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ORIGINAL ARTICLE

ERCC2 Lys751Gln rs13181 and *XRCC2* Arg188His rs3218536 gene polymorphisms contribute to susceptibility of colon, gastric, liver, lung and prostate cancer

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Summary

Purpose: *Cancer is the leading cause of death in economically developed countries and the second leading cause of death in developing countries. The relationship between genetic polymorphisms and cancer risk has been extensively researched. In the present study, we evaluated the association between polymorphisms in two DNA repair genes, ERCC2 Lys751Gln (rs13181) and XRCC2 Arg188His (rs3218536) and the risk of colorectal, stomach, liver, prostate and lung cancer.*

Methods: *This study was planned by the Medical Biology Unit and Department of Internal Medicine, Pathology and Surgical Medicine Sciences of Ataturk University. A total of 40 colon cancer, 40 gastric cancer, 40 hepatocellular carcinoma (HCC), 40 prostate cancer, and 40 lung cancer patients and 40 healthy individuals over 18 years of age were enrolled in the study (Controls). All patients and healthy subjects underwent ERCC2 Lys751Gln rs13181 and XRCC2 Arg188His rs3218536 genotyping. After collection of 10 ml venous blood from the patients, DNA was isolated and single nucleotide polymorphism (SNP) analysis was performed using Roche 480 Real-Time PCR device. Results were analyzed using SPSS version 23.0 software.*

Results: *There were statistically significant differences in ERCC2 Lys751Gln rs13181 polymorphism variants GG colon and GT in the colon control and GG,TTprostate cancer groups when compared with the control group. GG variant of XRCC2 Arg188 rs3218536 was higher in the gastric patient group. AG variant of XRCC2 Arg188 rs3218536 was higher in the gastric control group.*

Conclusion: *The results of the present study demonstrate that ERC22 Lys751Gln polymorphisms may be associated with the development of colon and prostate cancers in the Turkish population. This was a small-scale study, and the results should be corroborated with further research including larger groups of patients with each cancer type and more healthy controls.*

Key words: *colon, ERCC2, gastric, liver, lung, prostate cancer*

Introduction

Cancer is a complex disease that arises due to uncontrolled cell division and proliferation, and is influenced by genetic and environmental factors [1]. The incidence of cancer varies by region, country, and even different areas within a country. The age-standardized rate of cancer in Turkey in 2015 was 247.6 per 100,000 persons in males and 177.5 per 100,000 persons in females. The total cancer incidence was 212.6 per 100,000 persons. A total of 167,463 people in Turkey were diagnosed

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with new cancers. Analysis of data from the past 5 years showed a decrease in the incidence of cancer among males [2]. According to statistics, a total of 1,658,370 new cancer cases and 589,430 cancer deaths were projected to occur in the United States in 2015 [3,4].

Single nucleotide polymorphisms (SNPs) are changes of a single nucleotide in a genomic sequence. SNPs account for most of the 0.1% structural diversity in the human genome. SNPs provide important information that increases our understanding about the degree of disease susceptibility and individual differences in treatment response [5].

Polymorphisms of genes involved in DNA repair such as *OGG1, ERCC1, XRCC1, XRCC2, XRCC3, XPC, XPD, XPF, BRCA2, MRE11, NBS1, Ku70/80, LIG4,* and *RAD* can alter protein function and the individual's capacity to repair damaged DNA. Impaired repair capacity can result in genetic instability and consequently, the development of cancer [6]. However, DNA repair gene polymorphisms alone are not sufficient to explain cancer risk diversity.

The relationship between genetic polymorphisms and cancer risk has been studied extensively. Excision repair cross-complementing group 2 (*ERCC2*) and x-ray repair cross-complementing group 2 (*XRCC2*) genes play important roles in the nucleotide excision repair pathway [7].

ERCC2 is found on chromosome 19q13.3 and contains 23 exons and approximately 54,000 base pairs [6]. The *ERCC2* gene encodes a protein called xeroderma pigmentosum group D (XPD), which is a subunit of the protein complex known as general transcription factor IIH (TFIIH). TFIIH has two main functions: it is involved in gene transcription and in the repair of damaged DNA [7].

There are two major SNPs in *ERCC2*. The Lys751Gln (rs13181) polymorphism was reported to contribute to genetic susceptibility to certain types of cancer. In addition, there have been many cancer studies investigating the Asp312Asn (rs1799793) polymorphism. There are data in the literature related to head/neck, esophageal, pancreatic, brain, bladder, lung, and colon cancers [8-13].

The *XRCC2* gene is located on chromosome 7q36.1 and has 31,387 base pairs. This gene encodes a member of the family of proteins related to RecA/Rad61, which is involved in homologous recombination to repair DNA double-strand breaks and maintain chromosomal stability. In total, approximately 622 SNPs have been reported in *XRCC2*. The most important *XRCC2* SNPs are rs3218536 (Arg188His), rs718282, rs3218384, rs3218550, rs3218408, rs2018699, and rs3218499 [14,15].

In the present study, we examined the relationship between common cancer types and the DNA repair genes SNPs *ERCC2* Lys751Gln rs13181 and *XRCC2* Arg188His rs3218536.

Methods

Sample collection

The study included a total of 200 patients over 18 years of age (40 colon, 40 gastric, 40 hepatocellular carcinoma (HCC), 40 lung, and 40 prostate cancer) who presented to the Internal Medicine Oncology Outpatient Clinic and General Surgery Outpatient Clinic of the Erzurum Ataturk University Health Research and Application Center and were diagnosed with cancer in 2018. In addition, 40 unrelated healthy individuals who had no systemic diseases and did not use any medication were enrolled as the control group.

Table 1. Demographic, clinical features and disease characteristics of the cancer patients

Features	*Patients* *n*
Age, years (mean ± SD)	50.43 ± 57.79
Gender	
Male	131
Female	69
Family history of cancer	
Yes	190
No	10
Smoking	
Never	109
Ever	91
Tumor site	
Colon	40
HCC	40
Prostate	40
Stomach	40
Lung	40
Chemotherapy regimens	
Colon	Altuzan + campto + leucovorin teva Eloxatin + campto + leucovorin teva Oxaliplatin + 5-fluorouracil + leucovorin teva
Stomach	Capecitabine Epirubicin + capecitabine + oxaliplatin Docetaxel + 5-fluorouracil + oxaliplatin
HCC	None
Lung	Cisplatin + etoposide Carboplatin + taxol Sindaxel + carboplatin
Prostate	Docetaxel

Patients' clinical findings, age, and sex were recorded (Table 1). The patients' current treatment regimens were not altered for the study. The study protocol was approved by the Atatürk University Faculty of Medicine Ethics Committee in Erzurum, Turkey, and was carried out in accordance with the 1989 revision of the Declaration of Helsinki.

DNA isolation and molecular analysis

DNA was isolated from the 240 frozen blood samples (2 mL) using the QIAGEN EZ1 Blood Kit (Qiagen, Hilden, Germany) according to the manufacturer's protocol.

Table 2. Reaction mixtures prepared for ERCC2 rs13181 and XCC2 rs3218536 SNP analysis

Contents: Real-time PCR	*Volume (μl)*
DNA (~50 ng)	5
LightSNiP typing assay	2
FastStart DNA Master HybProbe	2
25 mM $MgCl_2$	1.6
H_2O	9.4
Final volume	20

ERCC2 Lys751Gln (rs13181), XRCC2 Arg188His (rs3218536)

Using the reaction conditions specified in the optimized protocol, *ERCC2* and *XRCC2* fragments containing the rs13181 and rs3218536 SNPs were amplified using a primer and probe set. The polymerase chain reaction (PCR) and melting curve analyses were performed under the same conditions in a 96-well plate on a Light Cycler 480 (Roche Diagnostics, Penzberg, Bavaria, Germany). Genotyping was carried out with the LightSNiP typing assay (TIB-MolBiol, Berlin, Germany) by analyzing the melting curves with the LightCycler 480 II system (Roche Applied Science, Mannheim, Germany) (Table 2).

Samples

Real-time PCR was performed under the following conditions: After the amplification phase, a melting curve analysis was performed at 95°C for 30 s, 40°C for 2 min, 75°C for 0 s, followed by cooling phase at 0.1°C/s to 40°C for 30 s. Collected data were analyzed using LightCycler480 Gene Scanning software version 1.2 (Roche Diagnostics Penzberg, Bavaria, Germany) (Table 3).

Table 3. Real-time PCR protocol for ERCC2 Lys751Gln rs13181 and XRCC2 Arg188His rs3218536 SNPs

Analysis mode	*Cycle number*	*Segment*	*Target temperature 0°C*	*Duration*	*Acquisition mode*
Preincubation	1		95	10 min	-
Amplification					
		Denaturation	95	10 s	-
	45	Annealing	60	10 s	Single
		Extension	72	15 s	-
Melting curve					
		Denaturation	95	30 s	-
	1	Annealing	40	2 min	-
		Melting	75	0 s	Continuous
		Slope=0.2°C/s			
Cooling					
	1		40	30 s	-

Table 4. Distribution of ERCC2 rs13181 and XRCC2 rs3218536 genotypes and allele frequencies in colon cancer patients and controls

ERCC2 rs13181	*Colon cancer (n)*	*Control (n)*	*p value*
TT	14	21	>0.05
GG	16	0	<0.001
GT	10	19	<0.005
XRCC2 rs3218536			
AA	0	0	>0.05
GG	36	30	>0.05
AG	4	10	>0.05

Table 5. Distribution of ERCC2 rs13181 and XRCC2 rs3218536 genotypes and allele frequencies in gastric cancer patients and controls

ERCC2 rs13181	*Gastric cancer (n)*	*Control (n)*	*p value*
TT	28	21	>0.05
GG	0	0	>0.05
GT	12	19	>0.05
XRCC2 rs3218536			
AA	0	0	>0.05
GG	40	30	<0.001
AG	0	10	<0.001

A melting curve of the amplification products was plotted by denaturation at 95°C for 20 s, holding the sample at 40°C for 10 s, and then slowly heating the sample to 80°C with a ramp rate of 0.1°C/s and continuous fluorescence acquisition. The two SNPs were detected with a commercially available LightSNiP assay according to the manufacturer's protocol (Tables 2,3).

Statistics

The study data were analyzed using SPSS version 23.0 (IBM Corp. Armonk, NY, USA) statistical software package. Frequency distribution and standard deviation values were used in comparisons. P values less than 0.05 were considered statistically significant.

Table 6. Distribution of ERCC2 rs13181 and XRCC2 rs3218536 genotypes and allele frequencies in HCC patients and controls

ERCC2 rs13181	*HCC cancer (n)*	*Control (n)*	*p value*
TT	24	21	>0.05
GG	0	0	>0.05
GT	16	19	>0.05
XRCC2 rs3218536			
AA	0	0	>0.05
GG	36	30	>0.05
AG	4	10	>0.05

Table 7. Distribution of ERCC2 rs13181 and XRCC2 rs3218536 genotypes and allele frequencies in lung cancer patients and controls

ERCC2 rs13181	*Lung cancer (n)*	*Control (n)*	*p value*
TT	16	21	>0.05
GG	0	0	>0.05
GT	20	19	>0.05
XRCC2 rs3218536			
AA	0	0	>0.05
GG	34	30	>0.05
AG	6	10	>0.05

Table 8. Distribution of ERCC2 rs13181 and XRCC2 rs3218536 genotypes and allele frequencies in prostate cancer patients and controls

ERCC2 rs13181	*Prostate cancer (n)*	*Control (n)*	*p value*
TT	6	21	<0.001
GG	14	0	<0.001
GT	20	19	>0.05
XRCC2 rs3218536			
AA	0	0	>0.05
GG	36	30	>0.05
AG	4	10	>0.05

Results

In the present study we investigated the frequency of two SNPs in two different DNA repair genes in 40 colon, 40 gastric, 40 HCC, 40 lung, and 40 prostate cancer patients and a control group of 40 healthy individuals. Frequencies of the *ERCC2* rs13181 and *XRCC2* rs3218536 variants in the patient and control groups are summarized in Table 1. Each cancer group in the study was compared with the control group. There are three *ERCC2* rs13181 variants: GG, GT, and TT. Statistically significant differences in TT,GG and GT were detected between the colon cancer and control group ($p<0.05$) and between the prostate cancer and control group ($p<0.05$), The three variants of the *XRCC2* gene are AA, AG, and GG. There was a statistically significant difference between the gastric cancer and control group in terms of GG.AG ($p<0.05$). The colon, HCC, prostate, and lung cancer groups showed no significant differences in terms of the AA, AG, GG variants of *XRCC2* rs3218536 polymorphism compared to the control group ($p>0.05$) (Tables 4, 5, 6, 7, and 8). Analysis of *ERCC2* rs13181 SNP variants in all cancer groups revealed that the frequency of the TT variant was significantly higher in the gastric,HCC cancer. The frequency of the GG variant was significantly higher in the colon ,prostate,cancer group, while this variant was not detected in the gastric,HCC and lung cancer groups. In addition, the frequency of the GT variant was higher in the lung and prostate cancer groups compared to the colon and gastric cancer groups.

Discussion

In the present study, we evaluated the relationship between polymorphisms in the DNA repair genes *ERCC2* and *XRCC2* and colon, HCC, prostate, gastric, and lung cancers. Our findings demonstrate associations between *ERCC2* and *XRCC2* polymorphisms and colon, HCC, prostate, gastric, and lung cancers in the Turkish population.

Identifying cancer risk markers is difficult. Oncogenes, tumor suppressor genes, and DNA repair genes play very important roles in the cancer induction process. [14,15].

Statistically significant association was areported of the single nucleotide polymorphism (SNP) rs13181 (*ERCC2*) with predisposition to squamous cell carcinomas of the Head and Neck (SCCHN) and breast cancer in the north Indian population [15].

DNA must remain stable to perform its critical physiological functions. However, it is known that DNA is vulnerable to various endogenous and/or exogenous damage that can result in mutations, and that damaged DNA can be carcinogenic. DNA repair genes correct this damage and restore gene function. The other function of DNA repair genes is to eliminate the cell via apoptotic or necrotic pathways if repair has not occurred. However, losses of function in this important gene group results in the cell becoming cancerous [15].

Research is ongoing into whether the genetic polymorphisms observed in many populations contribute to the induction and/or progression of cancer. SNPs of DNA repair genes have been identified [5] and associated with sporadic carcinogenesis [6,7].

The *ERCC2* protein, which has both single-strand DNA-dependent ATPase and 5'-3' DNA helicase activity, was found to interact with most of the components of the nucleotide excision repair (NER) short patch pathway and participate in the coordination of the NER pathway required for the excision of bulky DNA lesions. It adds DNA, thereby contributing to cellular defense against various structurally unrelated DNA lesions [16,17]. In general, genetic polymorphisms and mutations in *ERCC2* can lead to faulty NER signal and reduced DNA repair capacity by affecting activity of the corresponding protein, and may thereby modulate cancer susceptibility [18]. It was recently determined that the Gln allele of ERC22 Lys751Gln (rs13181) polymorphism is associated with higher DNA adduct levels and lower DNA repair activity [16,19]. Moreover, a series of epidemiological studies have shown that the ERC22 Lys751Gln (rs13181) polymorphism plays a critical role in the susceptibility to various types of cancer [7].

In the literature search performed for our study, we found an article by Ming Yin et al [16] entitled "*ERCC1* and *ERCC2* polymorphisms predict clinical outcomes of oxaliplatin-based chemotherapies in gastric and colorectal cancer: A systemic review and meta-analysis", in which significant differences in *ERCC1* rs11615C>T and *ERCC2* rs13181T>G SNPs were reported in gastric and colorectal cancer patients in the group under combination therapy with oxaliplatin and fluoropyrimidine [16].

A study by Li et al [20] on the cancer survival in gastric cancer patients with *ERCC1* and *ERCC2* variants showed that the functional SNP variants of *ERCC1* and *ERCC2* affected the clinical outcomes of gastric cancer patients receiving chemotherapy.

In a study including 74 patients with gastric cancer, Shokrzadeh et al [21] reported a significant difference in the prevalence of the *ERCC2* rs13181 (G>T) genotype in patients with gastric cancer and concluded that TT allele frequency was important in terms of cancer risk. Liu et al [18] investigated the association between *ERCC2* polymorphisms and prostate cancer in Asian population and found that *ERCC2* rs13181 variants were not associated with risk of prostate cancer. Agalliu et al [22] were unable to detect any association between prostate cancer and *PEX1, BRCA2, ERCC2, ERCC4, MGMT, MUTYH, OGG1, XPC,* or *XRCC1* SNPs in US population.

Few studies have investigated the association between *ERCC2* SNP rs13181 and HCC. Wang et al [23] reported no significant correlation between *ERCC2* rs13181 variants and HCC risk.

We found numerous studies on the *ERCC2* rs13191 Lys751Gln polymorphism in the literature. Analysis of lung cancer case-control studies revealed that the *ERCC2* Lys751Gln gene polymorphism was found to be a significant risk factor for lung cancer in only one or two studies but was not significant in the others. Of the latter studies, Benhamou et al [24] could not detect a clear association between *ERCC2* Lys751Gln gene polymorphisms and lung cancer. In another comprehensive study, Spitz et al [25] observed no significant difference between the lung cancer group and controls in terms of *ERCC2* Lys751Gln. Studies performed in various ethnic groups demonstrated no statistically significant association between lung cancer and *ERCC2* Lys751Gln gene polymorphisms.

In contrast, Lys751Gln and Asp312Asn gene polymorphisms of XPD were associated with lung cancer in a 22-case-control study by Zhan et al [26]. Among the Caucasian population and smokers, the Lys751Gln allele of XPD increases the risk of disease development.

In the present study we evaluated the association between two polymorphisms in two DNA repair genes, *ERCC2* rs13181 Lys751Gln and *XRCC2* Arg188His rs3218536 polymorphism, and colon, HCC, prostate, gastric, and lung cancer. There are 3 *ERCC2* rs13181 variants: GG, GT and TT. Statistically significant differences in TT, GG and GT were detected between colon cancer and control group ($p<0.05$) and between prostate cancer and control group ($p<0.05$). Statistically significant differences in TT and GT were detected between gastric cancer and control group ($p<0.05$).

RAD51 is a RecA homologue and contains 339 amino acids. The *RAD51* gene is found on 15q15.1 in humans and is very polymorphic. *RAD51* has 5 paralogues: *RAD51B, RAD51C, RAD51D, XRCC2,* and *XRCC3*, which are all defined in the human genome [27].

XRCC2 is involved in the homologous recombination repair (HRR) pathway of double-stranded DNA, which repairs chromosomal fragmentation, deletions, and translocations [7 9]. In total, ~622 SNPs have been described in *XRCC2*, including rs3218536 (Arg188His), rs718282, rs3218384, rs3218550, rs3218408, rs2040639, and rs3218499 [13,27].

Associations between the rs3218536 (Arg188His) SNP in the *XRCC2* gene and cancer susceptibility has been investigated extensively. According to the results of a meta-analysis [28] including 30,868 cases and 38,656 controls, the *XRCC2* Arg188His polymorphism may contribute to increased risk of breast cancer and aerodigestive tract cancers.

When we analyzed previous studies on *XRCC2* Arg188His rs3218536 polymorphism and colon, gastric, HCC, lung, and prostate cancer groups, we found that Krupa et al in his study found a significant relationship between colon cancer and *XRCC2* Argis 88His rs3218536 polymorphism [29].

Curtin et al [30] reported an association between *XRCC2* and colorectal cancer in their meta-analysis of UK and US studies, while Cetinkunar et al [31] investigated *RAD51* and *XRCC2* gene polymorphisms in 71 colorectal cancer patients and 86 healthy controls in Turkish population using the PCR-RFLP technique. Their results also indicated that *RAD51* and *XRCC2* gene polymorphisms may be associated with colon cancer incidence in this population. Xu et al [32] showed that the *XRCC2* rs3218536 polymorphism reduced disease susceptibility in colon cancer cell cultures. Moreno et al [33] conducted SNP analysis of 15 DNA repair genes in 377 colon cancer patients and 329 healthy controls and reported no significant difference in the *XRCC2* Arg188His rs3218536 SNP between the groups. According to the results of a meta-analysis by Eskandari et al [34], *XRCC2* rs3218536 A/G was not associated with risk of colon cancer.

Gok et al [35] demonstrated significant differences in polymorphism frequency between cancer patients and the healthy control group, and concluded that the polymorphisms increased gastric cancer risk.

There are very few studies in the literature on the association between *XRCC2* (rs3218536) and prostate cancer risk. They mostly focus on mRNA-miRNA expression studies. Nowacka-Zawisza et al [36] analyzed *RAD51* (rs1801320), *XRCC2* (rs3218536), *RAD51B* (rs10483813and rs3784099), and *XRCC3* (rs861539) polymorphisms in 101 patients with prostate adenocarcinoma and 216 control patients using PCR-RFLP and Real-time PCR analysis and reported no significant correlation between *XRCC2* (rs3218536) and increased prostate cancer risk.

Previous studies on *XRCC2* (rs3218536) and HCC risk are also very limited, and focus mostly on expression studies [37].

Hung et al [38] compiled the results of 14 studies with 2,073–13,955 for 18 sequence variants of a total of 12 DNA repair genes, including *XRCC2* (rs3218536) *APEX1, OGG1, XRCC1, XRCC2, XRCC3, ERCC1, XPD, XPF, XPG, XPA, MGMT,* and *TP53.* They reported no significant association between lung cancer and *XRCC2* (rs3218536) variants. Zienolddiny et al [39] investigated the role of *XRCC2* (Arg188His) polymorphism in small cell lung carcinoma. When compared with controls having the Arg188Arg genotype, there was a 3-fold higher risk of lung cancer among heterozygous *XRCC2* Arg188His carriers, as well as the combined heterozygote and homozygote groups. In the present study, a statistically significant difference was detected between the gastric cancer group and control group in terms of the *XRCC2* Arg188His rs3218536 GG variant.

Conclusion

The *ERCC2* Lys751Gln and *XRCC2* Arg188His polymorphisms may have different roles in the carcinogenesis of various types of cancer. More comprehensive future studies are needed in order to determine whether there is a direct association between the polymorphisms found to be significant in our study and susceptibility to colon, prostate and gastric cancers. Our study adds to the literature on this topic and may provide direction for further research.

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Conflict of interests

The authors declare no conflict of interests.

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