RESEARCH ARTICLE

Null Glutathione S-transferase T1 and M1 Genotypes and Oral Cancer Susceptibility in China and India - a Meta-analysis

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Abstract

Objective: Genetic variation is considered to strongly impact on detoxification of carcinogens and therefore is related to cancer risk. However, findings for the null genotypes of GSTT1 and GSTM1 have not always been consistent. Therefore the present meta-analysis was conducted. Methods: We accessed the reported study at different research areas and used various databases, including PubMed and Wanfang Med Onlion from 1990 to May 1st 2013. We calculated the odds ratio (OR), 95% confidence interval (CI) and *P* value for oral cancer by using Review Manager 5.1 and STATE 12. Results: We found that there was no increased oral cancer risk among subjects carrying GSTM1 and GSTT1 null genotype (OR=1.35, 95%CI=0.68-2.68, *P*=0.39) and (OR=1.41, 95%CI=0.72-2.77, *P*=0.31) in the Chinese population. In contrast, in studies in India a significant correlation between GSTM1 null genotype and oral cancer was observed (OR=1.59, 95%CI=1.20-2.11, *P*=0.001), but not in GSTT1 (OR=1.21, 95% CI = 0.84-1.74, *P*=0.31). Conclusion: We discovered that GSTM1 deletion polymorphism had a significant effect on the susceptibility of oral cancer in the Indian population.

Keywords: Glutathione S-transferase - GSTT1 - GSTM1 - oral cancer - variation

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Introduction

Oral cancer is one of the most common cancers in the world (Petersen, 2009). The incidence of oral cancer has increased obviously in the last few years in different Asian populations (Sato et al., 1999; Masood et al., 2013). Despite the advances in diagnosis and treatment, the 5-year survival rate for patients is still low. A better understanding of etiology may improve the secondary prevention strategies.

Some studies had demonstrated that smoking and alcohol consumption were two risk factors of oral cancer (Katoh et al., 1999; Xie et al., 2004; Sugimura et al., 2006;Cha et al., 2007; Halawany et al., 2013; Menezes et al., 2013). However, other studies were focus on genetic polymorphisms. These genes included glutathione S-transferase (GST). Glutathione S-transferases are a family of phase II xenobiotic metabolizing enzymes and involve in detoxification of carcinogens. GST includes GSTM1 and GSTT1. Three alleles have been identified at GSTM1 locus: GSTM1*0, GSTM1*A, and GSTM1*B. Two alleles have been identified at GSTT1 locus: GSTT1*1 and GSTT1*0. Previous studies demonstrated that null genotype of GSTM1 and GSTT1 was correlated to the susceptibility to oral cancer (Seidegard et al., 1988; Hayes and Pulford, 1995; Gronau et al., 2003; Ma et al., 2011). However, the evidence was not convincing.

To derive a more precise estimation of the association in different countries, we enlarged the number of cases and controls and performed this meta-analysis in China and India.

Materials and Methods

Literature inclusion and exclusion criteria

(1) The studies must be about Chinese and Indian; (2) Only case-control or cohort studies are considered; (3) The papers should include the risk of oral cancer and GSTT1 or GSTM1 null genotype; (4) The papers must provide the sample size, the OR and 95% confidence interval or provide the related information such as genotype frequency that can calculate OR and 95% CI; (5) When more than one paper used the same study population, only most complete study is included. Exclusion criteria (1) The studies are no controls; (2) The controls are with other malignancies; (3) The studies are reviews; (4) The studies' data is overlapped.

Search strategy

PubMed and Wanfang Med Online were searched (last accessed on May 1st, 2013) by using key words: ''oral cancer''; ''GSTM1''; ''GSTT1''; ''glutathione S-transferase T1''; ''glutathione S-transferase M1''.

Study selection and data extraction

According to the criteria of inclusion and exclusion, a

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Table 1. Information of Eligible Studies

First author	Year	Country	No. of cases (GSTM1/GSTT1)	No. of controls (GTSM1/GSTT1)
Hung HC	1997	China	41/41	123/123
Liu CJ	2005	China	114/114	100/100
Chen MK	2010	China	164/164	274/274
Guo LK	2012	China	0/300	0/300
Zhang CX	2012	China	600/0	600/0
Sreelekha TT	2001	India	98/98	60/60
Buch SC	2002	India	297/297	450/450
Majumder M	2005	India	310/310	348/348
Sharma A	2006	India	40/40	87/87
Anantharaman D	2007	India	451/456	727/726
Bathi RJ	2009	India	30/30	60/60
Sharma R	2010	India	0/73	0/201
Yadav DS	2010	India	136/136	270/270
Ruwali M	2011	India	170/170	500/500
Mondal R	2013	India	25/25	25/25

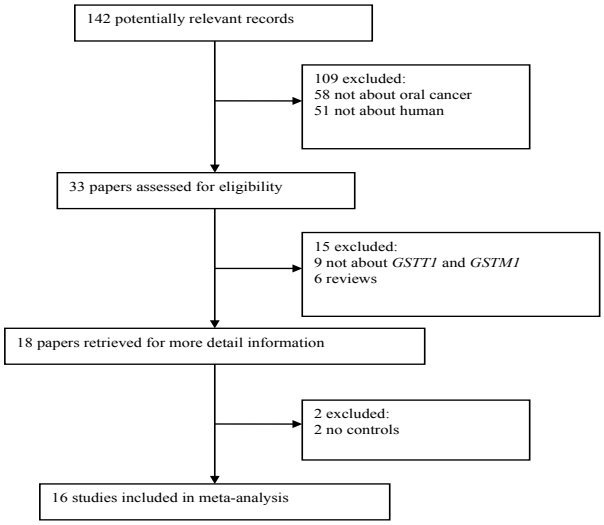

Figure 1. The Flow Chart of the Included Studies

double-check procedure was carried out to make sure the data accuracy. The following information was extracted from the studies: first author, published year, country, and the number of cases and controls. The information of studies was summarized in Table 1.

Statistical analysis methods

Statistical analysis was did by Review Manager5.1 and STATA 12. OR and 95% CI were calculated to measure the strength of association between GSTT1 and GSTM1 polymorphism and oral cancer. A 95% CI without 1 indicated a significant correlation. Q test was performed to check heterogeneity, and the heterogeneity was considered significant when P<0.10 or I^2>50%. The

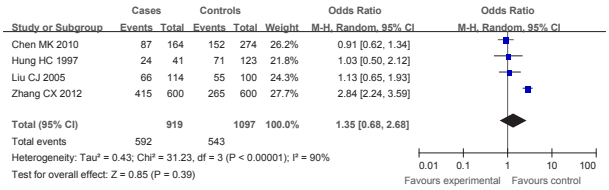

Figure 2. Forest Plot for the Association Between GSTM1 Null Genotype and Oral Cancer in Chinese Population

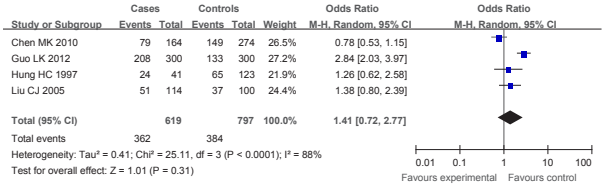

Figure 3. Forest Plot for the Association Between GSTT1 Null Genotype and Oral Cancer in Chinese Population

fixed effects model was used when P>0.10 and I^2<50%, while a random effects model was selected when P<0.10 and I^2>50%. Egger's test and Begg's test were done to check the publication bias. All the tests were two-sided, a P value of 0.05 was considered to be statistically significant.

Results

Characteristics of studies

According to the search strategy, 15 papers were selected in this meta-analysis in Figure 1. 10 studies included 1630 cases and 2728 controls were about GSTM1 and oral cancer in India population. 10 studies included 1562 cases and 2526 controls were about GSTM1 and oral cancer in India population. 5 studies included 919 cases and 1097 controls were about GSTM1 and oral cancer in Chinese population. 5 studies included 619 cases and 797 controls were about GSTT1 and oral cancer in Chinese population.

Meta-analysis Results

We observed a significant correlation between GSTM1 null genotype and oral caner in Indian population (OR=1.59, 95%CI=1.20-2.11, P=0.001) in Figure 4. However, there was no association between oral cancer and GSTT1 in Indian population (OR=1.21, 95% CI = 0.84-1.74, P=0.31) in Figure 5, and we found that there was not an increased oral cancer risk among subjects carrying GSTM1 and GSTT1 null genotype (OR=1.35, 95%CI=0.68-2.68, P=0.39) and (OR=1.41, 95%CI=0.72-

Table 2. Results of Meta-analysis

Characteristics	No.	Cases/controls	Heterogeneity test		P Egger's test	P Begg's test
			P	I^2		
Chinese popualtion						
GSTM1	4	919/1097	0.00001	90%	0.22	1.00
GSTT1	4	619/797	0.0001	88%	0.47	0.73
India population						
GSTM1	10	1630/2728	0.0001	74%	0.44	1.00
GSTT1	9	1562/2526	0.0001	74%	0.45	0.60

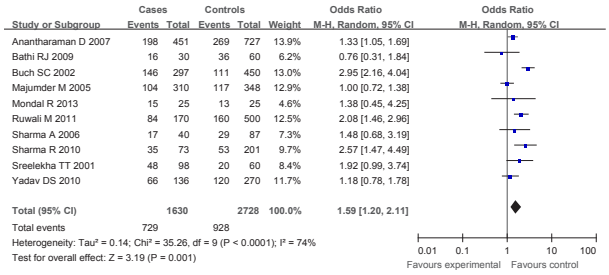

Figure 4. Forest Plot for the Association Between GSTM1 Null Genotype and Oral Cancer in Indian Population

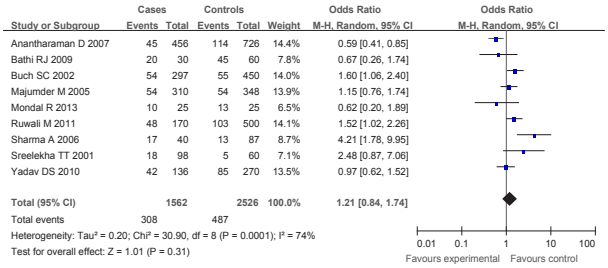

Figure 5. Forest Plot for the Association between GSTT1 Null Genotype and Oral Cancer in Indian Population

2.77, *P*=0.31) in Chinese population in Figure 2 and Figure 3. We caught a conclusion that GSTM1 null genotype and oral cancer had a significant correlation in Indian population.

Evaluation of Heterogeneity

The heterogeneity was showed in Table 2. $P_{\text{Heterogeneity}}$ of all groups indicated that heterogeneity could not be ignored ($P_{\text{Heterogeneity}}$<0.01). The detail information was not obtained, such as smoking status, so we could not investigate the source of heterogeneity.

Publication Bias

Egger's test and Begg's test were selected to assess the publication bias of the studies in Table 2. All the results of $P_{\text{Egger's}}$ and $P_{\text{Begg's}}$ were more than 0.05. It indicated that there was no publication bias in this meta-analysis.

Discussion

Oral cancer is a serious cancer in the world. To find more effective preventions and treatments, it is important to understanding the effect of genes. Genetic polymorphisms could contribute to the etiology of oral cancer (Zheng et al., 2007; Jiang et al., 2013; Wang et al., 2013), such as GSTM1 and GSTT1. Several studies had suggested that null genotype of GSTM1 and GSTT1 was related to the susceptibility to oral cancer in China and India. However, the results were inconsistent. Considering the different incidence of oral cancer in China and India, it might be not reasonable to perform a meta-analysis by group of Asian continent. Therefore, it was convincing to perform this meta-analysis by group of China and India.

15 papers were selected in this meta-analysis, and 10 studies included 1630 cases and 2728 controls were about GSTM1 and oral cancer in India population. 5 studies included 919 cases and 1097 controls were about GSTM1 and oral cancer in Chinese population. We found that there was not an increased oral cancer risk among subjects carrying GSTM1 and GSTT1 null genotype (OR=1.35, 95%CI=0.68-2.68, *P*=0.39) and (OR=1.41, 95%CI=0.72-2.77, *P*=0.31) in Chinese population. In India population, a significant association between GSTM1 null genotype and oral cancer was observed (OR=1.59, 95%CI=1.20-2.11, *P*=0.001), but it was not significant in GSTT1 (OR=1.21, 95% CI = 0.84 - 1.74, *P*=0.31). The association between GSTM1 null genotype and oral cancer was diverse in China and India.

We made a hypothesis. India and China are in the same stage of social development, and have similar environmental problems, such as industrial pollution. More important, they are yellow. Therefore, we made the hypothesis that GSTM1 deletion polymorphism might be correlated with oral cancer in Chinese population. The number of research literatures limited the efficiency of inspection, and more literatures were need to confirms this hypothesis.

There are some limitations in this meta-analysis. Firstly, the role of environmental interactions is crucial, so detailed information such as smoking status is needed. Secondly, the heterogeneity is difficult to exclude. It may be decided by confounding factors, such as gender and genetic diversities. However, the information is difficult to collect completely. Thirdly, only 4 studies are included in group of Chinese population, so large number of cases and controls is needed.

In a word, GSTM1 null genotype and oral caner has a significant correlation in Indian population. However, further studies should be carried out with larger sample size to confirm the result and hypothesis.

Acknowledgements

All authors declare that we have no conflict of interest.

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