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Evidence of association of glutathione-S-transferase *GSTT1* and *GSTM1* null genotypes with susceptibility to oral cancer based on meta-analysis

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ABSTRACT. The development of oral cancer results from interactions between genetic and environmental factors. Glutathione-*S*-transferase gene null polymorphisms have a strong impact on the detoxification of carcinogens; therefore they are expected to be related to oncogenic risk, including oral cancer. Various studies have evaluated a possible association of *GSTT1* and *GSTM1* null genotypes with oral cancer, including their relationship with tobacco smoking; though the findings have been inconsistent. We analyzed the available publications concerning association of tobacco smoking and *GSTT1* and *GSTM1* null polymorphisms and how they relate to the risk of developing oral cancer. A systematic review of the

literature was conducted in the PubMed database using combinations of the following descriptors and Boolean operators 'GSTM1 and GSTT1', [AND] 'oral cancer', [AND] 'polymorphism'. A meta-analysis of *GSTT1* and *GSTM1* null polymorphisms in patients with oral cancer (cases) and cancer-free individuals (controls) from each of the studies was performed. The data of each study were analyzed, and the odds ratio, the 95% confidence interval, and the number of patients were determined for each study and for all studies combined. The number of individuals analyzed was 7,839, 44.3% presenting with oral cancer and 55.7% healthy controls. The meta-analysis showed that *GSTT1* and *GSTM1* were associated with protection against oral cancer. A significant association of *GSTT1* and *GSTM1* null polymorphisms with an increased risk of developing oral cancer was observed. These findings point to a synergistic relationship between environmental and genetic factors in the development of oral cancer tumors.

Key words: Oral cancer risk; *GSTT1*; *GSTM1*; Polymorphisms; Glutathione-*S*-transferase

INTRODUCTION

Oral cancer is considered a public health problem worldwide; it affects gums, buccal mucosa (cheeks), hard palate (roof of the mouth), tongue and mouth floor (region below the tongue), base of the tongue, soft palate, tonsils, and lateral and posterior regions of the throat. In Brazil, the estimates were 11,172 and 3,528 new oral cancer cases in men and women, respectively, in 2018–2019 (INCA, 2017).

The development of oral carcinomas is considered a multifactorial disorder, since it results from interactions between genetic and environmental factors. Among them, alcohol consumption and tobacco smoking are the most relevant risk factors for this disease (IARC, 2007; Galbiatti et al., 2013; INCA, 2017). Tobacco has potentially carcinogenic substances and elements with genotoxic effects, which can cause alterations in the genetic information (IARC, 2007; Haholu et al., 2013; Lin et al., 2013).

Additionally, gene deletions cause null polymorphisms in the glutathione-*S*-transferase (*GST*) genes *GSTT1* and *GSTM1*, which encode enzymes involved in the biotransformation of carcinogens. Therefore, *GSTT1* and *GSTM1* null polymorphisms are relevant to the development of oral carcinomas, due to the absence of the activity of the enzymes that play a role in the detoxification of tobacco smoke metabolites, a major risk factor associated with this type of cancer (Leme et al., 2010; Ruwali et al., 2011; Haholu et al., 2013; Singh et al., 2014), leading to a higher risk of developing oral and several other types of cancer (Leme et al., 2010; Ruwali et al., 2011; Singh et al., 2014). However, the results of studies of the association *GSTT1* and *GSTM1* null genotypes with oral cancer are not consistent, which justifies carrying out this meta-analysis.

The influence of environmental risk factors in the development of oral cancer has already been well established. In contrast, studies aiming to elucidate an association between environmental factors and genetic polymorphisms have shown divergent and

contradictory results. It is crucial to conduct investigations in order to establish possible relationships between cancer risk factors and associated genetic polymorphisms, since estimates of new cases of oral cancer have significantly increased in recent years (IARC, 2007; INCA, 2017). These findings can be important tools to optimize oral cancer prevention and treatment programs. Thus, this study aimed to assess case-control trials that included *GSTT1* and *GSTM1* gene analysis in cases of oral cancer and, using meta-analysis, investigate the relationship between null polymorphisms the greater risk of developing oral cancer.

MATERIAL AND METHODS

A systematic review of the literature performed in the second half of 2018 was conducted in the PubMed database following the methodological recommendations of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (Moher et al., 2009). The search was carried out using combinations of the following descriptors and Boolean operators '*GSTM1* and *GSTT1'*, [AND] 'oral cancer', [AND] 'polymorphism'.

The study included publications from 2006 to 2018 and selected case-control trials in English or Portuguese, excluding analytical studies and literature reviews. Tobacco smoking was one of the external risk factors assessed in the studies. Only *GSTT1* and *GSTM1* genotypes were considered, even if the selected articles included other genotypes.

A meta-analysis of the reported *GSTT1* and *GSTM1* null polymorphisms in patients with oral cancer (cases) and cancer-free individuals (controls) from each of the studies selected was performed. The data of each study were statistically analyzed and the Odds Ratio (OR), 95% confidence interval (CI), and weight (relevance of the study in the meta-analysis) were determined for each of them and for all of them combined. For the analysis, the chi-square test of heterogeneity and the DerSimonian-Laird test were used and P-values < 0.05 were considered statistically significant. The DerSimonian-Laird test is a meta-analysis test, with a random effect. The statistical tests were applied using the BioEstat® 5.3 software.

RESULTS

To perform the meta-analysis, 14 articles that met the inclusion criteria established in the design of this study were selected. Molecular analysis data obtained from the investigations of *GSTT1* and *GSTM1* null polymorphisms in patients with oral cancer (cases) and cancer-free individuals (controls) were extracted from these articles (Table 1). The, total number of individuals analyzed was 7,839, among which 44.3%had oral cancer and 55.7% were healthy controls.

In the group of patients with cancer, *GSTT1* was absent (null allele) in 30.0% of them and *GSTM1*, in 57.3% (Tables 2 and 3). In the control group, composed of individuals without cancer, *GSTT1* was absent in 23.1% of them and *GSTM1*, in 46.2% (Tables 2 and 3). The results obtained in the meta-analysis showed that the presence of the genes *GSTT1* (OR = 0.688, 95%CI = 0.475–0.998, $p = 0.0491$) (Figure 1) and *GSTM1* (OR = 0.671, 95%CI = 0.524–0.859, $p = 0.0016$) (Figure 2) constituted a protective factor against oral cancer.

Table 1. Relevant data from selected case-control studies for systematic review of the relationship between null polymorphisms (*GSTM1* and *GSTT1*) and a risk of developing oral cancer.

Author (year)	Country	Case (n)	Control (n)	Tissue analyzed	Most frequent tumor site	Method	Risk factor analyzed	Null genotype	Genotype frequency (%)		OR	P
									Case	Control		
Biselli et al. (2006)	Brazil	60	60	Peripheral blood	Oral cavity	PCR multiplex	Tobacco, alcohol	GSTM1	41.7	48.3	–	0.582
								GSTT1	33.3	23.3	–	0.311
Gattás et al. (2006)	Brazil	103	102	Peripheral blood	Pharynx	PCR multiplex	Tobacco, alcohol	GSTM1	57.3	38.2	2.20	–
								GSTT1	24.3	17.6	1.50	–
Peters et al. (2006)	USA	692	753	Peripheral blood	Oral cavity	PCR	Tobacco, alcohol	GSTM1	58.2	53.7	1.20	–
								GSTT1	17.6	21.5	0.77	–
Sharma et al. (2006)	India	40	87	Tumor (case) Peripheral blood (control)	Oral cavity	PCR	Tobacco, alcohol	GSTM1	52.5	33.3	2.20	0.060
								GSTT1	42.5	14.9	4.20	0.002
Sugimura et al. (2006)	Japan	122	241	Peripheral blood	–	PCR	Tobacco, alcohol	GSTM1	48.3	52.3	0.87	0.547
								GSTT1	37.7	43.6	0.78	0.282
Anantharaman et al. (2007)	India	458	729	Peripheral blood	Oral cavity	PCR	Tobacco	GSTM1	44.0	37.0	1.29	0.050
								GSTT1	10.0	16.0	0.57	0.004
Buch et al. (2008)	USA	197	416	Blood	Oral cavity	PCR	Tobacco, alcohol	GSTM1	64.3	66.7	–	0.500
								GSTT1	34.4	29.5	–	0.220
Amtha et al. (2009)	Indonesia	81	162	Peripheral blood	Oral cavity	PCR multiplex	Tobacco, alcohol, betel quid	GSTM1	60.5	55.6	1.19	0.527
								GSTT1	45.7	41.4	1.19	0.463
Yadav et al. (2010)	India	136	270	Peripheral blood	Oral cavity	PCR multiplex	Tobacco, betel quid	GSTM1	49.0	44.0	1.02	0.480
								GSTT1	31.0	31.0	1.18	0.930
Ruwali et al. (2011)	India	500	500	Blood	Oral cavity	PCR multiplex	Tobacco, alcohol	GSTM1	47.2	32.0	1.95	0.020
								GSTT1	27.0	20.6	1.39	0.040
Singh et al. (2014)	India	122	127	Blood	Oral cavity	PCR	Tobacco	GSTM1	43.4	33.1	1.55	0.117
								GSTT1	23.0	13.4	1.92	0.060
Zakiullah et al. (2015)	Pakistan	200	151	Blood	Oral cavity	PCR	Tobacco	GSTM1	80.0	57.0	3.01	0.000
								GSTT1	48.0	23.0	3.01	–
Dong et al. (2016)	China	750	750	Blood	Oral cavity	PCR	Tobacco, alcohol	GSTM1	69.0	44.0	2.83	0.001
								GSTT1	47.0	20.0	3.54	–
Rao et al. (2017)	India	15	15	Blood	Oral cavity	PCR	Tobacco	GSTM1	80.0	73.0	–	–
								GSTT1	13.0	7.0	–	–
Total		3,476	4,363									

Case, patient with oral cancer. Control, cancer-free individuals. PCR, polymerase chain reaction.

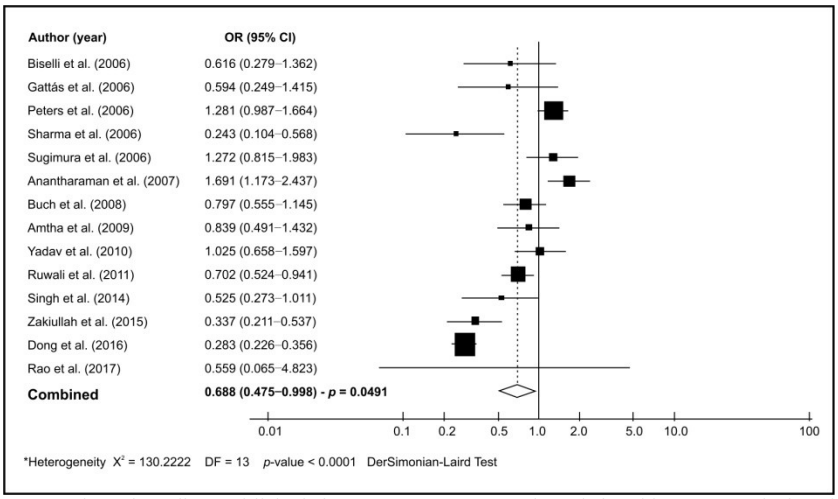

Figure 1. Forest plot of studies published from 2006 to 2018 selected for this meta-analysis with data on polymorphisms of the gene *GSTT1* in patients with cancer and controls.

Table 2. Analysis of the polymorphisms of the gene *GSTT1* in patients with cancer and controls in the studies published from 2006 to 2018 selected for this meta-analysis.

Author (year)	Country	Case					Control					OR	95% CI		Weight
		GSTT1 (+)	*f* (%)	*GSTT1* (-)	*f* (%)	Total	*GSTT1* (+)	*f* (%)	*GSTT1* (-)	*f* (%)	Total		Inf	Sup	
Biselli et al. (2006)	Brazil	40	66.7	20	33.3	60	46	76.7	14	23.3	60	0.616	0.279	1.362	6.10
Gattás et al. (2006)	Brazil	28	73.7	10	26.3	38	84	82.4	18	17.6	102	0.594	0.249	1.415	5.10
Peters et al. (2006)	USA	568	82.3	122	17.7	690	588	78.4	162	21.6	750	1.281	0.987	1.664	56.26
Sharma et al. (2006)	India	23	57.5	17	42.5	40	74	85.1	13	14.9	87	0.243	0.104	0.568	5.34
Sugimura et al. (2006)	Japan	76	62.3	46	37.7	122	136	56.4	105	43.6	241	1.272	0.815	1.983	19.46
Anantharaman et al. (2007)	India	411	90.1	45	9.9	456	612	84.3	114	15.7	726	1.691	1.173	2.437	28.76
Buch et al. (2008)	USA	128	65.6	67	34.4	195	292	70.5	122	29.5	414	0.797	0.555	1.145	29.26
Amtha et al. (2009)	Indonesia	44	54.3	37	45.7	81	95	58.6	67	41.4	162	0.839	0.491	1.432	13.44
Yadav et al. (2010)	India	94	69.1	42	30.9	136	185	68.5	85	31.5	270	1.025	0.658	1.597	19.53
Ruwali et al. (2011)	India	365	73.0	135	27.0	500	397	79.4	103	20.6	500	0.702	0.524	0.941	44.86
Singh et al. (2014)	India	94	77.0	28	23.0	122	110	86.6	17	13.4	127	0.525	0.273	1.011	8.94
Zakiullah et al. (2015)	Pakistan	105	52.5	95	47.5	200	116	76.8	35	23.2	151	0.337	0.211	0.537	17.64
Dong et al. (2016)	China	395	52.7	355	47.3	750	598	79.7	152	20.3	750	0.283	0.226	0.356	73.69
Rao et al. (2017)	India	13	86.7	2	13.3	15	14	93.3	1	6.7	15	0.559	0.065	4.823	0.83
Combined		2,384	70.0	1,021	30.0	3,405	3,347	76.9	1,008	23.1	4,355	0.688	0.475	0.998	p = 0.0491

Case, patient with oral cancer. Control, cancer-free individuals.

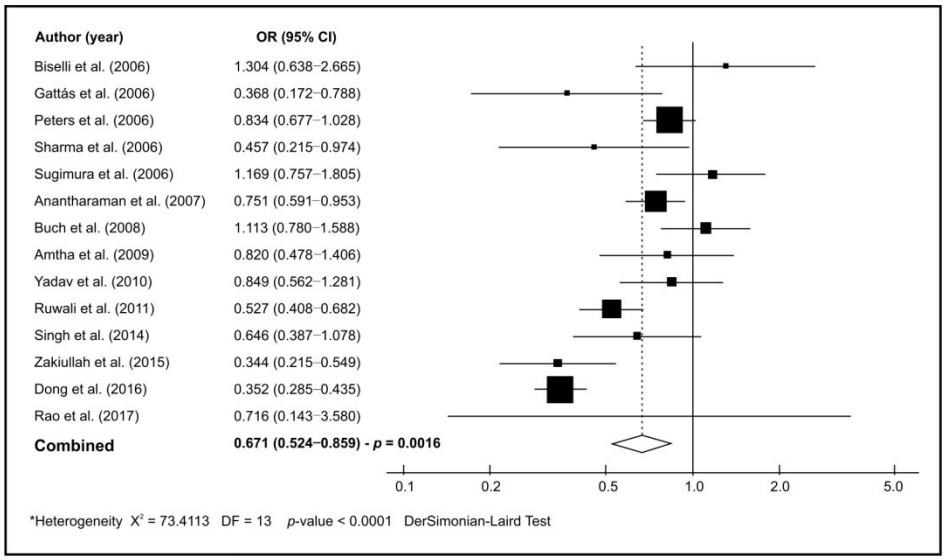

Figure 2. Forest plot of studies published from 2006 to 2018 selected for this meta-analysis with data on polymorphisms of the gene GSTM1 in patients with cancer and controls.

Table 3. Analysis of the polymorphisms of the gene *GSTM1* in patients with cancer and controls in the studies published from 2006 to 2018 selected for this meta-analysis.

Author (year)	Country	Case					Control					OR	95% CI		Weight
		GSTM1 (+)	*f* (%)	*GSTM1* (-)	*f* (%)	Total	*GSTM1* (+)	*f* (%)	*GSTM1* (-)	*f* (%)	Total		Inf	Sup	
Biselli et al. (2006)	Brazil	35	58.3	25	41.7	60	31	51.7	29	48.3	60	1.304	0.638	2.665	7.52
Gattás et al. (2006)	Brazil	14	36.8	24	63.2	38	63	61.8	39	38.2	102	0.368	0.172	0.788	6.63
Peters et al. (2006)	USA	287	41.6	403	58.4	690	345	46.1	404	53.9	749	0.834	0.677	1.028	88.32
Sharma et al. (2006)	India	19	47.5	21	52.5	40	58	66.7	29	33.3	87	0.457	0.215	0.974	6.72
Sugimura et al. (2006)	Japan	63	51.6	59	48.4	122	115	47.7	126	52.3	241	1.169	0.757	1.805	20.36
Anantharaman et al. (2007)	India	253	56.1	198	43.9	451	458	63.0	269	37.0	727	0.751	0.591	0.953	67.23
Buch et al. (2008)	USA	70	35.7	126	64.3	196	138	33.3	276	66.7	414	1.113	0.780	1.588	30.37
Amtha et al. (2009)	Indonesia	32	39.5	49	60.5	81	72	44.4	90	55.6	162	0.820	0.478	1.406	13.19
Yadav et al. (2010)	India	70	51.5	66	48.5	136	150	55.6	120	44.4	270	0.849	0.562	1.281	22.64
Ruwali et al. (2011)	India	264	52.8	236	47.2	500	340	68.0	160	32.0	500	0.527	0.408	0.682	58.22
Singh et al. (2014)	India	69	56.6	53	43.4	122	85	66.9	42	33.1	127	0.646	0.387	1.078	14.64
Zakiullah et al. (2015)	Pakistan	41	20.5	159	79.5	200	65	43.0	86	57.0	151	0.344	0.215	0.549	17.48
Dong et al. (2016)	China	231	30.8	519	69.2	750	419	55.9	331	44.1	750	0.352	0.285	0.435	85.87
Rao et al. (2017)	India	3	20.0	12	80.0	15	4	26.7	11	73.3	15	0.716	0.143	3.580	1.48
Combined		1,451	42.7	1,950	57.3	3,401	2,343	53.8	2,012	46.2	4,355	0.671	0.524	0.859	P = 0.0016

Case, patient with oral cancer. Control, cancer-free individuals.

DISCUSSION

Risk factors associated with oral cancer have been intensively studied in recent years and are now well established. Many studies have analyzed the risk factors, associating as many variables as possible, such as types of tobacco or alcoholic drink, frequency of use, time of exposure, age, and gender (Sugimura et al., 2006; Anantharaman et al., 2007; Buch et al., 2008; Anantharaman et al., 2011; Ruwali et al., 2011; Singh et al., 2014;). Based on these findings, it is possible to determine more accurately the influence of risk factors on oral cancer.

In the articles selected for the present review, all authors confirmed that smoking is an important risk factor for cancer. Moreover, alcohol consumption was also indicated as a relevant risk factor. Although alcohol consumption is more associated with other types of polymorphisms, its combination with tobacco can result in a higher incidence of oral cancer (Asakage et al., 2007).

So far, frequent divergences remain between the results of studies designed to establish a correlation between *GSTT1* and *GSTM1* null polymorphisms and increased risks of different types of cancer, including oral cancer. Some investigations suggest lack of correlation between them, while others indicate that null alleles are associated with a higher risk of developing cancer. Therefore, since the results of the association of *GSTT1* and *GSTM1* null genotypes and oral cancer have shown to be conflicting, the present meta-analysis was carried out in the expectation of solving this matter.

A recent meta-analysis, including 46 studies, concluded that *GSTT1* and *GSTM1* null genotypes are associated with an increased risk of developing hepatocellular carcinoma (Li et al., 2019). Another study showed the association of *GSTT1* null genotype with a greater risk of developing osteosarcoma (Moghimi et al., 2019).

Regarding oral cancer, some authors reported an association of the two null genotypes, *GSTM1* and *GSTT1*, with an increased risk of developing cancer (Anantharaman et al., 2011; Ruwali et al., 2011; Singh et al., 2014). Others established this association only for *GSTM1* null genotype and indicated *GSTT1* null genotype as a protective factor against the development of oral cancer (Peters et al., 2006; Anantharaman et al., 2007) or the association of *GSTM1* with a higher number of cancer cases (Gattás et al., 2006). Lastly, some authors did not find an association of *GSTM1* and *GSTT1* null genotypes with a greater risk of oral cancer (Biselli et al., 2006; Sharma et al., 2006; Sugimura et al., 2006; Buch et al., 2008; Amtha et al., 2009; Yadav et al., 2010).

Ethnic-geographic differences may explain part of this discrepancy in the results of the association between *GSTT1* and *GSTM1* null polymorphisms and oral cancer. This fact can be proven in two meta-analyses that included Asian populations (Peng et al., 2014; Li et al., 2018). In one of them (Peng et al., 2014), increased risk of oral cancer was not identified among individuals with *GSTM1* (OR = 1.35; 95% CI = 0.68-2.68) and *GSTT1* (OR = 1.41; 95% CI = 0.72-2.77) null genotypes in the Chinese population. However, in India, a significant correlation was identified between *GSTM1* null genotype and oral cancer (OR = 1.59; 95% CI = 1.20-2.11), but not for *GSTT1* null genotype (OR = 1, 21; 95% CI = 0.84-1.74). The hypothesis of the authors is that, although India and China are in the same stage of social development, have similar environmental problems, and belong to the same ethnic group (Asian), the number of Chinese individuals evaluated (due to scarcity of literature) was much lower than that of Indians. According to the authors, this fact influenced the statistical power of the analyses to find an association.

Similarly, in the study conducted by Li et al. (2018), no significant association was found between *GSTT1* and *GSTM1* null polymorphisms and oral cancer in the Chinese population. Nevertheless, in subgroup analyses per geographic area, a significant risk was found between *GSTM1* null genotype and oral cancer in mainland China (OR = 2.715, 95% CI = 2.17-3.38), strengthening the hypothesis of geographic diversity.

However, the present meta-analysis showed an association of *GSTT1* and *GSTM1* null genotypes with an increased risk of developing oral cancer. One of the probable reasons for this is the number of articles included (n = 14) and, consequently, the combined sample universe (n = 7,839), in the calculations of the meta-analysis.

CONCLUSIONS

Based on the results of this meta-analysis, we observed a significant association of *GSTT1* and *GSTM1* null polymorphisms with an increased risk of developing oral cancer. These results elucidate the synergy between environmental and genetic factors

in the development of oral tumors. However, most studies included in this meta-analysis were conducted in Asian populations, which have a specific genetic profile. Therefore, meta-analyses including more heterogeneous populations should be performed.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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