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# Relationship between the *Glutathione-S-Transferase P1, M1,* and *T1* Genotypes and Prostate Cancer Risk in Korean Subjects

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**Purpose:** The *glutathione-S-transferase (GST)P1, GSTM1,* and *GSTT1* genotypes have been associated with an increased risk of prostate, bladder, and lung cancers. The aim of this study was to investigate the association between the *GSTP1, GSTM1,* and *GSTT1* genotypes and the risk of prostate cancer in Korean men.

**Materials and Methods:** The study group consisted of 166 patients with histologically confirmed prostate cancer. The control group consisted of 327 healthy, cancer-free individuals. The diagnosis of prostate cancer was made by transrectal ultrasound-guided biopsy. Patients with prostatic adenocarcinoma were divided into organ-confined (≤ pT2) and non-organ-confined (≥pT3) subgroups. The histological grades were subdivided according to the Gleason score. The *GSTP1, GSTM1,* and *GSTT1* genotypes were determined by using polymerase chain reaction-based methods. The relationship among *GSTP1, GSTM1,* and *GSTT1* polymorphisms and prostate cancer in a case-control study was investigated.

**Results:** The frequency of the *GSTM1* null genotype in the prostate cancer group (54.2%) was higher than in the control group (odds ratio=1.53, 95% confidence interval=1.20-1.96). The comparison of the *GSTP1, GSTM1,* and *GSTT1* genotypes and cancer prognostic factors, such as staging and grading, showed no statistical significance.

**Conclusions:** An increased risk for prostate cancer may be associated with the *GSTM1* null genotype in Korean men, but no association was found with the *GSTT1* or *GSTP1* genotypes.

***Key Words:*** *Glutathione S-transferase M1; Glutathione S-transferase P1; Glutathione S-transferase T1; Prostatic neoplasms*



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## INTRODUCTION

The biotransformation enzymes, *glutathione-S-transferases (GSTs)*, are members of a multigene family; their gene products are phase II enzymes with both catalytic activities, including glutathione conjugation of electrophiles, and noncatalytic functions. The presumed function of these enzymes is to protect tissues against toxic and carcinogenic compounds that enter the body as either food additives or drugs [1]. In addition to their catalytic activities, *GSTs* are thought to engage metabolites and steroid hormones, which are important determinants in the development of prostate cancer [2,3]. The *GSTs* are involved in the detoxification of electrophilic compounds (such as carcinogens and cytotoxic drugs) by glutathione conjugation [4,5]. In addition, these enzymes are thought to play a role in the protection of DNA from oxidative damage [6]. GSTP1 inactivation may lead to increased cell vulnerability to oxidative DNA damage and to the accumulation of DNA base adducts, which allows tumors to acquire other relevant genetic alterations during prostate carcinogenesis [7].

*GSTM1* detoxifies carcinogenic polycyclic aromatic hy-

drocarbons, such as the smoke carcinogen benzopyrene, whereas *GSTT1* detoxifies smaller reactive hydrocarbons, such as ethylene oxide. The *GSTM1* null genotype has a decreased capacity to detoxify certain carcinogens and has been linked with an increased risk for solid tumors [8,9]. Examination of the *GSTT1* gene may provide insights into the dangers of exposure to common environmental or dietary agents that produce chromosomal damage. Indeed, persons with the *GSTT1* null genotype show a reduced ability to detoxify the metabolites of ethylene oxide [7]. The *GSTT1* null genotype has been associated with increased risk for ovarian, bladder, and lung cancers [10-13]. However, other studies have not confirmed the association between the *GSTT1* null genotype and cancer. The aim of this study was to investigate the association between the *GSTP1, GSTM1,* and *GSTT1* genotypes and the risk of prostate cancer in Korean men.

## MATERIALS AND METHODS

### 1. Patients and DNA samples

The DNA samples were provided by the Biobank of Wonkwang University Hospital, which is a member of the National Biobank of Korea; this Biobank is supported by the Ministry of Health, Welfare and Family Affairs. After approval from the institutional review board and informed consent from the participants, genomic DNA was obtained from 166 patients with prostate cancer and from 327 healthy controls. The healthy controls were selected by having a prostate-specific antigen (PSA) value below 2.5 ng/ml, a normal digital rectal examination, and no hypoechoic lesions in transrectal ultrasonography (TRUS). The mean age in the cancer group was 69.6 years (range, 51-87 years), and the mean age in the healthy controls was 68.3 years (range, 50-86 years) (Table 1). Genomic DNA was extracted from the leukocytes of the peripheral blood by means of a standard phenol-chloroform method or with the use of a Genomic DNA Extraction kit (iNtRON Biotechnology, Korea) according to the manufacturer's directions. The diagnosis of prostate cancer was histologically confirmed by TRUS-guided prostate biopsy. The patients were classified on the basis of tumor stage and grade.

**TABLE 1.** Distribution of the prostate cancer patients and controls according to age

| Age (yr) | No. of prostate cancer (%) | No. of control (%) |
|---|---|---|
| 50-59 | 17 (10.24) | 79 (24.23) |
| 60-69 | 68 (40.96) | 70 (21.47) |
| 70-79 | 58 (34.94) | 131 (40.18) |
| 80-89 | 23 (13.86) | 46 (14.11) |
| Mean | 69.6 | 68.3 |

### 2. Genotype analysis with the Taq-Man probe

The assay reagents for rs1695 and rs1138272 in the *GSTP1* gene were designed by Applied Biosystems (Applied Biosystems, USA). The reagents consisted of a 40x mix of unlabeled polymerase chain reaction (PCR) primer and TaqMan MGB probes (FAM and VIC dye-labeled). The reaction in 10 μl was optimized to work with 0.125 μl 40x reagents, 5 μl 2x TaqMan Genotyping Master mix (Applied Biosystems, USA), and 2 μl (50 ng) of genomic DNA. The PCR conditions were as follows: one cycle at 95°C for 15 min and 40 cycles at 95°C for 10 s and 60°C for 45 s. The PCR was performed in the Rotor-Gene thermal cycler RG6000 (Corbett Research, Australia). The samples were read and analyzed by using the Rotor-Gene 1.7.40 software (Corbett Research, Australia).

### 3. Genotype analysis by PCR

The *GSTT1* and *GSTM1* genotypes were determined by PCR. The primer pairs used for PCR amplification were 5'-GAAC TCCCTGAAAAGCTAAAGC-3' and 5'-GTTGGGCTCAAA TATACGGTGG-3' for GSTM1 and 5'-TTCCTTACTGGTC CTCACATCTC-3' and 5'-TCACCGGATCATGGCCAGCA-3' for GSTT1 (Table 2). PCR reactions were carried out for 30 cycles, each including a 10-s denaturation step at 98°C, a 15-s annealing step at 60°C, and a 20-s extension step at

**TABLE 2.** Primer sequences for genotyping SNPs of *GSTP1, GSTM1,* and *GSTT1*

| Primer | Primer sequence (5'→3') | Product size/Regions |
|---|---|---|
| GSTP1 | | |
| rs1695-AGF | CCTGGTGGACATGGTGAATGAC | rs1695 |
| rs1695-AGR | CAGATGCTCACATAGTTGGTGTAGA | |
| rs1695-AGV1 | TGCAAATACATCTCCC (VIC dye) | |
| rs1695-AGM1 | TGCAAATACGTCTCCC (FAM dye) | |
| GSTM1 | | |
| GSTM1-F | GAACTCCCTGAAAAGCTAAAGC | 218 bp |
| GSTM1-R | GTTGGGCTCAAATATACGGTGG | /exon 7 deletion |
| GSTT1 | | |
| GSTT1-F | TTCCTTACTGGTCCTCACATCTC | 459 bp |
| GSTT1-R | TCACCGGATCATGGCCAGCA | /intron 4 deletion |

SNP: single-nucleotide polymorphism, GST: glutathione-S-transferases

72°C. The PCR program included an initial denaturation time of 5 minutes at 95°C and an extension time of 10 minutes at 72°C after the last cycle. The PCR products were separated by electrophoresis by using a 2% agarose gel and were visualized by ethidium bromide staining. The presence of bands at 218 and 459 bp corresponded to intact genomic GSTM1 (Fig. 1) and GSTT1 (Fig. 2), respectively, whereas the absence of the bands implied the null state.

### 4. Statistical analysis

The correlations between the *GSTP1, GSTM1,* and *GSTT1* genotypes and clinico-pathological factors for prostate cancer were analyzed by using SPSS ver. 15.0 (SPSS Inc., Chicago, IL, USA) and analyze software (Dynacom, Yokohama, Japan). The chi-square test was used to calculate the p-values and 95% confidence intervals (95% CIs) for the odds ratios (ORs).

## RESULTS

Among the GSTP1 polymorphisms, two single-nucleotide polymorphisms (SNPs; rs1695 and rs1138272) were selected for large sample genotyping on the basis of their locations. The genotype and allele frequencies of rs1695 (g.1375A>G, based on NC_000011.9) were not significantly different between the patients with prostate cancer and the healthy controls (Table 3). The SNP rs1138272 (g.2265C>T), from the NCBI SNP database, was also analyzed for genotype; however, when 96 samples were analyzed, there was only one genotype. These findings suggest that the rs1138272 of *GSTP1* might be a very rare polymorphism or a monomorphism in the Korean population.

The frequencies of the *GSTM1* null and *GSTT1* null genotypes were 38.2% and 49.8% in the control population and 54.2% and 51.2% in the prostate cancer group, respectively. The *GSTM1* null genotype was more common in the

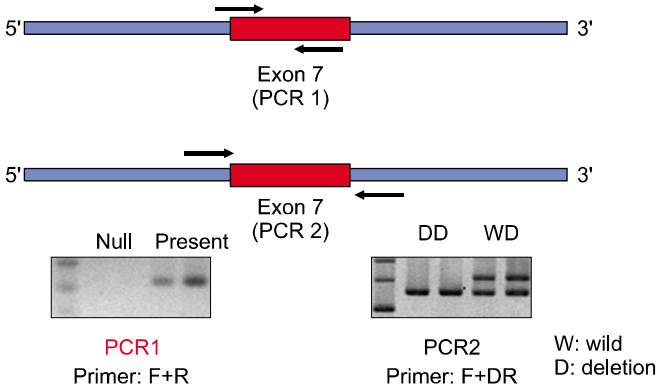


**FIG. 1.** Methods and results - glutathione-S-transferaseM1. PCR: polymerase chain reaction.

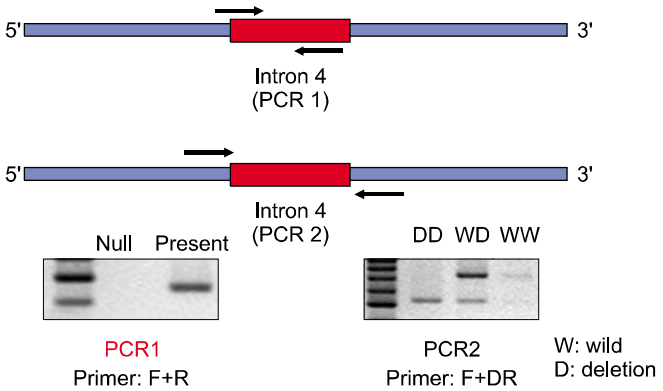


**FIG. 2.** Methods and result - glutathione-S-transferaseT1. PCR: polymerase chain reaction.

**TABLE 3.** Genotype and allele analysis of *GSTP1* polymorphisms in patients with prostate cancer and controls

| Position | Genotype /Allele | No. of control (%) | No. of PC (%) | p-value vs. PC |
|---|---|---|---|---|
| g.1375A>G (rs1695) | AA | 209 (63.91) | 117 (70.48) | 0.346 |
| | AG | 101 (30.89) | 42 (25.30) | |
| | GG | 17 (5.20) | 7 (4.22) | |
| | A | 519 (79.76) | 276 (83.13) | 0.077 |
| | G | 135 (20.64) | 56 (16.87) | |

Calculated from the translation start site. GST: glutathione-S-transferase, PC: prostate cancer

**TABLE 4.** Association between *GSTM1* and *GSTT1* genotypes and prostate cancer

| | No. of prostate cancer (%) | No. of control (%) | OR (95% CI) | p-value |
|---|---|---|---|---|
| *GSTM1* | | | | |
| Null | 90 (54.22) | 125 (38.23) | 1.53 (1.20-1.96)[a] | 0.001 |
| Present | 76 (45.78) | 202 (61.77) | | |
| *GSTT1* | | | | |
| Null | 85 (51.20) | 163 (49.85) | 1.04 (0.81-1.33) | 0.849 |
| Present | 81 (48.80) | 164 (49.80) | | |

The data were analyzed by the chi-square test. GST: glutathione-S-transferase, OR: odds ratio, CI: confidence interval, [a]: $p<0.05$

**TABLE 5.** Correlation of the clinical and pathological features of prostate cancer with *GSTP1* genotypes

| Pathological features | *GSTP1* | | | p-value |
|---|---|---|---|---|
| | No. of A/A (%) | No. of A/G (%) | No. of G/G (%) | |
| Stage | | | | |
| High (≥T3 or N1 or M1) | 55 (70.5) | 21 (26.9) | 2 (2.6) | 0.407 |
| Low (T1-T2 or No or M0) | 62 (70.5) | 21 (23.9) | 5 (5.7) | |
| Gleason score | | | | |
| ≥7 | 89 (71.8) | 31 (25.0) | 4 (3.2) | 0.226 |
| ≤6 | 28 (66.7) | 11 (26.2) | 3 (7.1) | |

The data were analyzed by the chi-square test. GST: glutathione-S-transferase

**TABLE 6.** Correlation of the clinical and pathological features of prostate cancer with *GSTM1* genotypes

| Pathological features | *GSTM1* | | OR (95% CI) | p-value |
|---|---|---|---|---|
| | No. of null (%) | No. of present (%) | | |
| Stage | | | | |
| High (≥T3 or N1 or M1) | 39 (50.0) | 39 (50.0) | 1.51 (0.82-2.80) | 0.212 |
| Low (T1-T2 or No or M0) | 53 (60.2) | 35 (39.8) | | |
| Gleason score | | | | |
| ≥7 | 68 (54.8) | 56 (45.2) | 1.10 (0.54-2.23) | 0.858 |
| ≤6 | 24 (57.1) | 18 (42.9) | | |

The data were analyzed by the chi-square test. GST: glutathione-S-transferase, OR: odds ratio

**TABLE 7.** Correlation of the clinical and pathological features of prostate cancer with *GSTT1* genotypes

| Pathological features | *GSTT1* | | OR (95% CI) | p-value |
|---|---|---|---|---|
| | No. of null (%) | No. of present (%) | | |
| Stage | | | | |
| High (≥T3 or N1 or M1) | 40 (51.3) | 38 (48.7) | 0.79 (0.43-1.46) | 0.453 |
| Low (T1-T2 or No or M0) | 40 (45.5) | 48 (54.5) | | |
| Gleason score | | | | |
| ≥7 | 58 (46.8) | 66 (53.2) | 1.25 (0.62-2.52) | 0.530 |
| ≤6 | 22 (52.4) | 20 (47.6) | | |

The data were analyzed by the chi-square test. GST: glutathione-S-transferase, OR: odds ratio

prostate cancer group than in the control group (OR=1.53, 95% CI=1.20-1.96) (Table 4). No statistically significant correlations were identified between the *GSTP1, GSTM1,* and *GSTT1* genotypes and staging or Gleason score (Table 5-7).

## DISCUSSION

Prostate cancer is a multifactorial disease that likely involves both environmental and genetic factors. Collectively, most putative environmental and genetic risk factors have not shown a consistent association with prostate cancer risk, and little is known about the interaction of these factors. Prostate cancer risk varies most prominently with age, ethnicity, family history, and diet [14].

Individual differences in the susceptibility to carcinogens play an essential role in the development of sporadic cancer. The biochemical basis for the genetic susceptibility to environmental hazards is related to genetic polymorphisms that normally occur in the general population and involves a series of genes implicated in the metabolic activation or detoxification of environmental genotoxins. Several polymorphic genes encoding enzymes involved in the biotransformation of carcinogens have been studied as possible prostate cancer risk modifiers, including the *GST* system and the phase I cytochrome P450 (CYP) genes [15].

The *GSTs* are involved in the metabolism of a wide variety of potential carcinogens. The levels of *GST* isozymes in normal and tumor tissues are important for several reasons. High levels of *GST* have been shown to detoxify several chemical carcinogens efficiently and to protect tissues against DNA damage. The presumptive function of *GST* is to protect tissues against toxic or carcinogenic compounds that enter the body as food components, food additives, or drugs [4-7]. Considerable evidence suggests the existence of various biological defense systems against carcinogenesis. Individuals with homozygous deletions of the *GSTM1, GSTT1,* and *GSTP1* genes lack *GST* and therefore may be unable to eliminate electrophilic carcinogens efficiently, which may increase the risk of somatic mutations that lead to tumor formation [8-13,16]. The phenotypic absence of *GSTM1, GSTT1,* and *GSTP1* activities is due to homozygous inherited deletions of these genes, which is referred to as the null genotype [17].

Several population-based studies have reported prevalences ranging from 47% to 58% for the *GSTM1* deletion genotype and from 13% to 25% for the *GSTT1*-null genotype among Caucasian Europeans. For *GSTP1*, the prevalences of *Ile/Val* heterozygosity and *Val/Val* homozygosity were found to be between 38% and 45.7% and between 7% and 13%, respectively. Previous studies have shown that the *GSTM1* null genotype correlates with increased susceptibility to bladder and prostate cancers, as well as to lung cancer [18,19].

In a Southern European population, an analysis of the frequencies of the 670 alleles indicated that men carrying two B-alleles (*GSTM3*) have an increased risk for prostate cancer. The polymorphism in *GSTM3* may be an important biomarker for prostate cancer risk, especially in the definition of the genetic risk profile of populations of Southern Europe [20]. In Chilean prostate cancer patients, the frequency of the m2 variant allele and *GSTM1*(−/−) showed

statistically significant increases compared with the control group. Chilean people carrying single or combined *GSTM1* and *CYP1A1* polymorphisms are more susceptible to prostate cancer [21]. In a Brazilian population, the *GST* and *CYP1A1* genotypes were not associated with the susceptibility to prostate cancer or its outcome. Those authors said that they were unable to demonstrate any relationship between genotypes and parameters of aggressiveness at diagnosis or during the follow-up. Also, there was no relationship between the response to radiotherapy and any other outcome [22].

In a Japanese population, the frequency of the *GSTM1* null genotype was also slightly higher in prostate cancer patients (49.6%) compared with the control value (42.5%), with an OR of 1.2 (95% CI=0.78-1.99). A *GSTT1*-positive genotype was thus associated with a 60% higher risk in the prostate cancer group (OR 1.6; 95% CI=0.99-2.51). That study showed a significant relation between the prostate cancer group and the genetic polymorphisms of *CYP1A1* alone and in combination with *GSTM1* [23]. The *GSTP1*-313 G polymorphism, and null alleles of *GSTM1* and *GSTT1*, are strong predisposing risk factors for sporadic prostate cancer in North India [24].

In the present study, we investigated the potential link between the *GSTM1, GSTT1,* and *GSTP1* null genotypes and prostate cancer risk. The results of our study showed an association between prostate cancer risk and the presence of the *GSTM1* null genotype (Table 3). These results suggest that elevated metabolic activation and decreased levels of detoxification of endogenous or exogenous carcinogens increase DNA adduct formation, thereby increasing the prostate cancer risk [1,19].

The major finding of the present meta-analysis provides support for the association of the genetic polymorphism of *GSTM1* (null vs. non-deleted) with the susceptibility to prostate cancer. However, the *GSTT1* polymorphism (null vs. nondeleted) and the *GSTP1* polymorphism showed no correlation with prostate cancer risk [19]. Although the results of our study show a statistically significant association between the *GSTM1* polymorphisms and prostate cancer, the clinical significance of this finding requires further investigation.

There was no significant association between the *GSTP1, GSTM1,* and *GSTT1* genotypes and the clinico-pathologic factors of prostate cancer. To better understand the role of the *GSTs* and to study their predictive value, tumor prognostic criteria should be examined, such as cancer-specific survival and overall survival.

## CONCLUSIONS

An increased risk for prostate cancer may be associated with the *GSTM1* null genotype in Korean men, but no association was found with the *GSTT1* or *GSTP1* phenotype. To better understand the role of the *GSTs* and to study their predictive value, tumor prognostic criteria should be examined, such as cancer-specific survival and overall survival.

**Conflicts of Interest**
The authors have nothing to disclose.

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