Bladder Cancer and Polymorphisms of DNA Repair Genes (*XRCC1*, *XRCC3*, *XPD*, *XPG*, *APE1*, *hOGG1*)

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Abstract. *Carcinogenic molecules from cigarettes are known to cause DNA damage to bladder epithelial cells, but such damage can be corrected by some DNA repair mechanisms such as base and nucleotide excision repair, double-strand repair and mismatch repair. Various gene products play a role in these DNA repair systems. The aim of this study was to investigate six of these genes (XRCC1, XRCC3, XPD, XPG, APE1, hOGG1) each of which has a separate role in these repair mechanisms. The study was performed on 83 bladder cancer patients and 45 healthy controls. The genes were amplified by polymerase chain reaction (PCR) and restriction fragment polymorphism determinations were used to elucidate the specific changes in the gene region. There was no difference in smoking status between patient and control groups. It was found that there was a statistical significance in XRCC3 T carriers between patient and control groups and so there was a 4.87-fold protective role by the XRCC3 T allele against bladder cancer. The AA genotype and A allele carriers of the APE gene were more frequent in the transitional epithelial carcinoma group than in the adenocarcinoma group. The genotype distribution for the APE gene was determined to be significantly different between local and invasive cases; G allele carriers for this gene were significantly higher in invasive cancer types.*

Exposure to tobacco smoke and occupational carcinogens is a major risk factor for urothelial cell carcinoma of the bladder. The carcinogenic molecules of cigarettes directly or indirectly create free oxygen radicals and cause DNA damage in bladder epithelial cells. DNA is a huge molecule that can be damaged by endogenous and exogenous mutagens, however the damage can be repaired through several ways such as base excision repair, nucleotide excision repair, double-strand repair and mismatch repair (1). Several different kinds of gene products play roles in these DNA repair systems. Apurinic endonuclease 1 (*APE1*), X-ray repair complementing defective repair in Chinese hamster cells 1 (*XRCC1*) and 8-oxoguanine DNA-glycosylase 1 (*OGG1*) genes express proteins for base excision repair (BER) (2). BER operates on slight damage such as oxidation or reduction. Polynucleotide kinase, apurinic/apyrimidinic endonuclease (APE), DNA polymerase-β and XRCC1 molecules are involved in the restoration phase of BER (3). Xeroderma pigmentosum D (*XPD*), excision repair cross-complementing rodent repair deficiency and complementation group 5 (*ERCC5*, *XPG*) genes express proteins having roles in the nucleotide excision repair (NER) pathway that can repair bulky lesions such as pyrimidine dimers, other photo-products, larger chemical adducts and cross-links. Double-strand breaks can also be produced by replication errors and by exogenous agents such as ionizing radiation; repair of those double-strand breaks is intrinsically more difficult than other types of DNA damage because no undamaged template is available (3). X-ray repair complementing defective repair in Chinese hamster cells 3 (*XRCC3*) gene expresses a protein that has a role in repair of double-strand DNA breaks by homologous recombination (4, 5).

The aim of this investigation is to study polymorphisms of *XRCC1, XRCC3, XPD, XPG, APE1* and *hOGG1* to determine whether there might be an increase in bladder cancer incidence in individuals with polymorphisms of these genes or not.

Patıents and Methods

Study Groups. The patient group consisted of 83 bladder cancer patients referred to Haydarpaşa Numune Hospital, Urology Department aged between 26-86 years and the control group

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Table I. *Details of PCR and RFLP procedures and expected products.*

Gene	Primers (forward and reverse)	PCR conditions	PCR product	Restriction enzyme	Restriction products
XRCC1 (6) *	5'-GCCAGGGCCCCTCCTTCAA-3' 5'-TACCCTCAGACCCACGAGT-3'	25 μL of PCR mixture: 1 Mm of each dNTP, 100 pmol/μL of each primer, 25 mM of $MgCl_2$, 1 U Taq polymerase 35 cycles: 95˚C 30 sec, 61˚C 35 sec, 72˚C 45 sec	485 bp	PvuII	Arg/Arg: 485 bp Arg/Trp: 485 bp, 399 bp, 194 bp Trp/Trp: 399 bp, 194 bp
XRCC3 (7)*	5'-GGTCGAGTGACAGTCCAAAC-3' 5'-TGCAACGGCTGAGGGTCTT-3'	25 μL of PCR mixture: 1 Mm of each dNTP, 100 pmol/μL of each primer, 25 mM of $MgCl_2$, 1 U Taq polymerase 35 cycles: 95˚C 1 min, 59˚C 1 min, 72˚C 1 min	456 bp	Hsp92 (NIaIII)	Thr/Thr: 456 bp Thr/Met: 456 bp, 315 bp, 141 bp Met/Met: 315 bp, 141 bp
XPD (8)*	5'-CCTCTCCCTTTCCTCTGTTC-3' 5'-CAGGTGAGGGGGGACATCT-3'	25 μL of PCR mixture: 1 Mm of each dNTP, 100 pmol/μL of each primer, 25 mM of $MgCl_2$, 1 U Taq polymerase 35 cycles: 95˚C 1 min, 52˚C 1 min, 75˚C 1 min	734 bp	PstI	Lys/Lys: 734 bp Lys/Gln: 734 bp, 646 bp, 88 bp Gln/ Gln: 646 bp, 88 bp
XPG (9)*	5'-GACCTGCCTCTCAGAATCATC-3' 5'-CCTCGCACGTCTTAGTTTCC-3'	25 μL of PCR mixture: 1 Mm of each dNTP, 100 pmol/μL of each primer, 25 mM of $MgCl_2$, 1 U Taq polymerase 35 cycles: 95˚C 1 min, 62˚C 1 min, 72˚C 1 min	271 bp	NIaIII	GG/GG: 271 bp GC/GC: 271 bp, 227 bp, 44 bp CC/CC: 227 bp, 44 bp
APE1 (10)*	5'-CTGTTTCATTTCTATAGGCTA-3' 5'-AGGAACTTGCGAAAGGCTTC-3'	25 μL of PCR mixture: 1 Mm of each dNTP, 100 pmol/μL of each primer, 25 mM of $MgCl_2$, 1 U Taq polymerase 35 cycles: 95˚C 30 sec, 52˚C 45 sec, 72˚C 45 sec	164 bp	FspBI (MaeI)	Asp/Asp: 164 bp Asp/Glu: 164 bp, 144 bp, 20 bp Glu/Glu: 144 bp, 20 bp
hOGG1 (11)*	5'-ACTGTCACTAGTCTCACCAG-3' 5'-GGAAGGTGCTTGGGGAAT-3'	25 μL of PCR mixture: 1 Mm of each dNTP, 100 pmol/μL of each primer, 25 mM of $MgCl_2$, 1 U Taq polymerase 35 cycles: 95˚C 1 min, 60˚C 1 min, 75˚C 1 min	200 bp	Fnu4HI	Ser/Ser: 200 bp Ser/Cys: 100 bp, 200 bp Cys/Cys: 100 bp

*Reference numbers for the methods.

consisted of 45 healthy individuals 48-83 years old that had no family history of bladder cancer. The bladder cancer patients were operated by transurethral resection or radical cystectomy. Questionnaires, medical records and pathology reports were received to confirm the diagnoses and cancer status. All study participants were informed about the study and their approval was obtained.

Polymorphism snalysis. From all participants, blood specimens were taken by using EDTA-containing tubes, and their DNA materials were prepared by using a salt-extraction method. All materials were protected in 4˚C refrigerators for later analyses. PCR-RFLP method was used to determine possible gene polymorphisms, the procedures of polymerase chain reaction (PCR) and restriction fragment polymorphism procedures (RFLP) are given in Table I (6-11). For each of the studied parameters, the appropriate primers were used to amplify the corresponding gene by PCR and the reaction products were digested by using the appropriate enzyme at 37˚C. Finally, DNA fragments were redissolved in agarose gels stained by ethidium bromide to be visualised. The expected results after restriction for each gene are given in Table I.

Statistically, univariate analysis was performed to compare the distribution of age and gender and the frequencies of alleles and genotypes. Multivariate logistic regression analysis with adjustment of age, gender and smoking status were then performed.

Results

The demographic information of the two groups and tumor status of the patient group are given in Table II. Each group was divided into age groups and respectively compared with regards to age, gender and smoking aspects. The patient group was further classified by their tumour types and grades. There was no significant difference between patient and

Table II. *Demographic information of both groups and tumor status of the patient group.*

	Control group (n: 45)	Patient group (n: 83)
Gender (M/F)	0/45	13/70
Age (years)	59.98±9.71	63.43±11.74
Age intervals		
<60 years	24 (53.3%)	29 (34.9%)
60-69 years	13 (28.9%)	29 (34.9%)
>70 years	8 (17.8%)	25 (30.1%)
Smoking	45 (100%)	75 (90.4%)
Non-smoking	0	8 (9.6%)
Grade	-	
1	-	33 (% 39.8)
2	-	35 (% 42.2)
3	-	15 (% 18.1)
Stage	-	
Local	-	31 (37.3%)
Invasive	-	52 (62.7%)
Pathological type	-	
Adenocarcinoma	-	4 (4.8%)
Transitional epithelial carcinoma	-	79 (95.2%)

Table III. *Genotype distributions of studied genes in control and patient groups.*

Genotype	Control group	Patient group
APE	n: 35	n: 75
AA	27 (77.1%)	50 (66.7%)
GG	4 (11.4%)	11 (14.7%)
AG	4 (11.4%)	14 (18.7%)
XRCC3	n: 39	n: 55
CC	5 (12.8%)	23 (41.8%)
TT	2 (5.1%)	5 (9.1%)
CT	32 (82.1%)	27 (49.1%)
XRCC1	n: 36	n: 57
Arg/Arg	20 (55.6%)	36 (63.2%)
Trp/Trp	1 (2.8%)	4 (7.0%)
Arg/Trp	15 (41.7%)	17 (29.8%)
XPD	n: 36	n: 39
LL	17 (47.2%)	20 (47.6%)
GG	2 (5.6%)	6 (14.3%)
LG	17 (47.2%)	13 (38.1%)
XPG	n: 40	n: 56
GG	18 (45%)	25 (44.6%)
CC	3 (7.5%)	3 (5.4%)
GC	19 (47.5%)	28 (50%)
hOGG1	n:36	n:58
Ser/Ser	18 (50%)	37 (63.8%)
Cys/Cys	0 (0%)	8 (13.8%)
Ser/Cys	18 (50%)	13 (22.4%)

control groups for age and smoking status ($p>0.05$). There was no significant difference between the ages of two groups for any of the genotype and/or allele determinations. No statistically significant difference was determined between the patient and control groups either in APE A allele carriers or *APE* G allele carriers ($p=0.771$; $p=0.264$) (Table III).

Although there was no significant difference between patient and control groups in *XRCC3* C allele carriers ($p=0.695$) it was found that there was a statistical significance in *XRCC3* T carriers between patient and control groups ($p=0.002$). It was also found that there is a 4.87-fold protective role of the *XRCC3* T allele from bladder cancer. There were no significant differences between any genotypes or alleles in the control and patient groups for *XRCC1*, *XPG* and *XPD* genes (Table III).

There was a statistically significant difference between the control and patient groups in genotype for *hOGG1 (p=0.003)* and *hOGG1* Ser allele carriers ($p=0.022$).

Grouping accordings to the pathological types of the tumours, the AA genotype ($p=0.01$) and A allele carriers ($p=0.04$) for *APE* gene were more frequent in the transitional epithelial carcinoma group than in the adenocarcinoma group (χ^2: 4.21; OR: 6.88; CI 95%: 0.86-55.19). There was no significant difference between other groups. The genotype distribution for the *APE* gene was determined to be significantly different between local and invasive cases ($p=0.002$); G allele carriers for this gene were significantly more frequent in invasive cancer ($p.0.001$). There were no other significant differences between any of the groups for any of the genes (Table IV).

Discussion

The bladder, due to being the urine collecting area, is prone to contact with carcinogens. It has been shown that smoking increases bladder cancer risk four-fold (12). It is thought that smoking increases the risk due to chemicals such as hydrocarbons, arylamines, nitrosamines and the formation of reactive oxygen species as by-products of the above compounds (13). It is very important to protect DNA from damage by these chemicals; DNA repair mechanisms are paramount in correcting the changes on DNA and provide unmutated DNA while replication goes on (14). It is known that there are more than a hundred genes participating in four main DNA repair mechanisms (15). Closas *et al*. determined the relationship of *XPC* and *ERCC1*-1 to -5 gene polymorphisms in bladder cancer (16). It is thought that the polymorphisms in DNA repair genes change their repair capacity, leading to cancer (3). The most frequent DNA damage caused by free oxygen radicals is the formation of 8-hydroxydeoxyguanosine (8-OHdG) and is normally repaired by 8-oxoguanine DNA glycosylase1 (hOGG1) by removing the bond between the damaged base and sugar, thereby creating an abasic region (17, 18). Kim *et al*. demonstrated that Ser326Ser and Ser326Cys genotypes had an increased probability of recurrency in bladder cancer over Cys326Cys

Table IV. *Genotype distributions of patient group according to the pathological types and stages of the tumors.*

	Pathological type		Stage	
	Adeno-carcinoma n (%)	Transitional epithelial carcinoma n (%)	Local n (%)	Invasive n (%)
APE				
AA	0 (0)	50 (70.4)	24 (92.3)	26 (53.1)
GG	2 (50)	9 (12.7)	1 (3.8)	10 (20.4)
AG	2 (50)	12 (16.9)	1 (3.8)	13 (26.5)
A+	2 (50)	62 (87.3)	25 (96.2)	39 (79.6)
G+	4 (100)	21 (29.6)	2 (7.7)	23 (46.9)
XRCC3				
CC	0 (0)	23 (45.1)	8 (36.4)	15 (45.5)
TT	1 (25)	4 (7.8)	1 (4.5)	4 (12.1)
CT	3 (75)	24 (47.1)	13 (59.1)	14 (42.4)
C+	3 (75)	47 (92.2)	21 (95.5)	29 (87.9)
T+	4 (100)	28 (54.9)	14 (63.6)	18 (54.5)
XRCC1				
Arg/Arg	2 (66.7)	34 (63)	13 (65)	23 (62.2)
Trp/Trp	0 (0)	4 (7.4)	3 (15)	1 (2.7)
Arg/Trp	1 (33.3)	16 (29.6)	4 (20)	13 (35.1)
Arg+	3 (100)	50 (92.6)	17 (85)	36 (97.3)
Trp+	1 (33.3)	20 (37)	7 (35)	14 (37.8)
XPD				
LL	0 (0)	20 (51.3)	7 (46.7)	13 (48.1)
GG	0 (0)	6 (15.4)	3 (20)	3 (11.1)
LG	3 (100)	13 (33.3)	5 (33.3)	11 (40.7)
L+	3 (100)	33 (84.6)	12 (80)	24 (88.9)
G+	3 (100)	19 (48.7)	8 (53.3)	14 (51.9)
XPG				
GG	1 (25)	24 (46.2)	13 (59.1)	12 (35.3)
CC	1 (25)	2 (3.8)	2 (9.1)	1 (2.9)
GC	2 (50)	26 (50)	7 (31.8)	21 (61.8)
G+	3 (75)	50 (96.2)	20 (90.9)	33 (97.1)
C+	3 (75)	28 (53.3)	9 (40.9)	22 (64.7)
hOGG1				
Ser/Ser	2 (50)	35 (64.8)	18 (75)	19 (55.9)
Cys/Cys	1 (25)	7 (13)	1 (4.2)	7 (20.6)
Ser/Cys	1 (25)	12 (22.2)	5 (20.8)	8 (23.5)
Ser+	3 (75)	47 (87)	23 (95.8)	27 (79.4)
Cys+	2 (50)	19 (35.2)	6 (25)	15 (44.1)

n=Number of patients.

cases. In this study, there was a statistically significant difference in genotype distribution between control and patient groups in hOGG1 Ser carriers, but there was no significance between hOGG1 Cys carrying cases (p=0.187).

Shen *et al*. previously determined that *XRCC3* codon Thr241Met variant genotype had protective effects for bladder cancer, but no relationship of *XRCC1* Arg399Gln and *XPD* Lys751Gln polymorphisms with bladder cancer (19). *XRCC1* gene is located on chromosome 13 and its protein is an important component in the repair of base excision caused by ionising radiation and alkylating agents (20). This protein recognizes single-strand breaks and binds onto those broken areas (21). Other studies on *XRCC1* gene polymorphisms in bladder cancer and smoking have yielded no meaningful results (21, 22). In parallel to these previous studies, no relationship between *XRCC1* gene polymorphisms and bladder cancer could be found in this study. *XRCC3* gene protein has a role in the repair of DNA double helix breaks by cross-binding homologous recombination, as well as a role in maintainig chromosome stability (23). Sanyal *et al*. could not find any statistically significant relationship between *XRCC1* Thr241Met polymorphism and bladder cancer (24). In the present study, a significant relationship between control and patient groups was found for *XRCC3* codon 241 polymorphism, but there was no relationship for the *XRCC3* C allele in those groups. Importantly, a 4.87-fold protection in *XRCC3* T allele carriers was found in this study indicating that *XRCC3* T allele carriers have 4.87 times more protection against bladder cancer.

Sanyal *et al*. previously investigated the relationship between several genes and bladder cancer and found that some *XPC* and *XPD* gene polymorphisms were increased in bladder cancer patients (24). XPD protein works in nucleotide excision repair to recognition and repair of tymidine dimers. *XPD* gene distortions increase repair and transcription defects and cause an abnormal response to apoptosis (25). There are various previous studies on the relationship between *XPD* genes and bladder cancer (24, 26, 27). In the present study, no difference in any of the *XPD* genotype and allele carriers between patient and control groups was found.

The *XPG* gene product has a role in nucleotide excision repair. It has been previously reported that the polymorphisms of this gene are related to lung cancer (9), but there was no obvious relationship between this polymorphism and bladder cancer (24). In parallel, no relationship was found in either genotype and allele distributions of this gene and bladder cancer.

The *APE1* gene product is the rate-limiting enzyme in base excision repair and works in coordination with the product of *XRCC1* gene. Damaged bases on DNA skeleton are removed by a specific glycosylase and an abasic region is formed (28).

This study is a rare investigation of several genes in bladder cancer in the Turkish population. The novel findings of this study require further investigation in larger study groups.

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