POLYMORPHISMS OF GSTT1 AND RELATED GENES IN HEAD AND NECK CANCER RISK

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Abstract: Background. Glutathione S-transferase T1 detoxifies some environmental carcinogens while activating others and is deleted in 15% to 38% of humans. We sought to determine whether GSTT1 genotype and genotypes of several related genes are associated with risk of squamous cell carcinoma of the head and neck (HNSCC).

Methods. Somatic genotypes for GSTT1, GSTM1, GSTP1, and CYP1A1 were determined in 283 individuals with HNSCC and 208 population-based controls.

Results. The OR for presence of GSTT1 was 1.6 (CI, 1.1–2.5, p = .03). HNSCC risk was not associated with GSTM1 null genotype, the presence of the GSTP1 Val/Val genotype, or the Val/Val homozygous genotype for CYP1A1. Stratified analysis revealed disparate ORs for women (OR, 3.0; CI, 1.5–6.3) and men (OR, 1.2; CI, 0.7–2.1) for the presence of GSTT1.

Conclusions. In this population, the presence of GSTT1 gene was associated with a significant increase in the risk of HNSCC.

Keywords: head and neck cancer; glutathione transferases; GSTT1; CYP1A1; GSTM1; GSTP1; epidemiology

Approximately 37,200 new cases and 11,000 deaths are expected as a consequence of head and neck cancer in 2002.1 Worldwide, head and neck cancer accounts for 6.1% of all malignancies.2 Tobacco and alcohol exposure are the most important environmental factors that contribute to the development of head and neck cancer.3 A deeper understanding of host genetic factors that may modulate the influence of environmental risk factors is needed.

Polymorphisms in the isoenzymes of the cytochrome P450s and of the glutathione S-transferases have been associated with tobacco-induced malignancies.4–7 Significant associations between the aforementioned polymorphisms and head and neck squamous cell carcinoma (HNSCC) have been seen, and evidence of polymorphism interaction with tobacco smoke and/or alcohol consumption

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has been reported. Excellent contemporary reviews of this subject are available.\(^8\)

**GSTT1**
The theta-class glutathione S-transferase T1 (GSTT1) null mutation is found in approximately 15% to 38% of the Caucasian population.\(^8\)\(^–\)\(^1\) A number of relatively small studies have sought to determine whether this mutation is associated with head and neck cancer. A study in Ashkenazi Jews and French-Canadians found an odds ratio (OR) of 5.00 (95% CI, 1.66–15.1) for the null mutation in HNSCC patients compared with controls.\(^1\) One larger study with about 175 French Caucasian cases and controls found a significantly increased OR among heavy smokers only (OR 3.3; 95% CI, 1.3–8.1).\(^1\) A US study looking at the joint effects of tobacco use and GSTT1 null mutation on HNSCC suggested interaction only for subjects with 40+ years of tobacco use.\(^1\) One additional study found a significantly elevated OR for the null mutation in German Caucasian patients with glottic tumors only.\(^1\) At least seven studies found nonsignificant associations.\(^1\)\(^5\)\(^–\)\(^2\)\(^1\) In contrast, one group in the Netherlands observed the GSTT1 null mutation more frequently in patients with benign head and neck lesions than in head and neck cancer patients, but no difference was seen comparing blood donor controls with HNSCC.\(^2\)

**GSTM1**
The glutathione S-transferase M1 isoenzyme (GSTM1) is a phase II detoxification enzyme homozygously deleted in about 50% of individuals in European and US populations.\(^2\)\(^3\)\(^–\)\(^2\)\(^5\) Evidence is still limited as to whether the GSTM1 null mutation is a risk factor for HNSCC. Four relatively small studies suggested an association between the null mutation and HNSCC, including 42 race-matched pairs in a US population (OR, 3.1; 95% CI, 1.2–7.8), a Japanese population with nonlaryngeal HNSCC (OR, 1.8; 95% CI, 1.0–3.0), a Spanish population of smokers with laryngeal cancer (OR, 2.5; 95% CI, 1.8–3.1), and a Thai population with oral cancer (OR, 3.6; 95% CI, 1.0–12.9).\(^1\)\(^5\)\(^–\)\(^2\)\(^6\)\(^,\)\(^2\)\(^7\) Other groups did not find a significant association.\(^1\)\(^1\)\(^,\)\(^1\)\(^2\)\(^,\)\(^1\)\(^7\)\(^,\)\(^1\)\(^9\)\(^,\)\(^2\)\(^1\)\(^,\)\(^2\)\(^8\)\(^–\)\(^3\)\(^0\)

**GSTP1**
Glutathione S-transferase P1 (GSTP1) is overexpressed in human carcinomas of the colon, stomach, urinary bladder, uterine cervix, esophagus, and lung (non-small cell).\(^3\)\(^1\) Ali-Osman and co-workers\(^3\)\(^2\) have described a polymorphism of GSTP1 resulting from a single base change at nucleotide 313 that produces an enzyme with reduced capacity for detoxifying a number of carcinogens. There is conflicting evidence regarding GSTP1 alleles and the risk of HNSCC. One study reported an association between the wild-type genotype and laryngeal cancer in a Japanese population (OR, 2.4; 95% CI, 1.0–5.9).\(^3\)\(^0\) Two studies reported the opposite finding with excess mutant alleles in oral/pharyngeal cancer in a German population (OR, 2.1; 95% CI, 1.0–4.3) and pharyngeal cancer in Caucasians alone or combined with the African-American subjects (OR, 2.6; 95% CI, 1.1–6.2 and OR, 2.4; 95% CI, 1.2–4.8).\(^3\)\(^3\)\(^,\)\(^3\)\(^4\) Three studies reported no significant association between the GSTP1 genotype and HNSCC in German, Chinese, and Northern European Caucasian populations.\(^1\)\(^9\)\(^,\)\(^2\)\(^1\)\(^,\)\(^3\)\(^5\)

**CYP1A1**
One cytochrome P450 1A1 (CYP1A1) gene polymorphism of interest consists of a single base change at codon 462 in exon 7 (Ile462Val) that codes for either an Ile or a Val.\(^3\)\(^6\) This base change has been shown to influence the risk for lung cancer, coding for a more inducible form of the enzyme.\(^3\)\(^6\)\(^,\)\(^3\)\(^7\) A single Japanese study found an association between the CYP1A1 Val/Val genotype and HNSCC at all locations (OR, 4.1; 95% CI, 1.1–15.0) and an even stronger association for pharyngeal carcinomas (OR, 5.7; 95% CI, 1.1–28).\(^3\)\(^0\) However, a number of studies, including those carried out in Western populations, have failed to demonstrate an association between HNSCC and CYP1A1.\(^1\)\(^2\)\(^,\)\(^1\)\(^3\)\(^,\)\(^1\)\(^7\)\(^,\)\(^1\)\(^9\)\(^,\)\(^3\)\(^3\)

The conflicting results may reflect a lack of contribution of these polymorphisms to cancer risk. Alternately, they may reflect the methodological limitations of the published studies. All these studies had limited sample sizes, and many were limited by lack of accurate assessment of confounding risk factors or problems with case or control group selection. Although many have matched for gender or included gender in multivariate analyses, only one other study has reported the GST polymorphisms stratified by genders.\(^3\)\(^8\) This study, with 491 Caucasian subjects, is one of the largest such studies reported to date in HNSCC. A distinction between prevalent and incident cases is made in this study. The known risk factors, such as tobacco use and alcohol, are assessed in cases and controls.
MATERIALS AND METHODS

Population Samples. Individuals with head and neck squamous cell carcinoma (cases) were recruited from the Head and Neck Oncology clinic at Oregon Health & Science University in Portland, Oregon. Controls were recruited by advertisement for adult smokers, and were from the same geographic area as the cases. Eligibility criteria for cases was age 18 years or older, histologically proven squamous cell carcinoma of the head and neck region, and ability to give informed consent. Eligibility for controls was age 18 years or older, lack of any malignancy (except nonmelanoma skin cancer or carcinoma in situ of the uterine cervix). After giving informed consent, study subjects were administered a questionnaire regarding age, race, tobacco use, alcohol use, and family history of cancer. This study was approved by the Institutional Review Board of Oregon Health & Science University.

DNA Preparation. DNA was isolated from peripheral blood lymphocytes by the Puregene method (Gentra Systems, Minneapolis, MN). DNA samples were serially numbered on arrival in the laboratory. To limit potential bias, an aliquot of each DNA sample was labeled with a random four-digit number, blinding the individual performing the assays as to the case/control status of each DNA sample.

PCR Techniques. Polymerase chain reaction (PCR) was carried out in a total volume of 50 μL including 0.2 μg of genomic DNA; 400 μM each of dATP, dCTP, dGTP, and dTTP; 1.5 mM of MgCl2; 0.5 μM of each primer; 1 unit of Taq DNA polymerase (Promega), and subjected to thermal cycling conditions optimized for each gene. Amplification products were resolved on a 2% agarose gel containing ethidium bromide, and DNA bands were visualized by ultraviolet transillumination.

GSTT1 Null Polymorphisms. The method for detecting the presence or absence of GSTT1 was as described by Pemble, et al10 and used primers 5’-TTTCTTACTGGTCCATCTCCT-3’ and 5’-TCACGGATCATGCGGACA-3’. The reaction was cycled 35 times at 95°C for 1 minute, and at 72°C for 15 minutes. Primers for human apurinic endonuclease (APE) (exon 5) were included as a positive internal control.

GSTM1 Null Polymorphism. The PCR assay for deletion of GSTM1 was performed essentially as described by Comstock and coworkers.39 Co-amplification of exon 4 of the hprt gene was used as a positive internal control. The primers were 5’-CTGCCCTACTTGATGGATGGG-3’ and 5’-CTGGATTGTACGATCATGC-3’, respectively. The reaction was cycled 35 times at 94°C for 20 seconds, 55°C for 1 minute, and 72°C for 1 minute.

GSTP1 (Ile105Val, A313G) Polymorphism. GSTP1 genotyping was done following the methods of Ali-Osman.32 This was a restriction fragment length polymorphism (RFLP) assay, which was designed to examine exon 5 for the presence of the mutation at amino acid 105 (Ile105Val). The exon together with segments of surrounding introns were amplified by PCR and subsequently digested by TaqI, which digested the mutant but not the wild type. The primers were 5’-CCA GGCTGGGCTCACAGACAGC-3’ and 5’-GCT CAGCCCAAGCACCCTGAGG-5’. The reactions were cycled for 94°C for 1 minute, 53.5°C for 1 minute, and 72°C for 1 minute.

CYP1A1 (Ile462Val, G4889A) Polymorphism. The CYP1A1 genotyping assay was designed using a mismatch PCR paradigm to amplify the region of codon 462 in exon 7. This reaction required two separate PCR reactions for each DNA sample. The common forward primer 5’-GAACACTGCACCTCAGCAGTCT-3’ was used in both reactions. Reverse primers were designed with the same sequence except for the last base with primer 5’-AAGACCTCCCGCGGCGAAT-3’, which anneals to the isoleucine allele or primer 5’-AAGACCTCCGGCGGCGAAT-3’, which anneals to the valine allele. PCR reaction was cycled 25 times at 95°C for 1 minute, followed by 72°C for 1 minute.

Statistical Analysis. ORs and 95% CIs were calculated by comparing genotype frequencies in the case population with the control population by standard methods.40 For the GSTT1 and GSTM1 polymorphisms, the referent genotype was the presence of at least one GSTM1 or GSTT1 gene (i.e., +/+ or +/−). For the GSTP1 polymorphism, the referent genotype was the homozygous Ile/Ile group. Likewise, the referent for the exon 7 polymorphism of CYP1A1 was the homozygous Ile/Ile group. Statistical analyses were performed...
RESULTS

Demographics. A total of 615 individuals were recruited to the study. Of these, 359 individuals with head and neck cancer (cases) were recruited from the Head and Neck Oncology clinics at Oregon Health & Science University (OHSU), and 256 controls were recruited by advertisements recruiting adult smokers. For this analysis, only cases with primary tumors of the oral cavity, larynx, and pharynx were included (patients with tumors of the lip, paranasal sinuses, and patients whose primary tumor could not be definitively determined were excluded). Because 95% of cases and 85% of controls were Caucasian, only Caucasians were included in the remaining analyses. DNA was analyzable from 90% of case and 99% of control subjects. The final study population (eligible and analyzable) consisted of 283 cases and 208 controls. Their characteristics are summarized in Table 1. The case subjects were significantly older and had used more tobacco and alcohol than the control group. The characteristics of the case group are further characterized in Table 2. Incident cases, defined as cases enrolled within 1 year of initial diagnosis, constituted 49% of the study population. The primary tumor site distribution reflects the distribution of primary tumor sites for the patient population of OHSU.

### Table 1. Demographics.

<table>
<thead>
<tr>
<th></th>
<th>Cases</th>
<th>Controls</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>283</td>
<td>208</td>
<td>—</td>
</tr>
<tr>
<td>Age (median)</td>
<td>63 (55–71)</td>
<td>53 (46–60)</td>
<td>p &lt; .001</td>
</tr>
<tr>
<td>Gender (male %)</td>
<td>195 (69)</td>
<td>118 (57)</td>
<td>p = .006</td>
</tr>
<tr>
<td>Industry use (ever-smoker %)</td>
<td>246 (87)</td>
<td>191 (92)</td>
<td>p = .1406</td>
</tr>
<tr>
<td>Tobacco use (median pack-years)</td>
<td>47 (27–67)</td>
<td>32 (15.50)</td>
<td>p &lt; .001</td>
</tr>
<tr>
<td>Alcohol use (median year of 1 ounce/day consumption)</td>
<td>27 (0–15)</td>
<td>6 (0–15)</td>
<td>p &lt; .001</td>
</tr>
</tbody>
</table>

### Table 2. Characteristics of cases.

<table>
<thead>
<tr>
<th></th>
<th>Number (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incident</td>
<td>140 (49)</td>
</tr>
<tr>
<td>Prevalent</td>
<td>143 (51)</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>111 (39%)</td>
</tr>
<tr>
<td>Larynx</td>
<td>100 (35%)</td>
</tr>
<tr>
<td>Pharynx</td>
<td>72 (25%)</td>
</tr>
<tr>
<td>Total</td>
<td>283 (100%)</td>
</tr>
</tbody>
</table>

*Percent do not total to 100 because of rounding.

Polymorphism Frequencies in Cases and Controls. Individual genes were first analyzed using chi square analysis. These results are summarized in Table 3. The OR for the presence of the GSTT1 gene was 1.6 (95% CI, 1.1–2.5; p = .03). An analysis limited to incident case (n = 149) was consistent with the findings in the entire cohort (OR, 1.8; 95% CI, 1.0–3.0; p = .04). Several additional analyses that stratified the population by age, gender, and smoking history further examined the relationship between GSTT1 genotype and the risk of head and neck cancer in all cases and incident cases (Table 4). Similar ORs were found when the population was stratified by median age of the total study population (59 years), although the study lacked statistical power for each individual strata. Stratification by gender revealed disparate
ORs for women (OR, 2.7; 95% CI, 1.3–5.7) and men (OR, 1.2; 95% CI, 0.7–2.1) for the presence of GSTT1. The disparity seemed greater when the analysis was limited to incident cases (women: OR, 4.2; 95% CI, 1.4–12.8; men: OR, 1.2; 95% CI, 0.7–2.3). When the GSTT1 data were stratified by smoking history, the association of HNSCC risk with the presence of a GSTT1 allele was significant only in smokers. There were no differences in GSTT1 genotype among the different tumor primary sites (data not shown).

HNSCC risk was not associated with GSTM1 null genotype (OR, 1.0; 95% CI, 0.7–1.5), the presence of the GSTP1 Val/Val genotype (OR, 1.1; 95% CI, 0.6–2.1), or the homozygous genotype for CYP1A1 (OR, 1.4; 95% CI, 0.3–6.9). This lack of association persisted after stratification of case and control groups by age, gender, and tobacco use. Similarly, an analysis by incident cases only revealed no significant differences in risk estimates.

**DISCUSSION**

The epidemiology of HNSCC is similar to the epidemiology of lung and bladder cancer in that it is strongly related to tobacco exposure. In addition, in most case-control studies, the risk of HNSCC has also been strongly influenced by exposure to ethanol.\(^3\) Tobacco exposure and alcohol exposure seem to act synergistically to increase the risk of the development of cancer in the mucosal surfaces of the mouth and esophagus.\(^3\)

Previous studies of gene polymorphisms and risk for other tobacco-associated cancers, such as lung carcinoma and bladder carcinoma, have defined gene polymorphisms that increase cancer risk in smokers.\(^41–48\) For this reason, it is of interest to examine the same genetic polymorphisms that are thought to alter the risk of lung cancer to determine whether these factors also increase the risk of HNSCC developing. Because of the strong relationship of risk of HNSCC developing to alcohol and tobacco risk, it is important to control for these risks in assessing the effect of genetic polymorphisms on HNSCC risk.

The results of this case-control study demonstrate an increased risk for head and neck cancer developing for carriers of the GSTT1 gene, with an OR of 1.6 (95% CI, 1.1–2.5). Because a genetic polymorphism could alter the prognosis of HNSCC, it was important to determine whether this OR was observed when the analysis was limited to incident cases of HNSCC.

A similar OR was observed when the analysis was limited to incident cases. In this study, the association between the presence of the GSTT1 gene and HNSCC was strongest among heavy smokers (≥41 pack-year smoking history) with an OR of 2.2 (95% CI, 1.2–4.3). This interaction of

### Table 4. Stratified analysis of the GSTT1 genotypes (ORs for the GSTT1 present vs absent.)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Cases T1 positive N (%)</th>
<th>Controls T1 positive N (%)</th>
<th>OR (95% CI)</th>
<th>p value</th>
<th>Cases T1 positive N (%)</th>
<th>Controls T1 positive N (%)</th>
<th>OR (95% CI)</th>
<th>p value</th>
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<tbody>
<tr>
<td>Unstratified</td>
<td></td>
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<tr>
<td>Age</td>
<td></td>
<td></td>
<td>1.6 (1.1–2.5)</td>
<td>.03</td>
<td>1.8 (1.0–3.0)</td>
<td>.04</td>
<td></td>
<td></td>
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<tr>
<td>Gender</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Male</td>
<td>154 (79)</td>
<td>89 (75)</td>
<td>1.2 (0.7–2.1)</td>
<td>.55</td>
<td>1.2 (0.7–2.3)</td>
<td>.61</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>75 (85)</td>
<td>61 (68)</td>
<td>2.7 (1.3–5.7)</td>
<td>.01</td>
<td>4.2 (1.4–12.8)</td>
<td>.02</td>
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<tr>
<td>Smoking history</td>
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<tr>
<td>Never smoker</td>
<td>27 (75)</td>
<td>12 (71)</td>
<td>1.3 (0.3–4.5)</td>
<td>.99</td>
<td>1.4 (0.3–7.3)</td>
<td>.98</td>
<td></td>
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<tr>
<td>Ever smoker</td>
<td>202 (82)</td>
<td>138 (72)</td>
<td>1.7 (1.1–2.7)</td>
<td>.02</td>
<td>1.8 (1.0–3.2)</td>
<td>.04</td>
<td></td>
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<tr>
<td>Alcohol use*</td>
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<tr>
<td>&lt; Median ounce yrs</td>
<td>43 (80)</td>
<td>66 (71)</td>
<td>1.6 (0.7–3.6)</td>
<td>.34</td>
<td>1.2 (0.8–5.6)</td>
<td>.16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ Median ounce yrs</td>
<td>82 (82)</td>
<td>32 (68)</td>
<td>2.1 (1.0–4.7)</td>
<td>.09</td>
<td>1.9 (0.9–4.0)</td>
<td>.12</td>
<td></td>
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</tr>
</tbody>
</table>

*Questions about alcohol use were added to the questionnaire late; therefore, these data are not available for all patients.

Median age for all cases and controls was 59. Median age for incident cases and control was 56. Median pack years for all cases and controls was 41. Median pack years for incident cases and controls was 40. Median ounce years for all cases and controls was 12. Median ounce years for incident cases and controls was 12.
the risks caused by the GSTT1 gene and smoking is consistent with a biochemical interaction of the GSTT1-1 enzyme and some component of tobacco smoke. Stratification by gender demonstrated disparate ORs for men and women (1.2 and 2.7). The increased risk for development of HNSCC in GSTT1-positive women was significant (p = .01).

HNSCC risk was not associated with GSTM1 null genotype, the presence of the GSTP1 Val/Val genotype, or the Val/Val homozygous genotype for CYP1A1. Although this is one of the largest case-control studies of the effect of genetic polymorphisms on HNSCC risk and the largest study conducted in a US population, the study is not powered to exclude a small effect of these genotypes on HNSCC risk.

Our finding that the positive GSTT1 genotype is associated with risk of HNSCC among smokers is at odds with several published reports. This study is, however, the largest study with non-hospital/clinic controls and the largest study in the United States. By not matching on gender, this study was able to include analysis by gender and thereby demonstrate a difference in the effect of the GSTT1 gene on HNSCC risk in men and women. Nonetheless, as is the case with any single study, this finding could represent a chance observation or be the result of unsuspected selection bias and should be confirmed in larger, well-designed studies.

Glutathione S-transferases are usually considered as detoxification enzymes that inactivate carcinogens by conjugation with glutathione. However, for particular chemical substrates, GSTT1-mediated glutathione conjugation can result in activation of a compound to an electrophile that is capable of mutagenesis. An example of such an interaction is GSTT1-mediated activation of halomethanes. Dichloromethane (DCM) is a well-studied example of a chemical that is activated to a mutagenic compound when conjugated to glutathione by GSTT1. DCM is used in a variety of industrial settings (paint and varnish strippers and production of plastics, film, and pharmaceuticals) but is not described as a byproduct of tobacco or alcohol exposure. GSTT1 activates DCM to a mutagen by converting it to formaldehyde. Although DCM has not been associated with tobacco, there may be other tobacco byproducts that gain carcinogenic function after GSTT1-mediated activation.

Interestingly, the presence of GSTT1 seems to interact with smoking in modulating the risk of heart disease. Two studies have shown a significant three-fold increase in the risk of coronary heart disease and peripheral vascular disease in smokers (≥20 pack-years) with the GSTT1 genotype.

Analogous to our findings indicating an interaction between gender and smoking, another group reported a gender difference in the risk of lung cancer from the GSTM1 null genotype that was potentiated by smoking. They reported an OR of 2.5 (95% CI, 1.09–5.72) for lung cancer in women and 1.4 in men (95% CI, 0.58–3.38). Women smokers were at an even higher risk from the combination of M1 null genotype and smoking (OR, 3.03; 95% CI, 1.09–8.40). The reason for gender-specific interactions between the GSTT1s and cancer risk is not known.

However, in rats there are different patterns of expression of hepatic GSTT1 in males and females, as well and gender-specific differences in halomethane metabolism. Additional studies to examine the relationship between gender, smoking, and the GSTT1 are needed to confirm the findings presented here.

In summary, to address the effect that different genotypes may have in altering the risk of head and neck cancer developing, we conducted a case-control study of four genetic polymorphisms and their association with head and neck cancer risk. Of the four polymorphisms studied, the homozygous deletion of the GSTT1 gene was associated with protection against the risk of developing head and neck cancer. This protection was most pronounced in the female population. We were unable to demonstrate an altered risk for the development of head and neck cancer in individuals bearing the null alleles of GSTM1 and GSTP1 or the Val/Val genotype of P4501A1.

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GSTT1 Polymorphism in Head and Neck Cancer Risk


