

## RESEARCH ARTICLE

# Predictive Role of Glutathione-S-transferase Gene Polymorphisms in Risk and Prognosis of Hepatocellular Carcinoma

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### Abstract

**Aim:** We conducted a prospective study in an Chinese population to detect associations of GSTM1, GSTT1 and GSTP1 polymorphisms with hepatocellular carcinoma (HCC), and analyze roles in determining survival outcome. **Methods:** A prospective follow-up study was conducted with 476 HCC patients and 481 controls collected from May 2005 to May 2007. All patients were followed up until the end of Dec. 2011. GSTM1, GSTT1 and GSTP1 genotyping were performed by PCR-CTPP methods. **Results:** Null GSTM1 carriers had a 1.64 fold risk of HCC compared with non-null genotype, while GSTP1 Val/Val carriers had a 93% increased risk over the GSTP1 Ile/Ile genotype. The median follow-up time for the 476 patients was 34.2 months (range: 1 to 78 months). Individuals with null GSTM1 genotype had better survival of HCC than non-null genotype carriers (HR=0.71, 95% CI=0.45-0.95). Similarly, GSTP1 Val/Val genotypes had significant better survival than the GSTP1 Ile/Ile genotype (HR=0.34, 95% CI=0.18-0.65). Individuals carrying null GSTM1 and GSTP1 Val/Val who received chemotherapy had lower risk of death from HCC than those without chemotherapy. **Conclusion:** This study indicated carriage of null GSTM1 and GSTP1 Val/Val genotypes to have roles in susceptibility to and survival from HCC.

**Keywords:** HCC - glutathione-S-transferases - polymorphisms - risk - survival

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### Introduction

Hepatocellular carcinoma (HCC) is the fifth most common cancer in men (523 000 cases, 7.9% of the total) and the seventh in women (226 000 cases, 6.5% of the total), and most of the burden is in developing countries, where almost 85% of the cases occur, and particularly in men. The overall sex ratio of male to female is 2.4. The regions of high incidence are Eastern and South-Eastern Asia, Middle and Western Africa, but also Melanesia and Micronesia/Polynesia (particularly in men) (IARC, 2008). The wide geographic variation at an international levels of EC in terms of incidence and mortality suggested the role of genetic and environmental factors in the pathogenesis of this cancer.

Recently evidence indicated that carcinogen-metabolizing genes and DNA-repair genes may play a critical role in determining individual susceptibility to cancers (Han et al., 2012). Polymorphisms in these genes encoding the enzymes, possibly by altering their expression and function, may increase or decrease carcinogen activation or detoxication and modulate DNA repair.

Xenobiotics can be detoxified by phase II enzymes, such as GSTM1, GSTT1 and GSTP1 which have been

suggested to be involved in detoxification of polycyclic aromatic hydrocarbons (PAHs) and benzo(a)pyrene (Schneider et al., 2004), which could detoxify carcinogens and reactive oxygen species (Rebbeck, 1997). Individuals who have homozygous deletions for GSTM1, GSTT1 and GSTP1 gene have reduced enzyme function. Lack of these enzymes may potentially increase cancer susceptibility due to a decreased ability to detoxify carcinogens such as benzo[ $\alpha$ ]pyrene-7,8-diol epoxide, the activated form of benzo[ $\alpha$ ]pyrene. The misses substitution Ile105Val results from an A3G base substitution at nucleotide 313. The Val105 form of the GSTP1 enzyme may be 2–3 times less stable than the canonical Ile105 form (Johansson et al., 1998) and may be associated with a higher level of DNA adducts (Ryberg et al., 1997). Number of published studies have focused on GSTM1, GSTT1 and GSTP1 genetic variation with respect to HCC, but yielded conflicting results. Whether GSTM1, GSTT1 and GSTP1 polymorphisms are risk factors for HCC remains largely uncertain.

Furthermore, GSTs play an important role in drug metabolism, including many cancer chemotherapeutic agents (Hayes and Pulford, 1995). Genotypic and phenotypic variation in GST activity has been noted, and is thought to affect risk and prognosis in several cancers

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(Wiencke et al., 1990; Pemble et al., 1994; Hayes and Pulford, 1995; Dalhoff et al., 2005; Yang et al., 2005; Goekkurt et al., 2006; Reszka et al., 2006; Shiga et al., 2006). The Single nucleotide polymorphisms (SNPs) of GST genes induced the different expression of the gene product, and GSTM1, GSTT1 and GSTP1 genotypes have been hypothesized to affect the risk of HCC (Zhang et al., 2005; White et al., 2008; Giera et al., 2010), and response to chemotherapy (Ott et al., 2008; Tahara et al., 2011). GSTM1 and GSTT1 polymorphisms result in the absence of the gene product, while the GSTP1 Ile105Val polymorphism results in the substitution of valine for isoleucine at codon 105. The non-synonymous substitution results in altered catalytic activity of the gene product (Watson et al., 1998; Srivastava et al., 1999). Despite the fact that GSTM1, GSTT1 and GSTP1 gene polymorphisms have been widely examined and related to the survival of several cancer, their role in the survival of HCC in Chinese population has not been established.

Therefore, based on the literature and current understanding, this study was designed to investigate the association of GSTM, GSTT and GSTP polymorphisms with HCC, and analyze their roles in determining survival outcome in Chinese population.

## Materials and Methods

### Patients

498 HCC patients were consecutively collected from May 2005 to May 2007. All HCC patients with newly diagnosed primary HCC in the hospital were invited for face-to-face interviews within one month after diagnosis. All cases recruited in our study were histologically confirmed. Among a total of 498 eligible cases, 476 were interviewed with a participation rate of 95.6%, including 297 males and 179 females. 513 controls were randomly selected from people who requested general health examinations in the same hospital during the same period, and 481 controls approved to participate our study with a participation rate of 93.8%. The controls were confirmed to have no malignancy, digestive diseases, chronic diseases and also no prior history of malignancy. The controls were matched with cases by ages within five years age. All the patients were followed up until the end of Dec. 2011.

### Genomic DNA Extraction

For DNA extraction, 5 ml blood were provided by each collected subjects. Blood samples were stored at -20 °C. DNA was extracted from whole blood or lymphoblastoid cell lines using the Qiagen Blood Kit (Qiagen, Chastworth, CA) according to the manufacturer's instructions. More than 80% of the genotypes were determined from DNA directly extracted from whole blood.

### Genotyping of GSTM1, GSTT1 and GSTP1

Genotyping was based upon duplex polymerase-chain-reaction with the confronting-two-pair primer (PCR-CTPP) method (Chen et al., 2010; Kao et al., 2010). Briefly, the sequences of primers used for polymorphism of GSTM1, GSTT1 and GSTP1 were amplified by

using the following primers. The primers of GSTM1 were 5'-GAACTCCCTGAAAAGCTAAGC-3' and 5'-GTTGGGGCTCAAATATACGGTGG-3'. The primers of GSTT1 were 5'-TTCCTTACTGGTCCTCATATCTC-3' and 5'-TCACCGGATCAGGCCAGCA-3'. The primers of GSTP1 were 5'-ACCCCAGGGCTCTATGGGAA-3' and 5'-TGAGGGCACAAGAAGCCCCT-3'. Each 30 µL reaction mixture contained 1.3 U Tag biocatalysts, 1.8 mmol/L Mg<sup>2+</sup>, 2.4 µL dNTPs, 8 primers, 15 pmol of each primer and 5-8Ml template. The PCR conditions were as follows: initial denaturation at 94 °C for 5 min, 35 cycles at 94 °C for 30 s, 62 °C for 30 s, and 72 °C for 30 s and a final extension at 72 °C for 5 min. After transient centrifugation, agarose electrophoresis was conducted.

### Statistical analysis

All analysis was performed by using the STATA statistical package (version 9, STATA, College Station, TX). Hardy-Weinberg equilibrium of alleles at controls was assessed by using exact tests. Categorical variables were compared with use of the chi-square test or Fisher's exact test (when one expected value was < 5). Unconditional logistic regression was undertaken to estimate odds ratios (ORs), and their 95% confidence intervals (95% CIs) after adjusting for potential confounding factors was described in previous studies. The primary death of HCC was defined as the failure event, and time of survival was defined as the time between diagnosis and death. The cause of death was reported by the hospital or cancer registration. If the patient died of other causes rather than HCC, he/she was censored at the date of death. The outcome for the study was overall survival, which was estimated using the Kaplan-Meier method. A univariate Cox's regression analysis was used to assess the association of GSTM1, GSTT1 and GSTP1 gene polymorphism and survival. The relative risk [hazard ratio (HR)] and 95% CI were calculated from the Cox regression model for all significant predictors from cancer diagnosis to the endpoint of the study (event). All statistical tests were two sided, and differences were taken as significant when the P value was less than 0.05.

## Results

### Characteristics of HCC cases

The demographic characteristics of subjects included and clinical features of HCC patients are shown in Table 1. The average age is 47.2±6.4 years in HCC cases, and is 47.6±6.9 years in controls. There was no significant difference for gender, age and smoking (P>0.05). The lower annual income and lower BMI were associated with a higher risk of HCC (P<0.05), and HCC patients have higher proportion of positive HBsAg and positive Anti-HCV than controls (P<0.05). The HCC patients had higher consumption of alcohol drinking than controls (P<0.05). Moreover, relatives have a history of HCC would increase the risk of HCC (P<0.05).

### Distribution of GSTs genotypes in HCC patients and controls

The frequency distributions of GSTs (GSTM1, GSTT1

**Table 1. Demographic Characteristics of the Study Population**

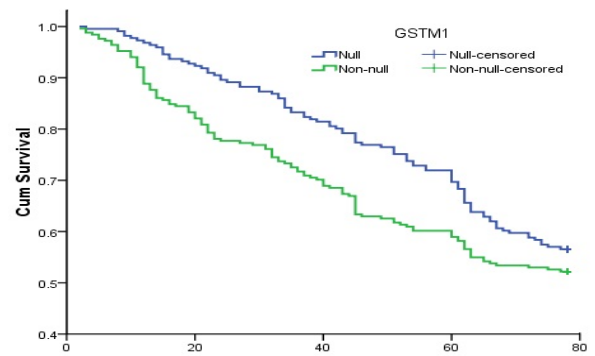
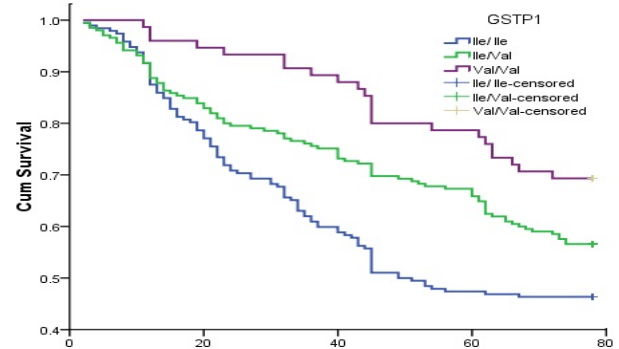
Parameter	Cases N=476(%)	Controls N=481(%)	P value
Gender			
Male	316(66.4)	309(64.2)	0.486
Female	160(33.6)	172(35.8)	
Age (mean±SD)	47.2±6.4	47.6±6.9	0.82
Annual income (RM)			
<5000	231(48.5)	167(34.7)	<0.001
5000-10000	193(40.6)	214(44.4)	
>10000	52(10.9)	101(20.9)	
BMI(Kg/m <sup>2</sup> ) (one year before)			
<18.5	170(35.7)	156(32.5)	<0.05
18.5-23.9	191(40.2)	174(36.1)	
≥24	115(24.1)	151(31.4)	
Smoking			
Ever	178(37.4)	157(32.6)	0.12
No	298(62.6)	324(67.4)	
Drinking			
Ever	278 (58.3)	165(34.2)	<0.001
No	198 (41.7)	316(65.8)	
HBsAg			
+	260 (54.7)	210(43.6)	<0.001
-	216 (45.3)	271(56.4)	
Anti-HCV			
+	64 (13.4)	12(2.5)	<0.001
-	412 (86.6)	469(97.5)	
First-degree history of HCC			
Yes	41 (8.7)	6(1.3)	<0.001
No	435 (91.3)	475(98.7)	

**Table 2. The Gene Frequencies of GSTs Genotypes in Cases and Controls**

Gene polymorphisms	Cases N=476(%)	Controls N=481(%)	OR	Adjusted OR <sup>†</sup>
GSTM1				
Non-null	231(48.7)	270(56.1)	1.0(Reference)	1.0(Reference)
Null	244(51.3)	211(43.9)	1.35(1.04-1.76)	1.64(1.23-2.04)
GSTT1				
Non-null	355(74.8)	387(80.4)	1.0(Reference)	1.0(Reference)
Null	120(25.2)	94(19.6)	1.13(0.79-1.54)	1.33(0.86-1.77)
GSTP1				
Ile/Ile	192(40.5)	211(43.9)	1.0(Reference)	1.0(Reference)
Ile/Val	205(43.1)	220(45.7)	1.14(0.79-1.46)	1.36(0.84-1.66)
Val/Val	78(16.4)	50(10.4)	1.71(1.12-2.63)	1.93(1.32-2.95)

and GSTP1) genotypes are shown in Table 2. Among controls, the frequencies of GSTM1, GSTT1 and GSTP1 Val allele are 43.9%, 19.6% and 56.1%, respectively, and they did not deviate from Hardy-Weinberg equilibrium ( $P = 0.22, 0.13$  and  $0.08$ , respectively). The null GSTM1 genotype is detected in 51.3% of the HCC cases, and the proportion of them was higher than controls ( $P < 0.05$ ). The frequencies of GSTP1 1a/1a, 1a/1b and 1b/1b in cases (40.5%, 43.1% and 16.4%) showed significant difference compared with those in controls (43.9%, 45.7% and 10.4%) ( $p < 0.05$ ). Null GSTM1 carriers had a 1.64 fold risk of HCC compared with non-null genotype. GSTP1 1b/1b carriers had the OR (95% CI) of 1.93 (1.32-2.95) for HCC risk. No significant difference was found in the GSTM1 genotypes between cases and controls ( $P > 0.05$ ). Kaplan-Meier survival analysis of HCC patients and the effect of GSTM1 and GSTP1 on survival outcome

Patients were followed from diagnosis until the end

**Figure 1. Kaplan-Meier Survival Analysis on the Effect of GSTM1 Polymorphism and Survival Outcome of HCC****Figure 2. Kaplan-Meier Survival Analysis on the Effect of GSTP1 Polymorphism and Survival Outcome of HCC****Table 4. Association Between GSTs Genotype and Survival by Chemotherapy**

Genotype	Chemotherapy		No chemotherapy	
	Deaths, n(%)	HR (95% CI)	Deaths, n(%)	HR (95% CI)
GSTM1				
Non-null	102(47.3)	1.0(Reference)	88(40.6)	1.0(Reference)
Null	114(52.7)	0.66(0.41-0.88)	128(59.4)	0.78(0.46-1.07)
GSTP1				
Ile/Ile	86(39.9)	1.0(Reference)	94(43.5)	1.0(Reference)
Ile/Val	82(38.1)	0.63(0.46-1.06)	92(42.6)	0.76(0.62-1.23)
Val/Val	48(22.0)	0.30(0.12-0.62)	30(13.9)	0.44(0.26-0.78)

of Dec. 2011. Of 476 patients, 5 patients were lost to follow-up due to migration, while the remaining 472 patients completed the study. The median follow-up time was 34.2 months (range: 1 to 78 months). A total of 216 patients (39.1%) died of HCC during the follow-up period. Individuals with null GSTM1 genotype had better survival of HCC than Non-null genotype carriers, and the HR(95% CI) was 0.71 (0.45-0.95) (Table 3). Similarly, GSTP1 Ile/Val or GSTP1 Val/Val genotypes had better survival than the GSTP1 Ile/Ile genotype, and the HR (95% CI) was 0.34 (0.18-0.65).

#### Interaction of GSTT1 and GSTP1 with chemotherapy

Results stratified by chemotherapy, present in Table 4, provide further evidence of interaction between GSTs genotypes and chemotherapy. Among those who did not receive chemotherapy, the HR (95% CI) associated with null GSTM1 genotype was approximately 0.66 (0.41-0.88), with 95% confidence interval consistently including 1.0. Among subjects who received chemotherapy, the HR (95% CI) associated with null GSTM1 was statistically

**Table 3. Kaplan-Meier Estimation of the 5-years Survival and HRs(95% CI) with Gene Polymorphism**

Gene polymorphisms		Cases, N=472(%)	Death, N=216(%)	Median survival (in months)	5-years survival rate	Adjusted GSTM1 HR(95% CI)
GSTM1	Non-null	230(48.7)	113(52.3)	56.1(52.7-59.4)	50.90%	1.0(Reference)
	Null	242(51.3)	103(47.7)	63.1(60.2-65.9)	57.40%	0.71(0.45-0.95)
GSTP1	Ile/ Ile	192(40.5)	103(47.9)	50.4(46.6-54.4)	45.90%	1.0(Reference)
	Ile/Val	205(43.1)	89(41.3)	58.8(55.1-62.4)	56.10%	0.69(0.51-1.12)
	Val/Val	78(16.4)	23(10.8)	67.3(62.9-71.6)	69.90%	0.34(0.18-0.65)

significant (HR=0.66, 95% CI=0.41-0.88). Moreover, those with GSTP1 Val/Val genotype showed a better survival compared with Ile/Ile genotype (HR=0.30, 95% CI=0.12-0.62). The P value for interaction between GSTT1 and GSTP1 genotype and chemotherapy was 0.04 and 0.012, respectively. Some evidence of dose-dependent effect was found in GSTP1 genotypes, but no significant difference was found.

## Discussion

This study firstly analyzed the influence of GSTM1, GSTT1 and GSTP1 gene polymorphisms on the susceptibility to HCC. Individuals carrying null GSTM1 or GSTP1 Val/Val genotype had a significant increased risk of HCC, while GSTM1 gene did not show significant association with risk of HCC. Moreover, association was found between the different genotypes of GSTT1 and GSTP1 and survival of HCC. Null GSTM1 and GSTP1 val/val carriers had a better survival among HCC patients with chemotherapy (HR=0.66, 95% CI=0.41-0.88 and HR=0.30, 95% CI=0.12-0.62, respectively). A significant interaction was found between GSTM1 and GSTP1 genotype and chemotherapy.

GSTs belong to a super-family of detoxification enzymes, which play a role in resisting a large variety of chemical carcinogens and environmental toxicants. The null GSTM1, null GSTT1 and GSTP Val/Val reduced function genotypes, one of the phase II enzymes, are known to link with increasing incidence of certain cancers, most likely due to inefficient carcinogen detoxification and therefore a higher risk of developing cancer. Previous meta-analysis studies indicated that null GSTM1, null GSTT1 and GSTP1 Val/Val genotypes might have a significant association with increased risks of breast cancer, lung cancer, gastric cancer and HCC in Chinese population (Sull et al., 2005; Saadat, 2006; Hosgood et al., 2007; Shi et al., 2008). In our study, we did not find the association of null GSTM1 and GSTT1 with HCC, and the GSTP1 Val/Val genotype frequency was associated with a 1.93 times higher risk of HCC than GSTP Ile/Ile genotype. In a recent meta-analysis, it was observed that null GSTT1 conferred a light increased risk (White et al., 2008). Previous epidemiological studies showed GSTP1 Val/Val genotype was considered as a factor increasing the susceptibility to and risk of HCC in Taiwanese (Chen et al., 2010), and null GSTT1 and GSTM1 genotypes did not show association with increased risk of HCC (Kao et al., 2010). However, the results of GSTs and risk of HCC are conflicting in studies conducted in other ethnicities (Abd et al., 2008; Kiran et al., 2008; Asim et al., 2010). The reason might be ethnic difference in the gene-susceptibility.

Increased evidence has suggested an important role for drug-metabolizing enzymes in determining interindividual variations in therapeutic response. GSTs are enzymes which detoxify a variety of electrophilic compounds. Few studies reported the genetic polymorphisms in GSTs gene influencing the efficacy of detoxifying cytotoxins generated by chemotherapeutics. Our results showed patients carrying null GSTM1 and GSTP1 Val/Val genotypes had a significant decreased risk of death from HCC. Previous studies showed the GSTM1 gene polymorphism might be a predictor factors for the prognosis of certain cancer among Asian population, including breast cancer, lymphoblastic leukemia, advanced oral cancer, non-small cell lung cancer and gastric cancer (Mahimkar et al., 2011; Saip et al., 2011; Suneetha et al., 2011; Borst et al., 2012; Zha et al., 2012). There still no report on the role the GSTs polymorphisms on the survival of HCC. We found increased survival in null GSTM1 and GSTP1 Val/Val genotypes which is obvious because the two genotypes carriers have reduced enzyme function and thus, may have decreased DNA repair function and enhance the effect of chemotherapy.

Overall, this study reported the carriage of null GSTM1 and GSTP1 Val/Val genotype have a role in susceptibility and survival of HCC. However, the gene susceptibility showed variable in different ethnicities and a lower number of patients with survival data. Therefore, further large sample studies are needed to confirm the genetic role of GSTs on HCC.

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