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Association of *CYP1A1* and *GSTM1* Polymorphisms With Oral Cancer Susceptibility

A Meta-Analysis

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Abstract: Our meta-analysis was aimed to evaluate the association of *CYP1A1* and glutathione-*S*-transferase M1 (*GSTM1*) polymorphisms with oral cancer susceptibility.

The related articles were searched in PubMed, Embase, and CNKI databases. Fifty eligible studies were included in our meta-analysis. Odds ratios (ORs) with 95% confidence intervals (CIs) were used to evaluate the relationship of *CYP1A1* (rs4646903 and rs1048943) and *GSTM1* polymorphisms with oral cancer risk. A random-effects model or fixed-effects model was employed depending on the heterogeneity.

In overall analysis, *CYP1A1* rs4646903 polymorphism was associated with the risk of oral cancer (CC vs TT: OR 1.65, 95% CI 1.33–2.05; CC vs TC+TT: OR 1.77, 95% CI 1.48–2.11; C vs T: OR 1.17, 95% CI 1.07–1.28), whereas rs1048943 showed no obvious association with oral cancer susceptibility. Moreover, subgroup analysis by ethnicity demonstrated that rs4646903 and rs1048943 both related with increased risk of oral cancer in Asians. Moreover, the analysis based on source of control suggested that rs4646903 could increase the risk for oral cancer in both population- and hospital-based populations, whereas no remarkable relationship of rs1048943 with oral cancer susceptibility was observed. For *GSTM1* gene, null genotype appeared to be a risk factor for oral cancer (null vs present: OR 1.23, 95% CI 1.12–1.34), which was also proved in the subgroup analysis.

The results demonstrated that *CYP1A1* rs4646903 and null genotype of GSTM1 polymorphisms might serve as risk factors for oral cancer.

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Abbreviations: CI = confidence interval, GSTM1 = glutathione-*S*-transferase M1, HWE = Hardy–Weinberg equilibrium, OR = odds ratio, PAH = polycyclic aromatic hydrocarbon, SNP = single nucleotide polymorphism.

INTRODUCTION

Oral cancer is one of the most common cancers in the world,[1] the incidence of which has increased obviously in the last few years among different populations.[2,3] It is generally considered that genetic polymorphisms and environmental factors including cigarette smoking, alcohol consumption, and betel quid chewing are of particular importance in the etiology of oral cancer.[4,5]

Genetic polymorphisms is prevalent and play a viral role in human diseases. Recently, the relationship of genetic polymorphisms and the risk of cancers have been researched widely. Among the genes, cytochrome *P450 1A1* (also known as *CYP1A1*) gene, located on chromosome 15, encodes aryl hydrocarbon hydrolase, which involves in metabolism of polycyclic aromatic hydrocarbons (PAHs).[6] For *CYP1A1*, rs4646903 polymorphism, a T to C transition in the 3′ noncoding region (a thymine/cytosine point mutation), has been confirmed to be related with the high risk of lung and head and neck cancers.[7,8] In addition, *CYP1A1* rs1048943 polymorphism, an amino acid substitution from isoleucine to valine at codon 462, shows the effects of enhancing catalytic activity and increasing the risk for lung cancer.[9,10] For glutathione-*S*-transferase M1 (*GSTM1*), the polymorphism includes present genotype and null genotype, which are associated with abnormal function of GSTμ enzyme that is an important member in the detoxification of carcinogens in tobacco smoking.[11,12] Moreover, the null genotype was reported to associate with increased risk of gastric, bladder, colon, and lung cancers.[13–16] It is worth mentioning that CYP1A1, phase I enzyme, and GSTM1, phase II enzyme, could affect individual variability in the metabolism of chemical substances and finally affect the susceptibility to cancers through increasing the activity of xenobiotic metabolizing enzymes.[17–20]

Up to now, several epidemiological studies have focused on the association of *CYP1A1* and *GSTM1* polymorphisms with oral cancer susceptibility.[2,21–69] However, the results remained conflicting. Therefore, the meta-analysis was carried out to gain more comprehensive evidences for the association.

METHODS

Search Strategy

The relevant articles were searched in PubMed, Embase, and CNKI databases using the keywords "*CYP1A1*" or "cytochrome P450 1A1," "*GSTM1*" or "glutathione-*S*-transferase M1," "polymorphism," and "oral cancer." The reference lists in retrieved papers were also screened manually for potential articles. All the selected studies should comply with the following inclusion criteria: case–control studies, studies about the association of *CYP1A1* and *GSTM1* polymorphisms with oral cancer susceptibility, and adequate data for estimating an odds ratio (OR) with 95% confidence interval (CI). When the same data existed in >1 publication, the largest or most recent publication was included. This study is a meta-analysis and does not involve populations; ethical approval was not required.

TABLE 1. Characteristics of Studies on *CYP1A1* Polymorphisms

First Author	Year	Country	Ethnicity	Control Source	Genotyping Method	Cases	Controls
CYP1A1 rs4646903							
Anantharaman [55]	2007	India	Asian	Hospital	PCR	446	727
Cha [45]	2007	Korea	Asian	Hospital	PCR-RFLP	72	163
Chatterjee [52]	2010	India	Asian	Population	PCR	102	100
Cordero [59]	2010	Chile	Other	Population	PCR-RFLP	48	124
Gattas [44]	2006	Brazil	Other	Hospital	PCR-RFLP	38	102
Gronau [41]	2003	Germany	White	Hospital	PCR-RFLP	73	129
Guo [53]	2012	China	Asian	Population	PCR	300	300
Kao	2002	China	Asian	Hospital	PCR-RFLP	106	146
Losi-Guembarovski [51]	2008	Brazil	Other	Hospital	PCR-RFLP	91	81
Lourenço	2011	Brazil	Other	Population	PCR	29	142
Matthias [46]	1998	UK	White	Hospital	PCR	122	205
Sato [21]	1999	Japan	Asian	Population	PCR	142	142
Sharma [61]	2010	India	Asian	Population	PCR-RFLP	73	201
Shukla [68]	2013	India	Asian	Hospital	PCR-RFLP	100	100
Shukla [63]	2012	India	Asian	Population	PCR	150	150
Singh	2013	India	Asian	Population	PCR	122	127
Sreelekha [39]	2001	India	Asian	Population	PCR	98	60
Tanimoto [37]	1999	Japan	Asian	Hospital	PCR-RFLP	100	100
CYP1A1 rs1048943							
Amtha [58]	2009	Indonesia	Asian	Hospital	PCR-RFLP	81	162
Hahn [40]	2002	Germany	White	Population	PCR	94	92
Kao	2002	China	Asian	Hospital	PCR-RFLP	106	146
Katoh [38]	1999	Japan	Asian	Hospital	Multiplex PCR	92	147
Leichsenring [24]	2006	Brazil	Other	Population	PCR	126	60
Lourenço	2011	Brazil	Other	Population	PCR	29	142
Marques	2006	Brazil	Mixed	Hospital	PCR-RFLP	231	212
Matthias [46]	1998	UK	White	Hospital	PCR	124	193
Sato2	2000	Japan	Asian	Population	Allele-specific PCR	142	142
Sharma [61]	2010	India	Asian	Population	PCR-RFLP	73	501
Singh	2013	India	Asian	Population	PCR	122	127
Sugimura [43]	2006	Japan	Asian	Hospital	PCR-RFLP	122	241
Varela-Lema [56]	2008	Spain	White	Hospital	PCR	53	66
Xie [42]	2004	Puerto Rico	Other	Population	PCR	132	143

HWE = Hardy–Weinberg equilibrium, PCR = polymerase chain reaction, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism.

Data Extraction

The following data were extracted from each study by 2 independent investigators: name of first author, publication date, country of origin, ethnicity, source of controls, genotyping methods, total number of cases and controls, genotype frequencies in case and control groups and Hardy–Weinberg equilibrium (HWE). Disagreements were solved by a discussion between the 2 investigators. The characteristics of the included articles were shown in Tables 1 and 2.

Statistical Analysis

We applied crude ORs with corresponding 95% CIs to evaluate the association of *CYP1A1* and *GSTM1* polymorphisms with oral cancer susceptibility. Heterogeneity assumption was estimated by the χ^2-based Q test. When $P < 0.05$, which indicated significant heterogeneity among studies, the pooled OR was calculated using the random-effects model; otherwise, the fixed-effects model was used. The pooled results of *CYP1A1* were analyzed under the following genetic models: 22 versus 11, 22 + 12 versus 11, 22 versus 11 + 12, 2 versus 1, and 12 versus 11. For *GSTM1*, null versus present and present versus null models were used. Sensitivity analysis was conducted to measure the stability of pooled results. Publication bias was assessed by Begg funnel plot and Egger test. HWE was checked by χ^2 test. Statistical data were performed using the STATA software (version 12.0; Stata Corporation, Texas, Tex, USA).

RESULTS

Study Characteristics

As displayed in Figure 1, a total of 243 articles were searched through databases in which 132 articles were excluded for obvious irrelevance, 34 articles were excluded for unrelated single nucleotide polymorphisms (SNPs), and 27 articles were eliminated for not having controls and original genotype data. Finally, 50 articles were included in our meta-analysis.[2,21–69]

TABLE 2. Principle Characteristics of Studies on *GSTM1* Null/Present

First Author	Year	Country	Ethnicity	Control Source	Genotyping Method	Cases	Controls
GSTM1 Null/Present							
Anantharaman [55]	2007	India	Asian	Hospital	PCR	451	727
Bathi [57]	2009	India	Asian	Hospital	PCR	30	100
Buch [29]	2002	America	White	Population	PCR	297	450
Cha [45]	2007	Korea	Asian	Hospital	PCR-RFLP	72	209
Chatterjee [52]	2010	India	Asian	Population	Multiplex-PCR	102	100
Chen [62]	2010	China	Asian	Population	PCR-RFLP	164	274
Cordero [59]	2010	Chile	Other	Population	PCR-RFLP	48	124
Coutelle [48]	1997	France	White	Hospital	PCR	21	37
Deakin [25]	1996	UK	White	Hospital	PCR	40	577
Drummond [30]	2004	Brazil	Other	Hospital	PCR	70	82
Gattas [44]	2006	Brazil	Other	Hospital	PCR-RFLP	38	102
Gronau [41]	2003	Germany	White	Hospital	PCR-RFLP	73	129
Hahn [40]	2002	Germany	White	PB	PCR	94	92
Hatagima [34]	2008	France	White	Hospital	PCR-RFLP	231	212
Huang [35]	2006	China	Asian	PB-HB	Multiplex PCR	87	87
Hung [50]	1997	China	Asian	Population	PCR	41	123
Jourenkova-Mironova [26]	1999	Swiss	White	Hospital	PCR	67	172
Katoh [38]	1999	Japan	Asian	Hospital	Multiplex PCR	92	147
Kietthubthew [28]	2001	Thailand	Asian	Population	PCR	53	53
Liu [32]	2005	China	Asian	Population	PCR	114	100
Losi-Guembarovski et al [51]	2008	Brazil	Other	Hospital	Multiplex-PCR	91	81
Lourenço	2011	Brazil	Other	Population	Multiplex-PCR	29	142
Majumder [54]	2005	India	Asian	Hospital	PCR-RFLP	310	348
Masood [64]	2011	Pakistan	Asian	Hospital	PCR-SSCP	228	150
Matthias [46]	1998	UK	White	Hospital	PCR	122	178
Mondal [67]	2013	India	Asian	Hospital	PCR	124	140
Nomura [49]	2000	Japan	Asian	Hospital	PCR	114	33
Park [27]	2000	America	Other	Population	PCR	63	132
Park [27]	2000	America	White	Population	PCR	101	212
Park [36]	1997	America	White	Population	3 Primer-based PCR	133	133
Sato2	2000	Japan	Asian	Population	PCR	142	142
Sharma [33]	2006	India	Asian	Population	PCR	40	87
Sharma [61]	2010	India	Asian	Population	Quantitative real-time assay	73	201
Shukla [68]	2013	India	Asian	Hospital	PCR	94	100
Shukla [63]	2012	India	Asian	Population	PCR-RFLP	150	141
Sikdar	2004	India	Asian	Hospital	PCR	256	259
Singh	2013	India	Asian	Population	PCR	122	127
Sreelekha [39]	2001	India	Asian	Population	PCR	98	60
Sugimura [43]	2006	Japan	Asian	Hospital	PCR-RFLP	122	241
Tanimoto [37]	1999	Japan	Asian	Hospital	PCR-RFLP	100	100
Varela-Lema [56]	2008	Spain	White	Hospital	PCR	53	130
Xie [42]	2004	Puerto Rico	Other	Population	PCR	132	143
Yadav [65]	2012	India	Asian	Population	Multiplex PCR	136	270
Zhang [69]	2012	China	Asian	Population	PCR	600	600

GSTM1 = glutathione-*S*-transferase M1, PB = population-based study, PCR = polymerase chain reaction, PCR-RFLP = PCR-restriction fragment length polymorphism, PCR-SSCP = single-strand conformation polymorphism.

Meta-Analysis

The results were shown in Tables 3 and 4. Overall, *CYP1A1* rs4646903 polymorphism was closely associated with the increased risk of oral cancer according to the pooled ORs (CC vs TT: OR 1.65, 95% CI 1.33−2.05; CC vs TC+TT: OR 1.77, 95% CI 1.48−2.11; C vs T: OR 1.17, 95% CI 1.07−1.28). Using the CC+TC versus TT model and the TC versus TT

model, we did not find any significant association (Table 3). Subgroup analysis by ethnicity showed similar association of rs4646903 with oral cancer in Asians in the same genetic models tested (CC vs TT: OR 1.70, 95% CI 1.35−2.13; CC vs TC+TT: OR 1.83, 95% CI 1.52−2.20; C vs T: OR 1.17, 95% CI 1.06−1.29) but not in whites. Further subgroup analysis by source of control revealed that rs4646903 was significantly

TABLE 3. *CYP1A1* Polymorphisms and Oral Cancer Risk

SNPs (Number of Cases/Controls)		22 vs 11		22 + 1 vs 11		22 vs 11 + 12		2 vs 1		12 vs 11	
		OR (95% CI)	Ph/P_{OR}	OR (95% CI)	Ph/P_{OR}	OR (95% CI)	Ph/P_{OR}	OR (95% CI)	Ph/P_{OR}	OR (95% CI)	Ph/P_{OR}
CYP1A1 rs4646903											
Ethnicity	Asian (1811/2316)	1.70 (1.35, 2.13)	0.073/<0.001	1.10 (0.98, 1.23)	0.050/0.111	1.83 (1.52, 2.20)	0.056/<0.001	1.17 (1.06, 1.29)	0.018/0.002	1.01 (0.88, 1.15)	0.242/0.925
	White (195/334)	0.75 (0.11, 5.13)	0.832/0.770	1.13 (0.71, 1.78)	0.328/0.609	0.73 (0.11, 5.01)	0.861/0.770	1.09 (0.71, 1.68)	0.308/0.690	1.01 (0.88, 1.15)	0.317/0.548
	Other (206/449)	1.32 (0.58, 2.99)	0.597/0.502	1.22 (0.89, 1.68)	0.723/0.214	1.14 (0.52, 2.50)	0.399/0.502	1.23 (0.87, 1.75)	0.935/0.245	1.29 (0.82, 2.03)	0.448/0.265
Source of control	Hospital (1148/1753)	1.53 (1.15, 2.05)	0.854/0.004	1.04 (0.91, 1.19)	0.443/0.584	1.67 (1.26, 2.20)	0.789/<0.001	1.12 (0.99, 1.25)	0.239/0.068	1.00 (0.87, 1.17)	0.228/0.955
	Population (1064/1346)	1.81 (1.31, 2.51)	0.019/<0.001	1.23 (1.04, 1.46)	0.145/0.013	1.84 (1.46, 2.32)	0.011/<0.001	1.26 (1.09, 1.46)	0.065/0.002	1.09 (0.89, 1.33)	0.455/0.409
Total (2212/3099)		1.65 (1.33, 2.05)	0.206/<0.001	1.11 (1.00, 1.23)	0.177/0.047	1.77 (1.48, 2.11)	0.116/<0.001	1.17 (1.07, 1.28)	0.070/0.001	1.03 (0.92, 1.17)	0.342/0.592
CYP1A1 rs1048943											
Ethnicity	Asian (738/1466)	1.91 (1.20, 3.04)	0.050/0.007	1.16 (0.97, 1.38)	0.083/0.098	1.76 (1.10, 2.80)	0.236/0.017	1.27 (1.07, 1.50)	0.052/0.005	1.21 (0.99, 1.48)	0.042/0.057
	White (271/351)	0.30 (0.01, 6.37)	0.000/0.442	1.10 (0.70, 1.72)	0.114/0.677	0.31 (0.01, 6.53)	0.000/0.452	0.71 (0.40, 1.27)	0.884/0.251	0.79 (0.43, 1.45)	0.749/0.440
	Other (518/557)	1.15 (0.49, 2.70)	0.224/0.748	1.12 (0.85, 1.47)	0.573/0.420	1.11 (0.48, 2.61)	0.248/0.804	1.13 (0.87, 1.47)	0.189/0.347	1.12 (0.83, 1.51)	0.472/0.442
Source of control	Hospital (809/1167)	1.83 (0.68, 4.92)	0.053/0.228	1.04 (0.82, 1.31)	0.189/0.762	1.54 (0.78, 3.04)	0.287/0.210	1.09 (0.86, 1.39)	0.052/0.480	1.07 (0.81, 1.42)	0.155/0.620
	Population (718/1207)	1.42 (0.50, 4.03)	0.142/0.514	1.22 (0.97, 1.54)	0.381/0.094	1.34 (0.49, 3.65)	0.167/0.563	1.20 (0.95, 1.52)	0.179/0.133	1.27 (0.92, 1.74)	0.168/0.145
Total (1527/2374)		1.63 (0.84, 3.15)	0.063/0.145	1.14 (0.99, 1.31)	0.244/0.062	1.50 (0.89, 2.54)	0.246/0.131	1.14 (0.98, 1.34)	0.069/0.105	1.15 (0.98, 1.35)	0.128/0.085

11 = wide-type homozygote, 12 = heterozygote, 22 = rare homozygote, CI = confidence interval, NA = not available, OR = odds ratio, Ph = P value of heterogeneity test, SNP = single nucleotide polymorphism.
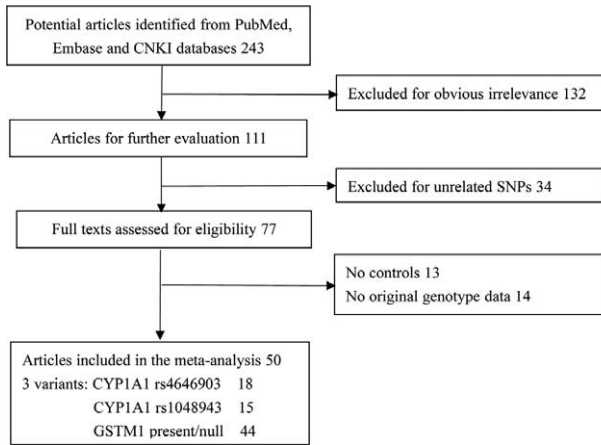
FIGURE 1. Flow diagram of included studies for the meta-analysis. CNKI = China National Knowledge Infrastructure, SNP = single nucleotide polymorphism.

related with oral cancer susceptibility in hospital-based population (CC vs TT: OR 1.53, 95% CI 1.15–2.05; CC vs TC+TT: OR 1.67, 95% CI 1.26–2.20) and population-based population (CC vs TT: OR 1.81, 95% CI 1.31–2.51; CC+TC vs TT: OR 1.23, 95% CI 1.04–1.46; CC vs TC+TT: OR 1.84, 95% CI 1.46–2.32; C vs T: OR 1.26, 95% CI 1.09–1.46), as shown in Figure 2. For *CYP1A1* rs1048943, subgroup analysis by ethnicity indicated that it was related with increased risk of oral cancer in Asians (GG vs AA: OR 1.91, 95% CI 1.20–3.04; GG vs GA+AA: OR 1.76, 95% CI 1.10–2.80; G vs A: OR 1.27, 95% CI 1.07–1.50) but not in whites and other ethnic groups (Figure 3). However, no significant relationship was found between the *CYP1A1* rs1048943 polymorphism and oral cancer risk in overall analysis and subgroup analysis by source of control.

With respect to *GSTM1* polymorphisms, null genotype showed obvious relevance to oral cancer susceptibility (OR 1.23, 95% CI 1.12–1.34), especially in Asians (OR 1.27, 95% CI 1.15–1.41), compared with present genotype. Moreover, it was demonstrated that null genotype could affect individual susceptibility to oral cancer in both hospital- and population-

based populations (OR 1.11, 95% CI 1.01–1.21; OR 1.38, 95% CI 1.18–1.61), as displayed in Figure 4.

Sensitivity Analysis

Sensitivity analysis was performed to evaluate the influence of each individual study on the pooled ORs. The recalculated ORs were not substantially influenced, which suggested our results were stable.

Publication Bias

Egger test and Begg funnel plot were conducted to estimate publication bias. The shape of the funnel plot was relatively symmetrical (Figure 5). Additionally, the result of Egger test did not show statistical evidence for bias ($P = 0.656$). Thus, there was no obvious publication bias in our meta-analysis, and the results were credible.

DISCUSSION

Oral cancer has become a major health problem characterized by high incidence, poor survival rate, and severe functional and cosmetic defects accompanying the treatment.[70] Moreover, it has been demonstrated that genetic and environmental factors could affect individual susceptibility to oral cancer. Therefore, it is significant to investigate the association of *CYP1A1* and *GSTM1* polymorphisms with oral cancer risk.

CYP1A1 rs4646903 and rs1048943 polymorphisms contribute to increased enzyme activity of CYP1A1 and are crucial to the activation of PAHs.[6,39] The null genotype of *GSTM1* polymorphism could result in the inactivation of GSTM1 enzyme and thus decrease the capacity of detoxifying carcinogens.[71] So far, several epidemiological studies have evaluated the association of *CYP1A1* and *GSTM1* polymorphisms with oral cancer susceptibility. In our study, *CYP1A1* rs4646903 was verified to increase the risk of oral cancer, particularly in Asians, whereas CYP1A1 rs1048943 polymorphism did not show significant relationship with oral cancer susceptibility, when we pooled all data together, but demonstrated a statistically significant association when data were limited to Asians, which was consistent with the results of most previous studies.[2,24,37,40,45,47,53,56,58,71,72] However, there were some studies with opposite results to ours. Among them, Losi-Guembarovski et al[51] and Amtha et al[58] found that there was no significant association between *CYP1A1* rs4646903 polymorphism and

TABLE 4. *GSTM1* Null/Present and Oral Cancer Risk

GSTM1 Null/Present		Null vs Present		Present vs Null	
		OR (95% CI)	Ph/P_{OR}	OR (95% CI)	Ph/P_{OR}
Ethnicity	Asian (3915/4919)	1.27 (1.15, 1.41)	0.056/<0.001	0.83 (0.76, 0.91)	0.100/<0.001
	White (1232/2322)	1.13 (0.94, 1.35)	0.056/0.197	0.88 (0.78, 1.00)	0.621/0.050
	Other (471/806)	1.25 (0.87, 1.79)	0.016/0.235	0.89 (0.71, 1.13)	0.216/0.322
Source of control	HB (2799/4254)	1.11 (1.01, 1.21)	0.522/0.033	0.93 (0.86, 1.01)	0.892/0.095
	PB (2732/3706)	1.38 (1.18, 1.61)	0.005/<0.001	0.78 (0.69, 0.88)	0.088/<0.001
	PB-HB (87/87)	1.19 (0.91, 1.56)	0.295/0.322	0.88 (0.71, 1.11)	0.678/0.276
Total **(5618/8047)**		1.23 (1.12, 1.34)	0.004/<0.001	0.86 (0.80, 0.92)	0.163/<0.001

CI = confidence interval, GSTM1 = glutathione-*S*-transferase M1, HB = hospital-based study, OR = odds ratio, PB = population-based study, Ph = P value of heterogeneity test.
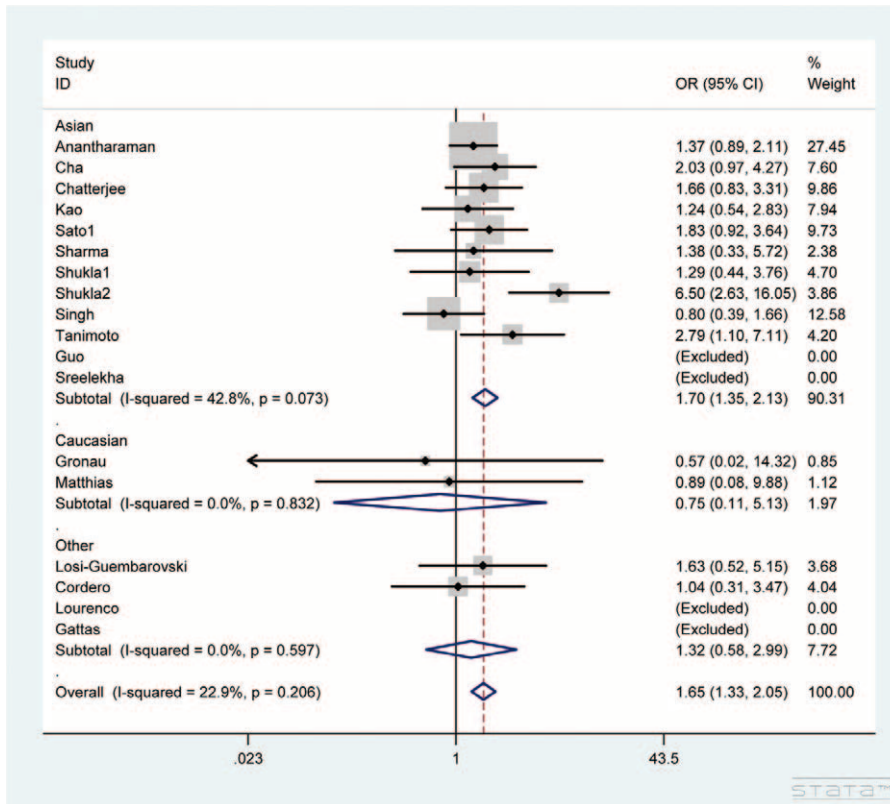
FIGURE 2. Forest plot of oral cancer susceptibility associated with CYP1A1 rs4646903 polymorphism under CC versus TT genetic model. CI = confidence interval, OR = odds ratio.
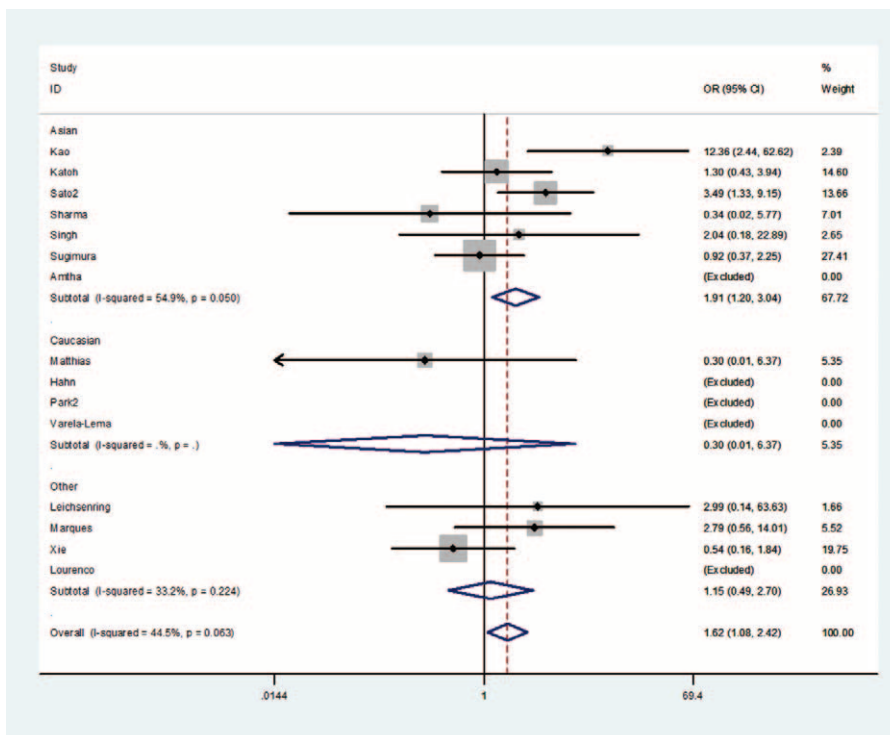

FIGURE 3. Forest plot of oral cancer risk related to CYP1A1 rs1048943 polymorphism in Asians under GG versus AA genetic model. CI = confidence interval, OR = odds ratio.
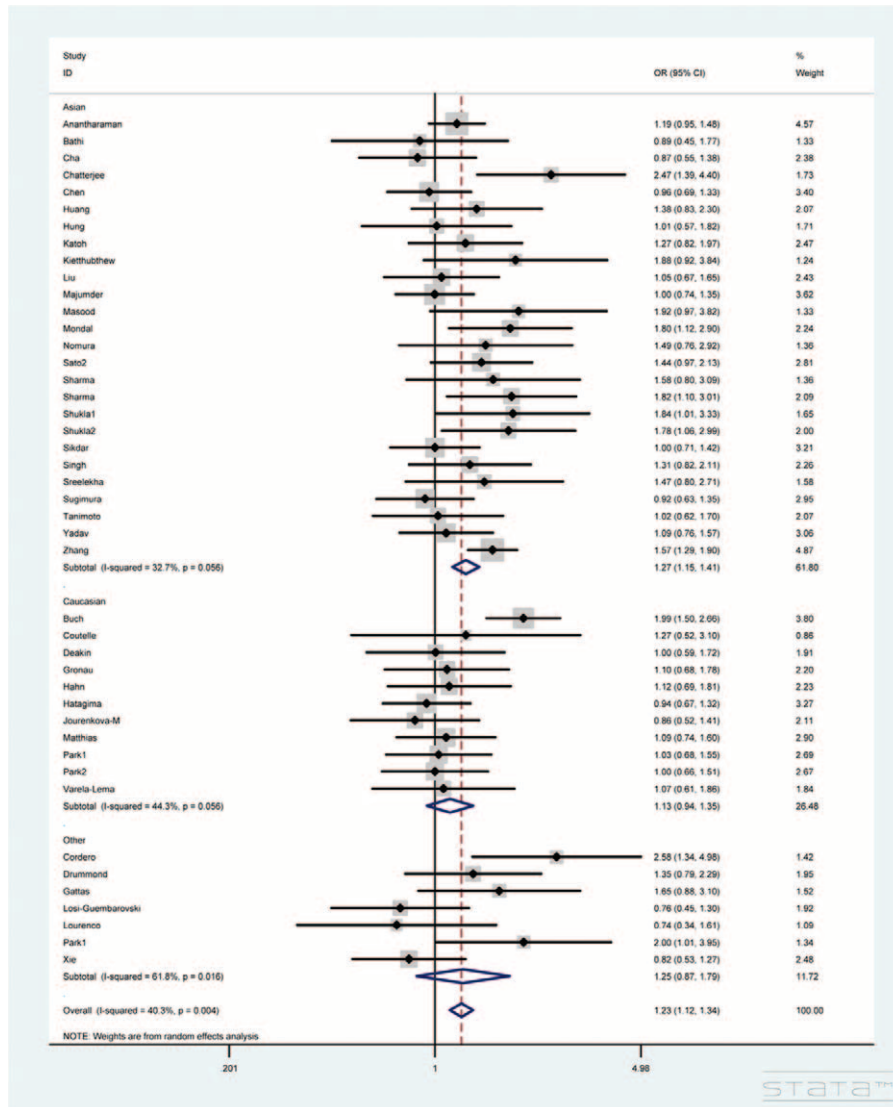
FIGURE 4. Forest plot of oral cancer risk associated with GSTM1 null/present. For each study, the estimates of OR and its 95% CI are plotted with square and a horizontal line. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI. GSTM1 = glutathione-S-transferase M1, CI = confidence interval, OR = odds ratio.

oral cancer risk. In the studies of Katoh et al[38] and Sreelekha et al,[39] *CYP1A1* rs1048943 showed no association with the susceptibility of oral cancer. Compared with the above studies, our study showed advantages in population composed of Asians, whites, and other ethnic groups and relatively lager sample size, which make our result much more credible.

For the association between null genotype of *GSTM1* polymorphisms and oral cancer risk, the results were also not conclusive.[25–31,33,34,41,44,63,65,66,68,73,74] Our meta-analysis demonstrated that null genotype of *GSTM1* polymorphisms was significantly associated with overall risk of oral cancer. However, the significance was lost in further analysis among whites.

The 3 polymorphisms analyzed in the present work have 1 thing in common. None of them demonstrated a significant association with genetic risk of oral cancer in whites. The null

results may be biased because the current sample is insufficient to determine whether there is an association in this population. Another possibility is that both *CYP1A1* and *GSTM1* polymorphisms modify oral cancer risk in an ethnic-specific fashion due to different genetic backgrounds. These possibilities clearly require to be investigated in future research.

Certain limitations in our study should be noted. First, our study was not stratified by smoking status, which was identified as a key factor in oral cancer risk.[54] Second, subgroup analysis of *CYP1A1* polymorphisms involved relatively fewer data in whites and other ethnic groups, which may produce some bias in the results. Finally, lack of original data about present genotype of *GSTM1* polymorphisms might influence the combined results.

In conclusion, our meta-analysis indicates that *CYP1A1* rs4646903, rs1048943, and null genotype of *GSTM1* polymorphisms are possible risk factors for oral cancer, especially
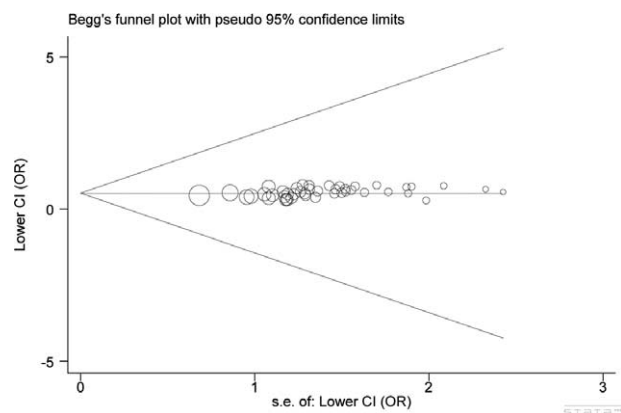
FIGURE 5. Begg funnel plot of publication bias. Each point represents a separate study for the indicated association. Log (OR), natural logarithm of OR; horizontal line, mean effect size. CI = confidence interval, OR = odds ratio.

in Asians. In the future, in-depth studies are required to further explore the association.

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