Genes Genom (2016) 38:235–241
DOI 10.1007/s13258-015-0382-2

RESEARCH ARTICLE

Association between glutathione S-transferases M1, T1 and P1 gene polymorphisms and prostate cancer in Koreans

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Received: 2 October 2015 / Accepted: 15 December 2015 / Published online: 28 December 2015

Abstract Prostate cancer (PCa) is the most commonly diagnosed cancer in the developed world, and the incidence of this cancer is rising rapidly in many countries. Several polymorphic genes encoding enzymes involved carcinogenesis have been studied as potential risk factor of prostate cancer. Genetic polymorphisms in glutathione S-transferases M1 (*GSTM1*), T1 (*GSTT1*) and P1 (*GSTP1*) genes have been constantly reported to have a meaningful effect on prostate cancer risk. But other surveys of this relationship have yielded inconsistent results. To assess the possible contribution of the *GSTM1*, *GSTT1*, and *GSTP1* gene polymorphisms in prostate cancer, we performed a population-based study of 139 prostate cancer patients and 115 healthy controls based on their genotype distributions of the genes. There were no differences in distributions of genotype frequencies of *GSTM1* and *GSTP1* polymorphisms between prostate cancer patients and controls (OR 1.60, 95 % CI 0.886–2.860 for *GSTM1* and OR 1.38, 95 % CI 0.739–2.577 for *GSTP1*). In contrast, the distribution of *GSTT1*-null genotype is significantly different between the prostate cancer case and controls (OR 0.26, 95 % CI 0.128–0.518, $p < 0.001$). Meanwhile, *GSTP1* I/V and V/V genotypes were significantly associated with prostate cancer where the PSA level was more than 10.0 (OR 2.73, 95 % CI 1.319–5.639, $p = 0.006$). Thus, our data imply that the *GSTT1*-null genotype may not be a risk factor but a protective factor of prostate cancer and *GSTP1* Val allele is a risk factor for the prostate cancer where the PSA level was high, although functional studies with larger sample size are necessary to elucidate these findings.

Keywords Association study · Prostate cancer · Glutathione S-transferase · *GSTM1* · *GSTT1* · *GSTP1*

Introduction

Prostate cancer is one of the most commonly diagnosed cancer among men in developed countries, and responsible for 25 % of all new case of cancer (Kim et al. 2007; Kim et al. 2008; Sissung et al. 2014; Mitchell and Neal 2015). In the western industrialized country, the prostate cancer is the second leading cause of cancer mortality (Kim et al. 2008; Safarinejad et al. 2011). It has reported that about 241,740 men in the USA were diagnosed of prostate cancer in 2012. Incidence of prostate cancer in Korea is relatively low when compared to the USA but it has been recently increased that prostate cancer is the fifth leading cancer in Korean men, moreover the mortality of the prostate cancer has also been elevated (Jung et al. 2013; Cho et al. 2015). Multiple variables such as, ethnic origin, environmental, and genetic factor are possibly linked to incidence of prostate cancer (Kim et al. 2008). Especially, the genetic factor may responsible for about 42 % of prostate cancer, according to studies that estimate the difference in the concordant occurrence of prostate cancer between monozygotic and dizygotic twin (Lichtenstein et al. 2000; Mitchell and Neal 2015).

Glutathione S-transferase genes are a multigene family that are classified into at least six classes, including alpha (α), mu (μ), omega (ω), pi (π), theta (θ) and zeta (ζ), that are encoded by the *GSTA*, *GSTM*, *GSTO*, *GSTP*, *GSTT* and *GSTZ* genes, respectively (Townsend and Tew 2003;

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Karagas et al. 2005; Safarinejad et al. 2011; Bansal et al. 2014). Glutathione S-transferases are members of the phase II enzymes, which are mediating the conjugation of harmful compounds such as chemical carcinogens, pesticides, and antitumor agents, with glutathione, resulting in neutralization (McIlwain et al. 2006; Pan et al. 2014; Zhou et al. 2014). Therefore deficiency in GST enzyme activity may be a risk factor for developing cancer when exposed to certain carcinogens (Zhao et al. 2015). Among glutathione S-transferase genes, *GSTM1* (OMIM: 138350), *GSTP1* (OMIM: 134660) and *GSTT1* (OMIM: 600436) are most widely analyzed for its genetic association with various cancers (Safarinejad et al. 2011; Bansal et al. 2014; Cai et al. 2013; Pan et al. 2014). The homozygous deletion (null genotype) of the *GSTM1* and *GSTT1* genes result in complete absence of enzyme activities and *GSTP1* Ile105Val polymorphism shows decreased enzyme activity (Mao et al. 2004; Safarinejad et al. 2011). *GSTM1* and *GSTT1* are critical components for the DNA repair pathway, thus absence of these enzymes possibly contribute to the higher risk of prostate cancer (Cai et al. 2013). Meanwhile, the *GSTP1* gene inactivation was frequently reported from many prostate tumor cases that the gene was silenced by hypermethylation in the promoter region (Lee et al. 1994; Cai et al. 2013). Despite these genetic associations between *GSTM1*, *GSTP1* and *GSTT1*, and prostate cancer, other surveys of this relationship have yielded inconsistent results (Kim et al. 2002, 2005; Ntais et al. 2005; Mittal et al. 2009; Mo et al. 2009; Konwar et al. 2010a, b; Wei et al. 2012; Cai et al. 2013; Zhou et al. 2014). Therefore, these discrepancies raised the question of whether or not *GSTM1*, *GSTP1*, and *GSTT1* polymorphisms are really the genetic risk factors for prostate cancer. The present study investigated an association between the *GSTM1*-null, *GSTT1*-null and *GSTP1* Ile105Val polymorphisms and the occurrence of prostate cancer by the case–control designed study in 139 prostate cancer case and 115 corresponding controls.

Materials and methods

Subject

The DNA samples included subsets of the samples examined by Kim et al. (2008). We analyzed a total of 139 Korean prostate cancer patients with histologically confirmed prostate adenocarcinoma (PCa), who were recruited for the study from the urology department of the Eulji University School of Medicine in Seoul and Daejeon, Korea. Histological classification of PCa was determined according to the World Health Organization (WHO) recommendations and the Gleason score (Table 1). In addition, a total of 115 Korean men who had been diagnosed as free of prostate cancer by the Eulji University hospital in Seoul and Daejeon, Korea were recruited as normal controls. These subjects were selected at random (and therefore likely to be unrelated) from the same geographical area as the cases. DNAs were prepared from the prostate cancer specimens of patients and whole blood samples of controls according to standard methods (Sambrook et al. 1989). The separate written informed consent was obtained for screening and for enrollment from all participants.

Clinicopathological characteristics

Information on clinical stage, Gleason score and PSA (prostate specific antigen) level were collected from medical records. According to clinicopathological grade, the patients were categorized into two subgroups: the low-grade PCa (Gleason score <7) and the high-grade PCa (Gleason score ≥ 7) (Safarinejad et al. 2011; Chen et al. 2014). In the Asian population, the detection rate of PCa has been shown to be much lower in the diagnostic gray zone of PSA 4–10 ng/ml (Chen et al. 2014). PSA levels were categorized into two subgroups: the low-grade (PSA ≤ 10 ng/ml) and the high-grade (PSA >10 ng/ml) (Kesarwani et al. 2009).

Genotyping

The *GSTM1* and *GSTT1* genotypes were determined by polymerase chain reaction. The primers used for PCR amplifications were 5′-CTGCCCTACTTGATTGATGG-3′ and 5′-CTGGATTGTAGCAGATCATG-3′ for *GSTM1*, 5′-TTCCTTACTGGTCCTCACATC-3′ and 5′-TCACCGG ATCATGGCCAGCA-3′ for *GSTT1*. And amplification of the albumin *(ALB)* gene with primers 5′-GCCCTCTGCTA ACAAGTCCT-3′ and 5′-GCCCTAAAAAGAAAATCG CC-3′ was used as an internal control.

Each PCR reaction was performed in a total volume of 20 µl containing 20 ng of genomic DNA, 10 pM each primer, 0.2 mM dNTPs, 2.0 mM $MgCl_2$, 10× PCR buffer and 1.0 U NV DNA polymerase (NAVI BioTech, Korea). The PCR amplification was conducted Bio-rad PCR system under the conditions: 94 °C for 5 min, followed by 35 cycles of 94 °C for 1 min, 58 °C for 1 min and 72 °C for 1 min, then a final extension at 72 °C for 10 min. Each PCR products were analyzed by electrophoresis on 2 % agarose gel. The length of PCR products were 273 bp for individuals with one or more *GSTM1* alleles, 480 bp for individuals with one or more *GSTT1* alleles and 350 bp for *ALB* as internal control.

Table 1 Distribution of studied clinicopathological characteristics among the prostate cancer patients and control group

Characteristic	Category	Prostate cancer (n = 139)	Control (n = 115)
Age (year)	≤55	5 (3.60 %)	36 (31.30 %)
	56–60	11 (7.91 %)	20 (17.39 %)
	61–65	24 (17.27 %)	32 (27.83 %)
	>65	99 (71.22 %)	27 (23.48 %)
		[70.6 ± 8.3][a]	[59.4 ± 10.7]
PSA (ng/ml)	≤4.0	15 (10.79 %)	108 (93.91 %)
	4.1–10.0	41 (29.50 %)	2 (1.74 %)
	10.1–20.0	24 (17.27 %)	3 (2.61 %)
	>20.0	59 (42.45 %)	–
	Not available	–	2 (2.61 %)
Gleason score	2–6	47 (33.81 %)	–
	7	35 (25.18 %)	–
	8–10	56 (40.29 %)	–
	Not available	1 (0.72 %)	–

PSA prostate-specific antigen

[a] Mean ± SD

The *GSTP1* genotype were determined by PCR–RFLP (restriction fragment length polymorphism) method. *GSTP1* was amplified using these primers 5′-ACCCCAGGGCTC TATGGGAA-3′ and 5′-TGAGGGCACAAGAAGCCCCT-3′. Each PCR reaction was performed in a total volume of 20 µl containing 20 ng of genomic DNA, 10 pM each primer, 0.2 mM dNTPs, 2.0 mM $MgCl_2$, 10× PCR buffer and 1.0 U NV DNA polymerase (NAVI BioTech, Korea). The PCR amplification under the conditions: 94 °C for 30 s, followed by 35 cycles of 94 °C for 90 s, 61 °C for 1 min, 72 °C for 30 s, then and a final extension at 72 °C for 10 min. After amplification, the PCR products were restricted by *BsmA*1. The fragments were separated by electrophoresis on 3 % agarose gel. Ile/Ile had single fragment of 176 bp, and Val/Val had two fragments of 85 and 91 bp, and Ile/Val had three fragment.

Data analyses

To test for association between all the samples for the prostate cases and the control groups, we used a frequencies, Chi squared tests implemented in SPSS 21 Statistics (IBM Korea, Korea). A test of proportion and odds ratio (OR) with 95 % confidence intervals (CI) in a 2 × 2 table were calculated using the statistical analysis on the internet (SISA, http://www.quantitativeskills.com/sisa/). ORs were adjusted for age by using the multivariate logistic regression models. The frequencies of combined genotype were estimated by counting.

A value of $p < 0.05$ was considered statistically significant. Bonferroni correction was used to adjust the α-level according to the number of independent comparisons.

Results

The mean ages of this study were 70.6 ± 8.3 and 59.4 ± 10.7 for the cases and the controls, respectively (Table 1). The level of PSA and Gleason score also presented Table 1. Eighty-three cases exceeded 10 ng/ml of PSA level and the Gleason score for 47 cases were more than 10.

Genotyping data of *GSTM1*, *GSTP1*, and *GSTT1* for the 139 prostate cancer cases and 115 controls are summarized in Table 2. The frequencies of *GSTM1*-null genotype for our study were 56.8 % in the prostate cancer group and 47.8 % in the controls. The adjusted odds ratio was 1.60 (95 % confidence interval 0.886–2.860, $p = 0.152$) which is not significant. The frequencies of valine related genotypes (I/V + V/V) of *GSTP1* were 33.9 % for the controls and 33.1 % for the case samples. The adjusted odds ratio was 1.38 (95 % CI 0.739–2.577, $p = 1.000$). Again, the value was not significant. However, the genotype distribution *GSTT1*-null was significantly different between the case group (57.5 %) and controls (79.1 %) ($p < 0.001$). The adjusted odds ratio and 95 % CI for the *GSTT1*-null genotype was 0.26 and 0.128–0.518, respectively. The result suggested that the *GSTT1*-null genotype is a protective factor for prostate cancer in our samples.

The effects from combined genotypes of *GSTM1*, *GSTP1* and *GSTT1* were analyzed (Table 3). Significant associations were observed among *GSTM1*-null + *GSTT1*-present ($p = 0.006$), *GSTT1*-null + *GSTP1*-I/I ($p = 0.006$), *GSTT1*-null + *GSTP1*-I/V or V/V ($p = 0.006$), *GSTM1*-null + *GSTT1*-present + *GSTP1* I/I ($p = 0.035$) and *GSTM1*-null + *GSTT1*-present + *GSTP1*-I/V or V/V ($p = 0.027$). However, no values were significant after applying the Bonferroni corrected significant level of

Table 2 Genotypes and allele frequencies of *GSTM1*, *GSTT1* and *GSTP1* gene in the prostate cancer patients and control group

Genotype	Prostate cancer (n = 139)	Control (n = 115)	Adjusted OR (95 % CI)[a]	*p* value[b]
GSTM1				
Present	60 (43.2 %)	60 (52.2 %)	1.0 (reference)	
Null	79 (56.8 %)	55 (47.8 %)	1.60 (0.886–2.860)	0.152
GSTT1				
Present	59 (42.5 %)	24 (20.9 %)	1.0 (reference)	
Null	80 (57.5 %)	91 (79.1 %)	0.26 (0.128–0.518)	<0.001***
GSTP1				
I/I	93 (66.9 %)	76 (66.1 %)	1.0 (reference)	
I/V + V/V	46 (33.1 %)	39 (33.9 %)	1.38 (0.739–2.577)	1.000

*** $p < 0.001$

[a] *Adjusted OR* adjusted in multivariate logistic regression models including age and GSTs genotypes

[b] The Chi square *p* value, using Bonfferoni correction for multiple testing, *p* values <0.0083 are statistically significant

Table 3 Combined genotype frequencies of the *GSTM1*, *GSTT1* and *GSTP1* polymorphisms in the prostate cancer patients and control group

GSTs	Genotype	Case (n = 139)	Control (n = 115)	*p* value[a]	Adjusted OR (95 % CI)[b]
M1 + T1	Both present	22 (15.83 %)	17 (14.78 %)	1.000	1.0 (reference)
	M1 present/T1 null	38 (27.34 %)	43 (37.39 %)	0.330	0.68 (0.317–1.473)
	M1 null/T1 present	37 (26.62 %)	7 (6.09 %)	0.006**	4.08 (1.464–11.398)
	Both null	42 (30.22 %)	48 (41.74 %)	0.309	0.68 (0.317–1.441)
M1 + P1	M1 present and P1 I/I	42 (30.22 %)	39 (33.91 %)	1.000	1.0 (reference)
	M1 present and P1 I/V or V/V	18 (12.95 %)	21 (18.26 %)	0.559	0.80 (0.370–1.712)
	M1 null and P1 I/I	51 (36.69 %)	37 (32.17 %)	0.426	1.28 (0.697–2.350)
	M1 null and P1 I/V or V/V	28 (20.14 %)	18 (15.65 %)	0.326	0.26 (0.332–1.444)
T1 + P1	T1 present and P1 I/I	38 (27.34 %)	16 (13.91 %)	1.000	1.0 (reference)
	T1 present and P1 I/V or V/V	21 (15.11 %)	8 (6.96 %)	0.845	1.11 (0.406–3.011)
	T1 null and P1 I/I	55 (39.57 %)	60 (52.17 %)	0.006**	0.39 (0.194–0.769)
	T1 null and P1 I/V or V/V	25 (17.99 %)	31 (29.96 %)	0.006**	1.18 (1.341–6.467)
M1 + T1 + P1	M1 present and T1 present and P1 I/I	12 (8.63 %)	10 (8.70 %)	1.000	1.0 (reference)
	M1 present and T1 present and P1 I/V or V/V	10 (7.19 %)	7 (6.09 %)	0.789	0.55 (0.234–3.020)
	M1 present and T1 null and P1 I/I	30 (21.58 %)	29 (25.22 %)	0.767	0.86 (0.323–2.302)
	M1 present and T1 null and P1 I/V or V/V	8 (5.76 %)	14 (12.17 %)	0.226	0.48 (0.142–1.593)
	M1 null and T1 present and P1 I/I	26 (18.71 %)	6 (5.22 %)	0.035*	3.61 (1.064–2.251)
	M1 null and T1 present and P1 I/V or V/V	11 (7.91 %)	1 (0.87 %)	0.027*	9.17 (1.003–83.766)
	M1 null and T1 null and P1 I/I	25 (17.99 %)	31 (26.96 %)	0.431	0.67 (0.249–1.810)
	M1 null and T1 null and P1 I/V or V/V	17 (12.23 %)	17 (14.78 %)	0.740	0.83 (0.284–2.442)

* $p < 0.05$, ** $p < 0.01$

[a] The Chi square *p* value, using Bonfferoni correction for multiple testing, *p* values <0.0041 (double), <0.0062 (triple) are statistically significant

[b] *Adjusted OR* adjusted in multivariate logistic regression models including age and GST genotypes

0.0041 and 0.0062 for a combination analysis of two loci and three loci, respectively.

The significant association was observed between GSTP1-I/V + V/V genotype and clinicopathological characteristics of prostate cancer (Table 4). This genotype was more frequently observed in the prostate cancer patients whose PSA level was more than 10 ng/ml (Table 4). The odds ratio was 2.73 (95 % CI 1.319–5.639, $p = 0.006$).

Discussion

The age was reported to be a major risk factor for prostate cancer (Zhou et al. 2014). Therefore, we adjusted the age for the statistical analyses in this study. There were no differences in the null genotype distribution of *GSTM1* and in the genotype distribution of *GSTP1* Ile105Val polymorphism between the prostate case samples and controls

Table 4 Association between the *GSTM1*, *GSTT1* and *GSTP1* polymorphisms and clinicopathological characteristics of prostate cancer

GSTs polymorphism	PSA level (ng/ml)		Gleason score	
	≤10.0 (n = 56)	>10.0 (n = 83)	≥7 (n = 91)	<7 (n = 47)
GSTM1				
Present	23 (41.1 %)	37 (44.6 %)	41 (45.1 %)	19 (40.4 %)
Null	33 (58.9 %)	46 (55.4 %)	50 (54.9 %)	28 (59.6 %)
p value[a]	Reference	0.682	Reference	0.603
OR (95 % CI)		1.15 (0.581–2.292)		0.83 (0.405–1.690)
GSTT1				
Present	26 (46.4 %)	33 (39.8 %)	36 (39.6 %)	23 (48.9 %)
Null	30 (53.6 %)	50 (60.2 %)	55 (60.4 %)	24 (51.1 %)
p value[a]	Reference	0.435	Reference	0.291
OR (95 % CI)		0.76 (0.384–1.511)		1.46 (0.720–2.977)
GSTP1				
I/I	30 (53.6 %)	63 (75.9 %)	62 (68.1 %)	30 (63.8 %)
I/V + V/V	26 (46.4 %)	20 (24.1 %)	27 (31.9 %)	17 (36.2 %)
p value[a]	Reference	0.006**	Reference	0.489
OR (95 % CI)		2.73 (1.319–5.649)		0.77 (0.364–1.622)

PSA prostate-specific antigen

[a] The Chi square *p* value

** $p < 0.01$

in this survey ($p > 0.05$), suggesting that these two polymorphisms do not significantly associated with a higher risk of prostate cancer in Korea. Earlier findings suggest that the *GSTM1*-null genotype is a risk factor for the occurrence of prostate cancer (Srivastava et al. 2005; Minelli et al. 2011; Haholu et al. 2013; Cai et al. 2013; Zhou et al. 2014). Wei et al. (2012) also supported these reports that the effect of *GSTM1*-null genotype is a mild risk factor for prostate cancer. Meanwhile, Srivastava et al. (2005) reported that *GSTP1*-313 A/G polymorphism, that the polymorphism replaces isoleucine at codon 105 with valine, is a strong predisposing risk factor for prostate cancer in North India. In addition, the *GSTP1* 105Val was found to be a moderately significant risk factor for prostate cancer among men of African descent (Ntais et al. 2005; Lavender et al. 2009; Safarinejad et al. 2011).

However, others reported the lack of association between the *GSTM1* and *GSTP1* polymorphisms and prostate cancer (Ntais et al. 2005; Så et al. 2014). Ntais et al. (2005) reported from their meta-analysis that *GSTM1*-null and *GSTP1* 105Val genotypes were not a risk for prostate cancer. Så et al. (2014) also could not find any association between the *GSTP1* 105Val polymorphism and increased risk of prostate cancer in a Brazilian population cohort. These findings are consistent with the present results (Table 2).

In contrast, we found a significant association between *GSTT1*-null genotype and prostate cancer that the null genotype was deficit among prostate cases (OR 0.26, 95 % CI 0.128–0.518, $p < 0.001$). It has reported that the *GSTT1*-null genotype is a strong risk factor of prostate cancer (Ntais et al. 2005; Srivastava et al. 2005; Safarinejad et al. 2011). However, the *GSTT1*-null genotype was not a risk factor for prostate cancer in our study. The frequencies of *GSTT1*-null genotypes are 57.5 % for prostate cancer cases and 79.1 % for controls (Table 2). This result means that the effect of *GSTT1*-null genotypes in Korean population is indeed protective. A similar association in Korean population was reported that the *GSTT1*-null genotype is a protective factor of bladder cancer (Kim et al. 2002). The author also suggested that *GSTT1*-present genotype is rather risk factor for bladder cancer in Koreans (Kim et al. 2005). Bansal et al. (2014) also reported that the *GSTT1*-null genotype was detected in 51.04 % for controls in comparison to 20.2 % of breast cancer patient, hence protective. Therefore, comprehensive analyses with larger sample sets are required to clarify the effect of *GSTT1*-null genotype in the prostate cancer.

Nominal associations between genotypes and cancer risk were observed in the combined analyses of these three markers (Table 3). The combined genotype of *GSTM1*-null/*GSTT1*-present showed that the risk increased ~fourfolds ($p = 0.006$). This result may support the previous result that the *GSTM1*-null and *GSTT1*-present genotypes are risk factors for bladder cancer in Korean population (Kim et al. 2005). The combined genotype of *GSTM1*-null, *GSTT1*-present and *GSTP1* I/V or V/V genotype increased the risk almost ninefolds ($p = 0.027$). In the previous report, *GSTP1* I/V or V/V genotype is a possible risk factor for prostate cancer (Safarinejad et al.

2011). Therefore, *GSTM1*-null, *GSTT1*-present and *GSTP1* I/V or V/V combined genotype can be a strong candidate risk factor for prostate cancer in Korea. However, none of them are survived after Bonferroni correction ($p = 0.0041$ for a combination of two loci and $p = 0.0062$ for a combination of three loci).

The genotype distributions of *GSTM1*, *GSTP1*, and *GSTT1* were compared to clinicopathological characteristics (Table 4). There is a significant surplus of *GSTP1* I/V + V/V genotypes in the prostate patients, whose PSA levels are exceeded 10 ng/ml (Table 4). Measuring PSA concentration in blood is a powerful tools to predict lifelong risk of prostate cancer in men (Vickers et al. 2013; Attard et al. 2015). But other studies reported lack of association between *GST* gene polymorphisms and prostate cancer status based on PSA level (Ashtiani et al. 2010; Qadri et al. 2011). Thus, additional survey of samples with various ethnicities and data of precisely estimate PSA level for each samples are the subjects for further analyses.

The present study has an inherent deficiency that the number of studied samples was relatively small. The sample numbers of this study were 139 prostate cancer cases and 115 controls. Despite the methodological limitation, this study has an advantage that both the prostate case group and controls in this study underwent strict clinical evaluation by urologists, therefore the purity of our samples is relatively high. Besides, this study conducted with 254 subjects and the calculated analysis power of our study was over 95 %. However, genetic association studies should be carefully interpreted, because the possibility of common errors contributed to statistical fluctuation, for example, GWAS approaches have a high rate of false negative because of the burden of multiple testing. Inversely, the candidate approaches that conducted in this study, typically showed a high rate of false positive and overestimation in genetic effects (Sissung et al. 2014). Therefore, further analyses with larger sample sizes and various genetic markers are required to exclude possible errors.

In conclusion, the statistically significant association was observed between *GSTT1*-null genotype and prostate cancer. Our results imply that the *GSTT1*-null genotype may be protective in Korean samples. In addition, we find a significant association between *GSTP1* I/V + V/V genotype and PSA level in patients.

Acknowledgments The present research was conducted by the research fund of Dankook University in 2013.

Compliance with ethical standards

Bioethical statements This study was approved by the Ethics Committee and institutional review boards of Eulji Medical Center of the Eulji University School of Medicine in Seoul, Korea.

Conflict of interest The authors declare no conflict of interest.

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