RESEARCH ARTICLE

Genetic Deletions of *GSTM1* and *GSTT1* in Head and Neck Cancer: Review of the Literature from 2000 to 2012

Nosheen Masood[1]*, Azra Yasmin[1], Mahmood A Kayani[2]

Abstract

Head and neck cancer is one of the leading causes of deaths worldwide. Two genes *GSTM1* and *GSTT1* involved in phase II of carcinogen detoxification have been frequently studied in the literature. Their null genotypes are thought to be associated with increased head and neck cancer risk. However, the published reviews are not up to date and many important papers have been skipped. The current literature review was restricted to the null genotypes of the *GSTM1* and *GSTT1* genes with special emphasis on the genotypic status. We found that the size of study sample varied greatly and the oral cavity cancer was more influenced by *GSTM1* and *GSTT1* gene deletions. With respect to ethnicity Asians are more prone to head and neck cancers with these null genotypes as compared to Europeans and Americans. The current review showed significant associations (OR=9.0, 95%CI; 1.4-9.5; OR=3.7, 95%CI; 1.4-9.5) of *GSTM1* and *GSTT1* null genotypes with head and neck cancers. Review confirms the data of previous reviews that *GSTM1* and *GSTT1* gene polymorphisms may be risk factors for cancer initiation.

Keywords: *GSTM1 -GSTT1* - head and neck cancer

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Introduction

Head and neck cancer incidence has risen significantly worldwide in the last few years (Toefil et al., 2007) and is now the fifth most common cancer worldwide (Jun et al., 2010). Head and neck cancer includes mainly the cancers of the oral cavity, pharynx and larynx. Cancer of oral cavity is common, followed by larynx and pharynx (Bhurgri et al., 2006). Its multifactorial etiology includes genetic susceptibility as well as environmental risk factors.

Xenobiotics are detoxified by phase II enzymes, such as glutathione S-transferases (GSTs) which are involved in detoxification of polycyclic aromatic hydrocarbons (PAHs) and benzo(a)pyrene (Schneider et al., 2004). GSTs are family of dimeric protein enzymes known to play an important role in the Phase II detoxification of several carcinogens (Hayes and Pulford, 1995). GSTs catalyze the conjugation reactions between glutathione and carcinogen substrates and facilitate its excretion. *GSTM1* and *GSTT1* are known to exhibit deletion polymorphisms (Egan et al., 2004). Persons with homozygous deletions of either the *GSTM1* or the *GSTT1* gene have no enzymatic functional activity of the respective enzyme and are known as null gene (Egan et al., 2004). Evidence suggests that genetic polymorphisms of these genes might increase individual susceptibility to HNC. Number of published studies have focused on *GSTM1* and *GSTT1* genetic variation with respect to HNC and have yielded conflicting results (Toru et al., 2008). Whether *GSTM1* or *GSTT1* polymorphism is a risk factor for HNC remains largely uncertain. The last previously published review on *GSTM1* and *GSTT1* gene deletions in relation to head and neck cancer was before July 2007 (Toru et al., 2008) and a number of published case control studies in populations are not included in this review. Therefore we conducted an updated review of *GSTM1* and *GSTT1* gene deletions in head and neck cancer in order to get conclusive results.

Materials and Methods

We carried out a search in Medline for case control studies covering published online papers reported from Jan 2000 up to Oct 2012. Language was not a limitation and keywords used were *GSTM1*, *GSTT1*, HNC, head and neck cancer, carcinoma, null allele, deletions. We focused on null alleles of *GSTM1* and *GSTT1* genes in head and neck cancer. The search was limited to human study. Articles clearly describing case control study with association of these genes to head & neck cancer were selected. Citation lists of retrieved articles were checked to ensure sensitivity of the search strategy. We excluded studies that presented aggregate data for several cancers but not of HNC. A total of 47 publications for *GSTM1* and 38 publications for *GSTT1* were selected after exclusion from 473 publications that were searched. Positive controls were mentioned for *GSTM1* and *GSTT1* null genotypes. A total of 8063 patients and 9438 controls for *GSTM1* and 6961 patients and 7954 controls for *GSTT1*

[1]*Environmental Sciences Department, Fatima Jinnah Women University, Rawalpindi,* [2]*Department of Biosciences, COMSATS Institute of Information Technology, Islamabad, Pakistan *For correspondence: nosheenmasood@hotmail.com*

were genotyped in these reports.

For each study we abstracted the publication date, country of research, ethnicity, statistical results, site of head and neck cancer, number of cases and controls.

Results

The literature search found 473 articles. After removal of duplicate entries and unrelated studies, 105 abstracts and 148 full-text articles were reviewed. Eventually, only 47 studies were identified that evaluated polymorphisms in *GSTM1* and *GSTT1* genes and HNC outcomes; the remaining abstracts and full-text articles did not pertain to HNC, polymorphisms or outcomes. All of these studies were case-control studies. For study size determination, we only included the subset of individuals who had genotyping done, not the entire study population. Study size varied widely for *GSTM1* and *GSTT1* genes (Table 1). The median of *GSTM1* and *GSTT1* cancer cases was 118 and 149, respectively and control was 144 and 180, respectively.

Table 2 gives an overview of *GSTM1* and *GSTT1* gene deletions with respect to year, ethnicity and site of cancer. Since 2000 to 2012, 36 studies of HNC, (including the subanatomic sites) ORs for *GSTM1* null genotype vs the positive genotype were>1, suggesting that the null *GSTM1* genotype may be associated with increased risk for HNC. Similarly for *GSTT1* 25 studies (ref) suggested ORs>1 for null genotype vs positive genotype (Table 3). Thus *GSTT1* may also be considered as a risk factor of cancer initiation.

For *GSTM1* null genotype in HNC 64% studies showed positive association with cancer and for larynx, pharynx and oral cavity the percentages were 62%, 86% and 84%, respectively. Similarly the percentages of positive association with HNC, larynx, pharynx and oral cavity for *GSTT1* null genotype were 60%, 50%, 72% and 100%, respectively.

Study populations were predominantly Caucasian or Asian (reported or inferred based on the academic affiliation of authors or hospital location). Less than half of the studies (29) evaluated a mixed population of HNC sites, whereas 20 focused on specific subanatomic sites, particularly oral cavity, pharyngeal and laryngeal lesions (Table 4). Stratified according to ethnicity we found increased risk of HNC in Asians with *GSTM1* and *GSTT1* null genotype (Table 3) compared with Americans and Europeans.

Conflicting data were present for *GSTM1* (Table 2) and *GSTT1* null polymorphism with HNC (Table 5). However, current review showed that *GSTM1* and *GSTT1* null genotypes were found to be significantly associated

Table 1. Number of Individuals Studied, Median and Range for GSTM1 and GSTT1 Genes

		n	Median	Range
GSTM1	Cases	8063	118	20-690
	Controls	9438	144	20-749
GSTT1	Cases	6961	149	20-690
	Controls	7954	180	20-749

Table 2. Characteristics of Studies Included in the Review

Author., (year of publication)	Country	Ethnicity	Site of cancer
GSTM1			
McWilliams JE et al., 2000	USA	American	HNC
Olshan AF et al., 2000	USA	American	HNC
Nomura S et al., 2000	Japan	Asia	OC
Sato M et al., 2000	Japan	Asia	OC
Park JY et al., 2000	USA	American	OC
Park JY et al., 2000	USA	American	OC
Hong YJ et al., 2000	Korea	Asia	L
Cabelguenne A et al., 2001	France	Europe	HNC
Sreelekha TT et al., 2001	India	Asia	OC
Ko Y et al., 2001	Germany	Europe	P
Hanna E et al., 2001	USA	American	L
Keitthubthew S et al., 2001	Thailand	Asia	OC
Buch SC et al., 2002	India	Asia	OC
Topcu Z et al., 2002	Sri Lanka	Asia	OC
To-Figueras J et al., 2002	Spain	Europe	L
Hahn M et al., 2002	Germany	Europe	OC
Cheng YJ et al., 2003	Taiwan	Asia	P
Bardakci F et al., 2003	Turkey	Asia	L
Gronau S et al., 2003	Germany	Europe	HNC
Risch A et al., 2003	Germany	Europe	L
Unal M et al., 2004	Turkey	Asia	L
Gaudet MM et al., 2004	USA	American	HNC
Drummond SN et al., 2004	Brazil	American	OC
Evan AJ et al., 2004	USA	American	HNC
Xie H et al., 2004	Puerto Rico	American	OC
Deng ZL et al., 2005	China	Asia	P
Sikdar N et al., 2005	India	Asia	OC
Majumder M et al., 2005	India	Asia	OC
Gajecka M et al., 2005	Poland	Asia	L
Tiwawech D et al., 2005	Thailand	Asia	P
Sugimura T et al., 2006	Japan	Asia	OC
Gattas GJ et al., 2006	Brazil	American	HNC
Oude OM et al., 2006	Netherland	Europe	HNC
Sharma A et al., 2006	India	Asia	OC
Biselli JM et al., 2006	Brazil	American	HNC
Bendjemana K et al., 2006	Brazil	Europe	P
Peters ES et al., 2006	USA	American	HNC
Acar H et al., 2006	Turkey	Asia	L
Capoluongo E et al., 2007	Italy	Europe	HNC
Boccia S et al., 2007	Netherland	Europe	HNC
Anantharaman D et al., 2007	India	Asia	OC
Cha IH et al., 2007	Korea	Asia	OC
Varela lema L et al., 2008	Spain	Europe	OC
Varela lema L et al., 2008	Spain	Europe	P
Guo X et al., 2008	China	Asia	NP
Amtha R et al., 2009	Indonesia	Asia	OC
Leme CV et al., 2010	Brazil	American	HNC
Masood N et al., 2010	Pakistan	Asia	HNC
GSTT1 Gene			
McWilliams JE et al., 2000	USA	America	HNC
Olshan AF et al., 2000	USA	America	HNC
Hamel N et al., 2000	Canada	America	HNC
Hong YJ et al., 2000	Korea	Asia	L
Sreelekha TT et al., 2001	India	Asia	OC
Ko Y et al., 2001	Germany	Europe	P
Hanna E et al., 2001	USA	America	L
Cabelguenne A et al., 2001	France	America	HNC
Kietthubthew S et al., 2001	Thailand	Asia	OC
To-Figueras J et al., 2002	Spain	Europe	L
Buch SC et al., 2002	India	Asia	OC
Cheng YJ et al., 2002	Taiwan	Asia	P

Table 2. Characteristics of Studies Included in the Review (continue)

Author., (year of publication)	Country	Ethnicity	Site of cancer
GSTT1 Gene (continue)			
Gronau S et al., 2003	Germany	Europe	HNC
Risch A et al., 2003	Germany	Europe	L
Unal M et al., 2004	Turkey	Asia	L
Evan AJ et al., 2004	USA	America	HNC
Gaudet MM et al., 2004	USA	America	HNC
Xie H et al., 2004	Puerto Rico	America	OC
Deng ZL et al., 2005	China	Asia	P
Sikdar N et al., 2005	India	Asia	OC
Majumder M et al., 2005	India	Asia	OC
Gajecka M et al., 2005	Poland	Asia	L
Drummond SN et al., 2005	Brazil	America	OC
Sugimura T et al., 2006	Japan	Asia	OC
Biselli JM et al., 2006	Brazil	America	HNC
Gattas GJ et al., 2006	Brazil	America	HNC
Oude OM et al., 2006	Netherland	Europe	HNC
Sharma A et al., 2006	India	Asia	OC
Peters ES et al., 2006	USA	America	HNC
Acar H et al., 2006	Turkey	Asia	L
Anantharaman D et al., 2007	India	Asia	OC
Capoluonge E et al., 2007	Italy	Europe	HNC
Boccia S et al., 2007	Netherland	Europe	HNC
Guo X et al., 2008	China	Asia	P
Amtha R et al., 2009	Indonesia	Asia	OC
Leme CVet al., 2010	Brazil	America	HNC
Masood N et al., 2010	Pakistan	Asia	HNC

*HNC head and neck cancer, P Pharyngeal cancer, L Laryngeal cancer, OC Oral cavity

Table 3. Number of Significant and Non Significant Studies Related to Genotypic Status of GSTM1 and GSTT1 Genes

	HNC	Larynx	Pharynx	Oral Cavity	
Non Significant	5	3	3	1	*GSTM1*
Significant	9	5	16	6	
Non Significant	6	4	3	0	*GSTT1*
Significant	9	4	8	4	

Table 4. Distribution of Publications According to Ethnicity, Subanatomic Site of Cancer and Gene

	HNC	Larynx	Pharynx	Oral Cavity	
Americans	8	1	1	2	*GSTM1*
	9	1	0	2	*GSTT1*
Asians	1	5	4	13	*GSTM1*
	1	4	3	9	*GSTT1*
Europeans	5	2	2	3	*GSTM1*
	5	2	1	1	*GSTT1*

Table 5 Number of Cases and Controls along with Statistical Details of Papers Included in the Review

Anantharaman D et al.,	458	729	0.57 (0.39-0.83)
Capoluonge E et al.,	100	100	1.20 (0.64-2.26)
Boccia S et al.,	210	245	0.97 (0.63-1.51)
Guo X et al.,	350	622	1.11 (0.85-1.46)
Amtha R et al.,	81	162	1.19 (0.72-2.05)
Leme CVet al.,	100	100	0.67 (0.34-1.35)
Masood N et al.,	388	150	2.04 (1.3-3.1)

(OR=9, 95%CI; 1.4-9.5; OR=3.7, 95%CI; 1.4-9.5) with head and neck cancers.

Discussion

Carcinogen detoxifying pathways are studied as a risk and prognostic factor of head and neck cancer. Two important genes of phase II detoxification process *GSTM1* and *GSTT1* have been found to be frequently deleted leading to null genotype of respective genes (Masood et al., 2011). *GSTM1* and *GSTT1* null genotype is associated with head and neck cancer risk.

In the current review, strikingly, the results of many studies showed contradictory associations between null genotypes and cancer risks. However we found significant association of *GSTM1* and *GSTT1* null genotype with head and neck cancers and sub sites of cancers in different ethnic groups also. Previous meta-analysis and pooled analysis have reported an association between the *GSTM1* and *GSTT1* null genotypes and head and neck tumors, but did not analyze ethnic specific or sub site specific differences and also many latest publications of 2010 were missing. Varela-Lema et al., (2008) evaluated ethnic specific and sub site specific differences in a pooled analysis and confirmed that there was no association of the *GSTM1* null genotype with oral and pharyngeal cancers in Caucasians although not statistically significant. But the data of Varela-Lema et al., (2008) was not up to date and included publications till 2007 and two genes were studied at a time.

Deletion of *GSTM1* and *GSTT1* contribute to the tumorigenesis and progression of head and neck cancer (Toru et al., 2008; Masood et al., 2010). For *GSTT1*, a gene that is highly conserved during evolution, major ethnic differences exist in frequency distribution (Cadoni et al., 2012). In Asia, highest percentages of individuals with the *GSTT1* null genotype have been reported as evident from the current review. Additionally, as only few studies have been published in previous reviews, it is likely that the discrepancy may be by chance because studies with few papers may have insufficient statistical power to detect a slight effect or may yield a fluctuated risk estimate.

The overall assessment of the publications, several common concerns emerged about the published studies representing the challenges of a maturing field. Firstly, inadequate reporting of main aspects of the underlying population was a problem. Most studies had at least one to several of the following key categories incompletely reported: country of study and source of population, inclusion/exclusion criteria for participants, study design, population characteristics for general demographic variables and clinically important prognostic factors, demographic comparisons of patients included against those excluded from analysis and detailed descriptions of both genotyping quality control measures and statistical methods. Therefore these criteria should be considered in the future publications in order to deduce conclusive and confirmative results from review studies.

In conclusion, we reviewed the field of polymorphism variants of *GSTM1* and *GSTT1* null genotype and outcomes in HNC. Published studies have all used a

standard candidate genetic polymorphism approach. We found that the genetic polymorphisms had consistent associations with HNC. Carcinogen detoxification pathways continue to be the most studied pathways for HNC outcomes. The vast majority of studies were exploratory in nature resulting in the need to validate or replicate results in larger, well-characterized populations of patients.

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