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Original Article

GSTM1 and *GSTT1* null polymorphisms and risk of salivary gland carcinoma

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Abstract: Glutathione S-transferase (*GST*) genes detoxify and metabolize carcinogens, including oxygen free radicals which may contribute to salivary gland carcinogenesis. This cancer center-based case-control association study included 166 patients with incident salivary gland carcinoma (SGC) and 511 cancer-free controls. We performed multiplex polymerase chain reaction-based polymorphism genotyping assays for *GSTM1* and *GSTT1* null genotypes. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated with multivariable logistic regression analyses adjusted for age, sex, ethnicity, tobacco use, family history of cancer, alcohol use and radiation exposure. In our results, 27.7% of the SGC cases and 20.6% of the controls were null for the *GSTT1* (P = 0.054), and 53.0% of the SGC cases and 50.9% of the controls were null for the *GSTM1* (P = 0.633). The results of the adjusted multivariale regression analysis suggested that having *GSTT1* null genotype was associated with a significantly increased risk for SGC (odds ratio 1.5, 95% confidence interval 1.0-2.3). Additionally, 13.9% of the SGC cases but only 8.4% of the controls were null for both genes and the results of the adjusted multivariable regression analysis suggested that having both null genotypes was significantly associated with an approximately 2-fold increased risk for SGC (odds ratio 1.9, 95% confidence interval 1.0-3.5). The presence of *GSTT1* null genotype and the simultaneous presence of *GSTM1* and *GSTT1* null genotypes appear associated with significantly increased SGC risk. These findings warrant further study with larger sample sizes.

Key words: Glutathione S-transferase (*GST*); single nucleotide polymorphism; salivary gland carcinoma (SGC); genetic susceptibility; molecular epidemiology

Introduction

Salivary gland carcinoma (SGC) is a rare malignancy with an incidence rate of approximately 1 per 100,000 population per year in the United States [1]. However, the incidence of SGC as a proportion of all head and neck cancers increased from 6.3% during 1974 through 1976 to 8.1% during 1998 through 1999 [1]. SGC may arise in major or minor salivary glands and may have a variety of histologic and biologic characteristics. The parotid gland is the most common anatomic site of origin, and mucoepidermoid carcinomas and adenoid cystic carcinomas are the most frequently occurring histologic types [2,3]. Although the etiology of SGC remains unclear, prior exposure to radiation has been the most clearly identified SGC risk factor [4-6]. This type of cancer is special because it is a diverse group of neoplasm with differing characteristics [7].

Glutathione S-transferase (*GST*) genes are important in detoxifying and metabolizing carcinogens [8]. The GSTs catalyze the glutathione conjugation of these toxic and mutagenic compounds with electrophilic functional groups to prevent adduct formation, and thus protect organisms from DNA damage or protecting chromosomes from oxidative damage [9, 10]. The human cytosolic *GST* system consists of 7 gene classes of isoenzymes, designated *GST-α, GST-μ, GST-π,*

GST-σ, GST-ω, GST-θ, and *GST-ξ*. Each gene class can include several genes [11]. For instance, the *GST-μ* family consists of *GST-μ1* through *GST-μ5*. The effect of *GST* polymorphisms on genetic susceptibility has been investigated for several *GST* isoenzymes, particularly *GST-μ1* (*GSTM1*gene) and *GST-θ1* (*GSTT1*gene). Both genes possess null genotypes with no enzyme activity. Epidemiologic studies have found that individuals with homozygous deletions of these genes (ie, *GSTM1* null or *GSTT1* null) have an increased risk of cancer at a number of different body sites, including the head and neck, lungs, breasts, and brain [12-16].

The frequency of *GSTM1* and *GSTT1* null genotypes may vary in different populations. In Caucasian populations, 40%~60% are homozygote for the *GSTM1* null genotype and 20%-30% are homozygote for the *GSTT1* null genotype [17]. In African American populations, 30% are homozygote for GSTM1 null genotype and in the general population, 15% are missing both *GSTM1* and *GSTT1* genes [18, 19]. These polymorphisms may result in differences in enzyme activity, which may provide a potential mechanism for increased susceptibility to cancers including SGC in different populations. In addition to *GSTM1* and *GSTT1* null genotypes being less efficient at processing carcinogens and radical oxygen species, the frequency of p53 somatic mutation is greater in patients with the *GSTT1* null genotype compared with patients carrying *GSTT1* gene [20]. Therefore, understanding the variation in individuals in genetic susceptibility to SGC caused by these two polymorphisms holds great promise for primary cancer prevention. Identifying markers of SGC risk would greatly enhance cancer prevention programs, which is currently extremely limited.

In this molecular epidemiologic case-control study, we explored the association between *GSTM1* and *GSTT1* null genotypes and the risk of SGC, with adjustments for age, sex, ethnicity, smoking, drinking, family cancer history, and radiation exposure. We hypothesized that the lack of *GSTM1* and *GSTT1* isoenzymes puts individuals at risk of SGC by limiting their ability to detoxify carcinogens resulting from exposures or products of oxidative stress.

Materials and methods

Study subjects

This was a tertiary cancer center–based, case-control study. From April, 1996 to July, 2007, patients who presented to the Head and Neck Surgery Clinic at The University of Texas M. D. Anderson Cancer Center with a diagnosis of SGC were recruited into a molecular epidemiologic study of nonsquamous cell carcinoma of the head and neck before undergoing definitive surgical therapy. Final histopathologic diagnoses were obtained from a review of the medical records. Patients who underwent surgical excision or biopsy and received a definitive histopathologic diagnosis were included in the study. We included cancer-free control subjects who had been recruited from among spouses and other visitors who accompanied patients for a molecular epidemiologic study of head and neck squamous cell carcinoma from November, 1996 to March, 2005. The final genotype analysis included 166 SGC cases and 511 cancer-free controls. Each study subject had completed a self-administered questionnaire, providing demographic, socioeconomic, risk exposure, and family medical history data. A positive family history of cancer was defined as reportedly having any first-degree relative with a history of cancer except for nonmelanoma skin carcinoma. Positive radiation exposure was defined as whole body or head-and-neck-specific radiation exposure.

Smokers were defined as those subjects who had smoked more than 100 cigarettes in their lifetimes. Subjects who had quit smoking more than 1 year before enrollment in the study were classified as former smokers, with all other smokers considered current smokers. Those who had used alcohol at least once a week for more than 1 year were defined as drinkers; those drinkers who had not drunk alcohol for more than 1 year before enrollment were defined as former drinkers; and all other drinkers were considered current drinkers. Ethnicity was categorized by the subject as non-Hispanic white or other (Hispanic, African American, or Asian). After institutional review board–approved informed consent had been obtained, each participant had donated 20 mL of blood for cell culture and DNA extraction.

Genotyping

A leukocyte cell pellet was obtained from the buffy coat by centrifugation of 1 mL of whole blood. The pellet was used for genomic DNA extraction with a DNA blood kit (Qiagen DNA Blood Mini Kit; Qiagen, Inc, Valencia, Calif) according to the manufacturer's instructions. We used a multiplex polymerase chain reaction (PCR) assay to simultaneously determine the presence or absence of the *GSTM1* and *GSTT1* genes and the dihydrofolate reductase (*DHFR*) gene as an internal control for amplification failure secondary to DNA degradation. The primers used for *GSTM1* were 5'-GAA CTC CCT GAA AAG CTA AAG C-3' and 5'-GTT GGG CTC AAA TAT ACG GTG G-3', generating a 480–base pair (bp) fragment. For *GSTT1*, the primers used were 5'-TTC CTT ACT GGT CCT CAC ATC TC-3' and 5'-TCA CCG GAT CAT GGC CAG CA-3', generating a 215-bp fragment. The primers used for *DHFR* were 5'-CATCGG CAAGAACG GGGACCT-3' and 5'-ACCGAAGCCTCCACCCAGT TG-3', generating a 280-bp fragment. The absence of a 480- or a 215-bp band in the PCR assay indicated the presence of a *GSTM1* null or a *GSTT1* null genotype, respectively. When no band was evident at 280 bp, the PCR assay was considered unsuccessful, most likely owing to degraded DNA because *DHFR* is typically easily amplified. The *GSTM1*, *GSTT1*, and *DHFR* genes were coamplified in a 40-μL reaction mixture containing 100 ng of genomic DNA as the template, 3.5 pmol of each *GSTM1* primer, 2.9 pmol of each *GSTT1* primer, 6.2 pmol of each *DHFR* primer, 0.1mM deoxyribonucleotide triphosphate, 1X PCR buffer (50mM potassium chloride, 10mM Tris hydrochloride [pH, 9.0 at 25°C], 0.1% Triton X-100, and 1.5mM magnesium chloride), and 1.0 U of *Taq* DNA polymerase (Sigma-Aldrich Corp, St Louis, Mo). The PCR profile consisted of an initial melting step of 95°C for 5 minutes; 35 cycles of 95°C for 30 seconds, 58°C for 35 seconds, and 72°C for 60 seconds; and a final elongation step of 72°C for 10 minutes. The PCR products were separated on a 2% agarose gel and photographed with a digital imaging system (IS-1000; Alpha Innotech Co, San Leandro, Calif.).

Statistical analysis

All statistical analyses were two-sided and performed with commercially available statistical analysis system software (version 9.1, SAS Institute, Cary, NC). A *P* value of .05 was preset as the level of significance. The demographic characteristics of the study participants were compared using the two-sided $\chi 2$ tests to assess differences in age, sex, ethnicity, family cancer history, tobacco use, alcohol use, and radiation exposure frequencies. The *GST* genotypes were first analyzed as a dichotomized variable, with 0 being the null genotype and 1 being the other genotype. Univariate analysis was performed to calculate crude odds ratios (ORs) and 95% confidence intervals (CIs) for various strata for the *GSTM1* and *GSTT1* genotypes. Adjusted ORs were calculated, with adjustment for age, sex, ethnicity, tobacco use, alcohol use, family cancer history, and radiation exposure, using a multivariable logistic regression analysis. For the logistic regression analysis, the *GST* genotype was recorded as a dummy variable (0.0 for both null, 0.1 for *GSTM1* null, and 1.0 for *GSTT1* null). To assess trends, the quartered variables were treated as continuous variables and fit into the logistic regression model.

Results

We included 166 new patients with SGC and 511 cancer-free controls in this study. The demographic characteristics of case subjects and controls are shown in **Table 1**. The cases and controls appeared to be adequately frequency-matched for sex, ethnicity, family cancer history, smoking and drinking status. The mean age of the controls was 49.1 ± 11.4 (median, 48; range, 20-82) years while the mean age for the SGC cases was 54.5 ± 14.7 (median, 54.0; range, 18-90) years. The SGC cases were significantly older than the controls ($P < 0.001$). Radiation exposure history was not available for all study control subjects (13 controls were not available for information on radiation exposure). However, all these variables were further adjusted in later multivariable logistic regression analyses to control for any residual effects. Among the SGC cases, the parotid gland was the most common anatomic site of origin for SGC (27.5%). The most frequently encountered histologic types of SGC were adenoid cystic carcinoma (38.4%), followed by mucoepidermoid carcinoma (29.0%), adenocarcinoma (8%), acinic cell carcinoma (7.3%) carcinoma expleomorphic adenoma (3.6%), and salivary

Table 1. Demographic and exposure characteristics for SGC case and control subjects

	SGC (n = 166)		*Controls (n = 511)*		*P* value[a]
Variable	n	%	n	%	
Age					<0.001
≤ 50	64	38.6	328	64.2	
> 50	102	61.4	183	35.8	
Sex					0.089
Male	67	40.4	245	48.0	
Female	99	59.6	266	52.0	
Ethnicity					0.793
Non-Hispanic whites	128	77.1	399	78.1	
Other	38	22.9	112	21.9	
Family cancer history[b]					0.231
No	79	47.6	272	54.4	
Yes	87	52.4	228	45.6	
Tobacco use					0.206
Current	28	16.9	104	20.4	
Former	50	30.1	114	22.3	
Never	88	53.0	293	57.3	
Alcohol use					0.759
Current	61	36.7	176	34.4	
Former	21	12.7	75	14.7	
Never	84	50.6	260	50.9	
Radiation exposure[c]					0.014
No	161	97.0	495	99.4	
Yes	5	3.0	3	0.60	

[a]Chi-square analysis comparing case subjects to control subjects; [b]Family cancer history unavailable for 11 control subjects; [c]Radiation exposure data unavailable for 13 control subjects.

duct carcinoma (3.6%), with the remaining 10.1% consisting of several other carcinomas.

Genotyping analysis results are presented in **Table 2**. The percentages of *GSTM1* and *GSTT1* null cases were higher in the SGC cases compared with the control group (53.0% vs 50.9% and 27.7% vs 20.6%, respectively), the differences were statistically borderline significant for *GSTT1* ($P = 0.054$) but not for *GSTM1* polymorphism ($P = 0.633$). The calculated crude ORs for the *GSTM1* null genotype as a risk factor for SGC showed a minimal, statistically insignificant risk increase (OR, 1.1, 95% CI, 0.8-1.5). However, the crude OR for the *GSTT1* null genotype as a risk factor for SGC was 1.5 (95% CI, 1.0-2.2) and was statistically borderline significant. A multivariable logistic regression analysis was then performed to adjust for the residual effects of the variables listed in Table 1, including age, sex, ethnicity, family cancer history, smoking status, alcohol status, and radiation exposure. After adjustment, having the *GSTT1* null genotype remained a significant risk factor for SGC (OR, 1.5 [95% CI,

Table 2. *GSTT1 and GSTM1* genotype frequencies and their associations with risk of SGC

	SGC (*n = 166*)		*Controls* (*n = 511*)		p[a]	Crude OR (95% CI)	Adjusted OR[b] (95% CI)
Genotype	*n*	%	*n*	%			
GSTT1					0.054		
Wild type	120	72.3	406	79.5		Reference	Reference
Null	46	27.7	105	20.6		1.5 (1.0 – 2.2)	1.5 (1.0 – 2.3)
GSTM1					0.633		
Wild type	78	47.0	251	49.1		Reference	Reference
Null	88	53.0	260	50.9		1.1 (0.8 – 1.5)	1.0 (0.7 – 1.5)

[a]Chi-square analysis comparing genotype distributions and polymorphic allele frequencies between case subjects and control subjects; [b]adjusted for age, sex, ethnicity, tobacco use, family history of cancer, alcohol use and radiation exposure. Family cancer history unavailable for 11 control subjects and radiation exposure data unavailable for 13 control subjects

Table 3. Combined *GSTT1 and GSTM1* genotype frequencies and their associations with risk of SGC

Combined genotypes	*SGC* (*n = 166*)		*Controls* (*n = 511*)		p[a]	Crude OR (95% CI)	Adjusted OR[b] (95% CI)
	N	%	*N*	%			
Both wild type[c](ref.)	55	33.0	189	37.0	0.176	Reference	Reference
T1 wild type/M1 null	65	39.2	217	42.5		1.0 (0.7 – 1.5)	1.0 (0.6 – 1.4)
T1 null/M1 wild type	23	13.9	62	12.1		1.3 (0.7 – 2.2)	1.2 (0.6 – 2.1)
Both null	23	13.9	43	8.4		1.8 (1.0 – 3.3)	1.9 (1.0 – 3.5)
Trend test						0.050	0.061

[a]Chi-square analysis comparing genotype distributions and polymorphic allele frequencies between case subjects and control subjects; [b]adjusted for age, sex, ethnicity, tobacco use, family history of cancer, alcohol use and radiation exposure. Family cancer history unavailable for 11 control subjects and radiation exposure data unavailable for 13 control subjects; [c]Ref.=reference group

1.0-2.3), and the associated risk of SGC with *GSTM1* was not statistically significant (ORs, 1.0, 95% CI, 0.7-1.5).

Because both the null-genotypes of the *GST* polymorphisms appeared to have a minor or no effect on risk of SGC, we then utilized information from the same biologic pathway to perform meaningful combined effect of the two polymorphisms. To analyze the two polymorphisms together in order to focus on modifying effects of the combined genotypes on risk of SGC, we quartered the data set into 4 groups (*GSTM1/GSTT1* positive; *GSTM1* null/*GSTT1* positive; *GSTM1* positive/*GSTT1* null, and *GSTM1/GSTT1* null (**Table 3**). Although the distribution of the combined genotypes was not statistically significant between the SGC cases and the controls (P = 0.176), the SGC cases had a higher percentage of both *GSTM1/ GSTT1* combined null genotypes than the controls. Compared with the combined *GSTM1/GSTT1* positive genotypes, the combined *GSTM1/GSTT1*null genotypes were associated with a statistically significant risk for SGC, with a crude OR of 1.8 (95% CI, 1.0-3.3) and adjusted OR of 1.9 (95% CI, 1.0-3.5). Additionally, there was a borderline significant dose-response relationship between the number of null

genotypes and the risk for SGC (P = 0.050 for crude and P = 0.061 for adjusted risk models).

Discussion

In this molecular epidemiologic case-control study of 166 SGC patients and 511 cancer-free subjects at M.D. Anderson Cancer Center, we examined the association of *GSTM1*and *GSTT1* null polymorphisms with the risk of SGC. We found that the *GSTT1* null genotype was associated with a significantly increased risk of SGC. Although we did not observe a significant association of the *GSTM1* null polymorphism with the risk of SGC, the polymorphism did appear to interact with the *GSTT1* null polymorphism. Indeed, we found that participants who possess both null genotypes had a nearly 2-fold increased risk, although such individuals were not common. To the best of our knowledge, this is the first association study of *GST* polymorphisms and SGC risk.

*GSTM*1 and *GSTT*1 genes are important in metabolizing carcinogens, and the genetic polymorphisms of these genes are related to cancer risks secondary to their differing abilities to activate and deactivate environmental carcinogens and mutagens. The *GST* enzymes have been shown to protect organisms from reactive oxygen compound damage through their abilities to bind with glutathione, and variations in the efficiencies of these enzymes may influence cancer risks [5, 6, 10]. Although considerable allele frequency differences exist among various ethnicities, we found a similar proportion of *GSTM1* and *GSTT1* null genotypes in the control population of our study (50.9% and 20.6%, respectively) compared with those reported by Rebbeck et al [17]. The fact that radiation exposure is a clear risk factor for SGC further implicates an organism's ability to neutralize reactive oxygen species as a potential risk factor for SGC.

As suggested by Ho et al, in a study differentiated thyroid cancer [21], we also found that subjects with simultaneous presence of *GSTM1* and *GSTT1* null genotypes had a statistically significantly elevated risk for SGC compared with the controls, although the magnitude of association was modest (adjusted OR, 1.9). This finding indicates a synergistic effect of the *GSTM1* and *GSTT1* null genotypes on the risk of SGC. This result should be plausible given the number and complexity of isoenzymes in the *GST* system and their variability in expression. Different GST isoenzymes can have overlapping specificity for substrates and a certain amount of redundancy in function, so a deficiency in the activity of a single GST isoenzyme may be compensated for by another isoenzyme. Consequently, lack of function in the *GST* system may be associated with increased cancer risk only if multiple isoenzymes are disabled. Although several association studies have suggested that *GSTM1* and *GSTT1* null genotypes are associated with the increased risk of several types of cancer [21-25], this is the only study that has focused on *GST* null genotypes and SGC. Therefore, the results should be confirmed in future studies with large sample sizes.

Like any hospital-based case-control study, ours also has several potential limitations. Because all participants were enrolled from MD Anderson Cancer Center, our SGC and control groups may not have reflected the genetic characteristics of similar groups in the general population. However, because the variant genotype frequencies we observed in our control population did not differ significantly from the frequencies in the general population, it is likely that our study population accurately represented the general population. The rarity of SGC means that the sample size is necessarily small, so it is possible that our findings were caused by chance. A larger sample size is needed to detect the differential effects of *GST* polymorphisms and thereby confirm the findings of the current study. Finally, it is possible that residual effect caused by other confounders exists for which we did not fully adjust, particularly because SGC has few known risk factors.

In summary, the findings of this molecular epidemiologic study suggest that the simultaneous presence of the *GSTM1* and *GSTT1* null genotypes is associated with an increased risk for SGC. This finding further implicates a possible relationship between alteration in the detoxification ability of the GST enzyme family and the development of SGC. These findings may aid in screening among individuals at risk for SGC and ultimately refine cancer prevention efforts.

However, prospective studies with larger sample sizes are needed to verify these findings.

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