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Research Paper

Glutathione S-transferase P1 Ile105Val Polymorphism and Oral Cancer Risk: A Meta-Analysis

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Abstract

Objective The glutathione S-transferase P1 (*GSTP1*) gene has been suggested to play an important role in the pathogenesis of oral cancer. However, the results have been inconsistent. In this study, we performed a meta-analysis to clarify the association of *GSTP1* Ile105Val polymorphisms with oral cancer risk.

Methods Published literature from PubMed and EMBASE were retrieved. Pooled odds ratio (OR) with 95% confidence interval (CI) was calculated using fixed- or random-effects model.

Results 13 studies (1803 oral cancer cases and 2998 controls) for *GSTP1* Ile105Val polymorphism were included in the meta-analysis. The results indicated that there was no significant association between *GSTP1* Ile105Val polymorphism and oral cancer in the overall population (OR=1.30, 95%CI=0.92-1.38, I^2=48.0%, *p* for heterogeneity=0.027). Further subgroup analysis by ethnicity suggested that *GSTP1* Ile105Val polymorphism was significantly associated with oral cancer only in East Asians (OR=1.64, 95%CI=1.16-2.31, I^2=0.0%, *p* for heterogeneity=0.525), but not in Caucasians (OR=1.16, 95%CI=0.73-1.82, I^2=7.5%, *p* for heterogeneity=0.299), Africans (OR=1.10, 95%CI=0.37-3.28), South Asians (OR=1.20, 95%CI=0.69-2.08, I^2=74.3%, *p* for heterogeneity=0.021) and mixed population (OR=0.91, 95%CI=0.70-1.20, I^2=39.7%, *p* for heterogeneity=0.174).

Conclusions The present meta-analysis has limited evidence to support the association of *GSTP1* Ile105Val polymorphism with HCC risk in the overall population. However, *GSTP1* Ile105Val polymorphism might be associated with risk of oral cancer in East Asians.

Key words: *GSTP1*; Polymorphism; Oral cancer; Meta-analysis.

Introduction

Oral cancer is a serious public health problem worldwide [1]. It is believed that oral cancer is a complex disease caused by both genetic and environmental factors, as well as their interactions. Epidemiology studies have indicated that environmental factors including tobacco smoking, alcohol consumption and betel-quid chewing contribute to the development of oral cancer [2]. In addition, genetic factors also play important roles in the pathogenesis of oral cancer.

Most tobacco carcinogens are metabolized by enzymatic complex mechanisms involving both activation (phase I) and detoxification (phase II) reactions [3]. The detoxification efficiency of GST enzymes is determined by the presence, amount, and nature of the isoenzymes coded by *GSTT1*, *GSTM1*, and *GSTP1* genes [4]. The deleted variants of the *GSTM1* and *GSTT1* loci result in loss of functional activity [5]. The polymorphism at codon 105 of *GSTP1* gene has been reported to cause differences in catalytic activity. In other words, electrophilic compounds are reported to be detoxified less efficiently in individuals with variant genotypes of *GSTP1* (Ile/Val and Val/Val) when compared with those with wild-type genotype [6]. Recently, a meta-analysis has indicated that the *GSTM1* null genotype may be associated with a higher risk of oral cancer in Asians but not in Caucasians; the *GSTT1* null genotype may not be associated with oral cancer [7]. However, no meta-analysis has examined the association between *GSTP1* Ile105Val polymorphism and risk of oral cancer, although many individual studies have been published with inconsistent results [8-18]. Thus, in this study, we performed a meta-analysis to clarify the association between *GSTP1* Ile105Val polymorphism and risk of oral cancer.

Materials and methods

Literature and search strategy

Literature databases including PubMed and Embase were searched. The search strategy to identify all possible studies involved the use of the following key words: (GSTP1 or glutathione S-transferase P1) and (variant or variation or polymorphism) and oral cancer. The publication language was restricted to English. The reference lists of retrieved articles were manually searched. If more than one article were published using the same data, only the study with largest sample size was included. The literature search was updated on December 12, 2012.

Inclusion criteria and data extraction

The studies included in the meta-analysis must meet all the following inclusion criteria: (1) evaluating the association between *GSTP1* Ile105Val polymorphism and oral cancer; (2) using case-control or cohort design; (3) providing sufficient data for calculation of odds ratio (OR) with 95% confidence interval (CI). The following information was extracted from each study: (1) name of the first author; (2) year of publication; (3) country; (4) ethnicity; (5) sample size of cases and controls; (6) source of controls; (7) covariates' adjusted OR with 95%CI under a dominant model; and (8) whether or not the genotypes in Hardy–Weinberg equilibrium (HWE) in controls. The two authors independently assessed the articles for compliance with the inclusion/exclusion criteria, resolved disagreements and reached a consistent decision.

Statistical analysis

The association between *GSTP1* Ile105Val polymorphism and oral cancer was estimated by calculating pooled adjusted OR with 95% CI under a dominant genetic model. The significance of pooled OR was determined by *Z* test ($p<0.05$ was considered statistically significant). Q test was performed to evaluate to the between-study heterogeneity. A random- (DerSimonian-Laird method [19]) or fixed- (Mantel-Haenszel method [20]) effects model was used to calculate pooled OR in the presence ($p<=0.10$) or absence ($p>0.10$) of heterogeneity, respectively. Subgroup analysis by ethnicity, whether adjustment for smoking status (no vs. yes), and number of cases ($n<150$ vs $n\geq150$) was performed. Publication bias was assessed by Begg's test [21] and Egger's test [22] ($p<0.05$ was considered statistically significant). Data analysis was performed using STATA version 11 (StataCorp LP, College Station, Texas, USA).

Results

Characteristics of the studies

A flow chart of inclusion/exclusion of the individual studies was presented as Figure 1. The literature search identified a total of 55 potentially relevant papers. Of these, 37 papers were excluded because of obvious irrelevance by reading the titles and abstracts. In addition, two papers were excluded because they examined the association between *GSTP1* Ile105Val polymorphism and head-and-neck cancer [23, 24]; one paper was excluded because it investigated the association between *GSTP1* Ile105Val polymorphism and the combined cancer including lip, oral cavity/oropharynx cancer [25]; one paper was excluded because it examined the association between *GSTP1* Ile105Val polymorphism and arsenic-induced cancer [26]. Then, 14 papers met the primary inclusion criteria [8-18, 27-29]. In addition, two papers were excluded because they did not provide sufficient data for calculation of OR with 95%CI [27,28]; one paper was excluded because it examined the association between *GSTP1* mitochondrial polymorphisms and oral cancer [29]. It should be noted that since the paper by Kotoh, et al. [9] provided the data stratified for smoking status and the paper by Park, et al. [10] provided the data stratified for ethnicity, they were considered as separate studies in the following data

analysis. At last, 13 studies (1803 oral cancer cases and 2998 controls) were included in the final meta-analysis. The characteristics of the included studies are listed in Table 1.

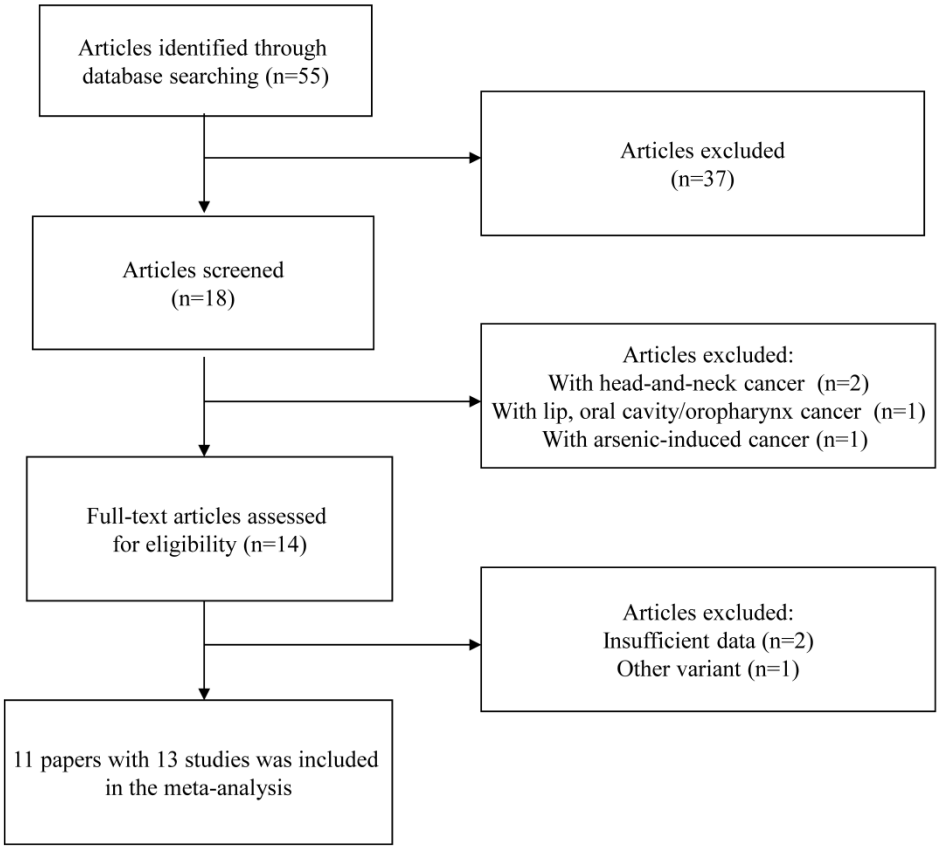

Figure 1. Flow chart of inclusion/exclusion of the individual studies

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

Study	Country	Ethnicity	No. of cases	No. of controls	Dominant model		Source of controls	Adjustment *	In HWE
					OR	95% CI			
Jourenkova-Mironova, 1999 [8]	France	Caucasian	67	172	1.50	0.80-3.00	Hospital-based	1, 2, 3, 4, 5	Yes
Kotoh,1999 (Non-smoker) [9]	Japan	East Asian	30	122	1.48	0.67-3.31	Hospital-based	1, 2	Yes
Kotoh,1999 (Smoker) [9]	Japan	East Asian	53	122	2.78	1.06-7.51	Hospital-based	1, 2	Yes
Park,1999 (Caucasian) [10]	USA	Caucasian	104	175	0.94	0.53-1.70	Hospital-based	3, 5	Yes
Park,1999 (African) [10]	USA	African	53	85	1.10	0.36-3.20	Hospital-based	3, 5	Yes
Sikdar, 2004 [11]	India	South Asian	256	259	2.00	1.00-4.00	Hospital-based	1,2,3	Yes
Leichsenring, 2006 [12]	Brazil	Mixed	72	60	1.40	0.70-2.79	Hospital-based	None	Yes
Peters, 2006 [13]	USA	Mixed	352	753	1.06	0.81-1.38	Population-based	1, 2, 3, 5, 6	Yes
Hatagima, 2008 [14]	Brazil	Mixed	231	212	0.78	0.56-1.17	Hospital-based	1, 2, 3, 5, 6	Yes
Chen, 2010 [15]	China	East Asian	164	274	1.53	1.01-2.31	Hospital-based	2	Yes
Yadav, 2010 [16]	India	South Asian	136	270	1.35	0.86-2.13	Hospital-based	3, 5, 7	Yes
Karen-Ng, 2011 [17]	Malaysia	Mixed	115	116	0.65	0.39-1.09	Hospital-based	1, 2, 4, 5, 6,,7	Yes
Ruwali, 2011 [18]	India	South Asian	170	500	0.75	0.54-1.12	Hospital-based	2, 3, 4,5	Yes

* 1, sex; 2; age; 3, tobacco consumption; 4, cigarette consumption; 5, alcohol consumption; 6, race; 7, betel quid chewing OR, odds ratio; CI, confidence interval; HWE, Hardy-Weinberg equilibrium.

Meta-analysis results

The results indicated that there was no significant association between *GSTP1* Ile105Val polymorphism and oral cancer in the overall population (OR=1.13, 95%CI=0.92-1.38, I^2=48.0%, *p* for heterogeneity=0.027, Fig 2 and Table 2). Further subgroup analysis by ethnicity suggested that *GSTP1* Ile105Val polymorphism was significantly associated with oral cancer only in East Asians (OR=1.64, 95%CI=1.16-2.31, I^2=0.0%, *p* for heterogeneity=0.525), but not in Caucasians (OR=1.16, 95%CI=0.73-1.82, I^2=7.5%, *p* for heterogeneity=0.299), Africans (OR=1.10, 95%CI=0.37-3.28), South Asians (OR=1.20, 95%CI=0.69-2.08, I^2=74.3%, *p* for heterogeneity=0.021) and mixed populations (OR=0.91, 95%CI=0.70-1.20, I^2=39.7%, *p* for heterogeneity=0.174) (Fig 3 and Table 2). In the stratified analysis by whether adjustment for smoking status, the effect size was significant in studies not adjusting for smoking status (OR=1.61, 95%CI=1.15-2.24, I^2=0.0%, *p* for heterogeneity=0.494), but was not significant in studies controlling for smoking status (OR=1.02, 95%CI=0.83-1.25, I^2=39.7%, *p* for heterogeneity=0.093) (Table 2). However, in studies with number of cases more than 150 or less than 150, the effect size was both not significant (Table 2).

Potential publication bias

No publication bias was detected for the association between *GSTP1* Ile105Val polymorphism and oral cancer (Begg's test: *p*=0.127; Egger's test: *p*=0.114).

Discussion

To our knowledge, this is the first meta-analysis investigating the association between *GSTP1* Ile105Val polymorphism and oral cancer risk. The present meta-analysis including 1803 oral cancer cases and 2998 controls did not support the significant association between *GSTP1* Ile105Val polymorphism and oral cancer risk in the overall population. However, *GSTP1* Ile105Val polymorphism was significantly associated with oral cancer in East Asians.

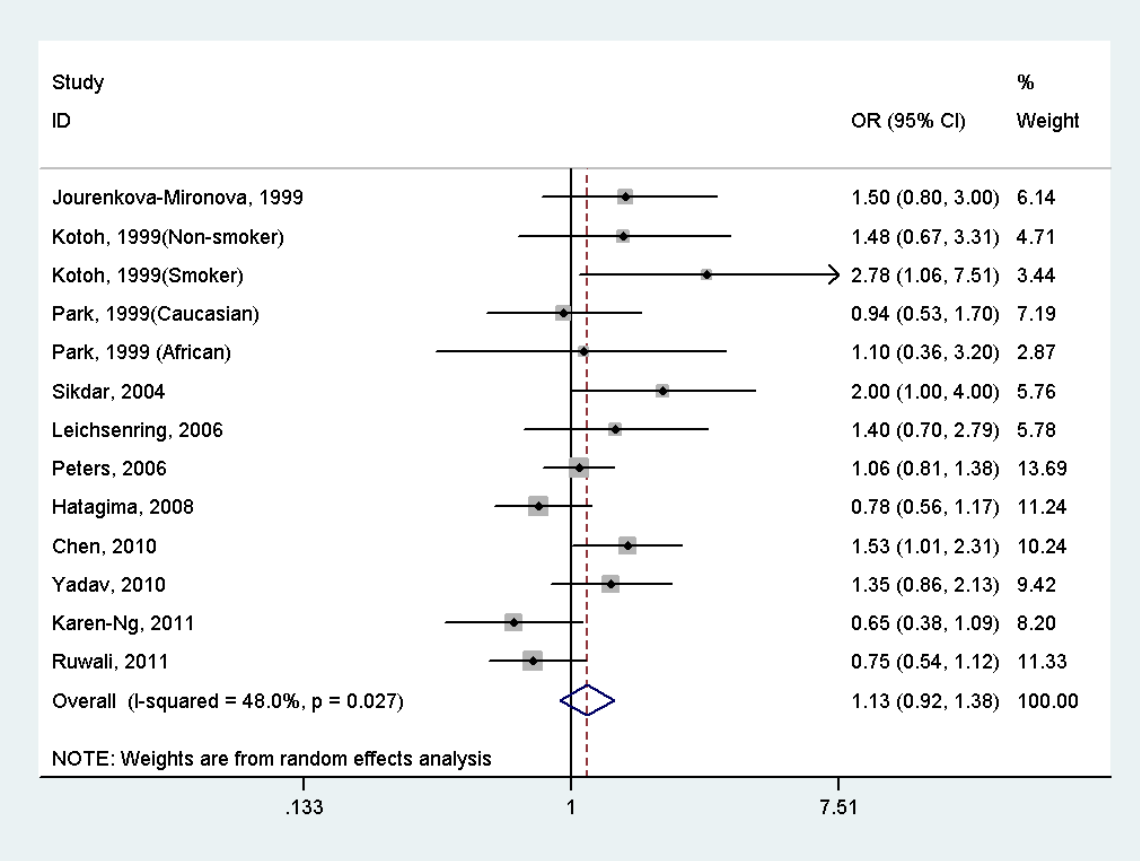

Figure 2. Forest plot of the meta-analysis of the association between *GSTP1* Ile105Val variant and oral cancer under a dominant model.

Table 2. Meta-analysis of the association between *GSTP1* Ile105Val variant and oral cancer under a dominant model.

	No. of studies	OR	95 %CI	*P* z	Statistical model	I^2 (%)	P_H
All	13	1.13	0.92-1.38	0.243	Random	48.0	0.027
Ethnicity							
Caucasian	2	1.15	0.74-1.79	0.523	Fixed	7.5	0.299
East Asian	3	1.64	1.16-2.31	0.005	Fixed	0.0	0.525
South Asian	3	1.20	0.69-2.08	0.524	Random	74.3	0.021
Mixed	4	0.93	0.77-1.13	0.703	Fixed	39.7	0.174
African	1	1.10	0.37-3.28	0.475	-	-	-
Adjustment for smoking							
No	3	1.61	1.15-2.24	0.005	Fixed	0.0	0.494
Yes	10	1.02	0.83-1.25	0.864	Random	39.7	0.093
No. of cases							
<150	8	1.17	0.93-1.47	0.171	Fixed	29.9	0.189
≥150	5	1.07	0.79-1.45	0.669	Random	67.1	0.016

Abbreviations: OR, odds ratio; CI, confidence interval. *P* z, *P* value for Z test. P_H, *P* value based on Q test for between-study heterogeneity.

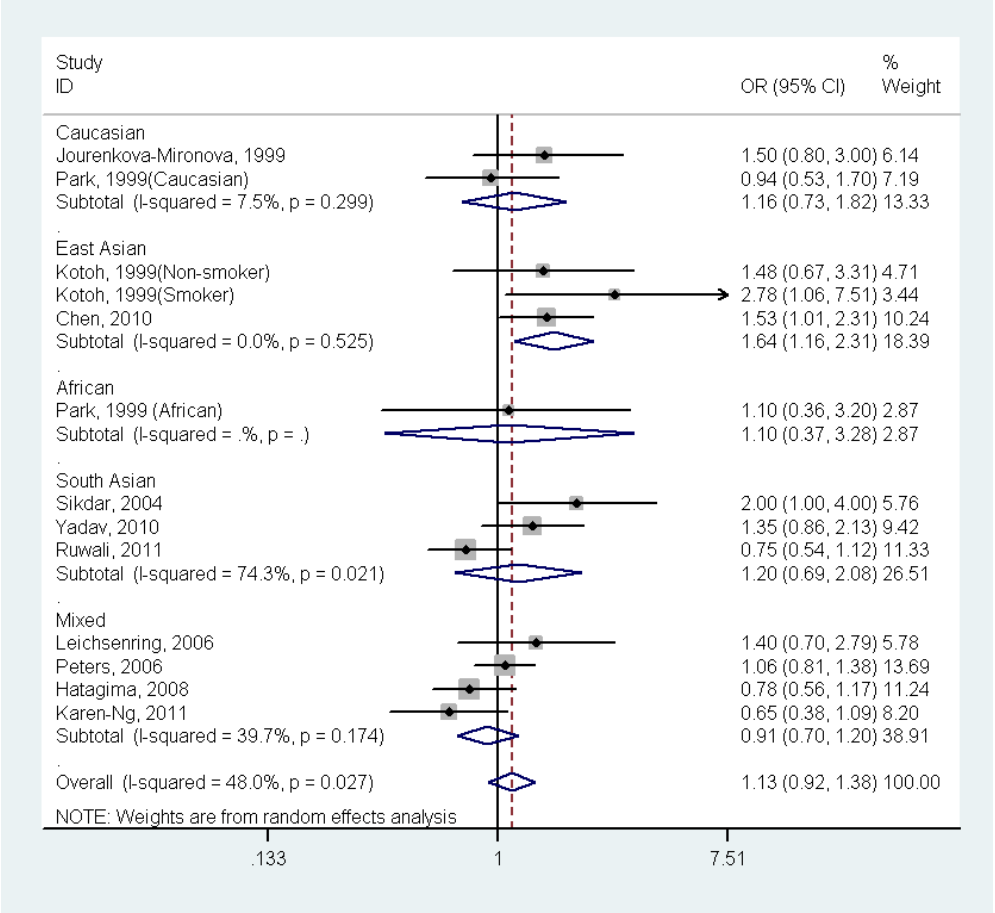

Figure 3. Forest plot of the meta-analysis of the association between *GSTP1* Ile105Val variant and oral cancer stratified by ethnicity under a dominant model.

Recently, many meta-analyses have been performed to investigate the association between *GSTP1* Ile105Val polymorphism and many types of cancer risk (e.g., prostate cancer [30], gastric cancer [31], esophageal cancer [32], head and neck cancer [33], lung cancer [34], breast cancer [35], ovarian cancer [36] and thyroid cancer [37]). The results indicated that *GSTP1* polymorphism was not significantly associated with prostate cancer [30], esophageal cancer [32], head and neck cancer [33], lung cancer [34], ovarian cancer [36] and thyroid cancer [37]; this polymorphism might contribute to the development of

gastric cancer [31] or breast cancer [35] in East Asians, but not in other ethnic populations. However, besides our study, these meta-analyses did not consider the effect of gene-gene and gene-environment interactions in the development of cancer. One polymorphism with modest effect may be not associated with cancer susceptibility, but the synthesis of many genes or gene gene-environment interactions might increase cancer risk.

In this meta-analysis, we used covariate's adjusted OR with 95% CI to calculate the pooled estimate, thus, more precise effect was obtained. However, some potential limitations in our study should be considered. First, gene-gene and gene-environment interactions were not addressed in our meta-analysis. However, we further performed subgroup analysis based on whether adjustment for smoking status. The result indicated that smoking strengthened the effect of the Ile105Val polymorphism on oral cancer. Second, most individual studies only provided adjusted OR with 95% CI under a dominant model. Thus, we are unable to estimate the effect of Ile105Val polymorphism under other genetic models, such as co-dominant model, recessive model and additive model. Third, there was significant between-study heterogeneity for Ile105Val polymorphism. We performed subgroup analysis based on ethnicity and the heterogeneity only existed in South Asians, suggesting this subgroup population is the source of between-study heterogeneity.

In summary, the present meta-analysis has limited evidence to support the association of *GSTP1* Ile105Val polymorphism with risk of oral cancer. However, *GSTP1* Ile105Val polymorphism might be associated with risk of oral cancer in East Asians. Further large-scale studies with the consideration for gene-gene/gene-environment interactions should be conducted to investigate the association.

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Competing Interests

The authors have declared that no competing interest exists.

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