LETTER TO JMG

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

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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.[1] In 1985, there were nearly 900 000 new cases of head and neck cancer registered worldwide.[1] 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.[2–4] The risk of head and neck cancer in smokers and alcohol users is more than twice that in non-smokers and non-alcohol users.[5–7] 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.[8] 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).[8] 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.[9] 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.[5 10]

GSTM1 and GSTT1 deficiency as risk factors for head and neck cancer were first reported in the middle 1990s.[11 12] Since then, a number of studies have confirmed or refuted an association between GSTM1 or GSTT1 deficiency and head and neck cancer.[4 6 7 11–41] 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.[42] 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.[43 44] 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.[45] 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[46] and a random effects model.[45] The fixed effects model assumes no significant heterogeneity between the results of the individual studies being pooled, whereas the random effects model

Abbreviations: GST, glutathione S-transferase; GSTM1, glutathione S-transferase M1; GSTT1, glutathione S-transferase T1

Table 1 Summary of studies on GSTM1 status and the risk of head and neck cancer

Author	Country	Cases	%GSTM1 deficiency	Controls	%GSTM1 deficiency	Control source	Tumour sites	Power (RR⩾1.5, α=0.05)	Power (RR⩾2, α=0.05)
Katoh, 1995[12]	Japan	32	50.0%	88	39.8%	population	oral cavity	16%	38%
Trizna et al, 1995[11]	USA	186	68.0%	42	48.0%	population	head and neck	22%	52%
Deakin et al, 1996[13]	UK	40	55.0%	577	54.8%	hospital	oral cavity	22%	50%
Jahnke et al, 1996[14]	Germany	269	56.0%	216	52.0%	not available	larynx	59%	95%
Hung et al, 1997[15]	Taiwan	41	58.5%	123	57.7%	population	oral cavity	23%	43%
Park et al, 1997[16]	USA	133	51.1%	133	51.1%	hospital	oral cavity	38%	79%
Oude Ophuis et al, 1998[17]	Netherlands	185	50.8%	207	51.7%	population	head and neck	50%	91%
Coutelle et al, 1997[18]	France	18	77.8%	37	48.6%	hospital	larynx	10%	21%
Coutelle et al, 1997[18]	France	21	61.9%	37	48.6%	hospital	pharynx	11%	23%
Kihara et al, 1997[19]	Japan	156	55.1%	472	48.7%	population	head and neck	58%	95%
Matthias et al, 1998[20]	Germany	265	57.0%	178	53.4%	hospital	larynx	54%	93%
Matthias et al, 1998[20]	Germany	122	58.2%	178	53.4%	hospital	oral/pharynx	39%	80%
Jourenkova et al, 1998[21]	France	129	60.5%	172	52.3%	hospital	larynx	40%	81%
Gonzalez et al, 1998[22]	Spain	75	58.7%	200	51.5%	population	head and neck	33%	68%
Morita et al, 1999[23]	Japan	69	43.5%	164	50.6%	population	larynx	28%	64%
Morita et al, 1999[23]	Japan	45	51.1%	164	50.6%	population	pharynx	28%	50%
Cheng et al, 1999[24]	USA	162	53.1%	315	42.9%	population	head and neck	55%	94%
Jourenkova-Mironova et al, 1999a[25]	France	67	44.8%	172	52.3%	hospital	oral cavity	28%	63%
Jourenkova-Mironova et al, 1999a[25]	France	50	52.0%	172	52.3%	hospital	pharynx	22%	50%
Tanimoto et al, 1999[26]	Japan	100	43.0%	100	42.0%	hospital	oral cavity	51%	67%
Katoh et al, 1999[27]	Japan	92	58.7%	147	46.3%	population	oral cavity	32%	73%
Sato et al, 2000[28]	Japan	142	64.8%	142	45.1%	population	oral cavity	39%	81%
Park et al, 2000;[29] African-American	USA	63	31.7%	133	15.9%	hospital	oral cavity	17%	48%
Park et al, 2000;[29] white	USA	101	50.5%	213	49.1%	hospital	oral cavity	38%	80%
Hong et al, 2000[30]	Korea	82	68.3%	63	52.4%	hospital	larynx	28%	51%
McWilliams et al, 2000[31]	USA	147	46.3%	129	46.5%	population	head and neck	39%	80%
Hamel et al, 2000[6]	Canada	90	56.7%	90	57.8%	hospital	head and neck	26%	58%
Olshan et al, 2000;[5] African-American	USA	63	31.7%	25	40.0%	hospital	head and neck	23%	30%
Olshan et al, 2000;[5] white	USA	109	50.4%	168	45.2%	hospital	head and neck	37%	79%
Kietthubthew et al, 2001[7]	Thailand	53	56.6%	53	37.2%	population	oral cavity	23%	37%
Sreelekha et al, 2001[32]	India	98	49.0%	60	33.3%	population	oral cavity	20%	71%
Cabelguenne et al, 2001[33]	France	162	49.4%	264	46.6%	hospital	head and neck	52%	92%
Ko et al, 2001[34]	Germany	312	53.2%	300	48.3%	population	head and neck	70%	98%
Hahn et al, 2002[35]	Germany	94	40.4%	92	46.7%	population	oral cavity	28%	65%
Buch et al, 2002[36]	India	297	49.2%	450	24.0%	population	oral cavity	46%	99%
To-Figueras et al, 2002[37]	Spain	204	47.1%	203	49.3%	population	larynx	52%	92%
Park et al, 2003[38]	USA	262	48.1%	414	47.8%	hospital	larynx	72%	99%
Cheng et al, 2003[39]	Taiwan	314	55.1%	337	50.1%	population	pharynx	72%	99%
Risch et al, 2003[4]	Germany	245	51.8%	251	53.8%	population	larynx	59%	95%
Gronau et al, 2003a[40]	Germany	73	56.2%	129	51.2%	hospital	oral cavity	17%	62%
Gronau et al, 2003b[41]	Germany	53	73.6%	139	48.9%	population	larynx	23%	54%
Gronau et al, 2003b[41]	Germany	117	52.1%	139	48.9%	population	oral, pharynx	36%	77%

allows for such heterogeneity, and it adds an empirical estimate of the between study variance τ^2 to the within study variance.[45 47] 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,[48] and Egger's test.[49] The results of the small studies are shown to be more widely scattered than those of the larger studies in the funnel plot. In the absence of publication bias the plot resembles a symmetrical inverted funnel.[50] The power of the studies was estimated as the probability of finding an association between GSTM1 or GSTT1 deficiency and head and neck cancer at the 0.05 significant levels, assuming that the genotype risk is 1.5 or 2. It was estimated on the basis of the method published by Schlesselman et al.[51] All analyses were conducted with KDE 1.8 software (InforSense, London).

RESULTS

Selected 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.[10 52 53] The studies of Khuri et al[3] and Worral et al[54] 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[29] and Olshan et al[5] 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.[18 20 23 25 41] Phenotype studies were excluded for our analysis to reduce possible misclassification of GSTM1 or GSTT1 status.[55 56]

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

Author	Country	Cases	%GSTT1 deficiency	Controls	%GSTT1 deficiency	Control source	Tumour sites	Power (RR⩾1.5, α=0.05)	Power (RR⩾2, α=0.05)
Trizna et al, 1995[11]	USA	127	44.9%	42	35.7%	population	head and neck	19%	47%
Deakin et al, 1996[13]	UK	34	11.8%	509	18.5%	hospital	oral cavity	16%	45%
Jahnke et al, 1996[14]	Germany	269	20.8%	146	19.2%	not available	larynx	26%	80%
Hung et al, 1997[15]	Taiwan	41	58.5%	123	52.8%	population	oral cavity	19%	46%
Oude Ophuis et al, 1998[17]	Netherlands	185	19.5%	207	20.3%	population	head and neck	40%	85%
Matthias et al, 1998[20]	Germany	263	19.4%	203	22.2%	hospital	larynx	46%	90%
Matthias et al, 1998[20]	Germany	122	27.7%	203	22.2%	hospital	oral/pharynx	36%	78%
Jourenkova et al, 1998[21]	France	129	19.4%	172	15.7%	hospital	larynx	27%	68%
Cheng et al, 1999[24]	USA	162	32.7%	315	17.5%	population	head and neck	41%	86%
Jourenkova-Mironova et al, 1999a[25]	France	67	22.4%	172	15.7%	hospital	oral cavity	14%	35%
Jourenkova-Mironova et al, 1999a[25]	France	50	52.0%	172	52.3%	hospital	pharynx	23%	53%
Katoh et al, 1999[27]	Japan	92	47.8%	147	51.0%	population	oral cavity	27%	71%
Hong et al, 2000[30]	Korea	82	57.3%	63	36.5%	hospital	larynx	28%	52%
McWilliams et al, 2000[31]	USA	142	16.9%	109	18.3%	population	head and neck	25%	62%
Hamel et al, 2000[6]	Canada	90	22.2%	90	10.0%	hospital	head and neck	24%	45%
Olshan et al, 2000;[5] African-American	USA	63	77.8%	25	80.0%	hospital	head and neck	10%	19%
Olshan et al, 2000;[5] white	USA	109	16.5%	168	12.5%	hospital	head and neck	22%	57%
Kietthubthew et al, 2001[7]	Thailand	53	34.0%	53	47.2%	population	oral cavity	17%	41%
Sreelekha et al, 2001[32]	India	98	18.4%	45	11.1%	population	oral cavity	20%	71%
Cabelguenne et al, 2001[33]	France	162	17.9%	264	19.3%	hospital	head and neck	40%	86%
Ko et al, 2001[34]	Germany	312	20.5%	300	20.3%	population	head and neck	56%	96%
Buch et al, 2002[36]	India	297	18.2%	450	12.2%	population	oral cavity	50%	93%
To-Figueras et al, 2002[37]	Spain	204	17.2%	203	23.6%	population	larynx	44%	89%
Cheng et al, 2003[39]	Taiwan	316	50.6%	336	51.8%	population	pharynx	72%	98%
Risch et al, 2003[4]	Germany	245	15.5%	251	13.9%	population	larynx	39%	84%
Gronau et al, 2003a[40]	Germany	73	15.1%	136	14.0%	hospital	oral cavity	20%	30%
Gronau et al, 2003b[41]	Germany	187	16.0%	139	15.1%	population	head and neck	27%	67%

to 747 individuals). In the control series, the frequencies of GSTM1 deficiency ranged from 24.0% to 57.7% in Asians, 46.6% to 53.8% in Europeans, and 15.9% to 57.8% in Americans. Similarly, the frequencies of GSTT1 deficiency ranged from 11.1% to 52.8% in Asians, 13.9% to 52.3% in Europeans, and 10% to 80% in Americans. None of the studies for GSTM1 and GSTT1 status were large enough to demonstrate a 1.5 fold increase in risk with 80% power, and 40.5% (17/42) and 37% (10/27) of the studies for GSTM1 and GSTT1 status were only large enough to find a two fold or greater risk, respectively.

Figs 1 and 2 show plots of the odds ratios (95% confidence interval) of head and neck cancer risk associated with GSTM1 and GSTT1 deficiency. The funnel plots were symmetrical. Both Egger's test (weighted regression, $p = 0.47$ for GSTM1 status; $p = 0.62$ for GSTT1 status) and Begg's test (rank correlation method, $p = 0.20$ for GSTM1 status; $p = 0.24$ for GSTT1 status) showed no evidence of publication bias in the funnel plots. The overall odds ratios of head and neck cancer risk associated with GSTM1 and GSTT1 deficiency are 1.27 (95% confidence interval, 1.13–1.42) and 1.14 (95% confidence interval, 1.00–1.31), respectively. Tests for heterogeneity between the studies showed an impression of heterogeneity related to GSTM1 ($p<0.005$) and GSTT1 ($p<0.05$) status. For GSTM1 status, exclusion of one outlying study[36] resulted in a Q statistic that was no longer statistically significant (a test of sensitivity). Its odds ratio is 1.20 (95% confidence interval: 1.15–1.24). Similarly, for GSTT1 status, exclusion of one outlying study[24] resulted in a Q statistic that was no longer statistically significant. Its odds ratio is 1.08 (95% confidence interval, 1.02–1.14).

To determine the effect of GSTM1 and GSTT1 deficiency associated with the distribution of tumour sites, we examined the associations of GSTM1 and GSTT1 deficiency with sites of head and neck cancer—for example, larynx, pharynx, and oral cavity. For GSTM1 status, the odds ratio is 1.14 (95% confidence interval, 1.05–1.21) for larynx (10 studies), 1.17 (95% confidence interval, 1.03–1.33) for pharynx (four studies), and 1.56 (95% confidence interval, 1.35–1.80) for oral cavity (15 studies). Tests for heterogeneity between studies of the oral cavity showed an impression of heterogeneity ($p<0.01$). Exclusion of three outlying studies[25 35 36] resulted in a Q statistic that was no longer statistically significant. Its odds ratio is 1.18 (95% confidence interval, 1.02–1.36). For GSTT1 status, the odds ratio is 1.05 (95% confidence interval, 0.94–1.16) for larynx (six studies), 0.96 (95% confidence interval, 0.83–1.16) for pharynx (two studies), and 1.16 (0.91–1.47) for oral cavity (eight studies).

All of these analyses were based on the pooling of data from the different ethnic groups. Subgroup analyses in the different ethnic groups were also performed. The overall odds ratios for GSTM1 status were 1.13 (95% confidence interval, 1.08–1.18) in whites, 1.55 (95% confidence interval, 1.18–2.11) in African-Americans and 1.53 (95% confidence interval, 1.19–1.97) in Asians. Tests for heterogeneity showed substantial evidence of heterogeneity in Asians ($p<0.005$). However, if we excluded three outlying studies,[7 28 36] the Q statistic showed that this was no longer statistically significant. Its odds ratio was 1.26 (95% confidence interval, 1.16–1.37). Similarly, the overall odds ratios for GSTT1 status were 1.13 (95% confidence interval, 0.97–1.32) in whites, 0.88 (95% confidence interval, 0.49–1.57) in African-Americans[5] and 1.19 (95% confidence interval, 0.87–1.63) in Asians. There was evidence of heterogeneity across the white and Asian studies ($p<0.05$). With the exclusion of one outlying study each of whites[6] and Asians,[30] the Q statistic indicated no evidence of heterogeneity between studies. Their odds ratios were 1.10 (95% confidence interval, 1.03–1.18) and 1.08 (95% confidence interval, 0.98–1.20), respectively.

Restricting analyses to geographic regions, the pooled odds ratios for GSTM1 status were 1.15 (95% confidence interval, 1.08–1.21) in Europe, 1.18 (95% confidence interval,

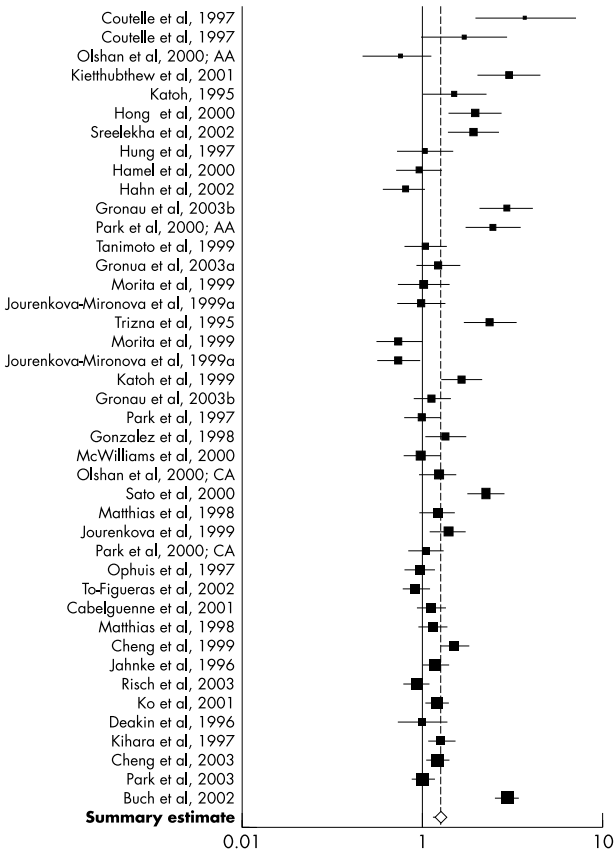

Figure 1 Funnel plot of odds ratio (OR) of GSTM1 deficiency and risk of developing head and neck cancer. Studies are stratified by sample size and are plotted according to the variance of log(OR). Each box represents the odds ratio estimate and its area is proportional to the weight of the study. The smallest study has a sample size of 55; the largest study has a sample size of 747. AA, African-American; CA, white.

1.09–1.28) in America and 1.53 (95% confidence interval, 1.19–1.97) in Asia. Tests for heterogeneity showed substantial evidence of heterogeneity in the studies of Asia ($p<0.005$). With the exclusion of one outlying study,[36] the Q statistic showed as no longer statistically significant. Its odds ratio was 1.33 (95% confidence interval, 1.23–1.44). Similarly, the pooled odds ratios for GSTT1 status were 0.98 (95% confidence interval, 0.91–1.08) in Europe, 1.55 (95% confidence interval, 1.08–2.22) in America, and 1.19 (95% confidence interval, 0.87–1.63) in Asia. However, there was evidence of heterogeneity in the studies of America and Asia ($p<0.05$). Exclusion of one outlying study each for America[6] and Asia[36] resulted in a Q statistic that was no longer statistically significant. Their odds ratios were 1.54 (95% confidence interval, 1.34–1.79) and 1.08 (95% confidence interval, 0.98–1.20), respectively.

Tables 1 and 2 show that population and hospital based controls were used in the different studies. Restricting analyses to population based studies, the pooled odds ratios of head and neck cancer associated with GSTM1 and GSTT1 status were 1.34 (95% confidence interval, 1.12–1.61) and 1.10 (95% confidence interval, 1.03–1.18), respectively. However, an impression of heterogeneity between studies was observed in the GSTM1 status by statistical analysis ($p<0.005$). Similarly, restricting analyses to hospital based studies, the pooled odds ratios of head and neck cancer associated with GSTM1 and GSTT1 status were 1.17 (95% confidence interval, 1.10–1.24) and 1.19 (95% confidence interval, 1.09–1.30), respectively.

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[11] 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

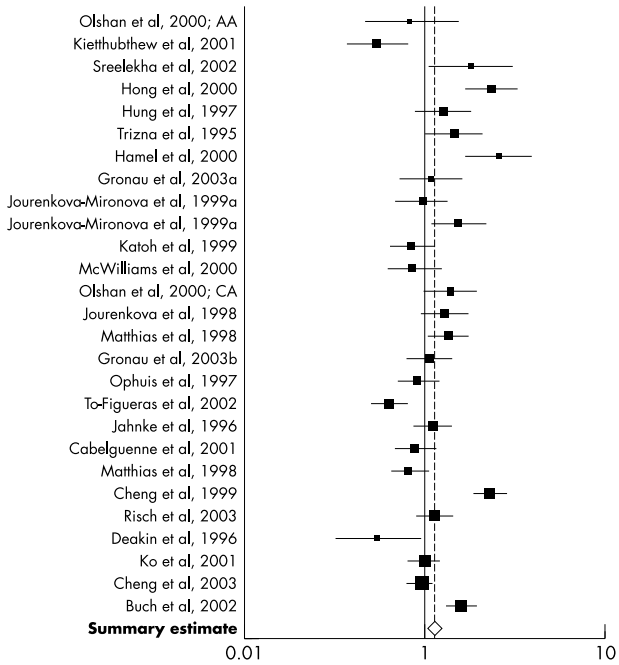

Figure 2 Funnel plot of odds ratio (OR) of GSTT1 deficiency and risk of developing head and neck cancer. Studies are stratified by sample size and are plotted according to the variance of log(OR). Each box represents the odds ratio estimate and its area is proportional to the weight of the study. The smallest study has a sample size of 88; the largest study has a sample size of 747. AA, African-American; CA, white.

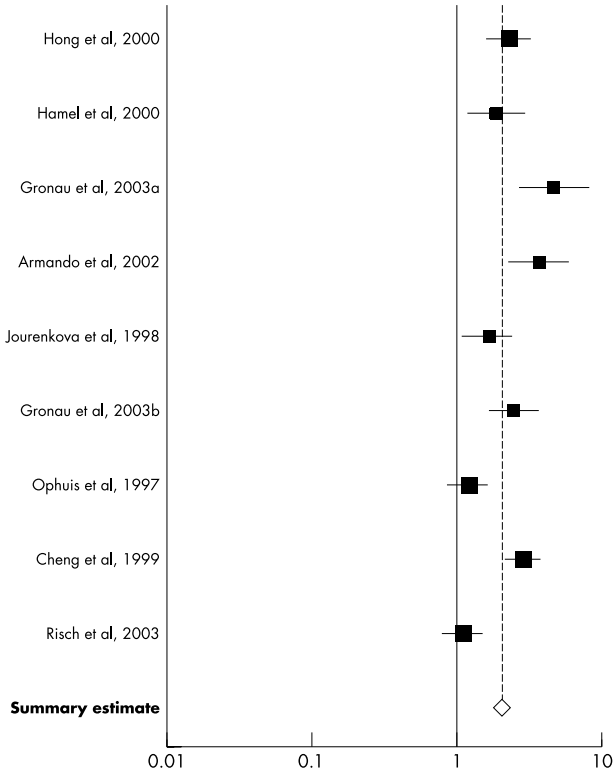

Figure 3 Funnel plot of odds ratio (OR) of both GSTM1 and GSTT1 deficiency and risk of developing head and neck cancer. Studies are stratified by sample size and are plotted according to the variance of the log(OR). Each box represents the odds ratio estimate and its area is proportional to the weight of the study. The smallest study has a sample size of 145; the largest study has a sample size of 496.

inconsistency about the effects of GSTM1 and GSTT1 deficiency on susceptibility to head and neck cancer prompted our meta-analysis to explore a possible association. Forty two studies used in our analyses provided data on over 13 000 and 8500 cancer cases and individual controls for GSTM1 and GSTT1 status, respectively. Based upon these data, the results of our analysis suggest that GSTM1 or GSTT1 deficiency are associated with a modest increased risk of head and neck cancer, particularly among individuals with both GSTM1 and GSTT1 deficiency. Cigarette smokers and alcohol users are at increased risk of head and neck cancer.

In the overview of all the studies, it is clear that the design of some studies in evaluating GSTM1 and GSTT1 deficiency as risk factor for head and neck cancer was less than optimal. In some studies failure to demonstrate a relationship may partly be due to a lack of statistical power. If GSTM1 and GSTT1 status are associated with two fold increased risk of head and neck cancer, many published studies are apparently underpowered to demonstrate such a moderate effect. To identify interplay between genotypes and cancer risk, a large sample size is crucial in the design of case control studies. Some of the case control studies analysed were based on a comparison of cancer cases and hospital based controls. Studies with hospital based controls might provide lower risk estimates since diseases of controls might be associated with the polymorphisms under study. The use of population based controls is, therefore, more appropriate. This was observed in our analysis. For example, the odds ratio of GSTM1 status is 1.34 (95% confidence interval, 1.12–1.61) for the population based studies and 1.17 (95% confidence interval, 1.10–1.24) for the hospital based studies.

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.[57 58] 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,[5–7 24 25 28 30 35 36] 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.[59] 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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