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Association of XRCC3 Thr241Met Polymorphism with Renal Cell Carcinoma in a Turkish Population

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ABSTRACT

Objective: Renal cell carcinoma (RCC) is considered as a major type of cancer of the kidney and is estimated to account for about 2-3% of all malignancies in adults. DNA repair mechanisms play a crucial role in defending genomic integrity against DNA damage, and defects in DNA repair mechanisms are associated with cancer susceptibility. The XRCC3 gene plays a pivotal role in the DNA repair system through homologous recombination and chromosomal activity. Therefore, our research aimed to clarify whether XRCC3 Thr241Met polymorphism affects the initiation and progression of RCC.

Materials and Methods: This study included 129 patients with RCC and 212 healthy individuals. The polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique was employed to analyze XRCC3 Thr241Met gene polymorphism using SPSS 23 software to facilitate data analysis.

Results: Our results revealed no remarkable differences in the genotype and allele frequencies of the Thr241Met polymorphism of XRCC3 between the patient and control groups. However, a greater risk of RCC was reported for the variant (Met/Met) genotype of XRCC3 gene polymorphism, particularly among smokers.

Conclusion: Although the XRCC3 Thr241Met polymorphism may not significantly influence RCC initiation and progression in a Turkish population, smoking seems to amplify the risk associated with the (Met/Met) genotype of XRCC3 gene polymorphism.

Keywords: Renal cell carcinoma, XRCC3, polymorphism, Thr241Met, PCR-RFLP.

INTRODUCTION

Renal cell carcinoma (RCC), which originates from renal epithelial cells, is the 16th most prevalent cancer, globally. According to GLOBOCAN data, 431,519 new cases were detected in 2020, constituting 2.2% of all malignancies (1, 2).

The etiology of RCC is multifactorial, with age, sex, obesity, high blood pressure, exposure to harmful chemicals at work, smoking, alcohol use, and their interactions being significant contributors (3, 4). Genetic variations, specifically single-nucleotide polymorphisms (SNPs), may also influence RCC risk. These DNA sequence variations may alter gene functions involved in DNA repair. Certain SNPs may be correlated with RCC risk modulation, treatment responsiveness, and patient survival (5).

DNA damage repaired by DNA repair systems may stem from a variety of factors, including environmental factors, internal metabolic reactions, errors during DNA replication, and random mutations. Disruption of DNA integrity may modify gene function and potentially lead to pathological conditions, including cancer (6). Among the most harmful forms of DNA damage are double-stranded DNA breaks (DSBs), which involve the cleavage of both DNA strands. Cells utilize nonhomologous end-joining

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(NHEJ) and homologous recombination (HR) as the main repair mechanisms for DSBs (7). These repair mechanisms involve different proteins and enzymes that recognize, process, and bring together destroyed ends of DNA strands.

The X-ray Repair Cross Complementing/3 (XRCC3) protein, a component of the Rad51-related family—which consists of XRCC2, XRCC3, RAD51B, RAD51C, and RAD51D—comprises 346 amino acids and participates in HR repair system (8). The HR repair system that is critical for maintaining genomic stability is a process that utilizes homologous DNA fragments as a template to restore DSBs (9). XRCC3 collaborates with RAD51C to form a complex known as CX3, and this complex acts downstream of RAD51 recruitment. RAD51C also binds RAD51B to join with RAD51D-XRCC2 dimer to form BCDX2 complex (10).

It has been indicated that XRCC3 Thr241Met (rs861539) gene polymorphism in exon 7 of the XRCC3 DNA repair gene results in a single nucleotide alteration from cytosine (C) to thymine (T). The exchange of threonine with methionine at codon 241 may modify the role of XRCC3 and its cooperation with other proteins (11). This polymorphism may alter the protein structure and consequently the efficiency of DNA repair (12). The inefficiency of HR repair mechanisms that leads to the accumulation of mutations may contribute to carcinogenesis. Studies have shown that XRCC3 gene polymorphism is linked to a variety of cancers, such as leukemia (13), gastric (14), lung (15), and colorectal cancer (16, 17). However, previous studies showing the influence of XRCC3 Thr 241Met polymorphism on RCC are limited. Therefore, in our study, we aimed to establish the correlation between the XRCC3 DNA repair gene variants and the initiation and clinicopathological factors of RCC in a Turkish population.

MATERIALS AND METHODS

Study Participants

Our study included 129 individuals (65.1% male and 34.9% female) diagnosed with RCC according to histopathological findings. Patients underwent either radical or partial nephrectomy at the Istanbul University, Istanbul Faculty of Medicine, Department of Urology. Each participant provided comprehensive information through a detailed questionnaire.

The control group was composed of individuals without cancer and compared with the patient group according to sex, age, body mass index (BMI), and smoking habits. There was no cancer history in the families of both patient and control groups. Classification of smoking status was based on a threshold of 20 packs/year, with those exceeding 20 packs/year was considered as smokers. On the other hand, individuals who smoked less than one cigarette/day or less than one year along their lifespan were considered as non-smokers. The staging of tumors was indicated based on tumor node metastasis (TNM) of the American Joint Committee on Cancer (AJCC), while tumor grade was defined using the Fuhrman grading system. RCC patients were categorized into localized (I+II) and advanced (III+IV) disease groups according to TNM staging. Based on the Fuhrman system, patients were categorized into low (I+II) and high (III+IV) grades. Ethical consent for the study was granted by Ethics Committee of Istanbul University, Faculty of Medicine, with informed permission acquired from all patients with RCC.

Genotyping

In this study, blood specimens were obtained from all participants, both patients with RCC and healthy controls, using tubes with EDTA. DNA was then isolated from the collected whole blood samples using the DNA extraction kit (Roche Diagnostics, Mannheim, Germany) and preserved at -20 °C for subsequent polymerase chain reaction (PCR) analysis.

Genotyping of the XRCC3 Thr 241Met (rs861539) polymorphism was performed according to the PCR-restriction fragment length polymorphism (RFLP) method. The PCR mix included 25 µL reactions with 10 pmol of each primer, 0.2 mM of dNTPs, 2 mM of $MgCl_2$, 100 ng of genomic DNA, 10× PCR buffer at pH 8.8, and 1.25 U of Taq polymerase (MBI Fermentas). The PCR cycling condition for XRCC3 was initial denaturation of 95°C for 5 min. followed by 30 cycles of denaturation at 84°C for 1 min, annealing at 58°C for 1 min and elongation at 72°C for 1 min and finally 5 min at 72°C. The 456-bp product was digested with Hsp92 restriction enzyme (Thermo Fisher Scientific), incubated overnight at 37°C (18). Fragment patterns for XRCC3 Thr 241Met genotypes were Thr/Thr (456 bp), Thr/Met (456 bp, 315 bp, 141bp), and Met/Met (315 bp, 141 bp). The digested products were subjected to gel electrophoresis on a 2% agarose gel and were subsequently stained with ethidium bromide to enable visualization under UV illumination.

Statistical Analyses

The statistical analysis was conducted with SPSS 23 software (SPSS-Inc, Chicago/ IL, USA). To assess mean differences between controls and RCC patients, Mann-Withney U test was utilized. The genotype distributions and allele frequencies were compared using chi-square tests. Odds ratios (ORs) and 95% confidence intervals (CI) were determined using logistic regression analysis. Verification of the Hardy–Weinberg equilibrium (HWE) for genotype distributions was accomplished using the chi-square test. The power of the study was assessed using "NCSS-2000" software (NCSS-Inc, Kaysville, UT, USA), aiming to define a size effect of 0.20 with two degrees of freedom at an alpha level of 0.05 (α: 0.05), achieving a power of 90%.

RESULTS

Table 1 represents clinical and demographic parameters of the RCC patient and control groups. Any remarkable differences were not detected between controls and patients with RCC according to age, sex, BMI, and smoking status. Disease staging showed that 65.2% of the RCC-patients were diagnosed at low stage (I+II), whereas 34.8% were at high stage (III+IV).

Table 1. Clinical and demographic parameters of the controls and RCC patients.

Parameters	Controls (n=212)	Patients (n=129)	[a]p value
Age (years; mean ± SD)	56.0 ± 9.07	54.7 ± 10.5	0.250
BMI (kg/m^2; mean ± SD)	27.2 ± 2.56	27.7 ± 4.46	0.178
Sex (%; Female /Male)	68 (32.1)/ 144 (67.9)	45 (34.9)/ 84 (65.1)	0.593
Smoking status (%; Never/Current)	65.4/34.6	55.8/44.2	0.077
Grade (n, %)			
I		27 (20.9)	
II		57 (44.2)	
III		31 (24.0)	
IV		14 (10.9)	
Stage (n, %)			
I		78 (60.5)	
II		6 (4.7)	
III		38 (29.5)	
IV		7 (5.3)	
Histology (n, %)			
Clear cell		102 (79.1)	
Papillary		11 (8.5)	
Chromophobe		16 (12.4)	

[a]p from Pearson's χ^2 test for categorical variables and Mann–Whitney U or Student's t-test for continuous variables. n: Number of subjects.

Moreover, 65.1% of the patients were classified as having a low grade(I+II) of the disease, whereas 34.9% had a high stage (III+IV), indicating a predominance of low stage and low grade diagnoses among RCC patients.

Table 2 includes the genotype and allele frequencies of Thr241 Met polymorphism of the XRCC3 gene in both controls and patients with RCC. The comparative analysis revealed that no significant differences were observed in the genotype distributions and allele frequencies of Thr241Met polymorphism of XRCC3 between controls and patients with RCC.

On the other hand, we assessed allele frequencies and genotype distributions in relation to RCC susceptibility among smokers versus non-smokers. According to our findings, carriers of Met/ Met genotypes exhibited a 2.22-fold increased risk (OR=2.22; 95%CI=1.10-4.47; p=0.025) of having RCC compared with wild-type (Thr/Thr) carriers among smokers. However, the variant (Met/ Met) genotype distribution was not observed to be high among non-smokers (OR=0.99; 95%CI=0.60-1.63; p=0.970; Table 3).

In addition, we examined the impact of Thr241Met polymorphism of XRCC3 on clinicopathological features, such as grade and T stage among RCC patients. In our study, we did not find any statistically significant association between the clinicopathological characteristics of RCC and this polymorphism, including T stage and grade among RCC patients (Table 4).

Table 2. Genotype and allele frequencies of XRCC3 Thr241 Met gene polymorphism in controls and RCC patients.

	Controls n (%)	Patients n (%)	p value	OR[a] (95% CI)
XRCC3 Thr241Met				
Thr/Thr	48 (22.6)	27 (20.9)		1.00*
Thr/Met	117 (55.2)	59 (45.7)	0.981	0.99 (0.51-1.92)
Met/Met	47 (22.2)	43 (33.3)	0.777	1.01 (0.90-1.14)
Thr/Met+Met/ Met	164 (77.4)	102 (79)	0.604	0.98 (0.96-1.01)
Allele				
Thr	213 (50.2)	113 (43.7)		1.00*
Met	211 (49.7)	145 (56.2)	0.102	1.29 (0.94-1.76)

[a]Odds ratios (OR) and 95% confidence intervals (CI) adjusted for age, sex, BMI, and smoking status

*Reference genotype. n: Number of subjects.

DISCUSSION

RCC is more frequently observed in males than females, and it is the predominant form of cancer affecting the urinary system, with a mortality rate ranging from 30% to 40%. In addition, chronic kidney disease, hypertension, smoking, and obesity are risk factors for RCC occurrence (19).

Genetic defects in DNA repair mechanisms frequently lead to an elevation in various types of cancer, including RCC. HR is an essential repair process for maintaining genomic stability against DSBs (14, 20). The Rad51 complex is known to exhibit DNA-induced ATPase activity and binds to single-stranded DNA. The presence of XRCC3 protein is essential for the stimulation of Rad51 complex formation within cells (11). There is a growing evidence that XRCC3 maintains genomic stability and prevents the generation of tumorigenic mutations in the HR repair pathway. The Thr241Met polymorphism is located within the ATP-binding domain of the XRCC3 gene, which is crucial for its function in DNA repair. The transition from threonine to methionine at 241 position has been implicated in reduced efficacy in repairing chromosomal aberrations caused by X-rays, likely due to alterations in the structure of the

Table 3. Genotype and allele frequencies of XRCC3 Thr 241Met polymorphism associated with smoking status.

		Controls n (%)	Patients n (%)	p value	OR[a] (95% CI)
Non-smokers	**XRCC3 Thr(241)Met**				
	Thr/Thr	32 (23.2)	17 (23.6)		1.00*
	Thr/Met	71 (51.1)	30 (41.7)	0.850	0.91 (0.38-2.22)
	Met/Met	36 (25.9)	25 (34.5)	0.970	0.99 (0.60-1.63)
	Thr/Met+Met/Met	107 (77.0)	55 (76.2)	0.884	0.94 (0.41-2.13)
	Allele				
	Thr	135 (48.5)	64 (44.4)		1.00*
	Met	143 (51.4)	80 (55.5)	0.610	1.12 (0.71-1.77)
Smokers	**XRCC3 Thr(241)Met**				
	Thr/Thr	15 (20.5)	10 (17.5)		1.00*
	Thr/Met	47 (64.4)	29 (50.9)	0.711	1.22 (0.41-3.60)
	Met/Met	11 (15.1)	18 (31.6)	0.025	2.22 (1.10-4.47)
	Thr/Met+Met/Met	58 (79.5)	47 (82.5)	0.498	1.41(0.51-3.86)
	Allele				
	Thr	77 (54.7)	49 (42.9)		1.00*
	Met	69 (47.6)	65 (57.0)	0.118	1.48 (0.90-2.42)

[a]Odds ratios(OR) and 95% confidence intervals(CI) adjusted for age, sex, and BMI; *:Reference genotype. n: Number of subjects.

XRCC3 protein (21). Therefore, it has been hypothesized that the exchange generated by Thr241Met polymorphism in the XRCC3 gene is related to disruption of the connectivity with the Rad51 protein involved in DNA repair (22).

XRCC3 gene polymorphism has been the subject of global investigation for its possible links to various cancers. Previous research by Osawa et al. (15) highlighted the influence of XRCC3 gene polymorphism on long-term outcomes in patients with lung cancer. A meta-analysis by Qin et al. (14) demonstrated a significant elevation in gastric cancer susceptibility among Asian populations due to XRCC3 gene polymorphism. According to Xie et al. (13), the Thr241Met polymorphism was found related to the incidence of leukemia in a Caucasian population. Wang and Zhang (17) and Procopciuc and Osian (16) reported that XRCC3 gene polymorphism may elevate the occurrence of colorectal cancer. Based on these findings, we presumed that XRCC3 gene polymorphism may also be involved in the risk of RCC in a Turkish population. According to our current knowledge, there exists no documented report investigating Thr241Met polymorphism of XRCC3 and its relationship with RCC susceptibility in a Turkish population. However, based on our study findings, (Met/Met) and (Thr/Met) genotypes of XRCC3 did not alter the risk of RCC. Our study outcomes were similar to the results obtained by Loghin et al. (23), who reported no relation of increased clear cell-renal cell carcinoma with Met/Met genotype of XRCC3 gene polymorphism in a Romanian population. In addition, Hirata et al. (24) did not detect any correlation between heterozygous (Thr/Met) genotype of XRCC3 gene polymorphism and RCC risk.

It has been demonstrated that tobacco consumption, including several harmful chemicals that modify DNA structure, may lead to mutations (25). Therefore, tobacco usage may be a major risk factor for various cancers, such as RCC. Many prior studies have demonstrated a significant relationship between XRCC3 gene polymorphism and smoking, such as colorectal (16, 26), bladder (27), lung (14), and breast cancer (28). Similar to previous studies, our results showed that the variant genotype of the XRCC3 gene was significantly linked to an elevated risk of RCC among smokers.

When stratified by disease stage and grade, the risk genotype (Met/Met) did not affect tumor staging and grading among patients with RCC. Our findings are in accordance with those of Loghin et al. (23) who determined no relationship between genotype distributions and clinicopathological factors of CCRCC.

Table 4. Genotype and allele frequencies of the Thr 241Met polymorphism of XRCC3 according to disease grade and stage.

	Low grade[a] n (%)	High grade[b] n (%)	p value	OR[e] (95% CI)
XRCC3 Thr 241 Met				
Thr/Thr	14 (16.7)	13 (28.9)		1.00*
Thr/Met	44 (52.4)	15 (33.3)	0.052	0.36 (0.14-0.95)
Met/Met	26 (31.1)	17 (37.8)	0.479	0.83 (0.51-1.36)
Thr/ Met+Met/ Met	70 (83.5)	32 (71.1)	0.103	0.49 (0.20-1.16)
Allele				
Thr	72 (42.8)	41 (45.5)		1.00*
Met	96 (57.1)	49 (54.4)	0.677	0.99 (0.53-1.30)
	Low stage[c] n (%)	**High stage[d] n (%)**	**p value**	**OR[e] (95% CI)**
XRCC3 Thr 241 Met				
Thr/Thr	17 (20.2)	10 (22.2)		1.00*
Thr/Met	41(48.8)	18 (40.0)	0.418	0.06 (0.21-1.90)
Met/Met	26 (31.0)	17 (37.8)	0.353	0.70 (0.34-1.46)
Thr/ Met+Met/ Met	67 (79.8)	35 (77.8)	0.392	0.63 (0.21-1.81)
Allele				
Thr	75 (44.5)	38 (42.2)		1.00*
Met	93 (55.3)	52 (57.7)	0.708	1.10 (0.65-1.85)

[a]Low grade(I-II); [b]High grade (III-IV); [c]Low stage (I-II); [d]High stage (III-IV) [e]Odds ratios (OR) and 95% confidence intervals(CI) adjusted for age, sex, BMI, and smoking status.
*Reference genotype. n: Number of subjects.

Although the current study has some novel findings, not evaluating the relationship between genotype distributions of other SNPs of XRCC3 gene and RCC was a limitation of our study. More SNPs of XRCC3 gene need to be studied in the future.

In conclusion, this study suggests no association between increased risk of RCC and genetic variants of the XRCC3 gene. However, smoking habits may influence the interaction between the variant genotype of XRCC3 gene polymorphism and the risk of RCC in a Turkish population. It is crucial to acknowledge that genetic polymorphisms may have different effects across different ethnic groups, and their contributions to cancer etiology are typically complex and multifactorial.

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Informed Consent: Informed consent was obtained from all participants included in the study.

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