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Review

The GST (M, T, P and A) genes polymorphisms in esophageal cancers

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Abstract. Glutathione S-transferases (GSTs) are a family of important enzymes which contribute to detoxifications of the cells, protecting the cells against toxic and genotoxic effect of exo- and endogenous substances. The GSTs catalyze the reaction of binding glutathione with a great number of pharmacologically active substances, including those with genotoxic properties. In recent years were much studied the alpha, mu, pi and theta classes of GST. The patients with a null genotype of GSTM1 and GSTT1 genes have a complete absence of the corresponding enzymes activity; in the case of other GSTs enzyme activity may decrease and this may lead to malignant alteration. We were able to observe links between many GST polymorphisms and diverse types of cancers, including digestive cancers. Our objective was to review data concerning the involvement of GST polymorphisms associated with the development of esophageal cancers. Although there have been many conflicting reports regarding this relationship, the current evidence indicates that some GST genotypes are associated with an increase in the risk of esophageal cancers depending on different ethnicities.

Key Words: esophageal cancer, GSTM1, GSTT1, GSTP1, GSTA1, polymorphisms.

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Introduction

The glutathione transferases, also being called glutathione S – transferases (Hayes et al 2005), are abbreviated "GST"s. We know that these enzymes catalyze the nucleophilic reaction of reduced glutathione (GSH) with nonpolar compounds having an electrophilic carbon, nitrogen, or sulphur atom. Among their substrates there are: halogenonitrobenzenes, arene-oxides, quinones, and α, β-unsaturated carbonyls. They are also part of the metabolism of cancer chemotherapeutic agents (Tew 1994; McLellan&Wolf 1999), insecticides (Tang&Tu 1994), herbicides (Dixon et al 1998), carcinogens, microbial antibiotics (Arca et al 1997) and provide protection against oxidative stress (Yin et al 2000). The enzymatic detoxification of xenobiotic compounds has been classified into three phases (Sheehan et al 2001): the first and the second phase consists of the conversion of a lipophilic, non-polar xenobiotic into a more water-soluble and less toxic metabolite, which can be more easily eliminated from the cell in the third phase. The first phase is mainly catalyzed by a family of microsomal proteins, the cytochrome P450 system (Guengerich&Shimada 1991), which is responsible for many reactions, oxidation being the most important. In the second phase enzymes catalyze the conjugation of activated xenobiotics to an endogenous water-soluble substrate, such as reduced glutathione which is catalyzed by the GSTs, UDP-glucuronic acid or glycine. In the human body, GSTs are grouped into three main families: cytosolic, mitochondrial (kappa-class GSTs) and membrane-bound microsomal. MAPEG (membrane-associated proteins in eicosanoid and glutathione metabolism) is a separate GST microsomal class, distinct from the cytosolic enzymes (Jakobsson et al 1999). The mammalian cytosolic GSTs are dimeric, having subunits of 199–244 amino acids in length. Presently there are seven known classes of mammalian cytosolic GSTs: Alpha, Mu, Pi, Sigma, Theta, Omega, and Zeta (Armstrong 1997; Hayes&McLellan 1999; Board et al 2000). Many other classes of cytosolic GST have been discovered in non-mammalian species (Sheehan et al 2001; Ding et al 2003): Beta, Delta, Epsilon, Lambda, Phi, Tau, "U" class. The GST isoenzymes share 75%-95% protein sequence identity (Pearson et al 1993) but members of different classes show less than 30% protein sequence identity. The null genotype of the GSTM1 or GSTT1 gene may cause a complete absence of GST enzyme activity, which decreases the ability of detoxifying electrophilic compounds, which in turn increases the susceptibility to many malignant tumors (Hayes&Strange 2000; Cheng et al 2012; Deakin et al 1996).

Implication of GST polymorphisms in esophageal cancer (EC)

GSTP1 Ile105Val was identified as a modest excess risk factor for Barrett esophagus (BE) and esophageal adenocarcinoma in Caucasian males (OR= 1.50, 95% confidence interval [CI] 1.16-1.95; OR (EAC)= 1.20, 95% CI 0.94-1.54) in a 2009 meta-analysis of 786 cases with EAC and 509 BE cases from 12 studies (Bull et al 2009).

Another 2009 meta-analysis (Zendehdel et al 2009) found that the GSTP1 polymorphism was associated with the risk of esophageal squamous cell carcinoma among Caucasians (OR= 1.4; 95% CI 1.0-2.2; p value for heterogeneity test 0.34).

The GSTM1 deletion was not associated with an increased esophageal cancer risk in a 2009 meta-analysis of 26 studies (Zhuo et al 2009). However, an increased risk was linked to only the CYP1A1 exon7 polymorphism in Asians but not in Caucasians.
A 2012 meta-analysis (Weng et al 2012) involving 11 studies with 2780 cases (1136 EC patients and 1644 controls) revealed a significant esophageal cancer risk in Chinese patients with a GSTT1 null genotype (OR= 1.31, 95%CI 1.12 to 1.53, p = 0.001).
Another 2012 meta-analysis (Sheng-Ming&Gui-Yu 2012) analyzing 5 studies with 1,626 EC patients and 2,216 controls found an increased risk for EC associated with the null genotype of GSTT1 in Asians (OR= 1.26, 95%CI=1.05-1.52).
There are studies which did not find an association of GST polymorphisms (GSTM1, GSTA1, GSTP1 I105V and A114V and GSTT1) with an increased risk for EC in a Caucasian population (Dura et al 2013).
A meta-analysis published in 2013 (Zhong et al 2013) studied 18 case-control studies involving 1,947 cases and 3,506 controls. It found an increased risk of EC in Chinese patients with a GSTM1 null genotype (OR= 1.49, 95 %CI = 1.11-2.00, P = 0.008).
Analyzing 203,112 patients with EC and 286,150 controls from two Indian regions, the risk of esophageal cancer almost doubled in patients from the Assam region showing a GSTM1 null genotype (OR= 2.1, 95 % CI, 1.44-3.13) and GSTT1 null genotype (OR= 1.7,95 % CI, 0.99-2.77), and tripled for patients from Delhi showing the GSTT1 null genotype (OR= 2.9, 95 % CI, 1.56-5.27). The study observed that the null GSTM1 genotype played a protective role (Sharma et al 2013).
A 2014 meta-analysis of 21 case control studies (Song et al 2014) did not find a significant association between GSTP1 Ile105Val polymorphism and the risk of EC (pooled OR= 1.25, 95% CI, 1.05-1.49). However, the homozygous variant of GSTP1 Val105Val was found to be associated with esophageal squamous cell carcinoma (pooled OR= 1.45, 95% CI, 1.07-1.96) particularly in the Caucasian population (pooled OR 1.41, 95% CI, 1.01-1.95).
A 2015 meta-analysis of 20 studies (Tan&Chen 2015) with 2,992 cases of esophageal cancer and 4,758 controls suggested that GSTP1 Ile105Val polymorphism significantly increased the risk of esophageal cancer in Caucasians (but not in Asians, Africans and mixed ethnicities) under three genetic models (G vs. A, OR= 1.146, 95 % CI 1.031-1.275, P = 0.012, I(2) = 30.40 %; GA vs. AA, OR= 1.208, 95 % CI 1.036-1.408, P = 0.016, I(2) = 50.30 %; GG+GA vs. AA, OR= 1.219, 95 % CI 1.053-1.410, P = 0.008, I(2) = 44.50 %).
A recent Indian study (Makhdoomi et al 2014) consisting of 492 pairs of esophageal squamous cell carcinoma (ESCC) cases and individually matched controls evidenced an association between the GSTT1 null genotype and ESCC risk (OR = 1.58; 95 % CI 1.04-2.39), but not for the GSTM1 null genotype.
A future study is needed to observe the influence of combinations of the different GSTM1, GSTP1 and GSTT1 genotypes on the susceptibility to esophageal cancer (Moaven et al 2010).
In recent years many studies investigated the relationship between GST genes and correspondent encoding enzymes, which are thought to play an important role in the pathogenesis of cancer disease. The GSTs are a family of phase II detoxifying enzymes that catalyze the conjugation of glutathione to a wide variety of electrophilic xenobiotic compounds (chemical carcinogens, environmental pollutants, antitumor agents, products of oxidative stress) to protect the cells against foreign compounds and cellular stress, inactivate endogenous alpha, beta-unsaturated aldehydes, quinones, epoxides, and hydroperoxides formed as secondary metabolites during oxidative stress (Hayes et al 2005; Sharma et al 2004).
The alpha class genes (GSTA1), located on chromosome 6p12.1, are the most abundantly expressed GST enzymes in the liver and have important functions of metabolizing bilirubin and certain anti-cancer drugs in the liver and also for glutathione peroxidase activity. GSTA contributes to the defense activity against oxidative stress due to Selenium-independent GSH peroxidase activity (Zhao et al 1999).
GSTM1 (Pearson et al 1993) is a polymorphic member of the mu class gene, located on the chromosome 1p13.3, and it has an important role in the detoxification of xenobiotic products. It is 5,950 bp long and has seven introns and eight exons, which encodes a cytosolic protein of 218 amino acid residues with a molecular weight of 21/25 kDa. The null GSTM1 genotype was found in 48%-51% of Japanese, in 35%-63% of Chinese, in 33%-36% of Asian Indians, in 50% of Caucasians and in 22%-35% of Africans (Rebbeck 1997).
The GSTP1 gene encodes the pi class of enzymes, is located on chromosome 11q13 and has nine exons. GSTP1 Ile105Val in the GSTP1 gene exon 5 (A1404G) results in an amino acid change from isoleucine (Ile) to valine (Val) and substantially reduced GSTP1 enzyme activity toward several substrates, including both chemotherapy agents carcinogens (Hayes and Strange 2000). Another extensively studied GSTP1 variant is exon 6 C2294T encoding a change of alanine (Ala) to Val at codon 114 (Ala114Val), which lower the levels of metabolic activity (Harris et al 1998). GSTP1 is involved in the metabolism of tobacco-related carcinogens (Nakajima et al 1996) and was associated with tobacco-related cancers (Lin et al 1998). GSTP1 has an effect upon benzo(α)pyrene and its major metabolites (Hu et al 1997), which are the major components of cigarette smoke (Lofroth 1989). The minor allele frequency of the Ile105Val variant can be found in 31% of Caucasians, 54% of African Americans and 17% of Asians; the Ala114Val minor allele is present in 10% of Caucasians, but it is absent in African Americans and Asians (Parker et al 2006).
The theta class of GSTs is encoded by the Glutathione S-transferase T1 (GSTT1) gene located on the long arm of chromosome 22 (22q11.23), is polymorphic and the homozygous deletion (null genotype) of GSTT1 gene causes a complete absence of GST enzyme activity (Hayes&Strange 2000). It was noted that the frequency of GSTT1 deficiency in humans measures 13–26% in Caucasians and 36–52% in Asians (Garte et al 2001). For the general population the prevalence of the GSTT1 null genotype (Nelson et al 1995) is highest among Chinese (64.4%), Koreans (60.2%), African-Americans (21.8%) and Caucasians (20.4%), and lowest among Mexican-Americans (9.7%).
An interesting observation may be the influence of the combinations of different GSTM1, GSTP1 and GSTT1 genotypes with the susceptibility to EC, which need to be evaluated in the future for EC and also for other digestive cancers.
The relationships between GST polymorphisms and the development of cancers of the gastrointestinal tract were much studied

in the last decade. They show an association with genetic differences between human races. It is difficult to understand and analyze the impact of all the factors related to life style and exposure to different environmental factors.

Meta-analysis provides a quantitative approach for combining the results of various studies on the same topic and for estimating and explaining their diversity. This is why we investigated mainly meta-analyses and combined our results with clinical studies where this was necessary. Individual genetic susceptibility may be critical in a variety of processes relevant to tumor genesis of digestive cancers (Gonzales et al 2002).

Conclusions

EC: there are differences between studies of the risk attributed to GST polymorphisms. In Asian populations, particularly Chinese and Indian, an increased risk for EC may be associated with a null variant of GSTT1. In Caucasian populations only the GSTP1 Ile105Val polymorphism was found to be associated with an increased risk of esophageal cancer.

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