RESEARCH COMMUNICATION

Polymorphisms at GSTM1 and GSTP1 Gene Loci and Risk of Prostate Cancer in a South Indian Population

Vijayalakshmi K1, Vettriselvi V1, Krishnan M1, Sunil Shroff2, Vishwanathan KN3, Vikram R Jayanth1, Solomon FD Paul1*

Abstract

Inter-individual differences in cancer susceptibility may be mediated in part through polymorphic variability in the bioactivation and detoxification of carcinogens. The glutathione S-transferases (GSTs), which are active in detoxification of wide variety of carcinogens, have been consistently implicated as cancer susceptibility genes in this context. We here assessed the association of GSTM1 and GSTP1 polymorphisms with susceptibility to prostate cancer in a case-control study of 75 patients and 100 age-matched controls in a South Indian population. The GSTM1 null polymorphism was detected by PCR and the GSTP1 Ile105Val polymorphism by PCR-RFLP using peripheral blood DNA. There was no significant link between the null genotype of GSTM1 and risk of prostate cancer (OR-1.79; 95% CI-0.78-4.11; P=0.18). However, the GSTP1 Ile/Val genotype was significantly associated with a decreased risk for prostate cancer (OR-0.36; 95% CI-0.18-0.73; P<0.001). Analysis of the variant GSTM1 and GSTP1 genotypes in combination did not reveal any significant difference between cases and controls, even with a stratified analysis tumor grades. Thus our study indicates that the GSTP1 Ile/Val genotype may decrease risk of prostate cancer in the South Indian population.

Key Words: GSTM1 - GSTP1 - polymorphisms - prostate cancer

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Introduction

Prostate cancer is the most common cancer in men worldwide and second leading cause of cancer related deaths (Jemal et al., 2003). Etiologically, Prostate cancer is a multifactorial disease in which several dietary, environmental and genetic factors may be involved; yet little is known about the interaction between these factors (Giovannucci et al., 1993; Ekmann 1999). Recent studies point to the important role that oxidative damage plays in prostate carcinogenesis (Fleshner and Kucuk., 2001). The prostate is replete with metabolic pathways such as prostaglandin synthetic pathways, which generate abundant oxygen free radicals. Diets rich in saturated fats have been shown to increase oxidative stress and to produce potentially mutagenic DNA adducts (Li and Randerath., 1992). Moreover, with increase in age the prooxidant-antioxidant state of many tissues, including the prostate, shift towards an oxidative state that leads to oxidative DNA damage (Baker et al., 1997). The metabolic reduction of these DNA-damaging electrophiles is done effectively by the antioxidants, of which the Glutathione S-transferases (GSTs) are important detoxifying antioxidants studied in association with prostate cancer.

The Glutathione S-transferases are a super family of genes, whose gene products are phase II metabolising enzymes, which act in coordination with Phase I metabolising enzymes in the carcinogen metabolism. The Phase I enzymes usually activate the carcinogens to reactive intermediates and the GSTs are active in the detoxification of a wide variety of these potentially toxic and carcinogenic electrophiles by conjugating them to Glutathione (Strange et al., 1998). The variations in metabolic activities in each phase or in the coordination of these two phases regulate the clearance of DNA toxic metabolites and might be partially responsible for individual host susceptibility to cancer.

In humans, eight distinct gene families encode the cytosolic soluble GSTs namely, alpha (GSTA), mu (GSTM), theta (GSTT), pi (GSTP), zeta (GSTZ), sigma (GSTS), kappa (GSTK) and Omega (GSTO) (Hayes and Strange., 2000). However, more attention has been focused on allelism in the mu, theta and pi families.

The GSTM1 gene belongs to the GST mu class gene

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family, members of which are clustered on chromosome 1p13. The presence or absence of the GSTM1 gene constitutes the polymorphism. Deletion of the GSTM1 gene, frequently affects both alleles, resulting in the so-called null genotype, GSTM1-/- . About 50% of both Caucasians and Japanese lack the GSTM1 gene due to inherited homozygous deletion of both alleles (Rebeck., 1997). The individuals with GSTM1 null polymorphism lack the ability of detoxifying specific substrate epoxide intermediates (Wiencke et al., 1990). The GSTM1null genotype is also positively associated with high DNA adduct levels, suggesting its role in carcinogenesis (Nazar Stewart et al., 1993). Homozygosity for the GSTM1null genotype has been found to confer risk for many cancers like lung, breast, bladder, and gastrointestinal cancers (Zhong et al., 1993; Aktas et al., 2001). However, reports on studies in prostate cancer have not been consistent.

GSTP1, member of the pi gene family, located at 1q13, is expressed predominantly in the basal layer of the normal prostate epithelium. Although normal prostate secretory cells do not routinely express GSTP1, they remain capable of expressing this enzyme and retain an unmethylated GSTP1 promoter (De Marzo et al., 1999). In contrast to most cancers prostate carcinogenesis is associated with marked downregulation of GSTP1. Events leading up to GSTP1 inactivation during prostate carcinogenesis remain unclear. Several investigators have speculated that the early loss of GSTP1 function leads to increased vulnerability to oxidant and heterocyclic amine carcinogens, both implicated in prostate carcinogenesis (De Weese et al., 2001; Nelson et al., 2001). Hence, heritable differences in GSTP1 function may also be associated with prostate cancer development. An A to G polymorphism at nucleotide 313 of GSTP1 results in an amino acid substitution (Ile105Val) in the substrate-binding site of GSTP1 (Ali-Osman et al., 1997). The substitution of the less bulkier and more hydrophobic valine results in substrate-dependent alterations of GSTP1 catalytic activity (Ali-Osman et al., 1997; Sunderberg et al., 1998). Positive associations have been reported between the GSTP1 I105V polymorphism and risk of oral and breast cancers (Ali-Osman et al., 1997; Sunderberg et al., 1998). Several investigators have speculated that the early loss of GSTP1 function leads to increased vulnerability to oxidant and heterocyclic amine carcinogens, both implicated in prostate carcinogenesis (De Weese et al., 2001; Nelson et al., 2001). Hence, heritable differences in GSTP1 function may also be associated with prostate cancer development. 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Materials and Methods

Subjects

The present case control study comprised of 75 histologically confirmed prostate cancer patients and 100 male control subjects. The Prostate cancer cases were patients admitted at the Urology Department of Sri Ramachandra Medical College and Research Institute, Chennai and the controls were recruited from out patient clinic. The controls were individuals with normal serum PSA levels (≤4ng/ml), digital rectal examination and with no previous history of cancer. The patients and controls were ethnically similar. The age of patients ranged from 50 to 85 years with mean age of 66. Control subjects were in the age group 50 to 81 years with mean age of 66 years. Pathological grading of the tumors by Gleason scores were obtained and the patients were stratified as low grade if their Gleason scores were less than 7 and high grade if their Gleason scores were greater than or equal to 7. The Gleason score was less than 7 in 43 patients and greater than or equal to 7 in 32 patients. All cases and controls were enrolled under informed consent. The study was approved by the Medical ethics committee of the Institute.

DNA Extraction and Genotyping

Blood sample (5ml) was collected from both the cases and control subjects in EDTA vials. Genomic DNA was isolated from the blood samples by standard phenol/chloroform extraction and ethanol precipitation, dissolved in TE buffer (pH 7.4) and stored at -20ºC.

The GSTM1 homozygous null genotype was determined by PCR with specific primers For GSTM1 5’ACTCCCTGAAAAGCTAAAGC3’ (Forward) and 5’GGTTGGGTCAAAATATACGAGG3’ (reverse) and amplification control primers (Forward primer 5’TGCGAAGTGGAGCACCAC3’, Reverse primer 5’GCATCTTGTCTCTGTGCAGAT3’) giving rise to a 796 base pair fragment from the third intron of HLA-DRB1 was included in the reaction.

Standard PCR reaction was performed in a total 25µl reaction volume containing 50-100ng of genomic DNA, 1X PCR buffer (1.5mM MgCl2, 10 mM Tris (pH 9.0), 50 mM KCl and 0.1% Triton X-100), 200µM dNTPs, 50pM of each primer and 1 U of TaqDNA polymerase. PCR chemicals were from Sigma chemicals Co., USA. The cycling condition were from Sigma chemicals Co., USA. The cycling condition were 95º C for 5min of one cycle; 95º C for 1min, 60º C for 1min and 72º C for 1min 30sec for 30 cycles and final elongation cycle of 72ºC for 5min. The PCR products were visualized by 2% agarose electrophoresis and the genotype was determined by the presence or absence of 220bp PCR amplicon of GSTM1 gene.

The GSTP1 Ile/Val polymorphism was determined by PCR followed by restriction fragment length polymorphism (PCR-RFLP). The exon 5 of GSTP1 was amplified by using specific primers 5’CAGGCTGGGGCTCAGACACC-3’ (Forward) and 5’GGTCAGGCCCAGCCACGTAGG-3’ (Reverse). The cycling conditions were 94º C for 5min of one cycle; 94º C for 45sec, 66º C for 45sec and 72º C for 1min for 30 cycles and final elongation cycle of 72ºC for 5min. The PCR amplicon of 306bp was subjected to restriction digestion using HpyCHIV enzyme (New England Biolabs, Inc., USA) at 37ºC for 1hour and the DNA bands were resolved by electrophoresis on a 3% agarose gel. The genotypes were determined based on the band pattern. The
Ile allele was resistant to digestion by HpyCHIV and so the Ile/Ile genotype resulted in an undigested band of 306 bp. The Val allele with HpyCHIV site resulted in two fragments of 183 bp and 123 bp. So an Ile/Val genotype was characterized by three fragments of 306 bp, 183 bp and 123 bp and a Val/Val genotype by two fragments of 183 bp and 123 bp.

Statistical Analysis

The allele frequency and genotype frequency of GSTM1 and GSTP1 gene were calculated for cases and controls. The relative risk of the variant genotypes was determined by calculating the Odds ratio (OR) and 95% confidence interval (CI). Stratified analyses were also carried out for the tumor grades by calculating the Odds ratio and 95% confidence interval based on the method described in (Mehta et al., 1983). All the statistical analyses have been carried out using Epi info-6 software.

Results

The distribution of GSTM1 and GSTP1 alleles and genotype frequency among the prostate cancer patients and controls are shown in Tables 1 and 2, respectively.

With respect to the GSTM1 null polymorphism, homozygous null allele frequency was 0.25 in prostate cancer patients and 0.15 in controls. Among the 75 prostate cancer cases the null genotype was seen in 18 cases (24%) and among the 100 controls 15 (15%) of them had null genotype. There was no statistically significant difference in the genotype frequency among the cases and controls (OR=1.79; 95%CI-0.78-4.11; P=0.18). This suggested that GSTM1 null genotype was not significantly associated with the risk of prostate cancer in the study population (Table 2).

For the Ile/Val polymorphism of GSTP1 gene, the frequency of the Val allele was 0.20 in cases, which was less than that in controls where the frequency was 0.31. Of the 75 prostate cancer cases analyzed, 49(66%) were homozygous wild type (Ile/Ile), 22 (29%) were heterozygous (Ile/Val) and 4 (5%) were Val/Val homozygous variant. In the controls 42 (42%) were Ile/Ile, 52 (52%) were Ile/Val and 6 (6%) were Val/Val. Thus the frequency of Ile/Val genotype was significantly higher in controls than the cases, suggesting GSTP1 Ile/Val genotype to be associated with decreased risk of prostate cancer (OR=0.36; 95%CI-0.18-0.73, P<0.001)(Table 2).

To evaluate the interaction between the genotypes, we examined the combined effect of the GSTM1 and GSTP1 genotypes (Table 3). Taking the risk of the combined wild

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**Table 1. Distribution of Allele Frequencies of GSTM1 and GSTP1 Polymorphisms in Control and Prostate Cancer Cases**

<table>
<thead>
<tr>
<th>Polymorphism</th>
<th>Group</th>
<th>No. Of Subjects (N)</th>
<th>Genotype</th>
<th>Allele Frequencies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Positive (+/+)</td>
<td>Negative (-/-)</td>
</tr>
<tr>
<td>GSTM1 Null polymorphism</td>
<td>Control</td>
<td>100</td>
<td>85</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Cases</td>
<td>75</td>
<td>57</td>
<td>18</td>
</tr>
<tr>
<td>GSTP1 Ile/Val polymorphism</td>
<td>Control</td>
<td>100</td>
<td>Ile/Ile</td>
<td>Ile/Val</td>
</tr>
<tr>
<td></td>
<td>Cases</td>
<td>75</td>
<td>49</td>
<td>51</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>6</td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Distribution of GSTM1 and GSTP1 Genotypes in Prostate Cancer Cases and Controls**

<table>
<thead>
<tr>
<th>Gene</th>
<th>Genotype</th>
<th>Subjects Cases (n=75)</th>
<th>Controls (n=100)</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>GSTM1</td>
<td>Positive (+/+)</td>
<td>57(76%)</td>
<td>85(85%)</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Null (-/-)</td>
<td>18(24%)</td>
<td>15(15%)</td>
<td>1.79</td>
<td>0.78-4.11</td>
<td>0.18</td>
</tr>
<tr>
<td>GSTP1</td>
<td>Ile/Ile</td>
<td>49(66%)</td>
<td>42(42%)</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Ile/Val</td>
<td>22(29%)</td>
<td>52(52%)</td>
<td>0.36</td>
<td>0.18-0.73</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>Val/Val</td>
<td>4(5%)</td>
<td>6(6%)</td>
<td>0.57</td>
<td>0.12-2.50</td>
<td>NS</td>
</tr>
<tr>
<td></td>
<td>Ile/Val+Val/Val</td>
<td>26(34%)</td>
<td>58(58%)</td>
<td>0.38</td>
<td>0.20-0.75</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

NS - Non significant

**Table 3. Combined Genotype of GSTM1 and GSTP1 and Relative Risk Of Prostate Cancer**

<table>
<thead>
<tr>
<th>GSTM1</th>
<th>GSTP1</th>
<th>Cases Control</th>
<th>OR</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>+/-</td>
<td>Ile/Ile</td>
<td>40(53%)</td>
<td>38(38%)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>+/-</td>
<td>Ile/Val</td>
<td>15(20%)</td>
<td>42(42%)</td>
<td>0.34</td>
<td>0.15-0.75</td>
</tr>
<tr>
<td>+/-</td>
<td>Val/Val</td>
<td>2(3%)</td>
<td>5(5%)</td>
<td>0.38</td>
<td>0.05-2.42</td>
</tr>
<tr>
<td>-/-</td>
<td>Ile/Ile</td>
<td>9(12%)</td>
<td>4(4%)</td>
<td>2.14</td>
<td>0.54-9.10</td>
</tr>
<tr>
<td>-/-</td>
<td>Ile/Val</td>
<td>7(9%)</td>
<td>10(10%)</td>
<td>0.66</td>
<td>0.20-2.15</td>
</tr>
<tr>
<td>-/-</td>
<td>Val/Val</td>
<td>2(3%)</td>
<td>1(1%)</td>
<td>1.9</td>
<td>0.13-55.36</td>
</tr>
</tbody>
</table>

NS - Non Significant
GSTM1 null genotype was neither associated with smoking and prostate cancer risk (Kaleda et al., 2000) nor with familial prostate cancer risk (Nakazato et al., 2003). However, our results are contradictory to studies on Chilean (Acevedo et al., 2003), Japanese (Murata et al., 2001) and North Indian (Srivastava et al., 2005) prostate cancer patients where significant association was found between the GSTM1 null genotype and risk of sporadic prostate cancer. These variations may be attributed to the underlying geographical and ethnic factors.

The GSTP1 Ile/Val polymorphism analyzed in the present study revealed a significant increase in the frequency of the homozygous wild type Ile/Ile genotype among cases than controls. In other words, there was a significant decrease in the Val allele (Ile/Val and Val/Val) among cases than the controls suggesting the Val allele to be associated with a decreased risk for prostate cancer (OR 0.38, P< 0.01). This is consistent with the study done by Gsur et al (2001) on Austrians where there was significant increase in homozygous wild type Ile/Ile among cases and the homozygous Val/Val was associated with a significant decrease in the risk for cancer (OR 0.23, P<0.01).

On the contrary, Swedish, Danish and German case control studies that evaluated the GSTP1 genotype failed to report an association between GSTP1 and prostate cancer risk (Wadelius et al., 1999; Autrup et al., 1999; Steinhoff et al., 2000). Also studies done on Caucasians in United States (Shepard et al., 2000), Portuguese men (Jeronimo et al., 2002) and on sporadic and familial prostate cancer in American families (Debes et al., 2004) found no associated risk between the GSTP1 Ile105Val polymorphism and cancer. However, the Ile/Val and Val/Val genotypes have been associated with a significant increase in the risk of prostate cancer in Japanese (Nakazato et al., 2003), Italian (Antognelli et al., 2004) and in a North Indian population (Srivastava et al., 2005). Kote-Jarai et al (2001) found that patients in the UK with the GSTP1 Ile105Val polymorphism were at higher risk for early onset prostate cancer. Thus it is evident that association of GSTP1 Ile105Val polymorphism with risk of prostate cancer differs widely among different populations suggesting the significance of ethnic differences and environmental factors towards prostate cancer susceptibility.

Based on previous studies (Zimniak et al., 1994; Johansson et al., 1998), the residue at codon 105 of the

type genotypes GSTM1+/+ and GSTP1 Ile/Ile as a baseline reference category, the odds ratios were calculated for the combination of the GSTM1 and GSTP1 genotypes. The analysis revealed no statistically significant difference among cases and controls when the variant genotypes occurred in combination. However when the variant GSTP1 (Ile/Val) genotype occurred in combination with the GSTM1 positive genotype the risk was significantly increased (OR-0.34; 95%CI- 0.15-0.75, P<0.01)

To determine whether the variant GSTs were associated with more aggressive disease, we performed stratified analyses on Gleason scores of the patients. There was no significant association of any of the variant GSTM1 genotypes and GSTP1 genotypes with either the low or high-grade cancer (Table 4).

**Discussion**

Alterations or absence of GST enzyme activity in individuals result in poorer elimination of DNA damaging electrophiles, which might lead to increased risk of somatic mutation leading to tumor formation (Rebbeck, 1997). Hence the present study was performed to analyze the polymorphisms altering GST activity towards susceptibility to Prostate cancer. The results of our study indicate the GSTP1 Ile/Ile genotype to be associated with increased risk for prostate cancer while no association was found between GSTM1 null genotype and prostate cancer.

Distinct ethnic differences exist in the prevalence of the GSTM1 null genotypes among different population; 22–35% in Africans, 38–67% in Caucasians, 33–63% in East Asian populations (Rebbeck, 1997) and 26% in an Indian population (Buch et al., 2001). However, in the present study, the frequency of homozygous absence of GSTM1 gene was 15% among the control subjects and 24% in cases suggesting no significant association between GSTM1 null genotype and prostate cancer. The lack of significant association of homozygous null GSTM1 gene in our study is consistent with reports from studies on Austrians (Gsur et al., 2001), German (Steinhoff et al., 2000), Danish (Autrup et al., 1999), American (Rebbeck et al., 1999), Portuguese (Medeiros et al., 2004), and Turkey men (Aktas et al., 2004) with prostate cancer. Moreover individual studies have revealed that, the GSTM1 null genotype was neither associated with smoking and prostate cancer. Moreover individual studies have revealed that, the GSTM1 null genotype was neither associated with smoking and prostate cancer. Moreover individual studies have revealed that, the GSTM1 null genotype was neither associated with smoking and prostate cancer. Moreover individual studies have revealed that, the GSTM1 null genotype was neither associated with smoking and prostate cancer. Moreover individual studies have revealed that, the GSTM1 null genotype was neither associated with smoking and prostate cancer.
GSTP1 protein defines the geometry of the hydrophobic substrate-binding site and influences the enzyme activity, suggesting that differences in allelic variants of GSTP1 may alter the detoxifying properties of cells (Johansson et al., 1998). The two naturally occurring isoforms, 105 Val and Ile were found to have different specific activity, catalytic activity, affinity and thermal stability based on the nature of electrophilic substrates. Functional studies by Sunderberg et al. (1998) have revealed that substitution of bulkier amino acid at the substrate binding site decreased the catalytic activity of the enzyme, thus GSTP1 Ile105Val was more active than GSTP1 Ile105Ile. The decreased risk associated with Ile/Val genotype in the present study could be attributed to the increased catalytic activity associated with Ile/Val genotype.

Although some substrates are metabolized by specific GST isoenzymes (Hayes and Pulford., 1995), they have overlapping substrate specificities; therefore combination of unfavorable genotypes could theoretically confer high risk. In the present study the combined variant genotypes of GSTM1 and GSTP1 did not magnify the risk of cancer suggesting that specific polymorphism of single genotype show significant association with cancer risk. Our results are consistent with that reported in Germans (Steinhoff et al., 2000). Moreover, our results indicate some weak evidence of an interaction between GSTP1 and GSTM1, reflecting the fact that the GSTP1 Ile/Val protective effect was stronger in GSTM1 positive individuals. Such interactions need to be interpreted cautiously in view of the absence of a significant effect of GSTM1 alone and the number of possible interactions that are being tested. However, in a few studies an increased risk was observed when a combination of the variant GST genotypes was present (Kote Jarai et al., 2001; Srivastava et al., 2005).

The stratified analysis of the variant GSTs on Gleason scores of the patients did not reveal any significant association suggesting that the genotypes are not associated with the stage or aggressiveness of cancer. This lack of association of GSTP1 and GSTM1 with Gleason score concurs with a few study reports (Debes et al., 2004; Acevedo et al., 2003).

In conclusion, our data reveals lack of association of GSTM1 null genotype and significant association of GSTP1 gene polymorphism towards the risk of Prostate cancer in the South Indian population. However further studies on the role of other GST enzymes as well as the Phase I metabolizing enzymes will enable us to get a complete picture on the role of carcinogen metabolizing enzymes in the etiology of prostate cancer.

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