Myeloperoxidase G-463A polymorphism and risk of lung and prostate cancer in a Turkish population

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Abstract. Myeloperoxidase (MPO) is a phase I enzyme that can bioactivate many specific procarcinogens, including polycyclic aromatic hydrocarbons and aromatic amines. The MPO gene contains a common single nucleotide polymorphism, for which the -463G>A substitution within the promoter region has been shown to reduce MPO expression and activity. We investigated the association between the *MPO* -463G>A polymorphism and lung and prostate cancer in a Turkish population. *MPO* genotypes in the study populations were determined using polymerase chain reaction-based restriction fragment length polymorphism assay. The allelic frequency was significantly different between the cases and controls for lung cancer (p=0.02), but not prostate cancer (p=0.30). No significant difference was noted between the lung and prostate cancer cases and control populations in terms of genotype distribution (p=0.07, p=0.53, respectively). Control groups of lung and prostate cancer were in Hardy-Weinberg equilibrium (p=0.87 and p=0.41, respectively). To determine the protective effect against lung cancer among individuals with the -463A allele, G/A and A/A genotypes were combined. Comparison of the G/G and G/A + A/A genotypes between the lung cancer cases and control groups showed a statistically significant relationship (p=0.032, OR=0.60, 95% CI 0.38-0.95). No gender-specific difference was found in terms of genotype distribution between the lung cancer patients and the controls (female, p=0.20; male, p=0.34). In the case of smokers, a difference in genotype distribution between the lung cancer patients and the controls was statistically significant (p=0.02), although this difference was not statistically significant for non-smokers (p=0.90). Overall, no statistically significant difference was found between the prostate cancer cases and the controls in terms of genotype combination (p=0.46, OR=0.83, 95% CI 0.51-1.36). Additionally, in smokers and non-smokers, no significant relationship was determined between the prostate cancer patients and the control population (p=0.21, p=0.91, respectively). These results suggest that the *MPO* -463A allele significantly contributes to a protective effect overall and in smokers against lung cancer.

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Introduction

Myeloperoxidase (MPO) is an oxidative lysosomal enzyme that is available in polymorphonuclear neutrophils and monocytes. MPO is a phase I enzyme that can bioactivate many specific procarcinogens, including polycyclic aromatic hydrocarbons and aromatic amines (1). The *MPO* gene is located on chromosome 17q23.1 and consists of 11 introns and 12 exons. The *MPO* gene contains a common, single nucleotide polymorphism (rs2333227) within the MPO -463 gene promoter. As a result of the G-463A polymorphism on the 5' untranslated region of the *MPO* gene, the SP1 binding site of *Alu* hormone components disappears and the -463A allele exhibits a 25-fold decreased MPO expression *in vitro* (1-3). Individuals with the -463A allele may be afforded protection due to the decreased transcriptional activity of MPO and subsequent decreased metabolic activation of procarcinogens.

Lung and prostate cancer are among the most common forms of cancer and are the cause of most cancer-related deaths worldwide (4). In the US, lung cancer accounts for approximately 15% of all cancer cases and 29% of all cancer-related deaths. Prostate cancer alone accounts for approximately 25% of all cancer cases and 10% of all cancer-related deaths in men (4). Some reports suggest that the risk of developing cancer is modified by both genetic and environmental factors, such as diet, hormone levels, drinking habits, ethnicity and genetic background (5). To the best of our knowledge, although several previous studies have reported a relationship between lung cancer risk and the *MPO* G-463A polymorphism, only one previous study investigated the association between the MPO G-463A polymorphism and prostate cancer (6-14). It has been suggested that the -463A allele has a protective effect against some cancer types due to a single base substitution (-463G>A) in the promoter region of *MPO*, which reduces transcription activity (1-3). It should be noted that the conclusions of these studies remain controversial. To date, the role of the *MPO* G-463A polymorphism in lung and prostate cancer has not been studied in a Turkish population.

The present study investigated the relationship between the myeloperoxidase G-463A polymorphism and lung and prostate cancer related to tobacco smoking in a Turkish population.

Materials and methods

Study population. To determine the relationship between the MPO G-463A polymorphism and lung cancer, 377 individuals (106 cases and 271 controls) were examined. Regarding prostate cancer, the number of studied individuals was 276 (114 cases and 151 controls). Lung and prostate cancer patients were admitted to the Cumhuriyet University Hospital (Central Anatolia, Sivas, Turkey) during 2001. They were newly diagnosed, histologically confirmed and previously untreated. The controls were selected at random from healthy individuals without any history of cancer. Prostate cancer patients and controls had elevated serum levels of prostate-specific antigen (PSA). The controls had serum levels of PSA <4 ng/ml. Both cases and controls were born in Turkey, and information concerning age, gender and smoking habits was collected using a standardized questionnaire by trained interviewers. Informed consent was obtained from the patients before the study, and the study was approved by the Local Ethics Committee on Human Research of Cumhuriyet University.

MPO G-463A genotyping. Genomic DNA of the studied populations was extracted from blood leukocytes using a standard phenol-chloroform method (15). MPO genotypes were determined using polymerase chain reaction (PCR)-based restriction fragment length polymorphism (RFLP) assay. PCR was carried out in a 25-ml vol containing 200 mM of each deoxynucleotide triphosphate (dATP, dCTP, dGTP and dTTP), 0.2 mM of each primer (F: 5'-CGG TAT AGG CAC ACA ATG GTG AG-3' and R: 5'-CAA TGG TTC AAG CGA TTC TTC-3'), ~100 ng template DNA, 1X reaction buffer [75 mM Tris-HCl (pH 8.8) at 25°C, 20 mM $(NH_4)_2SO_4$, 0.01% Tween-20; MBI Fermentas], 1.5 mM $MgCl_2$ and 2 units *Taq* polymerase (MBI Fermentas). The temperature profile for the 35-cycle amplification reaction using a thermal cycler (Techne, UK) was as follows: initial denaturation at 94°C for 5 min, denaturation at 94°C for 30 sec, annealing at 62°C for 30 sec and extension at 72°C for 30 sec, and a final extension at 72°C for 5 min. Following the PCR, 10 μl of 350-bp PCR product was digested with 10 U of *Aci*I restriction enzyme according to the manufacturer's instructions (MBI, Fermentas). The DNA fragments were separated on 3% agarose gel stained with ethidium bromide. The wild-type homozygous genotype (*GG*) yielded three bands (169, 120 and 61 bp), the heterozygous genotype (*GA*) yielded four bands (289, 169, 120 and 61 bp), and finally the mutant genotype (*AA*) yielded two bands (289 and 61 bp). In order to confirm the MPO genotypes, several wild and variant homozygote genotypes were selected for detection using the ABI 310 DNA sequencing system (Applied Biosystems, Iontek).

Statistical analysis. SPSS (Statistical Package for Social Sciences) release 13.0.1 software was used to perform the statistical analyses. Hardy-Weinberg equilibrium, genotype frequencies and allele frequencies were tested using the Pearson χ^2 test. The statistical significance of the differences between the *MPO* genotypes among the cases and controls was assessed using the χ^2 test. Probability values <0.05 were regarded as statistically significant. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using both an unadjusted and adjusted logistic regression analysis, adjusting several confounding variables such as age, gender and smoking status.

Results

Demographic parameters such as the gender, age and smoking status of lung and prostate cancer cases and controls are shown in Table I. The mean age of the lung cancer cases and controls was 53.4 (range, 30-85) and 49.9 (range, 26-82) years, respectively. The mean age of the prostate cancer cases and controls was 65.2 (range, 42-88) and 61 (range, 41-82) years, respectively. Distribution of gender and smoking status between the lung cancer cases and the controls was statistically significant (gender, p<0.001 and smoking status, p=0.001). In terms of smoking status among the prostate cancer patients, no significant difference was observed between the cases and controls (p=0.96).

The *MPO* G-463A allele and genotype distribution of the lung cancer cases, prostate cancer cases and controls is shown in Table II. Among the lung cancer cases and the controls, the frequencies of the -463A allele were 20.3 and 28.5%, respectively; in prostate cancer cases and controls, this frequency was 22.3 and 17.2%, respectively. Distribution of the allelic frequency was statistically significant between the lung cancer cases and the controls (p=0.02), but was not statistically significant between the prostate cancer cases and controls (p=0.30). In both the lung and prostate cancer cases, no significant difference was determined between the cases and control populations in terms of genotype distribution (p=0.07, p=0.53, respectively). Control populations of lung and prostate cancer were found to be in Hardy-Weinberg equilibrium (p=0.87 and p=0.41, respectively). To determine the potential protective effect against lung cancer of the -463A allele, the G/A and A/A genotypes were combined. Comparison of the G/G and G/A + A/A genotypes between the lung cancer cases and the control groups showed a statistically significant relationship (p=0.032, OR=0.60, 95% Cl 0.38-0.95) (Table III). The results indicated that the -463A allele provided a protective effect for 40% of lung cancer cases. Therefore, overall and in males, the AA genotype was determined to have a higher protective effect against lung cancer than the GA and the GA + AA genotype combination.

Additionally, the relationship between the *MPO* G-463A genotypes and lung cancer was analyzed on the basis of gender and smoking status (Table III). No statistically significant difference was determined in females or males in terms of genotype distribution between the lung cancer cases and the controls (female, p=0.20; male, p=0.34). In the case of smokers, genotype distribution between the lung cancer cases and the controls was found to be statistically significant (p=0.028, OR=0.51, 95% Cl 0.28-0.93), while this difference was found to be insignificant for non-smokers (p=0.90, OR= 0.95, 95% Cl 0.43-2.07).

Table I. Demographic parameters of the lung and prostate cancer cases and controls.

	Lung cancer		Prostate cancer	
	Cases, n (%)	Controls, n (%)	Cases, n (%)	Controls, n (%)
Sample size	106	267	114	151
Gender				
Male	88 (83.1)	126 (47.2)	114 (100)	151 (100)
Female	18 (16.9)	141 (52.8)	-	-
Age (years)				
Range	30-85	26-82	42-88	41-82
Mean	53.4±12.0	49.9±11.1	65.2±13.2	61±11.4
Smoking status				
Smoker	74 (68.8)	135 (50.5)	60 (52.6)	79 (52.3)
Non-smoker	32 (31.2)	132 (49.5)	54 (47.4)	72 (47.7)
PSA (ng/ml)	-	-	33.6±9.6	3.4±0.3

PSA, prostate-specific antigen.

Table II. Allele and genotype distribution of the lung and prostate cancer cases and controls.

	Lung cancer			Prostate cancer		
	Cases, n (%)	Controls, n (%)	P-value	Cases, n (%)	Controls, n (%)	P-value
Allele frequency						
G allele	169 (79.7)	382 (71.5)		175 (76.7)	220 (72.8)	
A allele	43 (20.3)	152 (28.5)	0.02	53 (22.3)	82 (17.2)	0.30
Genotype frequency						
G/G	67 (63.2)	136 (50.9)		67 (58.8)	82 (54.3)	
G/A	35 (33.01)	110 (41.1)		41 (36.0)	56 (37.0)	
A/A	4 (3.79)	21 (7.0)	0.07	6 (5.2)	13 (8.7)	0.53

Overall, no statistically significant difference was found between the prostate cancer cases and the controls upon comparison of the genotype combinations (p=0.46, OR=0.83, 95% CI 0.51-1.36) (Table III). However, the AA genotype was noted to have a protective effect of close to 45% against prostate cancer (OR=0.56, 95% Cl 0.20-1.56). In the smoker and non-smoker populations, no significant relationship was determined in terms of genotype distribution between the prostate cancer and control populations (p=0.21, p=0.91, respectively). However, in smokers, the presence of the GA and GA + AA genotypes provided a greater protective effect than in non-smokers (Table III). Overall, in the smokers and non-smokers, the AA genotype was found to have a higher protective effect than the GA and the GA + AA genotype combination for prostate cancer (Table III).

Discussion

Genetic polymorphisms in xenobiotic metabolizing enzymes, such as the CYP450 family, N-acetyltransferases (NAT), glutathione-s-transferases (GST) and sulfotransferases, have been thought to play an important role in the susceptibility of individuals to cancer (16). The MPO gene contains a common single nucleotide polymorphism (SNP) within the *MPO* -463 gene promoter. Allelic frequencies of variant *MPO*-463A differ widely among ethnic populations. In the present study, the frequency of the -463A allele in the lung cancer controls (n=271) was 28.5%. The frequency of the A allele was previously found to be 20.9% in Caucasians (n=1128), 26.7% in French-Canadians (n=217), 25% in Italians (n=214), 29.9% in African-Americans and 21.2% in Chinese populations (n=139) (6,10,17-21).

Since the *MPO* G-463A polymorphism was first reported by Austin *et al* in 1993, many subsequent studies have reported the relationship between different cancer types and this polymorphism (22). Many (but not all) of these studies reported a statistically significant relationship between the *MPO* G-463A polymorphism and different cancer types, including lung cancer (6-14,17-19,21). According to the present study, possession of the GA + AA genotype has a statistically

Table III. Risk estimates for MPO genotypes categorized by gender, smoking status and age.

Variables	Genotype combinations	Cases n	Controls n	χ^2	P-value	Unadjusted OR (95% CI)	Adjusted OR (95% CI)
Lung cancer							
Overall	GG	67	136			1.00 (reference)	1.00 (reference)
	GA	35	110	3.21	0.073	0.64 (0.40-1.04)	0.62(0.39-1.01)
	AA	4	21	3.00	0.083	0.38 (0.12-1.17)	0.41 (0.14-1.21)
	GA + AA	39	131	4.60	0.032	0.60 (0.38-0.95)	0.61 (0.39-0.97)
Gender							
Females	GG	11	64			1.00	1.00
	GA	7	65	0.83	0.36	0.62 (0.22-1.71)	0.60 (0.20-1.51)
	AA	-	12	-	-	-	-
	GA + AA	7	77	1.58	0.20	0.52 (0.19-1.44)	0.54 (0.21-1.53)
Males	GG	56	72			1.00	1.00
	GA	28	45	0.55	0.45	0.80 (0.44-1.43)	0.78 (0.41-1.38)
	AA	4	9	0.81	0.36	0.57 (0.16-1.95)	0.55 (0.13-1.85)
	GA + AA	32	54	0.90	0.34	0.76 (0.43-1.33)	0.75 (0.42-1.30)
Smoking status							
Smokers	GG	50	70			1.00	1.00
	GA	20	53	3.99	0.04	0.52 (0.28-0.99)	0.50 (0.27-0.98)
	AA	4	12	1.63	0.20	0.46 (0.14-1.53)	0.45 (0.12-1.48)
	GA + AA	24	65	4.82	0.028	0.51 (0.28-0.93)	0.49 (0.26-0.90)
Non-smokers	GG	17	66			1.00	1.00
	GA	15	57	0.95	0.95	1.02 (0.46-2.22)	0.98(0.33-1.95)
	AA	-	4	-	-	-	-
	GA + AA	15	61	0.14	0.90	0.95 (0.43-2.07)	0.93 (0.38-1.90)
Prostate cancer							
Overall	GG	67	82			1.00	1.00
	GA	41	56	0.17	0.67	0.89 (0.53-1.50)	0.85(0.48-1.45)
	AA	6	13	1.22	0.26	0.56 (0.20-1.56)	0.55 (0.18-1.53)
	GA + AA	47	69	0.52	0.46	0.83(0.51-1.36)	0.79 (0.49-1.33)
Smoking status							
Smokers	GG	38	51			1.00	1.00
	GA	18	34	0.89	0.34	0.71 (0.35-1.44)	0.68 (0.31-1.39)
	AA	4	9	0.66	0.41	0.59 (0.17-2.08)	0.57 (0.13-1.95)
	GA + AA	22	45	1.57	0.21	0.65 (0.33-1.27)	0.62 (0.29-1.19)
Non-smokers	GG	29	29			1.00	1.00
	GA	23	22	0.01	0.91	1.04 (0.48-2.27)	1.01 (0.39-2.11)
	AA	2	4	0.06	0.43	0.50 (0.85-2.94)	0.51 (0.82-2.83)
	GA + AA	25	24	0.01	0.91	1.04 (0.48-2.22)	1.02 (0.46-2.12)

significant protective effect against lung cancer (p=0.02). In addition, overall it was determined that the AA genotype had a greater protective effect than either the GA or the GA + AA genotype combination against lung cancer. This finding is in agreement with many previous studies (7-13). London *et al* were the first to report an association between a variant allele of *MPO* and the risk of lung cancer (11). In addition, a study by Schabath *et al* of 903 lung cancer patients reported that the -463A allele had a statistically significant protective effect (12). A meta-analysis showed that Caucasians carrying the -463A allele have an approximately 20-30% reduced risk for lung cancer (6). MPO is a phase I metabolic enzyme that has a polymorphic region upstream of the gene that appears to reduce transcriptional activity (3-5). Thus, individuals with the variant allele may be provided with a protective effect due to decreased metabolic bioactivation of carcinogenic compounds. This hypothesis is supported by the findings of the present study and many previous reports (3,23).

In the present study, the -463A allele was shown to have a statistically significant protective effect in smokers. A comprehensive study (3688 cases and 3874 controls) concluded that the myeloperoxidase G-463A polymorphism was significantly

protective in smokers, but not in non-smokers (23). It was also concluded that MPO converts tobacco smoke procarcinogens, such as benzo(α)pyrene and arylamines, into highly carcinogenic intermediates, such as benzo(α)pyrene dio-epoxide (1,3). Since the variant allele may be associated with weaker transcriptional activity, carcinogens contained in cigarette smoke will not be metabolically activated, therefore the -463A allele has been suggested to have a protective effect against the development of cancer related to smoking. The present study and a significant proportion of previous reports found similar results with regard to the MPO polymorphism and lung cancer related to tobacco smoking (6,8,15,23).

In the present study, no significant relationship was found in terms of the MPO genotype between lung cancer cases and controls, in either the male or female populations. However, the GG + GA genotype was found to have a 46% protective effect against lung cancer in females, and a 25% protective effect in males. Therefore, a 46% protective effect was found between the lung cancer cases and the controls for males with the AA genotype. Taioli *et al* conducted a meta-analysis of 10 studies and reported that an inverse association between lung cancer and the *MPO* G-463A polymorphism was found equally in males and females, with no differences in the association according to age in the two genders (23).

No statistically significant difference was found between the prostate cancer cases and the controls in terms of the *MPO* G-463A genotype. A review of the literature identified only one previous study indicating a relationship between the *MPO* G-463A polymorphism and prostate cancer (14). That study used 661 prostate cancer patients and 1310 control individuals, and found no statistically significant difference between the *MPO* G-463A polymorphism and prostate cancer. On the other hand, a 40% protective effect against prostate cancer was detected in males having the *MPO* AA genotype. In the present study, the risk of prostate cancer was found to be 45% lower among males with the *MPO* AA genotype. This finding is in close agreement with the findings of Choi *et al* (14). In addition, the present study found no statistically significant relationship in terms of genotype combinations between the prostate cancer patients and controls in either the smokers and non-smokers. On the other hand, smokers with the AA and AA + GA genotypes were found to have 43 and 38% protective effects, respectively, between the prostate cancer patients and controls. Our findings, suggesting a decreased risk of prostate cancer for males with the MPO AA genotype, which is associated with lower transcription and subsequent decreased metabolic activation of procarcinogens, are consistent with some (but not all) previous findings for several types of cancer including prostate cancer (17-19,21,23).

In conclusion, the relationship between the MPO G-463A polymorphism and lung and prostate cancer was evaluated in a Turkish population for the first time. In the cases overall and in smokers, the -463A allele was found to have a statistically significant protective effect against lung cancer. While no statistically significant relationship was found for prostate cancer, the AA genotype was shown to have a protective effect in these individuals. Further extensive studies are required, particularly regarding prostate cancer, in order to better clarify the role of the MPO genotype in mediating susceptibility to lung and prostate cancer.

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