ULUSLARARASI HEMATOLOJI-ONKOLOJI DERGISI ARTICLE International Journal of Hematology and Oncology

Influence of GSTM1, GSTP1, and GSTT1 Gene Polymorphisms on Prostate Cancer Risk in Turkish Population

Ufuk BERBER[1], Ismail YILMAZ[1], Omer YILMAZ[2], Aptullah HAHOLU[1], Zafer KUCUKODACI[1], Ferhat ATES[2], Dilaver DEMIREL[1]

[1] GATA Haydarpasa Training Hospital, Department of Pathology
[2] GATA Haydarpasa Training Hospital, Department of Urology, Ankara, TURKEY

ABSTRACT

We analysed glutathione S-transferase M1, T1, and P1 gene polymorphisms in a case control study to asses their susceptibility to prostate cancer in Turkish population. Polymorphisms were determined by PCR-based methods in 115 control subjects and 115 prostate cancer patients. The frequencies of polymorphisms were compared between patients and controls by logistic regression analysis. Possible associations of genetic profiles with respect to the Gleason score and patient age were also investigated. Besides GSTT1 null genotype has slightly increased prostate cancer risk (odds ratio(OR) = 1.50, 95% confidence interval (CI), 0.85-2.66), its association with prostate cancer risk was statistically significant among smokers (OR = 3.20, 95%CI, 1.06-9.70). GSTP1 Val/Val genotype was more common in cancer patients (OR = 1.63, 95%CI, 0.61-4.37). However, the combination of GSTP1 Ile/Ile and GSTT1 null genotype was associated with a higher risk (OR = 2.67, 95%CI, 1.00-7.10). Our results suggest that GSTT1 null genotype may modify prostate cancer risk among cigarette smokers seperately, and in combination with GSTP1 Ile/Ile genotype, irrespective of the smoking habit in Turkish population.

Keywords: Prostate cancer, GSTM1, GSTP1, GSTT1, Polymorphism

ÖZET

Türk Toplumunda GSTM1, GSTP1 ve GSTT1 Gen Polimorfizmlerinin Prostat Kanseri Riski Üzerine Etkileri

Türk toplumunda prostat kanseri riski üzerindeki etkilerini değerlendirmek amacı ile glutatyon S-transferaz M1, T1 ve P1 gen polimorfizmlerini bir vaka kontrol çalışması ile araştırdık. Polimorfizmler 115 kontrol ve 115 prostat kanseri hastasında polimeraz zincir reaksiyonuna dayalı yöntemler ile saptandı. Kontrol ve prostat kanseri gruplarında polimorfizmlerin sıklıkları lojistik regresyon analizi ile karşılaştırıldı. Ayrıca genetik profiller ile Gleason skoru ve hasta yaşları arasında bir ilişki varlığı araştırıldı. GSTT1 null genotipin prostat kanseri riskini hafif derecede artırdığı görülmekle birlikte (odds oranı (OR) = 1.50, %95 güven aralığı (CI), 0.85-2.66), sigara içenlerde prostat kanseri ile ilişkisinin istatistiksel olarak anlamlı olduğu saptandı (OR = 3.20, %95CI, 1.06-9.70). GSTP1 Val/Val genotipi vakalarda daha sıktı (OR = 1.63, 95%CI, 0.61-4.37). Ancak, GSTP1 Ile/Ile ve GSTT1 null genotip kombinasyonunda risk anlamlı derecede daha yüksek olarak bulundu (OR = 2.67, %95CI, 1.00-7.10). Bu sonuçlar, Türk toplumunda GSTT1 null genotipin sigara içen bireylerde prostat kanseri riskini artırdığını göstermiştir. Ayrıca GSTT1 null ve GSTP1 Ile/Ile genotip birlikteliğinin sigara kullanımından bağımsız olarak prostat kanseri riskini arttırdığını göstermiştir.

Anahtar Kelimeler: Prostat kanseri, GSTM1, GSTP1, GSTT1, Polimorfizm

INTRODUCTION

Prostate cancer incidence varies in a wide range between different populations. Environmental factors and genetic polymorphisms in metabolic pathways are supposed to be one of the major causes for the variable cancer development risk among different ethnic/social groups. Glutathione S-transferase (GST) enzymes that play a key role in detoxification of activated carcinogens are shown to be one of the potential modifiers of individualized risk for several cancer types.[1] Polymorphisms in GST gene family casue a decrease or loss in activity of the corresponding enzymes and lead to the accumulation of intracellular genotoxic metabolites, which resulted in impairment of the cancer prevention mechanisms. Three members of the GST enzymes; GSTM1, GSTP1, and GSTT1 catalyze the reactions with common carcinogens such as polycylic aromatic hydrocarbons and aminobiphenyls present in tobacco, air pollutants, and grilled meat.[2,3]

Inherited absence of two alleles (null genotype) in GSTM1 and GSTT1 genes result in lack of enzymatic activity. In addition, an A/G transition at codon 105 of the GSTP1 gene (rs1695) leads to the formation of variant enzyme with decreased enzymatic activity.[4] Besides these genotypes were found to be associated with prostate cancer,[4-7] GSTP1 gene silencing with methylation was also linked to prostate cancer development, and suggested to be a useful marker for noninvasive detection of tumors from voided urine samples.[8] However, GSTP1 Ile105Val polymorphism and its relation to prostate cancer risk among Turkish population has not been studied before. Moreover, the data about null genotypes of GSTM1 and GSTT1 genes and their relevance to prostate cancer in our population is limited with only two studies investigating the GSTM[15,9] and one investigating the GSTT1 genotypes.[9] Therefore, we conducted this causative association study to determine the modifying roles of polymorphisms in three major xenobiotic metabolizing enzymes on prostate cancer risk and contribute to the emerging data with these polymorphisms. Also the associations of these polymorphisms with patient age and Gleason score were examined to find out whether they have clinical utility.

PATIENTS AND METHODS

Study Subjects

One hundred and fifteen histologically diagnosed prostate cancer patients between years 2008 and 2011, and the same number age (± 5 years) and sex matched cancer-free control subjects were included in the study. Smoking habit and family history of cancer were obtained for all individuals. Controls and cancer patients were dichotomised as never smokers versus ever smokers by their smoking habit. Patients who had a history of prostate cancer in first degree relatives were excluded in this study. Institutional Ethics Committee approved the study in accordance with the Declaration of Helsinki, and appropriate informed consents were obtained from the participants according to the institutional guidelines.

Genotype analysis

For control group, genomic DNA was isolated from blood buffy coat by using QIAamp DNA Mini Kit (Qiagen). For patients, DNA was isolated from formallin fixed paraffin embedded (FFPE) nontumoral prostate tissues by using QIAamp DNA FFPE Tissue Kit (Qiagen), according to the manufacturer's instructions. Primer sequences used in this study are given in Table 1. Null genotypes of GSTM1 (UniGene ID Hs.301961) and GSTT1 (UniGene ID Hs.268573) genes were determined by multiplex PCR and subsequent melting curve analysis method as previously described with minor modifications:[10] We included only primer pairs of GSTM1 and GSTT1 amplicons in PCR tubes. With this approach both amplicons served as an internal control in each tube for PCR efficiency. Whenever an amplification was not observed (i.e. null and null genotype), seperate PCR amplifications were performed for both genes using bcl2 as an internal control gene to evaluate the DNA integrity. PCR amplifications were carried out on RotorGene Q 5-Plex (Qiagen) in a final volume of 20 μL containing 50 ng of genomic DNA, 1.5 mM $MgCl_2$, 0.4 µM each primer, 250 mM of each dNTP, 1U FjTaq polymerase (Genoks), 1 µL EvaGreen dye (Biotium). Amplification protocol was consisted of an activation step at 95°C for 10 minutes and 40 cycles with amplification steps at 95°C, 62°C, and 72°C for 30 sec each. After amplification steps, melting curves were generated to evaluate the PCR products. Mel-

Table 1. Primer sets used in the study.

Gene	Primer sequence (5'-3')	Amplicon length
GSTM1	F: GAACTCCCTGAAAAGCTAAAGC	
	R: GTTGGGCTCAAATATACGGTGG	219 bp
GSTP1	F: ACCCCAGGGCTCTATGGGAA	
	R: TGAGGGCACAAGAAGCCCCT	176 bp
GSTT1	F: TTCCTTACTGGTCCTCACATCTC	
	R: GGAAAAGGGTACAGACTGGGGA	258 bp
Bcl2	F: GCAATTCCGCATTTAATTCATGG	
	R: GAAACAGGCCACGTAAAGCAAC	350 bp

GSTM1: Glutathione S transferase M1; GSTP1: Glutathione S transferase P1; GSTT1: Glutathione S transferase T1; Bcl2: B-cell CLL/lymphoma 2.

ting curve data was acquired between 65°C to 95°C, at a ramping rate of 0.3°C/sec. Melting curves were visually compared to identify different melting patterns.

GSTP1 (UniGene ID Hs.523836) Ile105Val polymorphism was determined by PCR and direct sequencing method by using primers previously described.[11] PCR amplifications were performed in a final volume of 20 μL containing 50 ng of genomic DNA, 1.5 mM $MgCl_2$, 0.4 μM each primer, 200 mM of each dNTP, 1U FjTaq polymerase (Genoks). Amplification protocol was consisted of an activation step at 95°C for 10 minutes following with 40 cycles of amplification steps at 95°C for 30 sec, 58°C for 30 sec, and 72°C for 60 sec. PCR products were subjected to direct sequencing by Big Dye Terminator Cycle sequencing kit (Applied Biosystems) using forward primer on ABI Prism 3730 Sequencer.

Positive - negative controls and no-DNA templates were used in each assay, and tests were randomly repeated for 5% of samples.

Statistical Analysis

Case and control groups were compared for age by Student's "t" test. The genotype distributions of GSTP1 gene among control subjects were analysed to determine whether they were in Hardy-Weinberg equilibrium using chi-square test. The estimates of associations between each genotype and susceptibility to prostate cancer risk were obtained from logistic regression analysis using odds ratios (ORs) with a confidence interval of 95%. Crude ORs were performed separately for GSTM1, GSTP1, and GSTT1 polymorphisms. GSTP1 polymorphisms were dichotomised as major allele homozygous (Ile/Ile) versus heterozygous and homozygous variant (Ile/Val + Val/Val) in the multivariate logistic models where age and smoking status were used as adjusting variables. Gleason scores were dichotomised as ≤6 vs ≥7, and patient age at onset was dichotomised as < 65 years vs ≥65 years for statistical analysis. The difference of histological tumor grade and patient age distributions in different genotype groups were tested using Pearson's chi-square test. Fisher exact test was also used where appropriate.

Statistical analyses were performed using 'SPSS for Windows software version 11.5'. All p values were two-tailed, and $p < 0.05$ was considered as significant.

RESULTS

Main characteristics of the study population are included in Table 2. Case and control groups were similar in terms of age and smoking habit (both $p > 0.05$). Majority of the patients (n= 66, 57.4%) had a Gleason score ≥ 7. The distributions of GSTM1, GSTP1, and GSTT1 polymorphisms found in both groups, ORs and 95% CI are demonstrated in Table 3. The frequency of GSTP1 genotypes among control group were in Hardy Weinberg equilibrium (p= 0.26). The frequency of GSTM1 null genotype was 48.7% (56/115) in controls and 53.0% (61/115)

Table 2. Baseline characteristics of prostate cancer patients and control subjects

		Cases (n= 115)	Controls (n= 115)	p
Age (years)	Mean ± sd	62.77 ± 5.64	61.64 ± 5.55	0.130
	Median (range)	63 (45-74)	61 (49-75)	
Smoking habit, n (%)	Never	50 (43.5%)	61 (53.0%)	
	Ever	65 (56.5%)	54 (47.0%)	0.147
Gleason score	≤6	49 (42.6%)		
	≥7	66 (57.4%)		

sd: Standart deviation

in cases. GSTP1 Ile/Val and Val/Val allele frequencies were 40.0% and 9.6% in cases, compared with 45.2% and 6.1% in controls. We did not observe a significant increased risk for prostate cancer in analysis of the GSTM1 and GSTP1 polymorphisms seperately. However, as demonstrated in Table 4, combined analysis of genotypes revealed a significant increased risk for GSTP1 Ile/Ile and GSTT1 null combination (p= 0.049) (OR= 2.67, 95% CI, 1.00-7.13).

Although it did not reach the significancy level, the frequency of GSTT1 null genotype was slightly higher in patients (n= 27, 23.5%) than controls (n= 16, 13.9%) with an OR of 1.50 (95%CI, 0.85-2.66). Furthermore, a positive association between GSTT1 null genotype and smoking habit was observed for prostate cancer development (OR= 3.20, 95%CI, 1.09-9.42) (p= 0.04). Overall prostate cancer risk in different genotype groups stratified by smoking habit are presented in Table 5.

Age at onset and Gleason scores in prostate cancer patients did not reveal significant differences among each genotype group, neither in seperate nor in combined analysis (data not shown).

Table 3. Genotype distributions of prostate cancer patients and controls

Genotype		Controls n (%)	Cases n (%)	OR	95%CI	p
GSTM1	Positive	59 (51.3)	54 (47.0)	1.0	(reference)	
	Null	56 (48.7)	61 (53.0)	1.19	0.71-2.00	0.51
			1.10*	0.67-1.81	0.70*	
GSTT1	Positive	99 (86.1)	88 (76.5)	1.0	(reference)	
	Null	16 (13.9)	27 (23.5)	1.90	0.96-3.75	0.07
			1.50*	0.85-2.66	0.17*	
GSTP1	AA	56 (48.7)	58 (50.4)	1.0	(reference)	
	AG	52 (45.2)	46 (40)	0.81	0.48-1.36	0.42
	GG	7 (6.1)	11 (9.6)	1.63	0.61-4.37	0.33
	AG + GG	59 (51.3)	57 (49.6)	0.93	0.56-1.56	0.79
			0.80*	0.57-1.13	0.21*	

* OR adjusted for age and smoking status. GSTM1: Glutathione S transferase M1; GSTP1: Glutathione S transferase P1; GSTT1: Glutathione S transferase T1.

Table 4. Combined genotype distributions and associated overall prostate cancer risk

Genotype	Controls n (%)	Cases n (%)	Crude OR (95%CI)	Adj. OR* (95%CI)
GSTP1/GSTM1				
AA/Positive	31 (27.0)	28 (24.3)	1.0 (reference)	1.0 (reference)
AA/Null	25 (21.7)	30 (26.1)	1.33 (0.64-2.78)	1.32 (0.62-2.78)
AG+GG/Positive	28 (24.3)	26 (22.6)	1.03 (0.49-2.15)	1.02 (0.48-2.17)
AG+GG/Null	31 (27.0)	31 (27.0)	1.11 (0.54-2.26)	1.02 (0.50-2.11)
GSTP1/GSTT1				
AA/Positive	49 (42.6)	42 (36.5)	1.0 (reference)	1.0 (reference)
AA/Null	7 (6.1)	16 (13.9)	2.67 (1.00-7.10)	2.67 (1.00-7.13)**
AG+GG/Positive	50 (43.5)	46 (40.0)	1.07 (0.60-1.91)	1.02 (0.57-1.83)
AG+GG/Null	9 (7.8)	11 (9.6)	1.43 (0.54-3.77)	1.42 (0.54-3.77)

* OR adjusted for age and smoking status.
** p=0.049
GSTM1: Glutathione S transferase M1; GSTP1: Glutathione S transferase P1; GSTT1: Glutathione S transferase T1.

DISCUSSION

The incidence of prostate cancer varies in a wide range between different ethnic / social groups worldwide, however, little is known about the causes of racial differences.[12] Genetic factors are implied to be a probable reason for this difference. Polymorphisms in metabolic pathways are one of the major subjects that researchers have investigated in an effort to clarify polygenic models of cancer development. Unfortunately, the effects and interactions of low penetrence genes in cancer susceptibility are largely unknown due to the requirement of large numbers of patients to identify their roles.

GST genes are belong to such low penetrence genes and play a role in carcinogenesis of various tumor types. Previous studies revealed that about 50% of the Caucasians lack the GSTM1 and about 20% lack the GSTT1 genes due to the inherited loss of both alleles.[13] Both genes encode GST enzymes which are involved in the metabolic detoxification of several carcinogenes. For prostate cancer, their involvement in metabolism and intracellular transportation of steroid hormones, provide additional support for these genes to may have a role in prostate carcinogenesis.[14] GSTP1 is the major extrahepatic detoxification enzyme found in several tissues, and GSTP1 gene silencing by methylation is frequently observed in prostate cancer.[8] Although much is known about polymorphisms of GSTM1, GSTT1, and GSTP1 genes and their relevance to prostate cancer, the data for their susceptibility among Turkish population is limited for GSTM1 and GSTT1 gene polmyorphisms, and currently there are no published data for the GSTP1 polymorphism.

In the present study we investigated the influences of GSTM1, GSTP1, and GSTT1 polymorphic genotypes on prostate cancer development risk in Turkish men. The results of polymorphism frequencies for these genes found in our control group did not deviate from previous studies performed in Turkish population. Considering GSTM1 null genotype, its predisposing role in our population is conflicting; while a study reported a strong association[9], another study did not indicate a predisposing role.[5] Our findings were parallel to Aktas et al.[5] that there is no association between GSTM1 null genotype and prostate cancer risk. While Aktas et al.[5] did not examine the relationship between smoking habit and cancer risk, our results demonstrated that cancer risk does not differ with smoking habit in GSTM1 null individuals. Silig et al. also investigated the inherited absence of GSTT1 gene and its

Table 5. Distributions of genotypes in patient and control groups stratified by smoking habit

Genotype	Non smokers			Smokers		
	Cases	Controls	OR (95%CI)	Cases	Controls	OR (95%CI)
GSTM1						
Positive	23 (46.0)	32 (52.5)	1.0 (reference)	31 (47.7)	27 (50.0)	1.0 (reference)
Null	27 (54.0)	29 (47.5)	1.3 (0.61-2.74)	34 (52.3)	27 (50.0)	1.1 (0.53-2.26)
GSTT1						
Positive	39 (78.0)	50 (82.0)	1.0 (reference)	49 (75.4)	49 (90.7)	1.0 (reference)
Null	11 (22.0)	11 (18.0)	1.3 (0.50-3.26)	16 (24.6)	5 (9.3)	3.2 (1.09-9.42)*
GSTP1						
AA	26 (52.0)	37 (60.7)	1.0 (reference)	32 (49.2)	25 (46.3)	1.0 (reference)
AG+GG	24 (48.0)	24 (39.3)	1.4 (0.67-3.03)	33 (50.8)	29 (53.7)	0.9 (0.43-1.83)

*p= 0.04
GSTM1: Glutathione S transferase M1; GSTP1: Glutathione S transferase P1; GSTT1: Glutathione S transferase T1; Bcl2: B-cell CLL/lymphoma 2

modifying role on prostate cancer risk.[9] Their results did not demonstrate a significant increased risk for GSTT1 null genotype carriers. In our study group, the proportion of GSTT1 null genotype was slightly higher in cases (23.5%) than in controls (13.9%) (p= 0.07). However, prostate cancer risk was significantly increased in GSTT1 null genotype carriers among smokers with an OR of 3.2 (95% CI, 1.09-9.42).

Our study revealed an unexpected result for investigation of the GSTP1 Ile/Val polymorphism in prostate cancer patients. Due to the decreased enzymatic activity in the heterozygous and homozygous variant genotypes, an increase in the cancer risk was expected for the Ile/Val and Val/Val genotypes. Besides, we did not observe a significant difference in the allelic distribution of the codon 105 of GSTP1 gene between healthy controls and prostate cancer patients, the major homozygous genotype (Ile/Ile) was found to be more common in cases, and its specific combination with GSTT1 null genotype significantly increased the prostate cancer risk. Thus, GSTP1 codon 105 polymorphism may modify the prostate cancer risk in our population. A such influence of GSTP1 Ile/Ile genotype on bladder cancer risk was also indicated before.[15]

In the association studies we did not observe any significant differences between pathological tumor grades and age of the patients in different genotype groups. Mittal et al. found that ages between 50-60 years exhibited significant variation between the controls and the cancer patients for GSTT1 and GSTM1 null genotypes.[16] In addition, prostate cancer patients with a GSTM1 null genotype were found to be younger than those with the GSTM1 wild type genotypes in Chinese and Japanese.[17,18] A more recent study also demonstrated that GSTM1 null and GSTT1 null genotype was observed in a higher frequency in patients with a Gleason score >7.[19] A detailed analysis of GST gene polymorphisms and their association with clinicopathological parameters in prostatectomy specimens does not exist in our population. Therefore, whether these genes have prognostic impact on prostate cancer patients remains unknown for Turkish men.

On the other hand, growing number of studies have revealed the predisposing roles of single nucleotide polymorphisms in various genes for prostate cancer development in Turkish population. Recently polymorphic variants of genes involved in cell cycle control mechanisms (HPC2/ELAC2), interaction between chemokines and their related receptors (CXCR4, SDF-1, CCR2, CCR5), and, androgen metabolism pathways (SRD5A2, CYP17) are some of the reported candidates for prostate cancer susceptibility.[20-23] Although studies reporting null

association between some of the above-mentioned polymorphisms and prostate cancer risk exist,[24,25] it is possbile that the effects of these low penetrence genes could be masked by gene-gene interactions due to the limited number of the patient and control groups. However, our findings and the results of previous studies collectively support the nature of prostate cancer being a polygenic multifactorial disease in which genetic and environmental factors play a role in its etiology. Moreover, single nucleotide polymorphisms in several metabolic or cell signalling pathways seem to modify the individualized prostate cancer risk among Turkish men. Therefore, further studies with larger patient and control groups are needed to identify the relevant associations between genetic polymorphisms and prostate cancer risk in Turkish population.

In conclusion, despite the fact that relatively small number of individuals with specific genotype combinations limit the power of gene-gene interaction analysis, results of the present study suggest that GSTT1 null genotype may be associated with prostate cancer susceptibility especially among cigarette smokers in Turkish population, and GSTP1 Ile/Ile genotype may be of importance in the pathogenesis of prostate cancer in combination with GSTT1 null genotype.

REFERENCES

1. Ntais C, Polycarpou A, Ioannidis JPA. Association of GSTM1, GSTT1, and GSTP1 gene polymorphisms with the risk of prostate cancer: A meta-analysis. Cancer Epidemiol Biomarkers Prev 14: 176-181, 2005.
2. Guengerich FP, Their R, Persmark M, et al. Conjugation of carcinogens by class glutathione s-transferases: mechanisms and relevance to variations in human risk. Pharmacogenetics 5: 103-107, 1995.
3. Turesky RJ, Marchand LL. Metabolism and biomarkers of heterocyclic aromatic amines in molecular epidemiology studies: Lessons learned from aromatic amines. Chem Res Toxicol 24: 1169-1214, 2011.
4. Srivastava DSL, Mandhani A, Mittal B, Mittal RD. Genetic polymorphism of glutathione S-transferase genes (GSTM1, GSTT1 and GSTP1) and susceptibility to prostate cancer in Northern India. BJU International 95: 170-173, 2005.
5. Aktas D, Hascicek M, Sozen S, et al. CYP1A1 and GSTM1 polymorphic genotypes in patients with prostate cancer in a Turkish population. Cancer Genet Cytogenet 154: 81-85, 2004.
6. Kwon DD, Lee JW, Han DY, et al. Relationship between the glutathione-S-transferase P1, M1, and T1 genotypes and prostate cancer risk in Korean subjects. Korean J Urol 52: 247-252, 2011.
7. Sivonova M, Waczulikova I, Dobrota D, et al. Polymorphisms of glutathione-S-transferase M1, T1, P1 and the risk of prostate cancer: a case-control study. J Exp Clin Can Res 28: 32, 2009.
8. Meiers I, Shanks JH, Bostwick DG. Glutathione S-transferase pi (GSTP1) hypermethylation in prostate cancer: review. Pathology 39: 299-304, 2007.
9. Silig Y, Pinarbasi H, Günes S, et al. Polymorphisms of CYP1A1, GSTM1, GSTT1 and prostate cancer risk in Turkish population. Cancer Invest 24: 41-45, 2006.
10. Fatima M, García N, Munoz X, et al. Simultaneous genotyping of GSTT1 and GSTM1 null polymorphisms by melting curve analysis in presence of SYBR Green I. J Mol Diagn 12: 300-304, 2010.
11. Toruner GA, Akyerli C, Ucar A, et al. Polymorphisms of glutathione S-transferase genes (GSTM1, GSTP1 and GSTT1) and bladder cancer susceptibility in the Turkish population. Arch Toxicol 75: 459-464, 2001.
12. Center MM, Jemal A, Lortet-Tieulent J, et al. International Variation in Prostate Cancer Incidence and Mortality Rates. J Eur Urol 62: 1079-1092, 2012.
13. Mo Z, Gao Y, Cao Y, et al. An updating meta-analysis of the GSTM1, GSTT1, and GSTP1 polymorphisms and prostate cancer: A huge review. The Prostate 2009; 69: 662-688.
14. Listowsky I, Abramovitz M, Homma H, Niitsu Y. Intracellular binding and transport of hormones and xenobiotics by glutathione-Stransferases. Drug Metab Rev 19: 305-318, 1988.
15. Cao W, Cai L, Rao JY, et al. Tobacco smoking, GSTP1 polymorphism, and bladder carcinoma. Cancer 104: 2400-2408, 2005.
16. Mittal RD, Srivastava DSL, Mandhani A, et al. Polymorphism of GSTM1 and GSTT1 genes in prostate cancer: A study from North India. Indian J Cancer 41: 115-119, 2004.
17. Li M, Guan TY, Li Y, Na YQ. Polymorphisms of GSTM1 and CYP1A1 genes and their genetic susceptibility to prostate cancer in Chinese men. Chin Med J 121: 305-308, 2008.
18. Murata M, Shiraishi T, Fukutome K, et al. Cytochrome P4501A1 and glutathione S-transferase M1genotypes as risk factors for prostate cancer in Japan. Jpn J Clin Oncol 28: 657-660, 1998.
19. Safarinejad MR, Shafiei N, Safarinejad SH. Glutathione S-transferase gene polymorphisms (GSTM1, GSTT1, GSTP1) and prostate cancer: a case-control study in Tehran, Iran. Prostate Cancer Prostatic Dis 14: 105-113, 2011.
20. Izmirli M, Arikan B, Bayazit Y, Alptekin D. Polymorphisms of HPC2/ELAC2 and SRD5A2 (5_-Reductase Type II) genes in prostate cancer. BJMG 14: 31-36, 2011.

21. Isman FK, Kucukgergin C, Dasdemir S, et al. Association between SDF1-30A or CXCR4 gene polymorphisms with predisposition to and clinicopathological characteristics of prostate cancer with or without metastases. Mol Biol Rep 39: 11073-11079, 2012.
22. Kucukgergin C, Isman FK, Cakmakoglu B, et al. Association of polymorphisms in MCP-1, CCR2, and CCR5 genes with the risk and clinicopathological characteristics of prostate cancer. DNA Cell Biol 31: 1418-1424, 2012.
23. Gunes S, Bagci H, Sarikaya S, et al. Prostate-specific antigen and 17-hydroxylase polymorphic genotypes in patients with prostate cancer and benign prostatic hyperplasia. DNACell Biol 26: 873-878, 2007.
24. Onen IH, Ekmekci A, Eroglu M, et al. The association of 5alpha-reductase II (SRD5A2) and 17 hydroxylase (CYP17) gene polymorphisms with prostate cancer patients in the Turkish population. DNA Cell Biol 26: 100-107, 2007.
25. Tigli H, Yazici H, Dalay N. Cyp17 genetic polymorphism in prostate cancer and benign prostatic hyperplasia. Res Commun Mol Pathol Pharmacol 113-114: 307-314, 2003.

Correspondence

Dr. Ufuk BERBER

GATA Haydarpaşa Eğitim Hastanesi

Patoloji Bölümü

34668, Uskudar, İSTANBUL / TURKEY

Tel: (+90. 216) 542 20 20 / 4739

Fax: (+90. 216) 542 26 38

e-mail: patologub@gmail.com