CYP1A1 MspI polymorphism and the risk of oral squamous cell carcinoma: Evidence from a meta-analysis

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Abstract. Numerous case-control studies have investigated whether the *CYP1A1* gene polymorphism is involved in the occurrence of oral squamous cell carcinoma (OSCC); however, the conclusions are inconsistent. In order to further explore the correlation and obtain a strong conclusion, a meta-analysis was performed to systematically assess the association between the *CYP1A1* MspI polymorphism and risk of OSCC. In the present meta-analysis, the odds ratios (ORs) and the corresponding 95% confidence intervals (CIs) were used to assess the association. The statistical analyses were performed with STATA 11.0 software. The heterogeneity was assessed by Q test and I^2 test. The final analysis included 10 studies of 1,505 cases and 1,967 controls. The overall results suggested that the *CYP1A1* MspI polymorphism was significantly associated with an increased risk of OSCC (CC+TC vs. TT: OR, 1.31; 95% CI, 1.01-1.70; P=0.043; CC vs. TC+TT: OR, 2.38; 95% CI, 1.58-3.58; P<0.001; CC vs. TT: OR, 2.52; 95% CI, 1.60-3.96; P<0.001; and C vs. T: OR, 1.45; 95% CI, 1.15-1.83; P<0.001). In a stratified analysis by ethnicity, a statistically significant correlation existed in the Asian population, but not mixed-race and Caucasian populations. In conclusion, despite several limitations, the present meta-analysis established that the *CYP1A1* MspI polymorphism may be a risk factor for OSCC, particularly among the Asian population.

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Introduction

Oral cancer is one of the most common cancers in the world and causes a considerable problem to global public health due to high mortality rates and disfigurement (1,2). Approximately 90% of malignant oral neoplasms are oral squamous cell carcinomas (OSCC), followed by adenocarcinoma and, rarely, other types (3). Despite advances in treatment for OSCC, the 5-year survival rate remains poor (4-6). Therefore, investigating the risk factors and developing the early diagnosis for treatment and prevention of OSCC are urgently required.

Epidemiological studies have shown that OSCC is associated with high tobacco use and alcohol consumption (7-9). However, not all individuals with tobacco and alcohol habits develop these fatal diseases, suggesting that individual genetic factors may also be involved in disease etiology. The research results of the human genome project have demonstrated that 99.9% of the genomes are the same between individuals, with little difference in single nucleotide polymorphisms (SNPs). Therefore, interindividual differences in expression of SNPs may contribute to the variability in the risk towards various types of malignancies, including OSCC. Currently, the published evidence shows that there were significant associations of gene polymorphisms with the susceptibility of numerous cancers, such as *GST* and *CYP1A1* gene polymorphisms with squamous cell carcinoma of the lungs and head and neck cancer, and the 8q24 rsl3281615 polymorphism with the risk of breast cancer (10-15). However, the associations of OSCC with *CYP1A1* MspI genetic variants are inconsistent (16-25).

Cytochrome P4501A1 (CYP1A1) is a member of the CYP family that participates in the metabolism of xenobiotics and endogenous compounds, encoding for the aryl hydrocarbon hydrolase, which is involved in the activation of polycyclic aromatic hydrocarbon (PAHs) and aromatic amines, and is expressed in oral tissue (26). CYP1A1 is able to activate carcinogenic PAHs and its expression and function are affected by gene polymorphisms, with more attention focused on the

association of cancer and CYP1A1. According to the previous studies, the *CYP1A1* gene has several SNPs that may alter the activities of their enzymes and increase carcinogen activation and yield to carcinogenicity. The first allele variants of the *CYP1A1* gene (*CYP1A1**2A or *CYP1A1* MspI) are the most common polymorphisms, which are a transition from T to C in the 3' non-coding region resulting in the introduction of an MspI restriction site and association with an increase in enzyme activity, thus affecting the risks of carcinoma (27,28). The MspI restriction site polymorphism results in three genotypes; wild-type (TT), heterozygous variant (TC) and homozygous variant (CC) (29).

Considering the significance of the *CYP1A1* MspI polymorphism in the occurrence and development of malignancies, including OSCC, the role of the *CYP1A1* MspI polymorphism in OSCC patients was systematically evaluated through a meta-analysis.

Materials and methods

Search strategy. Pubmed, Web of Science, China National Knowledge Infrastructure (CNKI) and WANFANG databases were searched without language limitations, and the last search was updated on May 3, 2014. The CNKI and WANFANG databases provided studies in Chinese and English. The search process was designed to primarily identify all the relevant studies and the search strategies are as follows: (CytochromeP450 1A1 or P4501A1 or *CYP1A1* or *CYP1A1**2A or MspI or T3801C), (genotype or polymorphism or allele or variant) and (oral squamous cell carcinoma or OSCC or mouth neoplasm or oral cancer or oral carcinoma or oral tumor). The results were screened by two investigators according to the title, key words, abstract and type of study, and irrelevant studies were removed. A manual review of the references cited in the selected studies was undertaken to retrieve studies that may have been missed in the search. Subsequently, the relevant studies were downloaded and further screened to identify the potentially eligible studies. When essential data were not provided in the original studies, every effort was made to contact the authors for confirmation.

Inclusion/exclusion criteria. All the relevant case-control studies were included, irrespective of languages. In the meta-analysis, the following criteria were set and reviewed by two independent investigators: i) Studies should be concerned with the association of the *CYP1A1* MspI polymorphism with oral squamous cell carcinoma risk, and OSCC cases were histologically confirmed; ii) each trial should be an observational study (case-control or cohort) of human subjects; iii) studies must offer the size of the sample, and the genetic distribution or the original information that can help infer the results; and iv) when multiple studies from a particular research group reported data from overlapping samples, the study reporting the largest dataset was included.

Exclusion criteria included: i) Review studies, editorials or meta-analysis; ii) case reports or lack of case-control study; and iii) studies that estimated the risk of secondary tumors, recurrence or response to treatment. For a conflicting evaluation, an agreement was reached following a discussion. When a consensus could not be attained, another investigator was invited to resolve the dispute and a final result was generated by the majority. All the studies were viewed in accordance with the criteria defined above for further analysis.

Data extraction. All the data were independently reviewed and extracted with a standardized data-collection form by two investigators (Shang Xie and Chongdai Luo). Differences between the investigators were solved by discussion and when necessary, through consultation. The following characteristics were collected from each study: Ethnicity, country, sample size, control source, matching contents, Hardy-Weinberg equilibrium and the gene distribution of cases and controls. When the data were not clear or presented by the author in the publication, contact for further details was attempted.

Quality assessment. The Newcastle-Ottawa scale (NOS) quality evaluation criteria was performed to evaluate the methodological quality of the included studies and those with poor quality were excluded (30,31). The NOS system categorizes into three dimensions, which are selection, comparability and exposure (case-control studies), and the three dimensions included eight items. A star system was used to assess the quality of all the included studies. The NOS ranges from zero (the lowest) to nine (the highest) stars. The assessment was performed independently by two investigators and the discrepancy was resolved by a discussion.

Statistical analysis. All the data management and analysis for the meta-analysis was performed with STATA 11.0 software (Stata Corporation, College Station, TX, USA). The odds ratio (ORs) with corresponding 95% confidence intervals (CIs) were used to estimate the associations between the *CYP1A1* MspI polymorphism and OSCC risks. In order to calculate the heterogeneity of the studies, the χ^2 test was used and $P<0.05$ was considered to indicate a statistically significant difference (32). The inconsistency index, I^2, was calculated to assess the variation caused by heterogeneity. When the P-value of the heterogeneity test was >0.10, the fixed-effects model was performed to calculate the combined OR, which assumed the same homogeneity of effect size across all the studies. When the P-value of the heterogeneity test was <0.10, the between-study heterogeneity was considered to indicate a statistically significant difference, and a random effect model was used to estimate the pooled OR. The funnel plot was used to test the underlying publication bias, and the funnel plot asymmetry was estimated by Egger's linear regression (33). Sensitivity analyses were performed to identify the influence of the individual studies on the combined OR. In the analysis, each study was excluded to assess whether stability between the remaining studies was reached.

Results

Characteristics of included studies. A total of 212 studies were retrieved by the literature search. In total, 171 studies were excluded as they were irrelevant to *CYP1A1* MspI, OSCC or gene polymorphisms, and were not human studies. Two other potential eligible studies were obtained by screening the references of reviews. Following more detailed evaluations for the remaining 43 potential eligible studies,

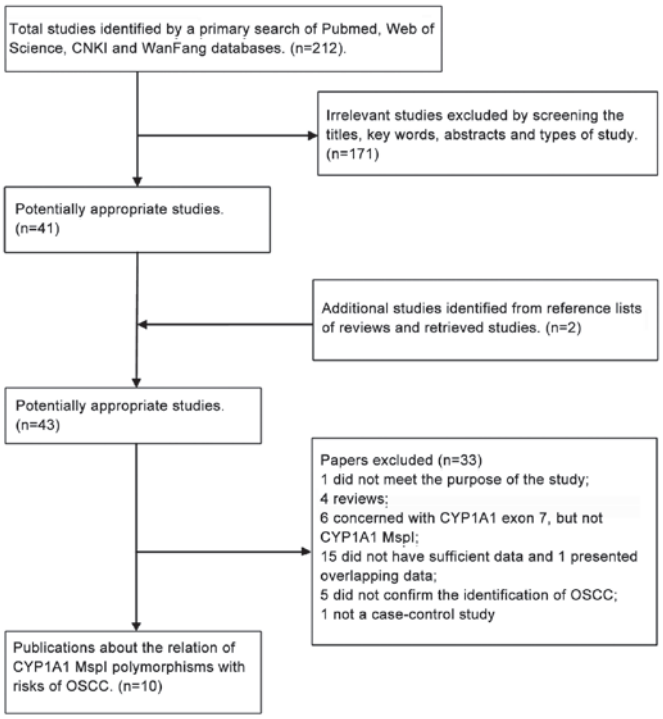

Figure 1. Flow diagram of the included/excluded studies.

one study obtained from references did not meet the purpose of the meta-analysis (34), and four were reviews (26,35-37). Following this, six studies only regarded *CYP1A1* exon 7, but not *CYP1A1* MspI (38-43). Another sixteen studies were excluded as one of them presented overlapping data (44) and 15 failed to provide sufficient genotyping data (45-59). In addition, there were five studies excluded as the cases were diagnosed as oral cancer only, and the identification of OSCC was not confirmed (60-64). One study was excluded as the study only contained the cases and lacked the controls (65). Finally, 10 studies conformed to the inclusion criteria and were included in the meta-analysis of *CYP1A1* MspI (16-25). The search process is shown in Fig. 1.

A database with regard to the information extracted from each included study was established. Summaries of these studies are presented in Table I, which includes the first author, ethnicity, country, number and characteristics of cases and controls, and other necessary information. Of the 10 studies included in the meta-analysis, seven studies were performed in Asian countries, two in American countries and one in European countries. The number of cases and controls in the studies included varied from 38-446 and 81-727, respectively. The frequency of the *CYP1A1* MspI homozygous variant allele (C/C) in the cases group varied from 0-30.0%, and 0-10.5% for the control group.

Results of quality assessment. According to the NOS system, all the included case-control studies were awarded a maximum of four stars in selection, two stars in comparability and three stars in exposure. The results of the assessment for the included studies ranged from six to eight stars (Table I), indicating that all the included studies were moderate-high qualities.

Test of heterogeneity and quantitative synthesis. A heterogeneity analysis was performed of the dominant (CC+TC vs. TT),

Table I. Characteristics of the excluded studies evaluating the effects of the *CYP1A1* MspI polymorphism on the susceptibility of OSCC.

			Quality assessment	Cases, n			Controls, n						HWE
Year	First author (ref)	Ethnicity	(NOS)	TT	TC	CC	TT	TC	CC	Cases, n	Controls, n	Control source	Matching	(control)
1999	Sato (18)	Asian	8/9	56	55	31	62	65	15	142	142	Healthy	Age, gender	0.738
1999	Tanimoto (16)	Asian	8/9	32	53	15	62	30	8	100	100	Hospital	Age, gender	0.126
2002	Kao (21)	Asian	6/9	40	52	14	53	79	14	106	146	Hospital	NA	0.046
2003	Gronau (22)	Caucasian	8/9	55	18	0	100	35	1	73	136	Hospital	Age, gender, tobacco and alcohol habits	0.260
2006	Gattás (23)	Mixed-race	8/9	25	13	(TC+CC)	63	39	(TC+CC)	38	102	Hospital	Age, gender	NA
2007	Anantharaman (25)	Asian	8/9	205	195	46	331	345	51	446	727	Hospital, dental clinic	Age, gender, tobacco habits	0.002
2007	Cha (24)	Asian	6/9	20	30	22	49	97	17	72	163	Hospital	NA	0.002
2008	Losi-Guembarovski (20)	Mixed-race	7/9	55	27	9	53	23	5	91	81	Hospital	Age, gender, tobacco habits	0.262
2008	Sam (19)	Asian	8/9	77	86	24	115	91	14	187	220	Hospital	Age, gender	0.475
2012	Shukla (17)	Asian	8/9	45	60	45	72	72	6	150	150	Hospital	Age, gender, tobacco habits	0.020

NA, not available; HWE, Hardy-Weinberg equilibrium; NOS, Newcastle-Ottawa scale.

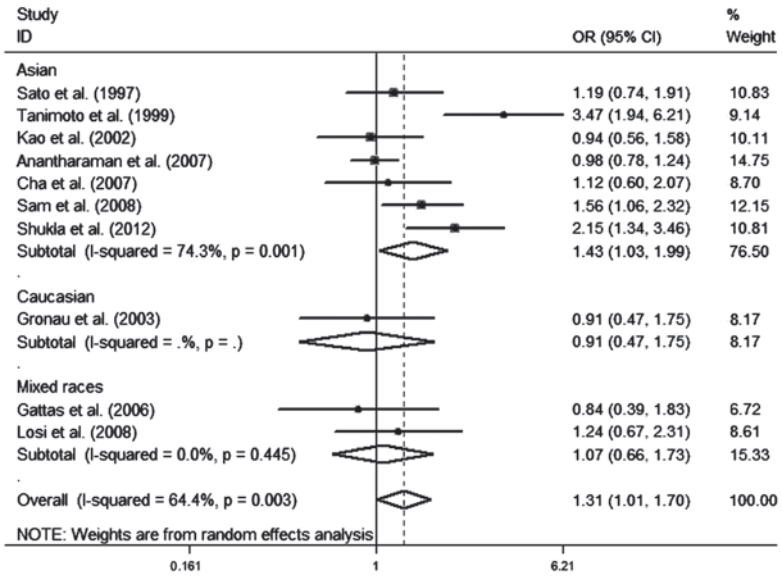

Figure 2. Forest plot of the association between the *CYP1A1* MspI polymorphism with the risk of OSCC (dominant model: CC+TC vs. TT; stratified by ethnicity). OSCC, oral squamous cell carcinoma.

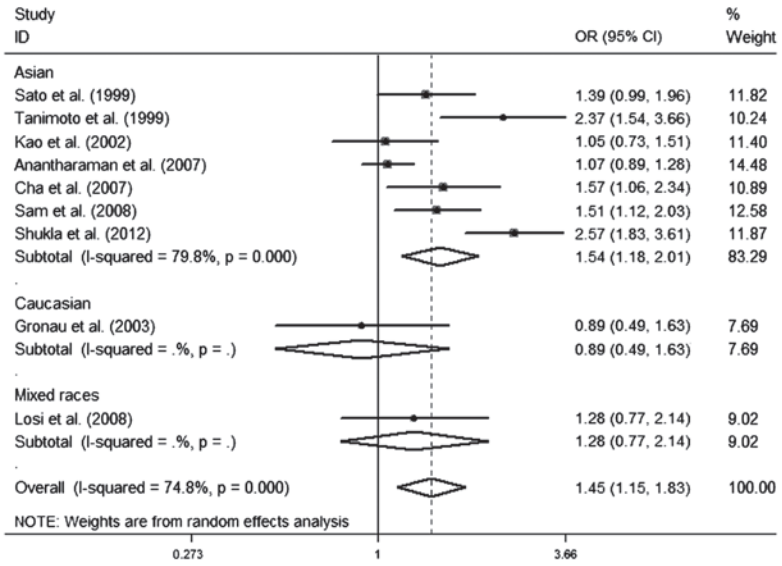

Figure 3. Forest plot of the association between the C allele of the *CYP1A1* MspI polymorphism and the risk of OSCC (allele model: C vs. T, stratified by ethnicity). OSCC, oral squamous cell carcinoma.

recessive (CC vs. TC+TT) and additive models (CC vs. TT), and the results are shown in Table II. Owing to the overall heterogeneity observed in the dominant (CC+TC vs. TT: I^2=64.4%, P=0.003), recessive (CC vs. TC+TT: I^2=57.9%, P=0.015) and additive models (CC vs. TT: I^2=61.0%, P=0.009), random-effect models were used to synthesize the data, respectively (Table II). The overall results suggested that the *CYP1A1* gene variants (TC+CC or CC) have an increased risk of OSCC compared to those individuals with the positive homozygous carriers (TT). In order to further explore the observed heterogeneity, subgroup analyses were performed by ethnicity and 10 studies were divided into three subgroups: the Asian, Caucasian and mixed-race groups. However, the heterogeneity remained in the Asian population, but not in the mixed-race and Caucasian populations. For ethnicity, a significant increased risk was associated with the genetic variants among the Asian population, while no associations were found among the mixed ethnic and Caucasian populations (Fig. 2 and Table II).

As for the C and T allele of *CYP1A1* MspI, the results of the heterogeneity test and quantitative synthesis of C vs. T model, the pooled OR, 1.447; 95% CI, 1.146-1.827; I^2=74.8%; $P_{Q\text{- test}}$=0.000; and P<0.05 (Fig. 3) suggested that the C allele was significantly associated with an increased OSCC risk.

Publication bias analysis. The Begg's funnel plot was used to assess the possible publication bias. The Egger's linear regression is for the quantitative evaluation of the meta-analysis funnel plot symmetry and the results were as follows: i) CC+TC vs. TT model: Begg's test, P=0.858>0.05 and Egger's linear

Table II. Main results of the heterogeneity test in the meta-analysis.

CYP1A1 MspI	No. of studies (case/controls)	CC+TC vs. TT				CC vs. TC+TT				CC vs. TT			
		OR (95% CI)	I^2 (%)	$P_{Q\text{-test}}$	P-value	OR (95% CI)	I^2 (%)	$P_{Q\text{-test}}$	P-value	OR (95% CI)	I^2 (%)	$P_{Q\text{-test}}$	P-value
Total ethnicity	3372 (1405/1967)	1.31 (1.01, 1.70)	64.4	0.003	0.043	2.38 (1.58, 3.58)	57.9	0.015	<0.001	2.52 (1.60, 3.98)	61.0	0.009	<0.001
Caucasian	209 (73/136)	0.91 (0.47, 1.75)	–	–	0.775	0.62 (0.02, 15.39)	–	–	0.770	0.60 (0.02,15.07)	–	–	0.758
Asian	2851 (1203/1648)	1.43 (1.03, 1.99)	74.3	0.001	0.032	2.52 (1.60, 3.98)	67.0	0.006	<0.001	2.70 (1.63, 4.49)	69.5	0.003	<0.001
Mixed-race	312 (129/183)	1.07 (0.66, 1.73)	0.0	0.445	0.798	1.67 (0.54, 5.20)	–	–	0.378	1.73 (0.55, 5.51)	–	–	0.351

OR, odds ratio; CI, confidence interval; I^2, variation in OR attributable to heterogeneity; $P_{Q\text{-test}}$ >0.05, heterogeneity was not statistically significant; P>0.05, no statistical significance.

regression test: t=0.85, P=0.419>0.05; ii) CC vs. TC+TT model: Begg's test, P=0.711>0.05 and Egger's linear regression test: t=1.05, P=0.335>0.05; iii) CC vs. TT model: Begg's test, P=0.266>0.05 and Egger's linear regression test: t=1.20, P=0.276>0.05; and iv) C vs. T allele model: Begg's test, P=1.000>0.05 and Egger's linear regression test: t=0.99, P=0.354>0.05. The data of the four models indicated that the funnel plots were symmetrical for all.

Sensitivity analysis. In order to assess the stability of the results and reflect the influence of each study on the pooled ORs, sensitivity analysis was performed by excluding each case-control study individually. All the estimates were included between the lower and upper CI limits, suggesting the stability of the results in the meta-analysis.

Discussion

Oral cancer is cancer of the mouth, including squamous cell carcinoma, adenocarcinoma and verrucous carcinoma. Different histopathological types of cancers may have different genetic susceptibilities, such as *CYP1A1* MspI polymorphism being a risk factor of squamous cell carcinoma of the lung, but varies in different histological types (13,66). Therefore, it is more reasonable to separately evaluate the association of gene polymorphisms with OSCC, oral adenocarcinoma and other cancer types.

To the best of our knowledge, this is the first meta-analysis to assess the association between the *CYP1A1* MspI genetic variants and risks of OSCC. Although there are two previous meta-analyses (67,68) regarding the *CYP1A1* MspI polymorphism and oral cancer, the results did not involve the single histopathological type and therefore cannot represent the association of *CYP1A1* MspI with the risks of OSCC. Oral cancer is known to include different histological types, including squamous cell carcinoma and adenocarcinoma, which may yield to different susceptibilities of cancer. Therefore, the previous studies' results may regard all types of oral carcinoma for only one selection. To obtain a powerful conclusion regarding the risks of OSCC and *CYP1A1* MspI polymorphism, a systematical meta-analysis was performed in the present study.

In the present meta-analysis, for the overall data the results of ORs and 95% CIs showed that the C allele of *CYP1A1* MspI played a significant role in the carcinogenesis process resulting in OSCC, and as for the genotypes, CC and CT+CC were identified as risk factors for developing OSCC. All the results indicated that the *CYP1A1* MspI polymorphism may increase the risks of OSCC. The heterogeneity among studies was observed in the dominant, recessive, additive and C versus T allele models, respectively. Following the subgroup analysis by ethnicity, the heterogeneity was not removed indicating that other factors, such as age, gender, country, source of controls, lifestyle, social status, smoking and alcohol habits, may also yield to heterogeneities.

In the subgroup analysis by ethnicity, a key association between the *CYP1A1* MspI polymorphism and risks of OSCC in the Asian population was confirmed in all four models, but not in the mixed-race and Caucasian populations, suggesting that the *CYP1A1* MspI gene variants may increase the OSCC susceptibility in the Asian population. The differences may be

attributed to different ethnicities sharing different gene-gene and gene-environmental backgrounds. Nevertheless, the conclusion regarding the mixed-race and Caucasian populations is not of a sufficient power for the few studies and subjects.

Publication biases were evaluated by funnel plots and their symmetries, and were further assessed by Begg's test and Egger's linear regression tests, respectively. No clear biases were observed, indicating that the publication may yield to little effects on the results. The sensitivity analysis showed that the importance of the corresponding pooled ORs was not significantly changed, suggesting that the pooled ORs were stable.

However, several limitations should be addressed. First of all, the original studies included data regarding the Asian, Caucasian and mixed-race populations, and only one study regarding Caucasian and two mixed-race populations. Secondly, a subgroup analysis was performed by ethnicity, but the other factors, such as gender, age, source of control and country, were not performed due to data limitations. Thirdly, the Asian population included India, Japan and China, but other Asian countries were not included. Fourthly, heterogeneity existed, which may weaken the reliability of the conclusions. In view of these limitations, the results should be considered with caution.

Overall, despite several limitations the results of the present analysis showed a clear association between the *CYP1A1* MspI polymorphism and OSCC risk, particularly among the Asian population. Future studies focusing on the *CYP1A1* MspI polymorphism containing larger sample sizes and well-matched criteria are required to improve the credibility of the conclusions.

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