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Review

The Glutathione S-Transferases (GSTS) gene polymorphisms in hepatocellular, pancreatic and gallbladder cancers

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Abstract. Polymorphisms of the glutathione-S-transferase (GST) genes are known risk factors for some environmentally-related diseases and cancer. The super family of GSTs is composed of multiple isozymes with significant evidence of functional polymorphic variation. GSTs are a superfamily of enzymes that are and is subdivided into 7 classes (α, μ, ω, π, σ, θ, ξ) and are known to protect cells by catalyzing the detoxification of electrophilic compounds, including exogenous products (carcinogens, therapeutic drugs, environmental toxins) and endogenous oxidative products, through conjugation with glutathione. The patients with a dual 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. Our objective was to review data concerning the involvement of GST polymorphisms associated with the development of liver, gallbladder and pancreatic cancers. Although there have been many conflicting reports regarding this relationship, the current evidence indicates that some GST genotypes are associated with an increased risk to develop an hepatocellular, gallbladder or pancreatic cancer.

Key Words: hepatocellular cancer, pancreatic cancer, gall bladder cancer, GSTM1, GSTT1, GSTP1, GSTA1, GSTO1, gene polymorphism.

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Introduction

The glutathione S -transferases, abbreviated "GST"s (Hayes et al 2005), are enzymes which catalyze the reaction of reduced glutathione (GSH) with nonpolar compounds having an electrophilic carbon, nitrogen, or sulphur atom. They participate in the metabolism of cancer chemotherapeutic agents (Tew 1994; McLellan and Wolf 1999; Jakobsson et al 1999; Hayes and Pulford 1995), insecticides (Tang and Tu 1994), herbicides (Dixon et al 1998), carcinogens, microbial antibiotics (Arca et al 1997) and provide protection against oxidative stress (Yin et al 2000). When consider the damage of electrophilic compounds to DNA, we may understand that the GSTs are important for maintaining genomic integrity. The xenobiotic compounds are detoxified into three phases (Sheehan et al 2001), the first phase being catalyzed by the cytochrome P450 system (Guengerich and Shimada 1991) and the second phase by the GSTs, UDP-glucuronic acid or glycine. In humans the 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). Presently there are seven known classes of mammalian cytosolic GSTs: Alpha, Mu, Pi, Sigma, Theta, Omega, and Zeta (McLellan and Wolf 1999; Arca et al 1997; Armstrong 1997; Hayes and McLellan 1999; Board et al 2000; McIlwain et al 2006). The GST isoenzymes share 75%-95% protein sequence identity (Pearson et al 1993) but members of different classes show less than 30% protein s equence 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 and Strange, 2000; Ayesh et al 1984; Seidegard et al 1986; Sugimura et al 1990; Strange et al 1991; Hayashi et al 1992; Wang et al 2003; Cheng et a 2012; Deakin et al 1996).

Hepatocellular carcinoma (HCC)

A 2006 study (Marahatta et al 2006) suggested that the GSTO1*A140D polymorphism may be a risk factor for the development of HCC, cholangiocarcinoma and breast cancer. A meta-analysis published in 2008 (White et al 2008) evaluated 15 case-control studies from which 14 analyzed GSTM1, 13 analyzed GSTT1 and 3 analyzed GSTP1; Each one analyzed GSTM2, GSTM3, GSTA1, GSTA4, GSTO1, and GSTO2, respectively. It showed high HCC incidence rates for Asian and African populations and medium HHC incidence rates in Europeans. The authors found a small excess risk of HCC with GSTT1 null (odds ratio (OR) = 1.19, 95% confidence interval (CI): 0.99, 1.44) and possibly GSTM1 null (OR = 1.16, 95% CI: 0.89, 1.53) genotypes.

A meta-analysis published in 2010 (Wang et al 2010), including 3349 cases of HHC and 5609 controls from 132 records and 24 case-control studies obtained an increased risk of HHC in patients with a null genotype of GSTM1 (OR=1.26, 95% CI 1.03-1.54, p(OR)=0.027), for a null genotype of GSTT1 (OR=1.28, 95% CI 1.09-1.51, p(OR)=0.002) and for associated null genotypes of GSTM1 and GSTT1 (OR=1.89, 95% CI 1.38-2.60, p(OR)<0.001). It also found a statistically significant association in patients of Asian ethnicity in high-rate areas and HBV-dominant areas.

A 2011 meta-analysis (Yu et al 2011) analyzed 19 studies of GSTM1 (2660 cases with hepatocellular carcinoma and 4017 controls) and 16 studies of GSTT1 (2410 cases and 3669 controls). The GSTM1/GSTT1 null genotypes were associated with an increased risk of HCC in a Chinese population (for GSTM1, OR = 1.487, 95% CI: 1.159 to 1.908, P = 0.002; for GSTT1, OR = 1.510, 95% CI: 1.236 to 1.845, P = 0.000).

Xiao and Ma (Xiao and Ma 2012) analyzed 25 case-control studies (2788 cases and 5548 controls) of GST (GSTM1 and GSTT1) polymorphisms and primary liver cancer, found an increase of the risk for primary liver cancer in a Chinese population (OR for null GSTM1 was 1.67 (95% CI: 1.39-2.01); OR for null GSTT1 was 1.59 (95% CI: 1.26-1.96); OR for both null genotypes was 3.34 (95% CI: 2.23-5.00).

A total of 34 studies (with 4,463 cases and 6,857 controls) were examined in a 2012 meta-analysis (Song et al 2012) concerning the association of HCC with GSTM1 and GSTT1 polymorphisms. In the case of a null GSTM1 genotype (OR = 1.29, 95% CI: 1.06-1.58; P = 0.01) or a null GSTT1 genotype (OR = 1.43, 95% CI: 1.22-1.68; P<10(-5) in an East Asian population and an Indian population it found significant associations, but not in a Caucasian or African population. The risk for HCC was significantly higher (OR = 1.88, 95% CI: 1.41-2.50; P<10(-4)) with both genotypes being null in 12 of these studies.

In 2012, analyzing 25 studies of the relation between polymorphic deletion of GSTM1 and HCC (3,547 patients and 6,132 controls) it was found that the null genotype of GSTM1 was associated with HCC risk in a Chinese population (OR 1.48, 95 % CI 1.19-1.85, P = 0.0004); null genotype of GSTT1 and null genotype of GSTM1/GSTT1 were associated with HCC susceptibility in an Asian\ population; the GSTP1 Ile105Val gene polymorphism was not associated with HCC risk in an Asian population (Chen et al 2012).

Analyzing a Chinese population, a 2013 meta-analyses (Liu et al 2013) found an increased risk for HHC associated with a GSTM1 null genotype (OR=1.47, 95% CI: 1.21 to 1.79, P<0.001), studying 26 articles concerning GSTM1 with 3712 cases and 6024 controls; associated with a GSTT1 (OR=1.38, 95% CI: 1.14 to 1.65, P<0.001) null genotype (OR=1.79, 95% CI: 1.26 to 2.53, P<0.001), studying 21 articles with 3378 cases and 5400 controls; In addition, an analysis of 12 articles with 1763 cases and 2537 controls with the dual null genotypes of GSTM1-GSTT1 found an increased risk for HHC (OR=1.79, 95% CI: 1.26 to 2.53, P<0.001).

The GSTP1 Ile105Val polymorphism was studied through a meta-analysis (Zhao et al 2013) of 6 studies with 1,843 participants, revealing no association with HC risk, but GSTP1 Val105Val (compared to Ile105Val/Ile105Ile) was associated with a lower risk of HC in a European population (OR = 0.44, 95 %CI 0.20-0.98, P = 0.044).

A 2014 meta-analysis (Chen et al 2014) evaluating 28 studies with 3,897 HCC patients and 6,117 controls revealed that the GSTT1 null genotype was associated with an increased risk for HCC only in an East Asian population (OR= 1.43 (95% confidence interval (CI) 1.22–1.68, P< 10(−5)); In addition, evaluating 10 studies (with 1,639 cases and 2,224 controls) which combined null genotypes of GSTT1 and GSTM1, they found a statistically significant increased risk for HCC (odd ratio = 1.85, 95% CI 1.37–2.49).

Another 2014 meta-analysis (Shen et al 2014) consisting of 33 studies with 4,232 cases and 6,601 controls found an increased risk for HCC in case of a null GSTM1 genotype (OR = 1.31, 95% CI = 1.07-1.61, P = 0.010, P heterogeneity < 10(-5)) and null GSTT1 genotype (OR = 1.47, 95% CI = 1.25-1.74, P < 10(-5), P heterogeneity < 10(-5)) in East Asians and Indians, but not in Caucasians and Africans. For the association of both genotypes it found an increased risk for HCC (OR = 1.88, 95% CI = 1.41-2.50, P < 10(-4), P heterogeneity = 0.004).

No interaction between a null GSTM1 and GSTT1 genotype has been found with the development of HCC in a 2014 meta-analysis (Sui et al 2014) involving 9 studies (1,085 cases and 2,396 controls). However, the individuals with at least one null genotype of GSTM1 and GSTT1 had a higher susceptibility to HCC (OR = 2.99, 95 % CI 2.21-4.02); in the control group the probability to develop HCC for patients with at least one null genotype of GSTM1 and GSTT1 was 0.6624, while in the case group the same probability increased to 0.1760 in a Chinese population.

Gallbladder cancer (GBC)

A 2006 Indian study (Pandey et al 2006) consisting of 106 GBC patients and 201 healthy controls revealed an increased risk for this type of cancer only for GSTP1 Ile-Val genotype (p=0.013, OR = 1.9, 95% CI = 1.1-3.1) and GSTP1 Val-Val genotype (p=0.027, OR = 1.5, 95% CI = 1.0-2.1), but not for GSTM1, GSTM3 and GSTT1.

A meta-analysis published in 2014 (Sun et al 2014) showed no association of the GSTM1 null genotype with GBC risk (OR = 1.13, 95% CI 0.88-1.46, P = 0.332) in both Caucasians and Asians. However, the meta-analysis of studies with adjusted estimations found an increased risk of gallbladder cancer (OR = 1.46, 95% CI 1.02-2.09, P = 0.038) with the GSTM1 null genotype. Patients with the GSTM1 null genotype showed no increased risk for GBC in an earlier meta-analysis (Srivastava et al 2011) of 44 published manuscripts and one unpublished report (with 1046 cases and 2310 controls) and also in other studies (Tsuchiya et al 2007; Tsuchiya et al 2010; Kimura et al 2008).

Pancreatic cancer (PC)

A GSTT1 null genotype was associated to an increased risk for PC in heavy smokers, especially in women: OR= 5.0 (95% confidence interval [CI] = 1.8 to 14.5) for women and 3.2 (95% CI = 1.3 to 8.1) for men; for heavy smokers with the GSTT1-present genotype they were 2.0 (95% CI = 1.0 to 4.0) for women and 2.1 (95% CI = 1.1 to 3.9) for men; in the case of both GSTT1-null and GSTM1-null genotypes the OR were similar

in magnitude to those among heavy smokers with the GSTT1-null genotype alone (Duell et al 2002).
The GSTP1*C ((105)Val-(114)Val)) variant conferred a possible protective effect against PC in older individuals and a significant survival advantage in patients who received 5-florouracil in a study concerning 352 patients with pancreatic ductal adenocarcinoma and in a control group of 315 healthy, analyzed for GSTM1, GSTT1 and GSTP1 polymorphisms (Jiao et al 2007).
An increased risk for PC was found in patients with a GSTT1 null genotype (OR = 1.38; 95%CI = 0.96-1.97) and GSTP1 Val105 allele variant (OR = 1.56; 95%CI = 0.93-2.61) in a case-control study with 253 cases and 403 controls (Vrana et al 2009).
A population-based study conducted on 455 PC subjects and 893 controls (Jang et al 2012) found an increased risk for PC in case of GSTM1 (rs737497)-GG (OR = 1.41, 95% CI: 1.02, 1.95), GSTM1 gene deletion (OR = 4.89, 95% CI: 3.52, 6.79) and GSTT1 gene deletion (OR = 4.41, 95% CI: 2.67, 7.29).
The null GSTT1 genotype but not the null GSTM1 genotype was associated with an increased risk of pancreatic cancer (OR = 1.61, 95 % CI 1.06-2.44, P OR = 0.025), with a significant association of GSTT1 polymorphism with pancreatic cancer risk in an Asian population (OR = 2.58, 95 % CI 1.67-3.98, P OR < 0.001), but not in a Caucasian papulation (OR = 1.16, 95 % CI 0.94-1.43, P OR = 0.170) in a 2013 meta-analysis of 10 studies (Fan et al 2013).
A Japanese study (360 patients and 400 control subjects) published in 2014 found no association between the GSTM1 and GSTT1 deletion polymorphisms and PC (Yamada et al 2014).

Discussion

Liver cancer (LC) occupied the fifth place in men (554,000 cases, 7.5% of the total) and the ninth in women (228,000 cases, 3.4%). In 2012 (Ferlay et al 2013) more than 80% of the estimated 782,000 new cancer cases worldwide occurred in less developed regions (50% in China alone). The regions of high incidence in men were East and South-East Asia (ASRs 31.9 and 22.2 respectively) and East Asia and West Africa for women (10.2 and 8.1 respectively). Also, LC was the second most common cause of death from cancer worldwide, estimated to be responsible for nearly 746,000 deaths in 2012 (9.1% of the total). Approximatively 85% to 90% of all primary LC are HCC. Known risk factors for HCC are: chronical B or C virus hepatitis, cirrhosis, alcohol abuse, smoking, exposure to aflatoxin B1 and genetic factors (Dragani 2009).
In 2012 pancreatic cancer was the seventh cause of death because of cancer (after lung, liver, stomach, bowel, breast and esophagus cancer) with 330,372 cases (Ferlay et al 2013). Pancreatic and lung cancer rates are higher in Black people than in Whites (Yadav and Lowenfels 2013). Among risk factors for pancreatic cancer there are: alcohol (Gapstur et al 2011; Lucenteforte et al 2012), smoking (Pandol et al 2012; Bosetti et al 2012), diet (Jiao et al 2009), obesity (Berrington de Gonzales et al 2003), diabetes (Ben et al 2011), non O blood type (Wolpin et al 2010), chronic pancreatitis and hereditary pancreatitis (Raimondi et al 2010).
Gallbladder cancer is considered to be the most common malignancy of the biliary tract, accounting 80%–95% of biliary tract cancers (Lazcano-Ponce et al 2001) and the 5th most common cancer of the digestive tract (Lai and Lau 2008). For year 2015 it was estimated by the American Cancer Society that there will be 10,910 new cases of diagnosed cancer of the gallbladder and nearby large bile ducts in the United States: 4,990 in men and 5,920 in women and 3,700 deaths from these cancers: 1,660 in men and 2,040 in women (American Cancer Society, 2015). The most common carcinogenetic pathway for the development of a gallbladder cancer is dysplasia-carcinoma sequence (Roa et al 2006; Dowling and Kelly 1986) and rarely an adenoma-carcinoma sequence (Maurya et al 2012). In a chronic inflamed gallbladder mucosa almost half of the cases have metaplasia. The gallbladder mucosal metaplasia may be of two types, pyloric and intestinal, the gallbladder cancer being associated with both types, but especially with the intestinal type (Duarte et al 1993). Tumor suppressor genes, such as p53, may be inactivated either by methylation or mutation, this event being the most common abnormality in human cancer and involves also the development of gallbladder cancer (Hughes and Bhathal 2013). In gallbladder cancer are implicated many genetic alterations, including oncogene activation (KRAS, EGFR, HER-2/neu), tumour suppressor gene inhibition (TP53, P16, FHIT), adhesion molecules and mucins (Cadherins, MUC1, CR1), cell cycle regulators (Cyclin D1, Cyclin E), apoptosis (Caspases, Bcl-2), microsatellite instability, and methylation of gene promoter areas (Kanthan et al 2015).
The GSTs take part of a superfamily of ubiquitous, multifunctional dimeric cytosolic enzymes that play a very important role in the Phase II detoxification pathway in humans and confer protection against a wide variety of toxic insults. The glutathione S-transferases have cytosolic and membrane-bound forms and they are encoded by two distinct supergene families: microsomal GSTs and cytoplasmic GSTs. 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). The mu class of enzymes participates in the detoxification of many electrophilic compounds, including carcinogens, therapeutic drugs, environmental toxins and products of oxidative stress, by conjugation with glutathione. The highly polymorphic genes encoding the mu class of enzymes are located on chromosome 1p13.3 (Pearson et al 1993). The null GSTM1 phenotype is unable to efficiently perform the conjugation reaction and also the elimination of toxic products through urine and bile. These genetic variations may change the susceptibility to carcinogens and toxins, and may affect the toxicity and efficacy of some drugs. Null mutations of this class mu gene have been linked with an increase in a number of cancers, possibly because of an increased susceptibility to environmental toxins and carcinogens (Xiao and Ma 2012). It was found a null GSTM1 genotype 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). Other members of the GST family may compensate for the absence of a functional GSTM1 enzyme (Bhattacharjee et al 2013). An interesting fact is that the deletion of the GSTM1 and GSTT1 may have offered a survival advantage for the cells (Parl 2005), since a protective effect of GSTM1 deletion has been found in a breast cancer study (Roodi et al 2004) and it was suggested the idea

of applying true GSTM1 genotyping (+/+; +/-; -/-) to additional or previously analyzed groups not only with breast cancer but also with other malignancies. GSTO1 is located on 10q25 and has glutaredoxin-like dehydroascorbate reductase and thiol transferase activities (Girardini et al 2002). Some GSTO polymorphisms are linked with cholangiocarcinoma, breast cancer and hepatocellular carcinoma (Marahatta et al 2006) and colorectal cancer (Masoudi et al 2011). The GSTP1 gene, located on chromosome 11q13 with nine exons, encodes the pi class of enzymes (Ali-Osman et al 1997). The genetic polymorphisms in the GSTP1 gene consist of nucleotide transitions which change codon 105 from Ile to Val and codon 114 from Ala to Val, forming four GSTP1 alleles: wild-type GSTP1*A (Ile105/Ala114), GSTP1*B (Val105/Ala114), GSTP1*C (Val105/Val114) and GSTP1*D (Ile105/Val114). High levels of GSTP were found in many tumors (ovarian, non-small cell lung, breast, colon, pancreas and lymphomas) and also in resistant cell lines and tumors (Tew 1994). In human prostate cancer a common somatic alteration was found to be the hypermethylation of the GSTP regulatory region, which leads to the loss of GSTP expression (Bakker et al 2002). 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 (Packer 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. 13–26% of Caucasians and 36–52% of Asians (Garte et al 2001) have a GSTT1 null genotype. In 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%).

It would be interesting to observe the influence of the combinations of different GSTM1, GSTP1 and GSTT1 genotypes with the susceptibility to hepatocellular, pancreatic and gallbladder cancers. There are many differences between races and lifestyle and environmental factors.

Conclusions

The results remain conflicting, even if the last large meta-analyses found statistical important implication of some of the GSTs polymorphisms to augment the risk for different types of digestive cancers. It is clear that cancer is a multistage and multifactorial disease, and many other changes, even genetic, influence the development of it. Future studies may further assess the possible gene-gene and gene-environmental interactions in this association with cancer risk.

HHC: the GSTM1 null genotype was a risk factor for HHC; the null GSTT1 genotype was a risk factor for HHC; also the association of both null genotypes offered an increased risk for HHC especially in Asians. The GSTP1 polymorphisms were not associated with an increased risk for HHC.

GBC: we found only a few numbers of meta-analyses concerning the implication of GSTs polymorphisms and we need to have more studies to confirm an increased risk especially for GSTP1.

PC: various studies evidenced an increased risk for PC in association with a null GSTM1 genotype; with a null GSTT1 genotype in both sexes, but especially in women (; with GSTP1 105 polymorphism; or no influence at all. The only meta-analysis found revealed increased risk only for Asians in connection with GSTT1 null genotype .

It is important for future studies to investigate the risk of hepatocellular, gall bladder and pancreatic cancer in relation with multiple combinations of genetic polymorphisms, knowing that the cancer disease is multifactorial.

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