Human & Veterinary Medicine
International Journal of the Bioflux Society HVM

OPEN ACCESS
Review

The risk of gastric cancer in patients with glutathione s-transferases (GSTS) gene polymorphisms. Review article

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Abstract. Glutathione S-transferases (GSTs) are among the most important enzymes which protect human cells against toxic and genotoxic effect of exogenous and endogenous substances, because of detoxification through catalyzing the reaction of binding glutathione with a great number of pharmacologically active substances. The locations for GST genes are different. The patients with dual null GSTM1+GSTT1 genotype exhibit a whole absence of their enzymes activity; genes changes in other GSTs determine alterations of enzyme activity which may be the trigger to malignant transformation. The present paper searched data dealing with the involvement of some GST polymorphisms in the development of gastric cancer. This relationship in time offered different conclusions, but some polymorphisms of the GSTs supergene family seem to be associated with an increase in the risk of gastric cancer depending on different ethnicities.

Key Words: gastric neoplasm, gastric cancer, gastric malignant tumor, GSTM1, GSTT1, GSTP1, GSTO1, gene polymorphism.

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Introduction

Gastric cancer (GC) is an important cause of cancer death worldwide. Despite advances in GC treatment (new antitumor agents, combined therapy) the outcome concerning survival remains poor. As it is with other cancers, in GC patients one way to decrease mortality is to identify the risk factors and prevent the occurrence of that specific cancer type. For GC there are many risk factors, among them Helicobacter pylori infection, environmental factors and also genetic factors. The host genetic polymorphisms in metabolic genes, which produce enzymatic and structural proteins in charge with metabolism and detoxification of different environmental carcinogens, were implicated into the alterations of their products, causing variable ability to metabolize and detoxify the carcinogens. An insufficient removal of carcinogens is thought to have a contribution to development of cancer and the individual variation may cause susceptibility to different cancer types (Lopez-Cima et al 2012). The GSTs (Glutathione S-transferases) are cytosolic phase II enzymes that catalyze the cleansing of possible carcinogens by conjugation with reduced glutathione. Currently, there are 7 classes of mammalian cytosolic GSTs: Alpha, Mu, Pi, Sigma, Theta, Omega, and Zeta (Armstrong 1997; Hayes &McLellan 1999; Board et al 2000) and the mitochondrial Kappa class (Morel et al 2004). Both GSTM1 and/or GSTT1 null genotypes may have the effect of an entire absence of that specific GST enzyme activity, that is why we encounter a reduced amount of the capacity to detoxify electrophilic compounds, which could favor the birth of many different malignant tumors. We are speaking about a polymorphism in GSTM1 or GSTT1 genes if there is absence of one allele or both alleles, in the last case we are speaking about a null genotype. An insufficient metabolism and elimination of toxic substrate in GSTM1 + GSTT1 null genotypes individuals may cause DNA damage, suggesting its role in carcinogenesis (Seidegard et al 1986; Strange et al 1988; Deakin et al 1996; Hayes&Strange 2000; Cheng et al 2012). Some of the most studied polymorphisms are those for GSTM1, GSTT1 and GSTP1.

Implication of GST polymorphisms in GC

A low risk (OR= 1.24; 95% CI 1.00–1.54; P=0.002) for GC associated with the null GSTM1 genotype was found in a 2005 meta-analysis of 15 studies (La Torre et al 2005), a significant risk for Asians (OR=1.22; 95% CI 1.04–1.43) and not a significant risk for Caucasians (OR=1.19; 95% CI 0.81–1.75); 4 studies from these 15 studies, with information about smoking habits revealed an OR= 2.93; 95% CI 1.56–5.47 for smokers. An year later, Saadat (Saadat 2006) found a non-significant 1.06-fold increased risk of GC for patients with a null GSTT1 genotype, through a meta-analysis of 16 studies (6717 subjects), however, the OR for the GSTT1 genotype was 1.27 in Caucasians (95% CI 1.03-1.57) and 0.98 in Asians (95% CI 0.86-1.13); dual GSTM1 + GSTT1 null genotype had a significant higher risk for developing GC (OR = 2.08, 95% CI 1.42–3.10) compared

with subjects with not null genotypes; an increased risk in case of a GSTM1 null genotype (OR= 1.43, 95% CI 1.12–1.83).
Another 2006 meta-analysis (Boccia et al 2006) of 18 case-control studies (2508 cases and 4634 controls) reported a slight risk for gastric cancer associated with an absent GSTT1 genotype (OR=1.09; 95% CI 0.97–1.21); in case of both null genotypes of GSTM1 + GSTT1 from 7 studies (with 319 cases and 656 controls) the risk for GC was increased (OR=1.95; 95% CI 1.42-2.67); in smokers the data from 6 of the 12 studies revealed an OR= 1.54 (95% CI 0.95–2.48; I 2= 59.2%, P for heterogeneity = 0.03) in GSTT1 deficiency.
A 2009 meta-analysis (Zhou et al 2009), which included 10 case-control studies with 1161 GC cases and 2847 controls, revealed a possible association with the GSTP1 105 polymorphism in Caucasians [GC patients had a significantly higher frequency of AA genotype (OR= 1.53, 95% CI 1.14-2.06) and lower frequency of AG (OR= 0.70, 95% CI 0.55-0.89) than controls among Caucasians].
No association with increased GC risk among Europeans, Americans, and East Asians (Chen1 et al 2010) was the conclusion of a 2010 meta-analysis. The study analyzed 36 studies with a total amount of 4,357 GC cases and 9,796 controls.
In the same year, another meta-analysis (Wang et al 2010) of 35 studies (4,505 GC patients and 9,062 controls) concluded the association of an increased risk of GC in individuals with no GSTM1 activity (OR= 1.15, 95% CI 1.02-1.29) among Asians (OR= 1.24, 95% CI 1.07-1.44) but not among Caucasians (OR = 1.04, 95% CI 0.88-1.24). Also, the analysis observed that in Caucasians a diffuse cancer was associated with a null GSTM1 genotype (OR= 4.80, 95% CI 1.65-13.94).
A 2010 meta-analysis (Chen2 et al 2010) using 49 studies with 7746 cases of GC and 13,230 controls found a significant association of the null GSTM1 genotype with gastric cancer in Asians, especially from China and Japan (for all studies OR= 1.26; 95% CI 1.14-1.39; p< 0.00001); in Asians (OR= 1.38; 95% CI 1.22-1.57; p<0.00001); but not in Caucasians (OR= 1.08; 95% CI 0.93-1.26; p=0.31); smoking, Helicobacter pylori infection made no changes in gastric cancer susceptibility. In addition, the same meta-analysis using data from 17 studies found an increased GC susceptibility for individuals having dual no GSTM1 and GSTT1 enzymes activity (OR= 1.50, 95% CI 1.19-1.90; p= 0.0007).
A 2011 meta-analysis (Qiu et al 2011) analyzing 44 studies with 5440 cases and 11607 controls found an increased GC risk in null GSTM1 genotype carriers (OR=1.19, 95% CI 1.08-1.33; in Asians (OR=1.31, 95% CI 1.11-1.54); but no statistical significance in Caucasians (OR=1.11, 95% CI 0.96-1.28).
A 2012 meta-analysis (Bao et al 2012) evaluating 20 studies containing 2,821 GC cases and 6,240 controls found in Asians an increased risk for GC in people with GSTP1 polymorphism (G vs. A, OR = 1.273, 95%CI=1.011-1.605; GG vs. AA, OR=2.103, 95%CI=1.197- 3.387; GG vs. AA+AG, OR =2.103, 95%CI=1.186-3.414); in Caucasians the only genetic model with increased risk for GC was AG vs. AA (OR=0.791, 95%CI=0.669-0.936).
In Caucasians, Indians and East Asians an increased risk for GC OR=1.23, 95%CI 1.13-1.35, p <0.001, I(2)=45.5%) was found for people with null GSTT1 genotype (Ma W et al 2013); the meta-analysis involved 48 studies (24,440 individuals).
A 2013 meta-analysis (Zhang et al 2013) of 27 case-control studies with 14,905 individuals involving 6,270 cases and 8,635 controls showed an increased risk of gastric cancer in Asians with a GSTT1 null genotype (OR=1.29, 95 % CI 1.16-1.44, P OR<0.001).
Zhao1 et al 2013 exposed the risk for GC (OR=1.26, 95 % CI 1.09-1.46, P OR=0.002) in Chinese with an absent GSTT1 genotype (20 case-control studies with 3,204 gastric cancer cases and 5,462 controls).
A 2013 meta-analysis (Ma Y et al 2013) investigating 12 studies with 2,552 cases of GC and 5,474 controls found that the Ile105Val polymorphisms of GSTP1 provided an increased GC risk in East Asians: for valine vs. isoleucine, OR=1.32, 95 %CI 1.05-1.66, P=0.015; for ValVal vs. IleIle, OR=2.00, 95 %CI 1.34-2.98, P=0.001; for the recessive model (ValVal vs. IleVal/IleIle), OR=1.96, 95 %CI 1.35-2.83, P<0.001).
Zhao2 et al (2013) found an increased risk for GC associated with an absent GSTM1 genotype (OR=1.217, 95% CI 1.113-1.331) through a meta-analysis of 46 studies (8138 GC cases and 13867 controls) in Asians (OR=1.273, 95% CI 1.137-1.426) but not in Caucasians; in those with an infection with H. pylori the risk was higher (OR=1.928). Another recent study, but not a meta-analysis, found an important risk for the variant allele Val-Val of the GSTP1 (Chen et al 2017).
A 2014 meta-analysis, evaluating 42 studies with a total of 8,203 GC cases and 13,866 controls found a significant association between the GSTT1 null allele and gastric cancer risk (OR = 1.24, 95% CI 1.14-1.36, P < 0.00001) in Europeans and Asians (Sun et al 2014).
Another 2014 meta-analysis of 46 studies involving 9012 GC cases and 14,215 controls associated the absent GSTT1 genotype with GC (OR of 1.20) in East Asians and Indians, but not in Caucasian, African and Middle Eastern populations; 19 studies offered an augmented risk for GC (OR = 2.04, 95% CI, 1.49-2.64; P < 0.05) in GSTT1+GSTM1 absent genotypes (Wang et al 2014).
In 2014 a meta-analysis (Meng et al 2014) of 47 case-control studies, which included 6,678 cases and 12,912 controls, found an increased risk for GC in cases with GSTM1 null genotype (OR=1.186, 95% CI 1.057-1.329, P=0.004) in Asians (OR=1.269, 95% CI 1.106-1.455, P=0.001), but not in Caucasians (OR=1.115, 95% CI 0.937-1.326, P=0.222).
Another 2014 meta-analysis (Lao et al 2014) consisting of 15,118 controls and 9,322 individuals with GC (54 studies) reflects GSTM1 null genotype as an important risk factor for gastric cancer (OR = 1.207). In association with a null GSTT1 genotype the risk was higher (OR = 1.505). The null GSTM1 genotype influenced the GC risk in Caucasians and Asians, but not in Africans.
In a Chinese smokers and non-smokers population a 2015 meta-analysis (25 studies with 3,491 cases of GC patients and 5,921 controls) revealed a significant association (OR=1.47) of GC risk with GSTM1 null enzyme activity (Zhang and Cui 2015).
The GSTO2 DD genotype was shown to decrease the risk of gastric cancer in individuals without a history of cancer in their first-degree relatives (Masoudi et al 2009), but the study did not involve a large population with GC.

Discussion

In 2012 GC occupied the 5th place for in the list of the world most common malignant tumors (Ferlay et al 2013), compared to 1975 when it had been the most common cancer. The developing countries declared 677,000 cases (more than 70%, the men being affected twice frequently than women); 50% of the cases were diagnosed in China and other East Asian countries. GC occupied the third place in the principal causes of death because of cancer (Ferlay et al 2013) in both males and females, noticing that like the incidence the more affected countries were in East Asia.

For GC a dramatic decline occurred, because in the 1930s this type of cancer accounted for 30% of male and 20% of female cancer deaths, respectively; meanwhile in 2012 was only about 2% for each. There are multiple reasons for the decrease in GC occurrence (Bertuccio et al 2009) in most other parts of the world: a lower prevalence of Helicobacter pylori infection (because of improved hygiene), promotion of a healthy lifestyle including dietary measures (lower salt intake, a higher consumption of fresh fruits and vegetables, the use of refrigeration, low alcohol intake), non-smoking, and sufficient physical activity (den Hoed & Kuipers 2016). But we have to mention that there were increasing rates for younger people and in some specific sites of the stomach (Camargo et al 2011), in particular ethnicities (Merchant et al 2017).

The occurrence of many gene transcriptions alterations and mutations, along with multiple inflammatory proteins overexpression may cause the appearance of GC (Oliveros-Bastidas et al 2015). As causal agents for GC the environment (infection with Helicobacter pylori and diet), smoking, the host genetic background, deprivation, illiteracy and occupation (Uthman et al 2013) are implicated.

The enzymes involved in protecting cells from the damages produced by reactive oxygen species are the glutathione peroxidase, superoxide dismutase and catalase. We know that the oxidative stress is in part responsible for the pathogenesis of many gastrointestinal cancers (Bhattacharyya et al 2014). Infection with H. pylori may increase the production of reactive oxygen species (Matthews &Butler 2005) and it is known that this infection represents a risk factor for GC (Xue et al 2001). Knowing that between ¼ to ½ of the entire population is infected with Helicobacter pylori and that almost 85% of non-cardial gastric cancers are related to this infection (Brenner et al 2004), the risk to develop a gastric cancer has been found to increase from 2.8-to 6-fold in patients with a chronic infection (Forman et al 1991, Nomura et al 1991).

In cancer disease development there is a lot of research investigating the influence of various genetic markers: Interleukin-17A IL-17A -197G>A polymorphism contributes to an increased risk of human digestive cancer, both in the Asian and Caucasian populations and especially for gastric cancer (Duan et al 2014); Interleukin-10 (IL-10), which is a multifunctional cytokine with immunosuppressive and anti-angiogenic properties with IL-10-1082A>G polymorphism, was associated with increased risk of cancer in an Asian population, lung cancer and non-Hodgkin's lymphoma (Wang et al 2012); another IL-10 polymorphism (the variant homozygote genotype AA of the IL-10-592C>A) seems to be associated with a moderately decreased risk of all cancer types (Ding et al 2013). Also, there are polymorphisms, such as the EPHX1 His139Arg polymorphism (Liu et al 2012), which may have a potential protective effect on the development of some digestive cancers.

The GSTs are considered the most important phase II enzymes of the xenobiotic pathway because these enzymes catalyze the conjugation of potentially mutagenic electrophilic compounds with nucleophilic glutathione forming less toxic and more water-soluble compounds, which can be excreted through urine or bile. That is why the GSTs protect human body from many harmful effects of carcinogens. In case of a reduction of their activity that individual may become more susceptible to various cancers. GSTs are divided into three major families, depending on the location inside a mammalian cell: cytosolic, mitochondrial (kappa-class GSTs), and microsomal GSTs (Hayes et al 2005). The cytosolic GSTs are the most abundant and are further grouped into several divergent classes on the basis of origin, sequence similarity, catalytic amino-acid residue, and substrate specificity. There are 7 mammalian GST classes known (Mannervik 2012), and the human genome contains 17 GST genes encoding soluble enzymes, one or two of which may be missing in some individuals (Mannervik et al 2005).

The GSTA1 (Alpha class), located on short arm of chromosome 6, in the position 6p12.2 (genecards.org) is involved in the bilirubin and some anti-cancer drugs metabolism in the liver and in ovarian tumors. It was linked with an increased risk for gastric cancer (Nguyen et al 2010).

GSTM1 (Pearson et al 1993), a polymorphic member of the mu class gene, is located on the chromosome 1p13.3. In the case of a homozygous deletion of GSTM1 there will be no enzyme activity and it will be impossible to eliminate many electrophilic carcinogens, which may increase the risk of somatic mutations. The null polymorphism of GSTM1 has been associated with lung cancer (Carlsten et al 2008), prostate cancer (Gong et al 2012), hepatocellular carcinoma (Song et al 2012), head and neck squamous cell carcinoma (Zhang et al 2012), breast cancer (Wan et al 2014), cervical cancer (Sun and Song 2016), esophageal cancer (Lu et al 2016). It is important to underline that the null GSTM1 genotype was found in 40–60% in Europeans (Garte et al 2001) and about 50% in Asians (Benhamou et al 2002), knowing that individuals homozygous for such gene deletion exhibit a loss of GSTM1 enzyme activity in all tissues.

GSTO1 and GSTO2, the members of the omega class gene, being composed of six exons and separated by 7.5 kb, are located on 10q24.3 (Whitbread et al 2003). GSTO1 polymorphisms was implicated in carcinoma of the liver (both hepatocellular and cholangiocarcinoma) and in breast cancer (Marahatta et al 2006).

Another polymorphic gene is the pi class of GST: GSTP1 located on the long arm of chromosome 11 (position 11q13). Two polymorphic sites were found in the coding DNA sequence of the GSTP1 gene: a transition of Adenine base to Guanine base located at nucleotide 313, which produces a replacement of an amino acid with another one (isoleucine to valine) at codon 105 (Ile105Val) in exon 5 and a C to G transition at nucleotide 341 which results in a replacement of alanine to valine amino acid of position 114 in exon 6. These will form four different alleles: the GSTP1*A allele (wild type Ile105 and Ala114), the GSTP1*B allele (Val105 and Ala114), the GSTP1*C allele (Val105 and Val114) and the GSTP1*D allele (Ile105 and

Val114) (Sharma et al 2014). The greatest proportion of people with variant Ile105Val are the African Americans (54%), then Caucasians (31%) and only 17% of the Asians were found to have it; the variant Ala114Val was not found in Asians and African Americans, but in only 10% of Caucasians (Packer et al 2006). GSTP1 enzyme activity is significantly lower in people with Val105 allele (Sharma et al 2014). It was associated with risk for bladder and testicular cancer (Harries et al 1997). GSTT1 (theta GSTs class) is located on the long arm of chromosome 22 (position 22q11.23). Polymorphism is also an attribute of this GST. A null GSTT1 genotype is found in 13.31% of Caucasians, in 14-57% of Africans and in 36–48% of Asians (Cotton et al 2000; Hayes et al 2005; Katoh et al 2008; Sharma et al 2012). In Europeans (Agudo et al 2006), the GSTT1 gene deletion occurs in 20% individuals (Spain and the Netherlands) and below 10% (in United Kingdom and Sweden). Like GSTM1 deletion, the GSTT1 deletion genotype display a loss of this kind of enzyme in all tissues. It was associated with colorectal (Katoh et al 1996) and esophageal cancers (Zendehdel et al 2009). The GSTZ1 gene is located on chromosome 14q24.3 (Blackburn et al 1998; Board &Anders 2005). The published studies showed no influence of the risk for gastric cancer (Karakas-Celik et al 2014) or breast cancer (Andonova et al 2010, Saadat et al 2012). It is now considered that GSTs genotypes with lower enzyme activity could offer advantage for the use of some chemotherapeutic agents because a reduced detoxification may increase the effect of the drugs.

Not all studies reported data concerning the H. pylori infection, smoking status, or family history of GC. In some studies, the above-mentioned risk factors did not modify the association between GST gene polymorphisms and GC risk (Chen2 et al 2010; Garcia-Gonzales et al 2012).

A possible explanation for the differences between studies is the significant variation (ethnic and geographic) observed in the GST profile of individuals (Garcia-Gonzales et al 2012). One possible reason for detecting conflicting results among diverse ethnicities could be that different populations have different genetic backgrounds and they may be exposed to diverse environment conditions which will determine changed effects on the GC risk. We wanted to use meta-analyses because of their statistical power to show an accurate effect. Future research has to make analysis of larger sample sizes gene–environment interactions in different geographic areas and ethnic groups to be able to assess the relevance of each factor in GC development.

Conclusions

Caucasians and Asians have an expanded hazard to create GC if there should arise an occurrence of a GSTM1 absent genotype, a GSTT1 absent genotype, additionally blend of these two null genotypes. In Asians, likewise the GSTP1 Ile105Val polymorphisms introduced an expanded hazard for GC.

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Citation	Chirila DN, Chirila MD, Micu BV, Istoan SA, Muresan MS, Gligor D, Pop TR. The risk of gastric cancer in patients with glutathione s-transferases (GSTS) gene polymorphisms. Review article. HVM Bioflux 2018;10(3):104-110.
Editor	Stefan Vesa
Received	2 June 2018
Accepted	26 July 2018
Published Online	3 August 2018
Funding	None reported
Conflicts/ Competing Interests	None reported