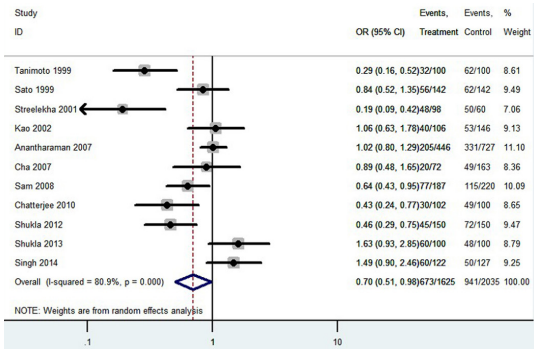

Figure 2. Forest plot of the genetic model m1/m1*vs* m1/m2 + m2/m2.

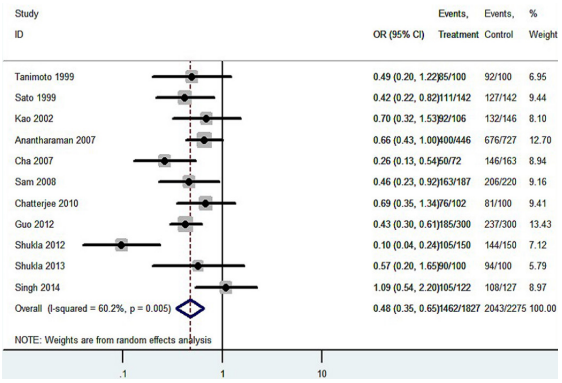

Figure 3. Forest plot of the genetic model m1/m1+m1/m2 *vs* m2/m2.

Sensitivity analysis

To assess the stability of the results of this meta-analysis, sensitivity analyses were used by random-effect methods, and the overall results showed no significant change in the three genetic models for any one study.

Publication bias

Egger's linear regression test was utilized to evaluate the symmetry of the funnel plot used to assess publication bias. The shape of the funnel plot did not display obvious asymmetry in any of the three genetic models. Furthermore, the Egger's test provided statistical evidence of funnel plot symmetry (m1/m1 *vs* m2/m2: t = -1.22, P = 0.258; m1/m1 *vs* m1/m2+m2/m2: t = -1.48, P = 0.173; m1/m1+m1/m2 *vs* m2/m2: t = -0.47, P = 0.651).

DISCUSSION

Oral cancer has been identified as the eighth most commonly diagnosed cancer worldwide (Alaizari and Al-Maweri, 2014). It results in serious damage to a person's oral aesthetic sensibility and function. It is well known that oral cancer is the result of the interaction between environmental and genetic factors; smoking tobacco and drinking alcohol are considered serious risk factors for oral cancer (Chatterjee et al., 2010). The nitrosamines and heterocyclic amines found in cigarettes are definite carcinogens. Such compounds require biotransformation and detoxification when they enter the human body, and the phase I metabolism activating enzyme cytochrome P450 (CYP) 1A1 is involved in the process (Cordero et al., 2010). The enzyme cytochrome P450 1A1 is encoded by the *CYP1A1* gene and regulated by the *CYP1A1 Msp*I polymorphism sites. The full-length *CYP1A1* gene is 5810 bp and is located on human chromosome 15. The CYP1A1 enzyme, which is also known as aryl hydrocarbon hydroxylase, is involved in the active metabolism of benzo (α) pyrene and other polycyclic aromatic compounds (Katsanou et al., 2014; Liu et al., 2014). *CYP1A1 Msp*I sites are polymorphic and can cause changes in the enzyme activity of CYP1A1, leading to individual differences in susceptibility to oral cancer.

Matthias et al. (1998) conducted the first case-control study of a Caucasian population

in Germany to explore the relationship between the *CYP1A1* MspI polymorphism and oral cancer risk. To date, several studies focusing on this association have been published, but have reported conflicting evidence about the association between the *CYP1A1 Msp*I polymorphism and oral cancer risk. To obtain a more precise evaluation of this association, it was necessary to perform a comprehensive meta-analysis.

In this meta-analysis, we ultimately included 12 articles comprising a total of 1925 oral cancer cases and 2335 controls. We calculated pooled ORs with their corresponding 95%CIs for the following three genetic models: m1/m1 *vs* m2/m2, m1/m1 *vs* m1/m2+m2/m2, and m1/m1+m1/m2 *vs* m2/m2. For the Asian populations, a marked association between the *CYP1A1 Msp*I polymorphism and oral cancer risk was seen. Subgroup analyses showed that the control source (HB or PB), the genotyping method (PCR or PCR-RFLP), the country in which the study was conducted, and HWE (Yes or No) were positively related to the association. Sensitivity analysis suggested that the overall results showed no significant change in the three genetic models when any one study was removed, and publication bias was undetected by the Egger test.

Our study had several limitations, which should be noted. First, in total, the sample size of the studies included in our meta-analysis was relatively small, particularly in the subgroup analysis of hospital-based controls. Only one study from the population-based controls was included, resulting in the possibility of bias risk. Therefore, more studies with large sample sizes are needed to more accurately assess the association. Second, the original data on certain genotypes such as m1/m1 and m2m2 in some studies were missing (Sreelekha et al., 2001; Guo et al., 2012). These studies only provided data about the number of patients with the m1/m1+m1/m2 or m1/m2+m2/m2 genotypes, which may have caused instability in the meta-analysis. Third, it has been shown that smoking tobacco, drinking alcohol, and chewing betel quid may be important etiologic risk factors for oral cancer. In addition, several other genetic polymorphisms have been assessed by meta-analysis and are regarded as possible risk factors for oral cancer. *MTHFR* C677T, *XRCC1* Arg194Trp, and *CYP2E1* Rsa I/Pst I polymorphisms are associated with oral cancer risk (Niu et al., 2012; Jia et al., 2014; Liu and Shen, 2014). Moreover, in this meta-analysis, gene-gene and gene-environment interactions were not discussed, so further studies are required to investigate those aspects.

Despite these limitations, our meta-analysis determined that the *CYP1A1 Msp*I polymorphism may be associated with oral cancer risk in Asian populations. However, to more accurately investigate the association between the *CYP1A1 Msp*I polymorphism and oral cancer risk in Asian populations, large, multi-center, multi-ethnic case-control studies are required.

Conflicts of interest

The authors declare no conflict of interest.

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