The significance of *P53* gene codons 72 and 213 polymorphisms in urinary bladder cancer in Central Poland

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KEY WORDS

urinary bladder ◗ bladder cancer ◗ P53 polymorphism ◗ codon 72 ◗ codon 213

ABSTRACT

Introduction. A major interest in human genetics is to distinguish functionally neutral mutations and polymorphisms from those that contribute to disease. Polymorphic variants of the P53 gene at codon 72 are associated with cancer susceptibility. The aim of our study was to characterize P53 polymorphism at codons 72 and 213 in bladder cancer patients and in a control group.

Materials and methods. Ninety-five patients with clinically diagnosed urinary bladder tumors were included in the study. Pathology classified 36 tumors as low grade and 59 as high grade. Tumor stage was pTa or lower in 30 patients and at least pT1 in 65 patients. The control included DNA samples from the blood of 84 cancer-free individuals. The demonstration of codon 72 and codon 213 P53 polymorphisms was performed using PCR and MSSCP techniques.

Results. In the group of healthy patients we found the following distribution of polymorphism: ARG/ARG – 58.3%, ARG/PRO – 40.5%, and PRO/PRO – 1.2%. In the group of patients suffering from urinary bladder cancer it was 56.8%, 43.2%, and 0.0%, respectively. Statistical analysis of the distributions by the G-test did not reveal any significant difference (table 2x2 G = 0.433)

Conclusions. Our study did not reveal that one of the polymorphic variants of the P53 gene codon 72 is a factor increasing the risk of urinary bladder cancer development in the Polish population. It needs to be mentioned, however, that the ARG/ARG genotype (leading to this kind of cancer, according to other researchers) is dominant in the tested population.

INTRODUCTION

The *P53* tumor suppressor gene has proven to be one of the most frequently mutated genes in human cancers [1]. Genetic polymorphisms at the genes involved in tumorigenesis may determine individual susceptibility to cancer. Germline *P53* mutations have been reported to be associated with inherited cancer risk. *P53* is a highly conserved gene and there are only three polymorphisms reported in the coding region; two in exon 4, residues 47 and 72; one in exon 6, residue 213; and one in exon 8, codon 248 [2, 3, 4]. The polymorphic variants of codons 47 and 72 have also been studied as potential genotypes susceptible to bladder cancer. *P53* polymorphisms are also found in the intronic regions: two being reported in intron 1, one in intron 2, one in intron 3, two in intron 6, and two in intron 7.

Urinary bladder cancer is the sixth leading cause of mortality due to malignant neoplasms in Polish men and is the third leading cause of morbidity [5]. Detection of *P53* gene mutations in cells of urinary bladder neoplasms may be regarded as an independent prognostic factor for progression and recurrence of tumors.

Codon 72 polymorphism of this gene, in connection with proline (PRO-codon CCC) and arginine (ARG-codon CGC) coding, is considered to be the factor increasing the risk of contracting cancers such as: lung, breast, ovarian, prostate, and adrenal cortical cancer. The distribution of this polymorphism (ARG/ARG and PRO/PRO homozygotes and AGR/PRO heterozygotes) varies ethnically. We decided to check this polymorphism's distribution in the Polish population, examining the groups of healthy people and people with urinary bladder cancer. As in the Greek population, it was shown that the presence of the ARG/ARG genotype is related to the increased risk of this cancer's development [6].

In the present study, we examined the relationship between the distribution of the *P53* codon Arg72Pro polymorphism, codon 213 (Arg/Arg) polymorphism, and mutation in the *P53* gene (exons 4-8) in bladder cancer cases and the control group.

MATERIALS AND METHODS

Sampling

The study included 95 surgically resected bladder cancer patients who were admitted to Pirogow Hospital between 2002 and 2004. The histology of tumor types and stages were determined according to the WHO classification method and Tumor-Node Metastasis system, respectively. Information about the smoking history of the bladder cancer patients was obtained from hospital records. The patients were classified into smoking and non-smoking groups, the former included both current smokers and ex-smokers.

DNA from blood of 95 patients with urinary bladder cancer (79 men and 16 women, aged 44-84 years, mean age 64) was collected, as previously reported [7]. The control DNA came from 84 cancer-free volunteers (Medical University students) without urological problems (76 males and 8 females, aged 22-25 years, mean age 23).

PCR conditions

For patients and controls, purified genomic DNA was amplified by PCR for exons 4 and 6 of the *P53* tumor suppressor gene. The PCR conditions and primer sequences were previously described by Soulitzis et al. [6] and by Phillips et al. [8]. The PCR reaction was

performed in 50 µl of solution containing 1µl of template DNA (approx 100 ng), 5 µl of 10x reaction buffer (Sigma-Aldrich), 3 µl of 2.5 mM dNTPs, 1mM $MgCl_2$, 2 µl of each primer pair (5 pmol/µl), 1U of Taq DNA polymerase (Sigma-Aldrich), and 36 µl of distilled water (thermocycler BioRad iQ5). All reactions contained a non-template control. The amplified DNA samples were separated on 2% agarose gel and stained with ethidium bromide.

MSSCP conditions

Aliquots of 5-9 µl of PCR reaction mixture were combined with 10 µl of MSSCP dye (95% formamide, 5 mM sodium hydroxide, 0.1% bromophenol blue, and 0.1% xylene cyanol) and heated at 55°C for 10 min, followed by cooling on ice. Fifteen microliters of each sample was loaded onto a 6-10% non-denaturing polyacrylamide gel (30:1). Electrophoresis was carried out under different electrophoretic conditions: combinations of gels with or without 5% glycerol and four temperature profiles (1 : 23°C – 120 min; 2 : 31°C – 20 min, 23°C – 20 min, 15°C – 20 min; 3 : 20°C – 5 min, 6°C – 25 min; and 4 : 15°C – 15 min, 10°C – 20 min, 5°C – 15 min), in order to increase the screening sensitivity. The running parameters for the gels were established at 600V and 40W in 0.5 x TBE buffer (pH 8.3). We used DNA Pointer (Kucharczyk T.E.), which controlled and changed the temperature thrice in each experiment. The bands of the screened PCR products were visualized by silver staining. Individual DNA fragments with shifted mobility were analyzed for mutations when compared with the control. The bands, possibly polymorphic or mutated in Multi-temperature Single-Strand Conformational Polymorphism (MSSCP), were extracted from the gels, amplified by 30 cycles of PCR to enrich the mutated alleles and sequenced.

RESULTS

The blood specimens from 95 patients with bladder cancer were analyzed for codon 72 polymorphism of the *P53* gene. The majority of specimens were obtained from male patients (79 out of 95). The results of this analysis as well as the clinical and histopathological data are shown in Table 1.

The Arg/Arg genotype of the *P53* codon 72 polymorphism was found in 54 patients (56.8%), the Arg/Pro genotype in 41 (43.2%). In order to determine whether the distribution of the *P53* codon 72 polymorphism in bladder cancer patients is different from the one in the general population we employed blood specimens from 84 healthy individuals. As *P53* allele frequencies have been shown to vary according to the ethnic group, controls and patients were from the same ethnic background. The Arg/Arg genotype was found in 49 individuals (58.3%), the Arg/Pro genotype in 34 (40.5%), and the Pro/Pro genotype in 1 (1.2%). The distribution frequency of the two alleles is not different between bladder cancer patients and healthy individuals. We carried out the statistical analysis with the help of the G-test (table 2x2 G= 0.433 – not significant).

Distribution of *P53* codon 72 polymorphism in the Polish population compared with other ethnic groups worldwide including the correlation with clinicopathological parameters of patients.

We studied a total of 179 individuals: 95 bladder cancer patients and 84 non-cancer controls. The frequencies of the three p53 genotypes Arg/Arg, Arg/Pro, and Pro/Pro found in the non-cancer controls in Poland were 58.3%, 40.5%, and 1.2%, respectively. The results are presented in figures 1 and 2. The genotype distribution was similar between male and female controls. The Arg/Arg genotype was strongly associated with ethnicity as compared with the distribution of the *P53* genotype in our controls with the data reported previously for other studied populations (Table 3). The genotype distribution also differed significantly between the Polish population and for example the Spanish or Greek populations, in which a higher frequency of Pro allele was found. However there was no significant difference between German and Polish people. Nevertheless, only in the Polish population one can observe such a high percentage of the Arg/Arg genotype – above 70%. Our results differ slightly from those obtained in previous tests on the Polish population and are more similar to the results of the tests on the German population. However, it has to be mentioned that the Pro/Pro genotype is very rare in the Polish population.

Table 1 shows the distribution of *P53* polymorphism by case/control status and clinicopathological parameters of bladder cancer patients. Overall, there was no difference in genotype distributions between non-cancer controls and bladder cancer patients. However, when the patients' group was stratified by sex, tumor stage, tumor grade, smoking habit, and age some interesting points were revealed (Tables 1 and 2).

An increased frequency of the Arg/Pro genotype was observed in patients (53.4%) when compared to non-cancer controls after adjustment by age.

As the bladder cancer patients were stratified according to sex, the Pro allele was over-represented in the female patients (50%) compared with non-cancer controls (40.5%).

Table 1. Distribution of *P53* polymorphism by case/control status and clinicopathological parameters of bladder cancer patients.

	Genotypes			
Characteristics	Arg/Arg n(%)	Arg/Pro n(%)	Pro/Pro n(%)	Total
Non-cancer control	49 (58.3)	34 (40.5)	1 (1.2)	84
Male	44 (57.9)	31 (40.8)	1 (1.3)	76
Female	5 (62.5)	3 (37.5)	–	8
Bladder cancer	54 (56.8)	41 (43.2)	–	95
Male	46 (58.2)	33 (41.8)	–	79
Female	8 (50)	8 (50)	–	16
Tumor stage				
Ta	15 (50)	15 (50)	–	30
≥T1	39 (60)	26 (40)	–	65
Tumor grade				
G1	21 (58.3)	15 (41.7)	–	36
≥G2	37 (62.7)	22 (37.3)	–	59
Smoking				
Yes	52 (57.7)	38 (42.3)	–	90
No	2 (40)	3 (60)	–	5

Table 2. Characteristics of cases and controls by *P53* genotype and age.

Cases				Controls			
Age (years)	Arg/Arg n(%)	Arg/Pro n(%)	Total	Arg/Arg n(%)	Arg/Pro n(%)	Pro/Pro n(%)	Total
>60	27 (46.6)	31 (53.4)	58	–	–	–	–
<60	27 (73)	10 (27)	37	49 (58.3)	34 (40.5)	1 (1.2)	84

When the patients' group was stratified according to smoking status, we found an increase in the Arg/Pro genotype frequency in bladder cancer patients who did not smoke (60%) compared with the non-cancer controls (40.5%), although the group of non-smokers was rather small (5 persons).

Distribution of the *P53* codon 213 polymorphism among healthy controls and bladder cancer patients

In six cases (6/95 – 6.3 %), polymorphism was found at codon 213 of the *P53* gene (Table 4). In the control group, polymorphism was diagnosed in 2 (2/84 – 2.4%) individuals.

Polymorphism at codon 213 appeared in four Arg/Arg genotype cases and in two Arg/Pro genotype cases. In the controls, we found one Arg/Arg genotype case and one Arg/Pro genotype case with the simultaneous presence of polymorphism at codon 213.

DISCUSSION

Bladder cancer has a high potential for recurrence and occasionally becomes invasive even in superficial cases. During the last two decades, a better understanding of the molecular mechanisms involved in carcinogenesis and tumor progression led to the determination of a large number of molecular markers of bladder cancer with potential diagnostic and prognostic value [2, 9, 10]. Since the original publication that *P53* homozygotes have a significantly higher risk of developing cancer, numerous studies have been conducted on cervical and other tumors [11, 12, 13, 14, 15, 16, 23]. The results are controversial with several groups confirming the original finding, while others have failed to find an association between *P53* Arg and cancer.

Table 3. Comparison of frequency distribution of the Arg/Arg, Arg/Pro, and Pro/Pro genotypes of the *P53* codon in populations from different regions of the world.

Population	N	Arg/Arg	Arg/Pro	Pro/Pro	References
USA	245	51.8	40.0	8.2	Hildesheim et al. 1998 [28]
USA	510	46.5	41.6	12.0	Fan et al. 2000 [25]
Chile	53	47.2	45.3	7.5	Ojeda et al. 2003 [29]
Brazil	82	40.2	54.8	4.9	Drummond et al. 2002 [24]
Japan	105	39.0	54.3	6.7	Suzuki et al. 2005 [31]
Taiwan	152	30.9	49.3	19.7	Wang et al. 1999 [33]
Spain	90	46.3	43.5	10.2	Beckman et al. 1994 [22]
Czech Republic	172	53.5	35.5	11.1	Tachezy et al. 1999 [32]
Holland	158	57.0	37.0	6.0	Hayes et al. 1998 [26]
UK	41	36.6	58.5	4.9	Storey at al. 1998 [30]
UK	246	62.6	30.5	6.9	Rosenthal et al. 1998 [34]
Greece	99	24.2	64.7	11.1	Soulitzis et al. 2002 [6]
Sweden	188	47.0	44.0	9.0	Anderson at al. 2001 [21]
Finland	171	56.7	38.0	5.3	Beckman et al. 1994 [22]
Norway	225	54.0	40.0	6.0	Helland et al. 1998 27]
Germany	193	59.0	34.0	7.0	Scheckenbach et al. 2004 [19]
Poland	52	73.1	23.1	3.8	Dybikowska et al. 2000 [17]
Poland	50	76	24	0	Ignaszak-Szczepaniak et al. 2006 [18]
Poland	84	58.3	40.5	1.2	Our work

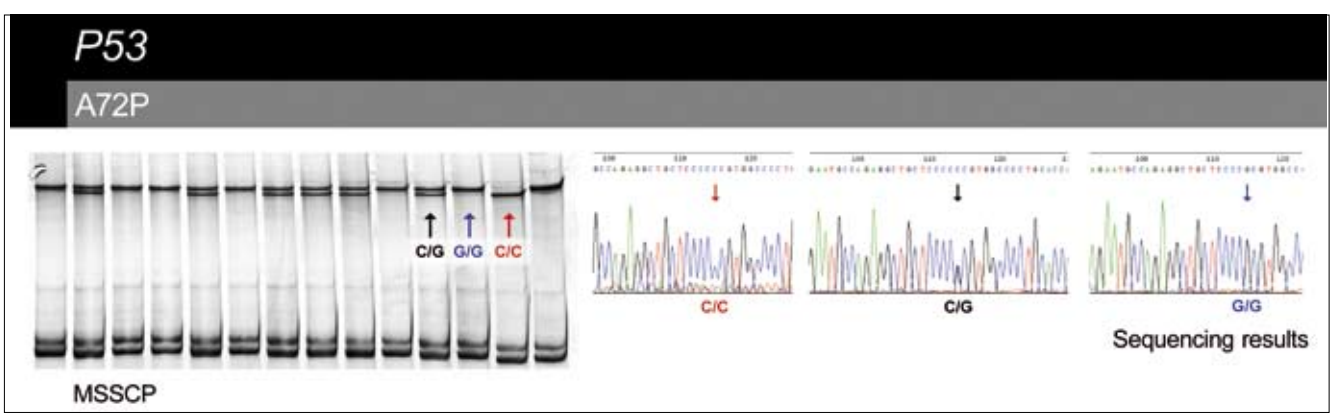

Fig. 1. MSSCP analysis and sequencing results of the P53 codon 72 Arg and Pro alleles.
Black arrows – heterozygotes Arg/Pro Blue arrows – homozygotes Arg/Arg, Red arrows – homozygotes Pro/Pro

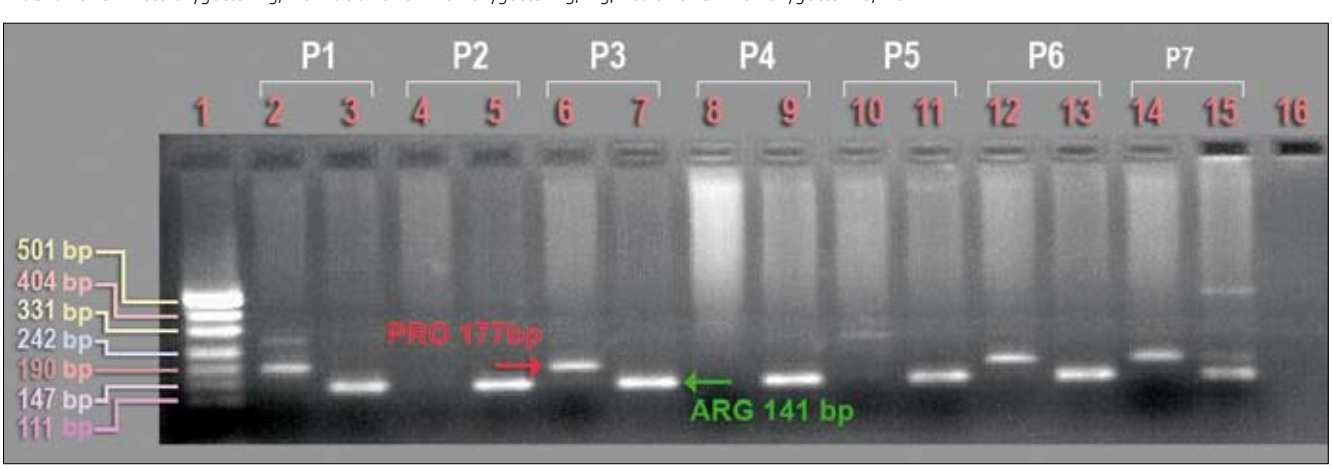

Fig. 2. PCR amplification of the P53 codon 72 Arg allele (141bp) and Pro allele (177bp). P1, P3, P6, P7 – heterozygotes Arg/Pro; P2, P4 – homozygotes Arg/Arg

Our research concentrated on polymorphisms at codons 72 and 213 of the *P53* gene. This study evaluates the association between the risk of developing cancer and the genotype distribution. The results show that the genotype distribution of the Arg/Pro allele *P53* polymorphism in the Polish population differs significantly from other reports in Sweden, Spain, and the United States (data in Table 3). We demonstrated ethnicity as an important confounding factor in epidemiological studies involving hereditary factors. This agrees with the finding of Soulitzis [6], who reported a significant correlation between the frequency of the Arg allele and an increased risk of developing bladder cancer in the Greek population. It has been suggested that the Arg/Arg allele may partly explain the incidence of bladder cancer among different ethnic groups, that is, the higher the Arg/Arg genotype frequency, the higher the bladder cancer incidence. According to the report by Dybikowska et al. [17], the genotype frequency among healthy people in the Polish population is 73.1% Arg/Arg, 23.1% Pro/Arg, and 3.8% Pro/Pro. The results published by Ignaszak-Szczepaniak in 2006 [18] (76% for Arg/Arg and 24% for Arg/Pro) are similar. Our results are slightly different: the Arg/Arg genotype in 58.3%, the Arg/Pro genotype in 40.5%, and the Pro/Pro genotype in 1.2% (1) of patients, but they are more similar to the distribution for the German population [19]. In our opinion, the study ought to be conducted on a larger group of people. Yet a fact worth emphasizing is that in all the findings concerning the Polish population Pro/Pro homozygotes appear extremely rarely.

We were also unable to show that one of the 72 codon genotypes goes with the CAG genotype at codon 213 more frequently. Tests on larger groups might allow the establishment of such correlations.

Recently we have also examined the mutation spectrum of the *P53* gene in bladder cancer patients in the Polish population (the same group Borkowska et al. 2007) and we have also found that patients with or without the *P53* mutation had a similar genotypic distribution of the *P53* gene, which suggests that *P53* codon 72 polymorphism may be unassociated with *P53* gene mutation [20]. Six out of 11 mutations were detected in tumors of the Arg/Arg genotype while the remaining 5 mutations were found in tumors of the Arg/Pro genotype (data in Table 4).

Table 4. Comparison of distribution of Arg/Arg and Arg/Pro genotypes in *P53* codon 72 polymorphism, *P53* codon 213 polymorphism, and *P53* mutation in bladder cancer cases.

Sample Symbol	Stage/ Grade	Codon 72 polymorphism	Codon 213 polymorphism	P53 mutation
P7	T2/G2	Arg/Pro		+
P20	T4/G2	Arg/Arg		+
P26	T2/G3	Arg/Arg		+
P55	T4/G2	Arg/Arg	+	+
P56	T1/G3	Arg/Arg		+
P69	T4/G2	Arg/Pro		+
P71	Ta/G1	Arg/Arg		+
P80	T1/G3	Arg/Pro		+
P86	T1/G3	Arg/Pro	+	+
P95	Ta/G2	Arg/Arg		+
P100	T2/G2	Arg/Arg		+
P103	T3/G3	Arg/Arg	+	
P104	T4/G3	Arg/Pro		+
P110	T1/G2	Arg/Pro	+	+
P137	Ta/G1	Arg/Arg	+	
P141	T2/G2	Arg/Arg	+	+

CONCLUSIONS

The results of our study show that there was no difference in distribution of genotype at codon 72 of the *P53* gene among patients diagnosed with cancer when compared with the control group. Neither have we determined any correlation between the presence of one of the codon 72 genotypes and polymorphism at codon 213 of the *P53* gene. In addition, our study did not confirm the correlation between the presence of *P53* mutation and one of the polymorphisms. Nevertheless, one has to notice that the Arg/Arg genotype in codon 72 of this gene (regarded as the factor leading to bladder cancer development) is dominant in our population (almost only Arg homozygotes or Arg/Pro heterozygotes are detected). This may explain the high rates of morbidity and mortality from urinary bladder cancer in Poland. Tests on both polymorphisms need to be conducted on a larger group of patients in order to find a complete answer to this question.

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