Distribution of nucleotide variants in the DNA sequence of ERCC1 and XRCC1 genes and the effect of phenotype in patients with gastric cancer

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ABSTRACT

Background/Aims: *Gastric cancers vary across countries and ethnic groups. They are the second most common type of cancer worldwide. Dietary and non-dietary factors as well as genetic and epigenetic alterations of many mechanisms are implicated in the development of gastric cancer. We aimed to determine the sequence of possible nucleotide changes, polymorphisms, and mutations, and to establish genotype and phenotype relation by performing whole DNA sequence analysis of the XRCC1 and ERCC1 genes belonging to base excision repair (BER) and nucleotide excision repair (NER) family of DNA repair genes in patients with gastric cancer.*

Materials and Methods: *We included 50 patients of both sexes who had received diagnosis of gastric cancer and 50 healthy people who showed same demographic traits that forms the control group. We analyzed the ERCC1 and XRCC1 genes by DNA sequence analysis on both groups. After the analysis, we compared the genotype-phenotype relation.*

Results: *Neither patients nor the control group has any nucleotide replacement in any exon of ERCC1 genes. We could not detect significant difference between patients and healthy groups when we correlated genotype contribution of mutations Arg194Trp, Arg208His, Arg399Gln detected in the XRCC1 gene and allele frequency.*

Conclusion: *According to our study, the ERCC1 gene in Turkish population is not getting mutation in patients with gastric cancer and healthy individuals. Three mutations were detected in the XRCC1 gene, and these mutations were not associated with gastric cancer.*

Keywords: *Gastric cancer, DNA repair genes, mutation*

INTRODUCTION

The DNA repair system plays a vital role in maintaining the stability of cellular functions and genetic integrity through the reversal of damaged DNA caused by various endogenous and/or exogenous factors, including therapeutic agents (1). Prokaryotic and eukaryotic organisms have various DNA repair mechanisms to protect their DNA. Different DNA repair pathways repair DNA damages in mammalian cells (2). During excision, the chemically altered, incorrectly matched, or unfavorable (such as uracil in DNA) bases are cut from the genomes and placed on the array bases toward their locations (3). Excision repair is divided into two families: base excision repair (BER) and nucleotide excision repair (NER). During the BER mechanism, the damaged bases are cleaved and removed as free base, and the damaged bases are cleaved as oligonucleotide fragments in the NER.XRCC1 (X-ray repair cross-complementing group1) is located on the long arm of the 19th chromosome and encodes the protein consisting of 633 amino acids. The XRCC1 protein functions as a complex with many other components to facilitate BER and single chain break-repair processes. In XRCC1, nine different SNPs (single nucleotide polymorphisms) have been identified, and all affect the coding region of XRCC1 (4). These coding polymorphisms have been identified in codons 194 (Arg>Trp), 280 (Arg>His), and 399 (Arg> Gln) in different cancers, but the genotype-phenotype relationship is not correlated (5). The ERCC1 gene functions in the NER pathway. This gene is required for the repair of DNA lesions induced by UV light or electrophilic compounds including cisplatin, and mapped in the 19q13.32 region, the long (q) branch at position 13.32 of the 19.3 chromosome (6). Gastric cancer is the fourth most common cancer worldwide and is the second most common cause of death among cancers after lung cancer. There are approximately 989,600 new cases per year, and 738,000 of them result in deaths (7). Etiologically, many risk factors, which we can classify as dietary and non-dietary, are responsible for the formation of gastric cancers (8). Dietary factors include food containing high

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nitrate and NaCl. It is also known that among the non-dietary factors, *Helicobacter pylori*, which has recently been implicated in the formation of gastric cancer, as well as the changes in genetic and epigenetic mechanisms in the intracellular cycle and signal pathway system, has emerged (9). These can be oncogenes, tumor suppression genes, or DNA repair genes. Many studies emphasize that mutations in DNA repair genes from the BER and NER family are associated with development of gastric cancer. In addition, the relationship between decreased DNA repair capacity and susceptibility to many cancers such as breast, lung, skin, liver, head, and neck has also been shown in epidemiological studies (10).

This study aimed to investigate the phenotypic relationship of polymorphism or mutation of nucleotide substitutions determined by DNA sequence analysis of XRCC1 and ERCC1 genes belonging to BER and NER families of DNA repair genes in patients with gastric cancer.

MATERIALS AND METHODS

Patient groups

After the decision of Ege University School of Medicine Ethics Committee (Date: April 27, 2012; No:12-3.1/1), patients diagnosed with gastric cancer who applied to the General Surgery Clinic of Ege University School of Medicine were included. All patients and healthy individuals were included in the study after their consent forms were obtained and the details of study were told to them. Individuals of both sexes were included in the study. The lower and upper age limits were 30 years and 85 years, respectively. The control group consisted of 50 healthy male and female individuals in the same age group with no malignancy.

Study method

The phenotype findings (tumor size, tumor localization, tumor histopathological type, lymph node metastasis rate) and patient sexes in patients with gastric cancer were statistically compared with genotype distribution and allele frequency detected in the XRCC1 and ERCC1 genes. One tube peripheral venous blood was taken from both patients and healthy subjects. We numbered tubes and then delivered them to the laboratory in a complicated manner to apply blindness. DNA repair genes, XRCC1 and ERCC1 gene sequence results, were taken into the database in the Microsoft Excel program, and then statistics were made.

Method of molecular analysis of ERCC1 and XRCC1 genes

For molecular genetic analysis, 2 ml peripheral blood was taken from healthy subjects who constitute the control group and gastric CA into tube with EDTA. Synthetic oligonucleotide primers for exon 17 of the XRCC1 gene encoding protein were made according to the NCBI Reference Sequence (NT_011109.16) GenBank sequence. The 2087 bp mRNA (NM_006297) was read according to the NCBI sequence. How the read sequences are reflected in the protein structure is interpreted according to the protein sequence (NP_006288) consisting of 633 amino acids. Synthetic oligonucleotide primers for 10 exons of the ERCC1 gene were made according to the NCBI Reference Sequence: NT_011109.16 GenBank sequence. The 10977 bp mRNA (NM_202001) was read according to the NCBI sequence. How the read sequences are reflected in the protein structure is interpreted according to the protein sequence (NP_933730) consisting of 323 amino acids.

DNA sequencing method

PCR amplification

A total of 27 PCR reactions were performed for each gene in each individual: 25 µL PCR reaction mixture; 100 ng of genomic DNA, 2.5 µL of 10× PCR buffer solution (Invitrogen Enhancer Buffer) 2.5 mM MgCl 2, 200 mM each of four dNTPs (Promega, Madison.US), 5 pmol forward and reverse primers each, and 1.0 U Platinum Taq Polymerase. PCR amplification was done by applying gradient thermal cycler program in Veriti PCR device. DNA was run on ethidium bromide 2% agarose gel electrophoresis to confirm PCR amplification product. For DNA sequence analysis, positive PCR products were subjected to enzymatic PCR purification.

Purification of PCR products

The PCR products were checked in agarose gel electrophoresis, and positive PCR fragments were purified using Exo-SAP enzyme mixture (Amersham Life Science, UK).

DNA sequence analysis

Purified PCR products were obtained by using a BigDye Terminator and 3.1 (Applied Biosystems U.S.A) kit for a second PCR analysis (cycle-sequencing PCR) for fluorescent labeling of nucleotides prior to DNA sequencing. The second round of PCR products to be obtained after cycle-sequencing PCR was purified from residual fluorescent stain using BigDyeXT kit (Applied Biosystems U.S.A). The re-purified PCR products were loaded into the ABI 3130XL Genetic Analyzer automated DNA sequencing system, and the nucleotide sequences were read according to the sequences set forth above. Evaluation was performed with the SEQSCAPE 2.0 computer program.

Statistical analysis

Statistical analyses were performed using Statistical Package for Social Sciences version 16.0. The groups were suitable for HWE equality. Chi-square, Mann-Whitney, Kruskal-Wallis tests were used to define nucleotide changes of XRCC1 and ERCC1 genes, DNA repair genes, demographic information of patients, and phenotype findings (age, sex, tumor location, tumor histopathology, tumor size, lymph node metastasis).

RESULTS

Phenotypic characteristics of the patient group

A total of 50 patients were enrolled in the patients group. The distribution of male/females was 37/13. Age distribution was 41-84 years (mean age 63 years) for men and 33-83 years (mean age 57 years) for women. Since 35 of our patients were operable, all demographic parameters and phenotype-genotype findings were recorded. Since 15 patients could not be operated or rejected the operation, the phenotype-genotype findings could not be recorded for them. Tumor localization was found distally in 22 patients (44%), proximally in 6 patients (12%), and corpusly in 22 patients (44%). Histopathologic evaluation was performed on LAUREN classification (intestinal, diffuse, and mixed type) in all our patients. In this classification, 18 (36%) patients had diffuse type, 29 (58%) patients had intestinal type, and 3 (6%) patients had mixed type adenocarcinoma. Fifteen patients underwent distal gastric resection. A total of 2 patients received proximal gastrectomy, 18 patients received total gastrectomy, and 15 patients were inoperable or refused surgery. We based the tumor diameter to >4 cm and <4 cm in patients. Tumor diameter was less than 4 cm in 15 patients (30%) and greater than 4 cm in 20 patients (40%). The evaluation was made in 35 patients. Because the other 15 patients could not be operated, the tumor diameters could not be recorded for them. The number of lymph nodes removed in operations performed on 35 patients was at least 4 and 42 lymph nodes. We detected at least 0 and no more than 23 metastatic lymph nodes as metastases.

Molecular findings

XRCC1 gene findings

The nucleotide sequence of the 17 exons encoding the protein structure of the 633 amino acids of the XRCC1 gene was analyzed by DNA sequencing for each individual in the patient and control group. In the DNA sequence analysis, mutations known only in codon 194, 280, and 399, which are known in the literature, were detected from 17 exons. Mutations in other exons of the XRCC1 gene were not detected. All three mutations of the XRCC1 gene at codons 194, 280, and 399 were compared between patients with gastric cancer and the healthy control group; and the following results were obtained. A homozygous mutation (Trp194Trp) was detected in 1 patient (2%) in the patient group, normal (Arg194Arg) genotypes were detected in 39 patients, and heterozygote (Arg194Trp) mutation was detected in 10 patients (18%). Normal genotype (Arg280Arg) was detected in 42 patients (84%) in codon 280 and heterozygote mutation (Arg280His) in 6 patients (12%) and homozygous mutation (His280His) in 2 patients (4%). In 13 patients (26%), codon 399 had normal (Arg399Arg) genotype, homozygous (Arg399Arg) mutation was detected in 14 patients (28%), and heterozygous (Arg399Gln) mutation was detected in 23 patients (46%). No other nucleotide substitutions were detected in the other 14 exons of the XRCC1 gene.

In healthy group, the normal genotype (Arg194Arg) was detected in 46 healthy individuals (92%) in XRCC1 gene codon 194, heterozygote (Arg194Trp) mutation was detected in 4 individuals (8%), and no homozygote (Trp194Trp) mutation was detected in any healthy individuals (0%). In codon 280, 47 normal individuals (94%) showed normal genotype (Arg280Arg), 3 individuals (6%) heterozygous (Arg280His) mutation, and no healthy individuals had homozygote (His280His) mutation. Codon 399 showed normal genotype (Arg399Arg) in 16 healthy individuals (32%), heterozygote (Arg399Gln) mutation in 21 individuals (42%), and homozygote (Gln399Gln) mutation in 13 individuals (26%). Allele distribution of the XRCC1 gene in patients and control groups was not statistically significant in comparison between patient and control group in alleles ratios of codons 194, 280, and 399 (p=0.065, p=0.082, p=0.671, respectively) (Table 1).

Phenotype-related findings of the XRCC1 gene

There was no statistically significant difference between the sexes of the patients; and the genotypes of XRCC1 gene in codon 194, codon 280, and codon 399 (p=0.248, p=0.181, p=1.000, respectively). No significant difference was found in the comparison of genotypes at the XRCC1 gene codons 194, 280, and 399 with the tumor location at the side (p=0.725). As a result of our study, mutations in the XRCC1 gene codons 194, 280, and 399 are not associated with tumor localization. We did not find a significant difference between the tumor diameters of the genotypes included in the XRCC1 gene codons 194, 280, and 399 (p=1.000). According to our results, the tu-

Table 1. Distribution of alleles in XRCC1 gene codons 194, 280, and 399 in patient and healthy group.

	XRCC1 codon 194			Alleles		
	Arg/Arg	Arg/Trp	Trp/Trp	Arg	Trp	p
Patient	39 (%78)	10 (%20)	1 (%2)	88 (%88)	12 (%12)	0.065
Control	46 (%92)	4 (%8)	0 (%0)	96 (%96)	4 (%4)	
	XRCC1 gene codon 280			Alleles		
	Arg/Arg	Arg/His	His/His	Arg	His	p
Patient	42 (%84)	6 (%12)	2 (%4)	90 (%90)	10 (%10)	0.082
Control	47 (%94)	3 (%6)	0 (%0)	97 (%97)	3 (%3)	
	XRCC1 gene codon 399			Alleles		
	Arg/Arg	Arg/Gln	Gln/Gln	Arg	Gln	p
Patient	13 (%26)	23 (%46)	14 (%28)	49 (%49)	51 (%51)	0.671
Control	16 (%32)	21 (%42)	13 (%26)	53 (%53)	47 (%47)	

mor diameter was not related to mutations in the XRCC1 gene codons 194, 280, and 399. There was no significant difference in the genotypes of the XRCC1 gene at codons 194, 280, and 399 compared to the tumor histopathologic type at the side (p=0.725). According to our study, mutations in the XRCC1 gene codons 194, 280, and 399 were not associated with tumor histopathologic type. Genotypes of XRCC1 codons 194, 280, and 399 were not significantly different in comparison with lymph node metastasis (p=0.725). According to our study, mutations in the XRCC1 gene codons 194, 280, and 399 are not associated with lymph node metastasis.

ERCC1 gene findings

The nucleotide sequence of the 10 exons encoding the protein structure of the 323 amino acids of the ERCC1 gene was analyzed by DNA sequencing for each individual in the patient and control group. As a result of these analyses, no nucleotide substitutions were found in the ERCC1 gene construct.

DISCUSSION

Today, gastric carcinogenesis is considered a multi-factorial and multi-stage process, and a possible mechanism that contributes to the process is molecular changes. Numerous epidemiological studies suggest that genetic predisposition is associated with gastric carcinogenesis. DNA damage may be involved in early stages of environmental carcinogenesis (11). If most of these damages are not repaired, they can result in genetic instability and mutagenesis. DNA repair mechanisms play an important role in the pathogenesis and progression of gastric cancer, providing the integrity and stability of the genome (11-12). Various DNA repair mechanisms such as NER, BER, mismatch repair, and recombination repair mechanisms control DNA damage. ERCC1 and XRCC1 are the major genes involved in the restoration of DNA damage, encoding the key protein of the basic excision repair. In some types of cancer, mutations in these genes have been reported to trigger cancer (13-15).

The human XRCC1 gene is located on the long arm of the 19th chromosome. Its length is approximately 33 kb. It consists of 17 exons. The XRCC1 protein is 69.5 kDa and consists of 633 amino acids. Polymorphisms in codon 194 (allele frequency 13%), codon 280 (allele frequency 7%), and codon 399 (allele frequency 27%) are intensively studied due to their high allele frequency and functional significance (16-17). Amino acid modification of arginine-tryptophan (Arg194Trp) in codon 194, arginine-histidine (Arg280His) in codon 280, and arginine-glutamine (Arg399Gln) in codon 399 occur (18). Bo Chen and colleagues emphasized in 2012 that the XRCC1 gene mutations in the meta-analysis involving 18 studies in different races and countries, 3915 patients with gastric cancer and 6759 control groups were not associated with gastric cancer alone, and multiple factors together constituted carcinogenesis in cancer development. Another study indicated that mutations in the codon 280 of XRCC1 gene were not associated with gastric cancer (19). Dai et al. (20) emphasized that mutations in XRCC1 codon 194 increase risk of gastric cancer. Huang et al.

(21) reported that mutations in the XRCC1 gene are not associated with breast cancer. Wang et al. (22) found no association between XRCC1 gene mutations and bladder cancer. Dai et al. (20) reported that the XRCC1 codon 194Arg/Trp mutation was associated with esophageal squamous cell carcinoma. In a particular study, the XRCC1 gene codon 399Arg/Gln mutation was found to be at risk for esophageal cancer (22). Shen et al. (23) investigated the risk of gastric cancer in Arg/Trp and Trp/Trp mutations at codon 194 of the XRCC1 gene in a study involving 503 patients and 503 control groups in China in 2009. In the study, the ratio of Arg allele was 609 (60.5%) in the patient group and 717 (71.3%) in the control group, and 397 (39.5%) in the patient group and 289 (28.7%) in the control group. There was no difference between the groups in the comparison of patients and control groups according to both allele distributions in the study (23).

The Arg/Trp and Trp/Trp polymorphisms of codon 194 of the XRCC1 gene were also found to be significant in gastric cancer studies. However, the same studies have emphasized that the Arg/Gln and Gln/Gln mutations of the codon 399 of the XRCC1 gene are not related to the risk of gastric cancer (23,24). Capella and colleagues in Europe in 2008 compared 245 patients with gastric cancer and 1175 control groups. In the study, mutations in codons 194 and 399 of the XRCC1 gene were investigated for gastric cancer. The ratio of Arg allele in codon 194 was 468 (98%) in the patient group and 2204 (93.7%) in the control group. Trp allele ratio was 22 (2%) in the patient group and 146 (8.3%) in the control group. A statistically significant difference was found between the patient and control group according to the distribution of both alleles (24).

Ratnasinghe et al. (22) in 2004 investigated the association of mutations in the codons 194 and 399 of the XRCC1 gene with gastric cancers. They included 86 patients with gastric cancer and 429 control groups. The ratio of Arg allele in codon 194 of the XRCC1 gene was 124 (72%) in the patient group and 628 (73%) in the control group; and Trp allele ratio was 48 (28%) in the patient group and 230 (27%) in the control group. There was a statistically significant difference between the patient and healthy groups compared to the distribution of both alleles (p=0.002). In the same study, the total Arg allele distribution in the codon 399 was found 132 (76.7%) in the patient group and 577 (62%) in the control group; and Gln allele ratio was 40 (23.7%) in the patient group and 259 (38%) in the control group (p=0.10). In this study, although the allele ratios of the XRCC1 gene in the 194th codon were related to the risk of gastric cancer, codon 399 mutations were found to be unrelated to gastric cancer risk (22).

Ye et al. (25) in 2006 investigated the gastric cancer association of the XRCC1 gene with codon 399 mutations in Sweden, which included 126 gastric cancer cases and 472 healthy control groups. In codon 399, the total ratio of Arg allele was 161 (63.8%) in the patient group and 602 (63.7%) in the control group. The Gln allele ratio was 91 (36.2%) in the patient group and 342 (36.3%) in the control group. There was a statistically significant difference between the patient and control group according to the ratio of both alleles (p=0.01). Mutations of Arg/Gln and Gln/Gln present in codon 399 of the XRCC1 gene according to Ye et al. (25) increase gastric cancer risk.

In our study, we also aimed to investigate the genotype and phenotype association of ERCC1 and XRCC1 genes in gastric cancer. We took 50 healthy individuals and 50 individuals diagnosed with gastric cancer. The sequence analysis of the ERCC1 and XRCC1 genes in both groups was performed on all gene exons in the genome and compared with the gastric cancer phenotype. In our study, we included 50 patients with gastric cancer and 50 control groups whose 10 exons of ERCC1 gene analyzed by DNA sequencing methods. We found no mutations in this gene and found that the ERCC1 gene was not associated with gastric cancer risk in the individuals in our study group.

Studies that emphasize that mutations in XRCC1 gene codon 194 are associated with gastric cancer risk, although our results are incompatible, are similar to many published studies. In our study, we did not find any significant difference in the genotype and allele distributions of the XRCC1 gene at codons 194, 280, and 399 with respect to sex, age, tumor localization, tumor size, histopathological type, and lymph node metastasis rate. We think that the XRCC1 gene is not related to these phenotypes. In our study, there was no significant difference in the correlation between the histopathological subtypes of gastric cancer (Lauren, diffuse type, intestinal type, and mixed type) XRCC1 mutations (codon 194 (p=0.109), codon 280 (p=0.391), and codon 399 (p=0.251)).

As the number of patients participating in the study is few, more extensive studies are needed to determine the relationship between gastric cancer and DNA repair genes.

This study aimed to determine the present mutations by DNA sequence analysis of entire XRCC1 and ERCC1

genes known as DNA repair genes in patients with gastric cancer and healthy control group individuals and to reveal the relationship between gastric cancer and genetic correlation between these two groups.

The XRCC1 gene exon 17 in all patients in the 50 patient group and 50 healthy control groups were examined by DNA sequencing analysis. In patients with gastric cancer and healthy controls, mutations known in the literature were detected in the XRCC1 gene codons 194, 280, and 399. (Arg/Arg normal genotype, Arg/Trp heterozygote mutation, Trp/Trp homozygous mutation in codon 194. Arg/Arg normal genotype, Arg/His heterozygote mutation, and His/His homozygous mutation at codon 280.) Codon 399 has Arg/Arg normal genotype, Arg/Gln heterozygous mutation, and Gln/Gln homozygous mutation.) No other mutations were detected in these three codons.

We did not find any statistically significant difference between these groups in terms of genetic correlations between the patient and control group according to allelic rates in the codons and the risk of gastric cancer. We did not find a statistically significant difference between the genotypes in the XRCC1 gene and the patient's sex, tumor size, tumor site, tumor histopathologic types and lymph node metastasis rates to reveal genotype-phenotype relation. Mutations in the XRCC1 gene were not associated with sex or gastric cancer phenotypic findings.

All of the 10 exon of ERCC1 genes in 50 patients and 50 healthy control subjects were examined by DNA gene sequencing. No mutations were detected in any exons of this gene in patients with gastric cancer and healthy subjects.

According to our study, the ERCC1 gene in Turkish population is not getting mutated in patients with gastric cancer and healthy individuals. Three mutations were detected in the XRCC1 gene, and these mutations were not associated with gastric cancer.

Ethics Committee Approval: Ethics committee approval was received for this study from the Ege University School of Medicine Ethics Committee (Date: April 27, 2012; No: 12-3.1/1).

Informed Consent: Written informed consent was obtained from patients who participated in this study.

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REFERENCES

1. Sancar, A. Mechanisms of DNA excision repair. Science 1994; 266: 1954-6. ***[CrossRef]***

2. Lindahl T, Karran P, Wood RD. DNA excision repair pathway. Curr Opin Genet Dev 1997; 7: 158-69. ***[CrossRef]***

3. Balajee AS, Bohr VA. Genomic heterogeneity of nucleotide excision repair. Gene 2000; 250: 15-30. ***[CrossRef]***

4. Hoeijmakers JH. Genome maintenance mechanisms for preventing cancer. Nature 2001; 411: 366-74. ***[CrossRef]***

5. Butkiewicz D, Rusin M, Enewold L, Shields PG, Chorazy M, Harris CC. Genetic polymorphisms in DNA repair genes and risk of lung cancer. Carcinogenesis 2001; 22: 593-7. ***[CrossRef]***

6. Olaussen KA, Mountzios G, Soria JC. ERCC1 as a risk stratifier in platinum-based chemotherapy for nonsmall-cell lung cancer. Curr Opin Pulm Med 2007; 13: 284-9. ***[CrossRef]***

7. Rugge M, Fassan M, Graham D. Epidemiology of Gastric Cancer. Strong VE, editor. Gastric Cancer. Switzerland: Springer Cham; 2015.p.23-34. ***[CrossRef]***

8. Correa P, Schneider BG. Etiology of gastric cancer: what is new? Cancer Epidemiol Biomarkers Prev 2005; 14: 1865-68. ***[CrossRef]***

9. Tsugane S, Sasazuki S. Diet and the risk of gastric cancer: review of epidemiological evidence. Gastric Cancer 2007; 10: 75-83. ***[CrossRef]***

10. Zabaleta J. Multifactorial etiology of gastric cancer methods. Mol Biol 2012; 863: 411-35. ***[CrossRef]***

11. Nagini S. Carcinoma of the stomach: A review of epidemiology, pathogenesis, molecular genetics and chemoprevention. World J Gastrointest Oncol 2012; 15: 4: 156-69. ***[CrossRef]***

12. Boer J, Hoeijmakers JH. Nucleotide excision repair and human syndromes. Carcinogenesis 2000; 21: 453-60. ***[CrossRef]***

13. Xu Z1, Hua LX, Qian LX, et al. Relationship between XRCC1 polymorphisms and susceptibility to prostate canser in men from Han, Soutern China. Asian J Androl 2007; 9: 331-8. ***[CrossRef]***

14. Torgovnick A, Schumacher B. DNA repair mechanisms in cancer development and therapy. Front Genet 2015; 6: 157. ***[CrossRef]***

15. Wang B, Wang D, Huang G, Zhang C, Xu DH, Zhou W. XRCC1 polymorphisms and risk of colorectal cancer: a meta-analysis. Int J Colorectal Dis 2010; 25: 313-21. ***[CrossRef]***

16. Goode EL, Ulrich CM, Potter JD. Polymorphisms in DNA repair genes and associations with cancer risk 2002; 11: 1513-30.

17. Huang J, FE Y, Chen H, Lu W, Xie X. The nonsynontmous single nucleotide polymorphisms of DNA repair gene XRCC1 and susceptibility to the development of cervical carcinoma and high-risk human papillomavirüs infection. Int J Gynecol Cancer 2007; 17: 668-75. ***[CrossRef]***

18. Duell EJ, Millikan RC, Pittman GS. Polymorphisms in the DNA repair gene XRCC1 and breast cancer. Cancer Epidemiol Biomarkers Prev 2001; 10: 217-22.

19. Xue H, Ni P, Lin B, Xu H, Huang G. X-ray repair cross-complementing group 1 (XRCC1) genetic polymorphisms and gastric cancer

risk: A HuGE review and meta-analysis. Am J Epidemiol, 2011; 173: 363-75. **[CrossRef]**
20. Dai L, Wang K, Zhang J, Lv Q, Wu X, Wang Y. XRCC1 gene polymorphisms and esophageal squamous cell carcinoma risk in Chinese population: A meta-analysis of case-control studies. Int J Cancer 2009; 125: 1102-9. **[CrossRef]**
21. Huang Y, Li L, Yu L. XRCC1 Arg399Gln, Arg194Trp and Arg280His polymorphisms in breast cancer risk: a meta-analysis. Mutagenesis 2009; 24: 331-9. **[CrossRef]**
22. Ratnasinghe LD, Abnet C, Qiao YL. Polymorphisms of XRCC1 and risk of esophageal and gastric cardia cancer. Cancer Lett 2004; 216: 157-64. **[CrossRef]**
23. Shen X, Zhang J, Yan Y, Yang Y, Fu G, Pu Y. Analysis and estimates of the attributable risk for environmental and genetic risk factors in gastric cancer in a Chinese population. J Toxicol Environ Health A 2009; 72: 759-66. **[CrossRef]**
24. Capellá G, Pera G, Sala N. DNA repair polymorphisms and the risk of stomach adenocarcinoma and severe chronic gastritis in the EPIC-EURGAST study. Int J Epidemiol 2008; 37: 1316-25. **[CrossRef]**
25. Ye W, Kumar R, Bacova G, Lagergren J, Hemminki K, Nyrén O. The XPD 751Gln allele is associated with an increased risk for esophageal adenocarcinoma: a population-based case-control study in Sweden. Carcinogenesis 2006; 27: 1835-41. **[CrossRef]**