LETTER TO JMG

Glutathione S-transferase M1, T1 status and the risk of head and neck cancer: a meta-analysis

Z Ye, H Song, Y Guo

Squamous cell carcinoma of the head and neck, including the larynx, pharynx, and oral cavity, is a relatively common human neoplasm and accounts for approximately 2% of deaths from cancer in the western world. In 1985, there were nearly 900,000 new cases of head and neck cancer registered worldwide. An increasing number of epidemiological studies indicate that tobacco and alcohol consumption are major aetiological factors increasing the risk of developing head and neck cancer. The risk of head and neck cancer in smokers and alcohol users is more than twice that in non-smokers and non-alcohol users. The enzymes involved in these carcinogens’ metabolism have thus received a reasonable level of attention.

Glutathione S-transferase (GST) M1 and T1 are two of a GST family which is involved in conjugation and detoxification reactions during the phase II metabolism of electrophilic compounds, including environmental carcinogens. Both of them have had a great deal of attention as possible genetic susceptibility factors for head and neck cancer. The GSTM1 gene is located on chromosome 1 (1p13.3), while the GSTT1 gene exists on chromosome 22 (22q11.2). Both of them are polymorphic. The GSTM1*0 (GSTM1 deficiency) and GSTT1*0 (GSTT1 deficiency) allele represent a deletion of the GSTM1 and GSTT1 gene and result in a loss of enzymatic activity. This suggested that individuals who lack these genes are more likely to develop cancer than those who have these genes, because of their inability to detoxify carcinogenic chemicals.

GSTM1 and GSTT1 deficiency as risk factors for head and neck cancer were first reported in the middle 1990s. Since then, a number of studies have confirmed or refuted an association between GSTM1 or GSTT1 deficiency and head and neck cancer. These disparate findings may be partly due to insufficient power in some studies, which have been based on only small sample sizes. To explore the possible association between GSTM1 or GSTT1 deficiency and the risk of head and neck cancer, we have performed a pooled analysis of all the available published case control studies from 1995 to September 2003 to address the controversy.

MATERIALS AND METHODS

Selection of studies

Studies with information on GSTM1 or GSTT1 deficiency and the risk of head and neck cancer were identified using two electronic databases: Medline (National Library of Medicine, Washington DC, USA) and EMBASE, from 1995 to September 2003, using the search terms “GSTM1” or “GSTT1”, “head and neck”, “oral-neoplasms”, “larynx”, “pharynx”, and “polymorphisms”. Additional articles were also checked via the references cited in these publications and in a review article. Articles selected for analysis were case control designs and their primary references, which did not obviously overlap cancer cases with other studies.

Key points

- Glutathione S-transferase M1 and T1 (GSTM1 and GSTT1) have been considered as risk factors for developing head and neck cancer in a number of studies, but the results are inconsistent.
- We performed a meta-analysis of 42 published case control studies to clarify the influence of GSTM1 and GSTT1 status on head and neck cancer. The pooled odds ratios were assessed using both a fixed effects and a random effects model.
- The pooled odds ratios of head and neck cancer associated with GSTM1 and GSTT1 deficiency were 1.27 (95% confidence interval: 1.13–1.42) and 1.14 (95% confidence interval: 1.00–1.31), respectively. The joint effect of both GSTM1 and GSTT1 null genotypes associated with the risk of head and neck cancer was observed with an odds ratio of 1.99 (95% confidence interval: 1.74–2.24).
- Our results support the hypothesis that GSTM1 and GSTT1 are important risk factors for head and neck cancer and suggest that GSTM1 and GSTT1 deficiency have an effect on the risk of developing head and neck cancer.

Statistical analysis

The odds ratios of head and neck cancer associated with GSTM1 or GSTT1 deficiency were recalculated for each study, and their corresponding 95% confidence intervals were estimated by the Woolf’s method. The results might be slightly inconsistent from those of some studies as difference criteria in the case control studies were performed in the statistical analysis. The homozygous allele of the GSTM1 or GSTT1 gene was used as the control group for each study. Each study was treated as a separate stratum. To take into account the possibility of heterogeneity across the studies, a statistical test for heterogeneity was performed based on the Q statistic, for which a p value >0.05 indicates a lack of heterogeneity. If heterogeneity between studies was present, a sensitivity analysis was performed based on the magnitude of Q statistic.

Meta-analyses were conducted by both a fixed effects and a random effects model. The fixed effects model assumes no significant heterogeneity between the results of the individual studies being pooled, whereas the random effects model takes into account the possibility of heterogeneity across the studies.
allows for such heterogeneity, and it adds an empirical estimate of the between study variance \( t^2 \) to the within study variance. \(^4^5 \) We reported results from the fixed effects model only if there was not heterogeneity between studies. The analyses were also conducted on subgroups of studies based on geographic region and ethnic origin. Geographic subgroups were defined as three regions (America, Europe, and Asia), while ethnic subgroups were considered as three ethnic groups (white, African-American, and Asian).

To identify publication bias, we assessed this bias using a funnel plot, Begg’s test,\(^4^8\) and Egger’s test.\(^4^9\) The results of the variance.\(^4^5\) \(^4^7\) We reported results from the fixed effects model because small studies are shown to be more widely scattered than the case control studies varied considerably (ranging from 55 to 75%).

### RESULTS

Characteristics of 42 case control studies for GSTM1 and GSTT1 status and the risk of head and neck cancer are summarised in Tables 1 and 2. Studies were rejected for our analysis if the same data were available in more than one study.\(^2^0\) \(^2^2\) \(^2^3\) \(^2^5\) \(^4^1\) The studies of Khuri et al\(^2^5\) and Worral et al\(^2^9\) were excluded because data on GSTM1 and GSTT1 status associated with the risk of head and neck cancer had not been ascertained. Park et al\(^2^9\) and Olshan et al\(^2^9\) reported GSTM1 or GSTT1 status in the African-American and white populations, respectively. They were treated as two case control studies for our analysis. Studies had data on larynx, pharynx, or oral cavity, which were considered as independent studies.\(^1^8\) \(^2^0\) \(^2^2\) \(^2^3\) \(^2^5\) \(^4^1\) Phenotype studies were excluded for our analysis to reduce possible misclassification of GSTM1 or GSTT1 status.\(^3^5\) \(^3^6\)

Of the 42 case control studies selected for meta-analysis, 19 studies were carried out in European countries, 13 in Asian countries and 10 in American countries. Hospital patients were used as controls in 19 studies (Table 1). The numbers in the case control studies varied considerably (ranging from 55
Table 2  Summary of studies on GSTT1 status and the risk of head and neck cancer

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The interactions between head and neck cancer and environmental exposures (cigarette smoking and alcohol drinking) or genotypes were examined in this study. Information on cigarette smoking and alcohol drinking was collected in 17 and 11 studies, respectively. The pooled odds ratios of head and neck cancer associated with ever having smoked cigarettes and ever having drunk alcohol were 4.09 (95% confidence interval, 2.66–6.30) and 1.23 (95% confidence interval, 0.76–2.00), respectively. An impression of heterogeneity between studies was observed by statistical analysis (both p<0.001). This may be partly attributable to misclassification of exposures. Information on cigarette smoking and alcohol drinking associated with GSTM1, but not GSTT1, status was collected in four and two studies, respectively. The pooled odds ratios of head and neck cancer associated with having smoked cigarettes and having drunk alcohol in relation to GSTM1 deficiency were 1.34 (95% confidence interval, 1.05–1.70) and 0.92 (95% confidence interval, 0.66–1.27), respectively.

Besides the effect analyses of GSTM1 and GSTT1 deficiency on head and neck cancer, we also performed pooled analysis of the joint effect of both GSTM1 and GSTT1 null genotypes associated with the risk of head and neck cancer. The common allele of GSTM1 and GSTT1 was used as the control group to evaluate the joint effect of the two genes. Nine studies evaluated a joint effect between the risk of head and neck cancer and GSTM1 and GSTT1 status. The pooled odds ratio is 1.99 (95% confidence interval, 1.74–2.24) (fig 3).

**DISCUSSION**

In 1995, Trizna et al. first evaluated a possible association between GSTM1 and GSTT1 deficiency and the risk of head and neck cancer. Since then, GSTM1 and GSTT1 deficiency have been regarded as risk factors for developing head and neck cancer by a number of researchers. However, some studies have produced inconsistent conclusions. This
It is well known that variation in the geographic and ethnic distribution between cases and control individuals among studies may be a considerable bias, which might confound the results of pooling analysis. We have observed such an imbalance in geographic and ethnic distribution. For GSTM1 status, the risk of head and neck cancer is higher in African-Americans and Asians than in whites, while the risk of head and neck cancer is higher in Asia than in America and Europe. Similarly, for GSTT1 status, the risk of head and neck cancer is higher in America than in Europe and Asia. However, the risk of head and neck cancer seems consistent in the different ethnic groups.

In our meta-analysis, the evidence of heterogeneity has been observed across the studies. Some studies contribute to major sources of heterogeneity, but the reasons for this are not clear. This might be due to uncontrolled confounding and bias inherent in study design. For example, misclassification of exposure was used in studies or hospital based controls were used. Selection bias is a possible major source of heterogeneity results from non-systemic, arbitrary acquisition of cancer samples and hospital based controls. We reduced such bias by removing studies in influence analyses. Although there is evidence of heterogeneity across the studies, which will produce an overestimate of the true association, studies that contribute to the heterogeneity do not significantly alter the estimate of the overall odds ratio and result in a type I error.

Although the overall risk of developing head and neck cancer in individuals with GSTM1 and GSTT1 deficiency may be modest, head and neck cancer is such a common malignancy that even a small increase in risk may well have considerable impact on head and neck cancer incidence. Based upon the results of our analyses in Asians, we calculate that a 1.58 and 1.16 fold increase in risk corresponds to a population attributable fraction of approximately 21% and 6% for GSTM1 and GSTT1 deficiency, respectively. Identification of individuals with GSTM1 and GSTT1 deficiency may eventually assist in the prevention of head and neck cancer by allowing early detection of individuals with a high risk, as well as effective treatment. Therefore, GSTM1 and GSTT1 deficiency are important public health issues.

In this study, we not only studied the association between GSTM1 or GSTT1 status and the risk of head and neck cancer but we also evaluated gene-gene and gene-environment interactions. We observed a positive association of GSTM1 status and the risk of head and neck cancer when stratified by cigarette smoking. However, these analyses were based upon small sample sizes. More studies including information on environmental exposures will be needed to enhance our understanding of gene-environment interaction.

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Conflicts of interest: none declared.

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