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Original Article

A pilot study assessing the association between paraoxonase 1 gene polymorphism and prostate cancer

Paraoksonaz 1 gen polimorfizmi ve prostat kanseri arasındaki ilişkinin değerlendirildiği pilot bir çalışma

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ABSTRACT

Objective: We aimed to show the relationship between paraoxonase 1 (PON1) gene polymorphism and the development of prostate cancer (PCa).

Material and methods: We investigated the association of single nuclotide polymorphisms of PON1 enzyme with the development of PCa risk. A total of 147 male patients were divided into PCa, and control groups. The control group was also divided into two subgroups according to serum prostate specific antigen (PSA) levels as non PCa-high PSA (>4 ng/mL) and non PCa-low PSA (≤4 ng/mL) groups.

Results: The mean ages of the patients were 64.81 years, 63.27 years and 64.22 years in PCa group, non PCa-low PSA and non PCa –high PSA groups, respectively. The mean PSA levels were 10.9 ng/mL, 1.16 ng/mL and 6.63 ng/mL for PCa group, non PCa –low PSA and non PCa –high PSA groups, respectively. In terms of PON1 polymorphisms and allele frequencies, there were no statistically significant differences between PCa and control groups. There was not a statistically significant difference between PCa and non PCa-high PSA groups as for genotypic and allelic frequencies. As a result of this small sample sized hypothetical study of polymorphism, a relationship could not be detected between PCa development and PON1 gene polymorphism.

Conclusion: According to the results of this preliminary study, it is thought that more comprehensive future studies are necessary to clarify the possible role of PON1 gene polymorphism in the etiology of PCa.

Keywords: Cancer; paraoxanase 1; polymorphism; prostate.

ÖZ

Amaç: Bu çalışmada Paraoksanaz 1 (PON1) gen polimorfizmi ve prostat kanseri (PCa) gelişimi arasındaki ilişkiyi göstermeyi amaçladık.

Gereç ve yöntemler: Bu çalışmamızda PON1 enziminin tek nükleotid polimorfizmi ile PCa gelişme riski arasındaki ilişkiyi araştırdık. Kliniğimize başvuran 147 erkek hasta, PCa grubu ve kontrol grubu olarak iki gruba ayrıldı. Ayrıca kontrol grubu serum PSA düzeylerine göre non PCa-yüksek prostat spesifik antijen (PSA) ve non PCa-düşük PSA olmak üzere kendi içinde iki alt gruba (>4 ng/mL ve ≤4 ng/mL PCa olmayan hastalar) ayrıldı.

Bulgular: Hastaların ortalama yaşları PCa grubunda 64,81 yıl, non PCa-yüksek PSA grubunda 64,22 yıl non PCa-düşük PSA grubunda 63,27 yıl olarak hesaplandı. Grupların ortalama PSA değerleri sırasıyla 10,9 ng/mL, 6,63 ng/mL ve 1,16 ng/mL olarak ölçüldü. PCa grubunda ortalama yaş ve ortalama PSA değerleri kontrol grubuna göre daha yüksek olarak tespit edildi. PON1 polimorfizmleri ve alel frekansları açısından, PCa ve kontrol grupları arasında istatistiksel olarak anlamlı bir fark tespit edilmedi. Ek olarak, PCa ve non PCa-yüksek PSA grupları arasında genotipik ve alelik frekansların karşılaştırılmasında, gruplar arasında istatistiksel olarak bir fark görülmedi. PON1 polimorfizmiyle PCa ilişkisinin araştırıldığı bu küçük örneklemli çalışmanın sonucunda; PCa gelişimi ile PON1 gen polimorfizmi arasında ilişki tespit edilmedi.

Sonuç: Bu ön çalışmanın sonuçlarına göre, PCa'nın etyolojisinde PON1 gen polimorfizminin olası rolünü açıklığa kavuşturmak için daha kapsamlı çalışmaların yapılması gerektiği düşünülmektedir.

Anahtar Kelimeler: Kanser; paraoxonaz 1; polimorfizm; prostat.

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Introduction

Prostate cancer (PCa) is the most commonly diagnosed malignancy in males over 70 years old in the industrialized countries and it is the second leading cause of cancer related mortality in the aged male population.[1] It is a major health concern, especially in developed

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countries due to greater proportion of elderly men in the general population. Early diagnosis and screening both imply detection of the disease at an early, pre-symptomatic stage when a man would have no reason to seek medical care or an intervention referred to as secondary prevention. The difference in incidence and mortality rates due to PCa in different geographical regions of the world has been attributed to varying environmental factors, diet, habitual factors and genetic differences. But the relationship between possible carcinogenetic mechanisms and these parameters has not been understood, yet. In the future, studies about this issue are warranted for further evaluation of these relationships.[2] Various molecular, genetic, clinical and experimental studies have been reported to reveal the pathogenetic mechanisms of cancer.

Elevation of reactive oxygen species (ROS) or free oxygen radicals during oxidative stress (OS) has been found to mediate carcinogenesis by causing metabolic malfunction and damaging biologic biomolecules including DNA. In this context, ROS induces oxidation of DNA bases, form mutagenic lesions and chromosome aberrations and activate chemical carcinogens into highly reactive compounds.[1] The association between the level of OS and ROS and the increased risk in the development of various types of cancers have been studied in numerous studies in the literature.[3] Human serum paraoxonase 1 (PON1) is an esterase enzyme which participates in the elimination of ROS by binding to high- density lipoprotein (HDL) and has highly lipophilic antioxidant characteristics. In addition to the preventive role of PON1 against OS, which is thought to contribute to carcinogenesis, PON1 also contributes to the detoxification of organophosphate compounds and carcinogenic lipid soluble ROS which are generated by lipid peroxidation.[4]

As a widely distributed esterase enzyme among all tissues of the body, PON 1 is also present in the blood plasma with a varying degrees of interindividual activities. The source of this functional variability has been shown to be the polymorphisms of the PON 1 gene in epidemiological and molecular studies. The most commonly studied functional genetic polymorphisms in the coding region of the PON1 are the polymorphisms at position 55 and 192 of the PON1 genes.[4]

In consideration of this antioxidant enzyme activity of PON1, it was hypothesized that the allelic variations of PON 1 due to polymorphisms may have an association with susceptibility to PCa. Therefore in present study, we aimed to assess whether there is any association between PON1 gene polymorphism and PCa.

Material and methods

Study design and study population

A total of 147 male patients who had presented to the clinic between April 2012, and April 2013 were included in the study. The written informed consents from all of the participants, and approval of the local ethics committee were obtained before the conduction of the study.

The PCa group (Group 1, n: 49) included the patients who had been histologically diagnosed as PCa with transrectal ultrasound (TRUS)- guided prostate biopsy specimens. The control group (Group II, n: 98) constituted of age matched males who were admitted to the same outpatient clinics. Furtherly, the main control group was divided into two subgroups as follows: one subgroup included the patients without further evaluations for PCa because of prostate- specific antigen (PSA) levels ≤4 ng/mL (Non PCa –Low PSA group) but the other subgroup included the patients with PSA levels >4 ng/mL but nonneoplastic prostatic disease according to TRUS- guided prostate biopsy results (Non PCa –High PSA group).

Patients with the history of any treatment (i.e. hormonotherapy, surgery, radiotherapy) for prostatic malignancy or the presence of another malignancy in the other parts of the body excluded from the study. None of the participants has been taking antioxidants, vitamins including selenium and alcohol during or 48 hours prior to blood collection for the examinations. Total serum PSA levels were measured with chemiluminescent enzyme immunoassay method in the biochemistry department, and evaluated based on the reference range of PSA/(0-4 ng/mL).

DNA isolation PON1 genotyping

Blood specimens were drawn into EDTA (ethylenediamine tetraacetic acid) containing tubes, and genomic DNA samples were extracted from the peripheral leukocytes of the collected venous blood by High Pure PCR Template Preparation Kit (Roche Molecular Biochemicals, Mannheim, Germany) according to manufacturer's instructions. The genotyping was carried out by means of the Real-Time PCR method using the LightCycler 480 II system (Roche Diagnostics, Mannheim, Germany). The PON1 L55M and PON1 Q192R genotyping method was based on previously developed methods. To detect the PON1 L55M the following the following primers, and probes were used: forward primer 5'-CCTGCAATAATATGAAACAACCTG-3'; reverse primer 5'-CTAGAACACAGAAAAGTGAAAGAAAAC-3'; donor probe 5'-CTCTGAAGACATGGAGATACTGCC-FL-3'; acceptor probe 5'- LCRed640-ATGGACTGGCTTTCATTAGC TCTGTGAGT-P-3' (Metabion international AG, Germany). To detect the PON1 Q192R the following primers, and probes were used: forward primer 5'-TATTGTTGCTGTGGGACCTGAG-3'; reverse primer 5'-CCTTCTGCCACCACTCGAAC-3'; donor probe 5'-CCCCTACTTACAATCCTGGGAGAT-FL-3'; acceptor probe 5'- LCRed640-ATTTGGGTTTAGCGTGGTCGTATG TTG-P-3' (Metabion international AG, Germany). A final Mg2+ concentration of 0.5 mmol/L and 0.8 μmol/L of each primer and 0.195 μmol/L of hybridization probes were used for the PCR. After amplification, the melting curve was recorded. Melting peaks of the PON1 L and M alleles were 59°C and 64°C, and of the PON1 Q and R alleles 64°C and 57°C, respectively.

Statistical analyses

Statistical analyses were performed using Statistical Package for the Social Sciences version 15.0 software for Windows (SPSS Inc.; Chicago, IL, USA). Normally distributed variables were evaluated with Kolmogorov–Smirnov test. Student's t-test was used to compare parametric variables, and the Mann-Whitney U test was used for nonparametric continuous variables. Categorical data and the frequencies of genotype and allele among the groups were compared using the *chi*-square test. To compare the observed genotype frequencies with those expected according to the Hardy–Weinberg equilibrium, a chi-square test with one degree of freedom was applied. A logistic regression analysis was performed to test the association between genotypes and BD. A multivariate logistic regression was performed to adjust for confounding variables. A p value of <0.05 was considered to be statistically significant. Odds ratios (ORs) and 95% confidence intervals (CIs) were also calculated.

Results

The mean ages of the patients were 64.81±6.77, 64.22±7.77, 63.27±8.08. years in PCa, Non PCa –Low PSA and Non PCa – High PSA groups, respectively. The mean PSA levels were 10.9 ng/dL, 1.16 ng/dL and 6.63 ng/dL for PCa, Non PCa –Low PSA, and Non PCa –High PSA groups respectively. The mean ages and serum PSA levels were higher in the PCa group compared to the control group (p<0.05). The distributions of PON L55 and 192Q/R polymorphisms and genetic and allelic variations in all groups are presented in Table 1-3. The distributions of genetic frequencies were consistent with Hardy-Weinberg equilibrium for all groups. In terms of PON1 polymorphisms and allele frequencies, there were no statistically significant differences between PCa and control groups (p>0.05). Additionally, in the comparison of genotypic and allelic frequencies between PCa and Non PCa-High PSA groups, a statistically significant difference was not found between groups (p>0.05).

Discussion

Prostate cancer is the most common incidental cancer and the second most common fatal cancer among men, not only in the USA but also in some developing countries.[5] The studies on the relationship between the genetic pathogenesis and the etiopathogenesis of cancer are gaining more interest nowadays. In those studies valuable data about the relationship between the pathogenesis of cancer and the genetic polymorphism have been obtained for bladder, liver, lung and kidney cancers. But there seems to be a limited number of studies on the relationship between PCa and genetic polymorphisms including PON-1 enzyme polymorphisms.[6]

The underlying molecular mechanisms for the initiation and development of different types of malignancies including PCa could not have been enlightened, yet. But, the role of OS and

Table 1. Distribution of PON1 polymorphisms in patients with prostatic cancer and Non-PCa controls

PON locus	Non-PCa n=98	PCa n=49	p
PON55L/M			
L/L	43 (43.9)	19 (38.8)	0.83
L/M	45 (45.9)	24 (49.0)	
M/M	10(10.2)	6 (12.2)	
Allele frequencies			
L	131 (66.8)	62 (63.3)	0.27
M	65 (33.2)	36 (36.7)	
PON192Q/R			
Q/Q	45 (45.9)	24 (49.0)	0.53
Q/R	42 (42.9)	17 (34.7)	
R/R	11 (11.2)	8 (16.3)	
Allele frequencies			
Q	132 (67.3)	65 (66.3)	0.43
R	64 (32.7)	33 (33.7)	

PON1: paraoxonase 1; PCa: prostate cancer

Table 2. Distribution of PON1 polymorphisms in patients with prostatic cancer and Non PCa-High PSA control group

PON locus	Non PCa High PSA n=49	PCa n=49	p
PON55L/M			
L/L	21 (42.9)	19 (38,8)	0.92
L/M	22 (44.9)	24 (49.0)	
M/M	6 (12.2)	6 (12.2)	
Allele frequencies			
L	64 (65.3)	62 (63.3)	0.38
M	34 (34.7)	36 (36.7)	
PON 192Q/R			
Q/Q	21 (42.9)	24 (49.0)	0.60
Q/R	22 (44.9)	17 (34.7)	
R/R	6 (12.2)	8 (16.3)	
Allel frequencies			
Q	64 (65.3)	65 (66.3)	0.44
R	34 (34.7)	33 (33.7)	

PON1: paraoxonase 1; PCa: prostate cancer

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Table 3. Distribution of PON1 polymorphisms in patients with prostatic cancer and Non PCa-Low PSA control group

PON locus	Non-PCa High PSA n=49	PCa n=49	p
PON55L/M			
L/L	22 (44.9)	19 (38.8)	0.67
L/M	23 (46.9)	24 (49.0)	
M/M	4(8.2)	6 (12.2)	
Allele frequencies			
L	67 (68.4)	62 (63.3)	0.23
M	31 (31.6)	36 (36.7)	
PON192Q/R			
Q/Q	24 (49.0)	24 (49.0)	0.64
Q/R	20 (40.8)	17 (34.7)	
R/R	5 (10.2)	8 (16.3)	
Allele frequencies			
Q	68 (69.4)	65 (66.3)	0.33
R	30 (30.6)	33 (33.7)	

PON1: paraoxonase 1; PCa: prostate cancer

polymorphisms of the antioxidant enzymes on carcinogenetic process has been studied extensively in recent years.[7-10] The L55M and Q192R functional polymorphisms are the two most common examples of PON1 polymorphism in the human serum that have been studied in the previous studies related with the cancer and polymorphisms. Two important mutations in 55 and 192 codons of PON1 which affect paraoxonase activities have been shown in molecular studies. The substitution of glutamine at position 192 of the PON1 gene by arginine leads to the formation of Q192R polymorphism of the gene, whereas the substitution of leucine at position 55 by methionine leads to the formation of L55M polymorphism.[11,12]

Up to now the relationships between various cancers and PON1 polymorphism have been studied. In the urinary system, the polymorphisms of PON1enzyme have been evaluated in kidney and bladder cancers. According to the results of the relevant previous studies, it has been shown that the functional alterations in PON1 activity may occur due to these genetic polymorphisms of the enzyme. For example, it has been demonstrated that PON1 activity is stronger in R allele carriers than Q allele carriers. Furthermore, more powerful PON1 activity in PON1 55L allele carriers than in M allele carriers was associated with difference in mRNA levels. The lower enzyme activity was suggested to be due to the decrease in protein stability of PON1 protein in PON1 55 M allele carriers, as well.[13-15]

Apart from cancers the decrease in the activity of PON1 enzyme has been shown in diabetes mellitus, cardiovascular disorders and hypertension. The relationship between polymorphisms of PON1 gene and the activity levels of these enzymes has been also studied in lung, breast and brain cancer patients.[16-18] Up to now the relationship between PCa and PON1 activity and polymorphisms has has been also investigated within the scope of similar studies. The study of Eroglu et al.[4] is an example of these studies, in which the increased activity of PON1 in Turkish PCa patients has been reported. Additionally, in another study which was performed in Italian population, polymorphisms of three genes (CYP17, GSTP1, and PON1) were described in 384 patients with newly diagnosed PCa and 360 age-matched control patients with benign prostatic hyperplasia (BPH). All polymorphisms were investigated by PCR/RFLP methods using DNA extracted from lymphocytes. The allelic frequency of PON1 192R and PON1 55M has been reported to be higher in PCa patients in comparison to benign prostatic hyperplasia patients.[19] In a meta-analysis evaluating the relationship between PON1 Q192R polymorphism and cancer risk, the accumulated data showed the decreased risk of breast cancer development due to Q192R polymorphism of PON1 gene. In this meta-analysis, the antitumoral effects of PON1 enzyme on breast cancer pathogenesis due to its scavenging activity on lipid peroxidation and its suppressor effects on malignant transformation of cells after an oxidative process has been also stressed by the authors. Furthermore, upon the analysis of homozygous and recessive subgroups of cancer patients, lower incidence of breast and PCa in individuals having PON1 Q192R alleles has also raised an idea of a possible protective role of PON1 Q192R polymorphism against breast and PCa carcinogenesis.[20] Moreover, in a previously published study of our group, Ala-9Val homozygous polymorphism of an antioxidant enzyme MnSOD has been found to be higher in PCa patients and patients with high PSA. As a result of that study, it has been reported that the high level of PSA with the existence of Val allelic variant of MnSOD in a patient should raise the suspicion of PCa.[21]

The most important limitation of this preliminary study about the relationship between the polymorphism of PON1 enzyme and PCa could be the small sample size and consequently very limited suggestive power of the results. So better designed epidemiological studies in different nations with larger populations are needed to delineate the relationship between PCa development and PON1 polymorphisms in detail.

In conclusion, as a result of this small sample- sized hypothetical study of polymorphism, a relationship between PCa development and PON1 gene polymorphism could not be determined, but conduction of further studies to clarify the possible role of PON1 polymorphism in the etiology of PCa is still needed.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of Gaziosmanpaşa University School of Medicine.

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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