

# The Association Between C194T and G399A Polymorphism of XRCC1 Gene and Susceptibility to Gastric Cancer in Population from Western Iran



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## ABSTRACT

**Background:** Gastric cancer is one of the most common malignancies in the world. It may result from a defect in the genes involved in DNA repair. One of the essential genes in the repair pathway is the XRCC1 gene that its polymorphisms in the human population play a role in gastric cancer susceptibility. The main purpose of this study was to investigate the association of 194C/T and 399G/A polymorphisms of the XRCC1 gene with gastric cancer in an Iranian population.

**Materials and Methods:** A total of 66 patients with gastric cancer and 67 control individuals were enrolled in our study. Following DNA extraction from blood samples, polymorphisms were analyzed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay.

**Results:** The allele frequencies of C/T of XRCC1-194C/T in the control and patients groups were 83.17% and 71.29%, respectively. Moreover, The allele frequencies of G/A of XRCC1-399G/A in control and patient groups were 66.34% and 62.38%, respectively. Our results indicated a significant positive association between the distribution T/C alleles and the risk of gastric cancer ( $\chi^2$ : 5.37 and  $P=0.02$ ), but no significant association was found in the distribution G/A alleles ( $\chi^2$ : 0.47 and  $P=0.48$ ).

**Conclusion:** Altogether, these findings indicate a positive association between the distribution of 194T/C alleles of XRCC1 and the risk of gastric cancer and the presence of the C allele may increase the risk of gastric cancer.

## Introduction

Gastric cancer is one of the causes of death worldwide [1]. Despite the decreasing incidence of this cancer in the world, it is still the second leading cause of cancer deaths in the world.

It is also the most common epithelial neoplasia with a multi-agent process [2]. There is a significant difference in the incidence of gastric cancer in various populations in the world. The difference in population genetic background and different lifestyles, especially eating habits such as consumption of salt and fast foods, are the main reasons for the prevalence of gastric cancer in differ-

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ent populations. One of the essential genetic factors is mutations and polymorphisms in oncogenes, tumor suppressor genes, genes involved in cell death, and genes involved in DNA repair [3-8].

DNA repair systems play a major role in the protection of the genome from carcinogenic agents, and the polymorphisms of DNA repair genes can affect DNA repair capacity in healthy individuals [9]. Single-Nucleotide Polymorphisms (SNP), which are the genetic variation that determines the phenotypic variation among individuals, are among the factors influencing cancer and various diseases [10, 11]. SNPs can be used as potential markers for determining the prognosis of cancer. Therefore, early detection of populations with high-risk of cancer by identifying cancer-related SNPs can be an effective strategy for reducing the number of people affected and even treating gastric cancer [12]. It has been shown that SNPs of the *XRCC1* gene, x-ray repair cross-complementing protein [1], are associated with thyroid [13], breast [14], esophagus [15], colorectal [16], prostate [2, 17], and stomach [18] cancers. The *XRCC1* gene with [17] exons and [16] introns, with a size of 39 kbp, is located in the chromosome position of 19q13.2-13.3 and encodes a 70-kDa protein with 633 amino acids [19]. It has been shown that the *XRCC1* protein plays a part in DNA repair mechanisms such as Base Excision Repair (BER) and Single-Strand Break Repair (SSBR) [20-22].

Among 300 single-nucleotide polymorphisms discovered in the *XRCC1* gene, Arg399Gln (in exon 10) and Arg194Trp (in exon 6) are the most important ones associated with cancer. There are different results for the association between these polymorphisms and the risk of cancer, regardless of the type of cancer. Although some studies have shown an association between *XRCC1* SNPs and susceptibility to gastric cancer, others have not found such a relationship. The main purpose of this study was to investigate the association of 194 and 399 polymorphisms in *XRCC1* with susceptibility to gastric cancer in an Iranian population. Gene polymorphisms of *XRCC1* may influence DNA repair capacity and thereby contribute to the susceptibility to cancer in humans [23].

## Materials and Methods

This case-control study was conducted on 66 patients with gastric cancer. The diagnosis of gastric cancer was based on the findings of the pathological and endoscopic examination. Patients with different types of gastric cancer were diagnosed and studied. Patients' clinical and pathological characteristics and stage of disease were recorded in a checklist (Table 1). The control group in-

cluded 67 healthy individuals with no clinical cancer and the same age, sex, and geographic location with the case group. All stages of the study were performed with the consent of the participants in the study and all participants were from the Kurdish population from Western Iran.

## DNA extraction

For DNA extraction, blood samples (2 mL) were taken from people with gastric cancer who referred to Taleghani Hospital in Bistoon or Kermanshah and Sanandaj Chemotherapy centers during 2015-2017. Genomic DNA was extracted from the blood using a commercially available kit (Zagros Bioidea Co., Iran). Concentration and DNA purity was measured using UV spectroscopy (NanoDrop, Thermo) and the integrity of extracted DNA samples was analyzed by 1% agarose gel electrophoresis.

## Genotyping

*XRCC1-194C/T* and *-399G/A* polymorphisms were investigated by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay. Primers used for the amplification of 491 and 614 loci were selected from the published papers [24, 25], and their sequences are listed in Table 2. PCR amplifications were carried out in 25  $\mu$ L reaction mixture containing 1 $\times$  PCR buffer, 100–500 ng of genomic DNA, three mM MgCl<sub>2</sub>, 100  $\mu$ M dNTP, two  $\mu$ M of each primer, and 1 U Taq DNA polymerase. Thermocycler conditions were listed in Table 3. About 10  $\mu$ L of PCR products were digested with MspI restriction enzyme for 15 h at 37°C. The PCR-RFLP products were separated by 3% agarose gel electrophoresis and the type of polymorphism was determined.

## Statistical analysis

The Chi-square test was used to assess the significance of the differences in genotype frequencies between the studied groups. The possible significant association of polymorphisms with periodontitis was statistically analyzed in SPSS v. 16 at  $P < 0.05$ .

## Results

Based on pathological records of 66 patients with gastric cancer, adenocarcinoma with 92.42% was the most common type of gastric cancer among patients. In terms of anatomical position, the cardiac region of the stomach (45%) was the most common position of the tumor, and the trunk and antrum were the second and third sites with 30% and 25%, respectively. A total of 133 people were

Table 1. Medical information of patients

Number	Age (y)	Sex	Pathology	Tumor Site	Family History	Tumor size (cm)	No.	Age (y)	Sex	Pathology	Tumor Site	Family History	Tumor Size (cm)
1	65	F	L - A	Antrum	-	2	34	40	M	A	Antrum	-	3.5
2	56	M	L - A	Cardia	-	3.5	35	45	M	A	Cardia	-	2
3	69	M	L - A	Antrum	-	4	36	65	M	A	Trunk	-	1.2
4	65	M	A	Cardia	-	2	37	66	M	A	Antrum	-	-
5	44	M	A	Trunk	-	4.8	38	38	F	A	Trunk	-	3.5
6	59	M	L - A	Cardia	+	2	39	45	M	A	Trunk	+	4
7	65	F	A	Antrum	-	2	40	42	M	A	Cardia	-	2
8	61	F	A	Cardia	-	1.2	41	44	M	A	Cardia	-	3.5
9	46	M	-	Antrum	-	-	42	46	F	A	Trunk	-	2
10	28	M	L - A	Cardia	-	3.5	43	72	M	A	Trunk	-	3.5
11	36	M	A	Trunk	-	4	44	69	M	A	Antrum	-	3.5
12	45	M	-	Trunk	-	2	45	71	M	A	Cardia	-	4
13	36	F	A	Antrum	-	3.5	46	69	M	A	Trunk	-	2
14	57	F	A	Cardia	-	2	47	64	F	A	Cardia	-	2
15	62	M	A	Cardia	-	3.5	48	42	F	A	Cardia	-	1.2
16	65	M	A	Antrum	-	3.5	49	68	M	A	Cardia	+	-
17	72	F	A	Cardia	-	4	50	40	F	A	Antrum	-	3.5
18	62	M	A	Trunk	-	2	51	75	M	A	Cardia	-	4
19	37	F	A	Trunk	+	3.5	52	67	M	A	Cardia	-	2
20	50	F	A	Antrum	-	2	53	70	M	A	Trunk	-	3.5
21	69	F	L	-	-	3.5	54	58	M	A	Trunk	-	2
22	69	M	A	Cardia	-	2	55	66	M	A	Trunk	-	3.5
23	50	F	A	Trunk	-	1.2	56	39	M	A	Cardia	-	3.5
24	55	M	L	Trunk	-	-	57	72	M	A	Antrum	-	4
25	50	M	-	Cardia	-	3.5	58	56	M	A	Cardia	-	2
26	49	M	A	Antrum	-	4	59	70	M	A	Antrum	+	3.5
27	45	M	A	Cardia	-	2	60	65	M	A	Cardia	-	2
28	48	M	A	Cardia	-	3.5	61	65	M	A	Cardia	-	3.5
29	55	M	A	Trunk	-	2	62	64	M	A	Trunk	-	3.5
30	57	F	A	Cardia	-	3.5	63	61	F	A	Trunk	-	4
31	39	F	A	Antrum	+	3.5	64	59	F	A	Trunk	-	4
32	42	M	A	Cardia	-	4	65	78	M	A	Cardia	-	2
33	43	M	A	Cardia	-	2	66	57	M	A	Cardia	+	3.5

F: Female; M: Male; L: Lymph; A: Adenocarcinoma

**Table 2.** The selected primers for polymorphism investigation in 194 and 399 loci of the *XRCC1* gene

Locus	Primer Name	Primer Sequence	Primer Annealing Temperature	Restriction Enzyme	Fragment Lengths of RFLP
XRCC1 - 194	X194-F	5'-GCCCCGTCAGGTA-3'	60	MspI	TT: 178+313 bp
	X194-R	5'-AGCCCCAAGACCTTCACT-3'			CC: 178+293+20 bp
XRCC1- 399	X399-F	5'-TTGTGCTTCTCTGTGTCCA-3'	60	MspI	AA: 614 bp
	X399-R	5'-TCCTCCAGCCTTTTCTGATA-3'			GG: 376+238 bp

**Table 3.** The PCR thermal cycling parameters and conditions for 194 and 399 loci amplification of the *XRCC1* gene

PCR Steps	194 T/C Locus			399 A/G Locus		
	Temperature (°C)	Time	Cycle	Temperature (°C)	Time	Cycle
Initial denaturation	94	5 min	1	94	5 min	1
Denaturation	94	45 s	35	94	50 sec	35
Primer annealing	60	45 s	35	52	50 sec	35
Extension	72	60 s	35	72	45 sec	35
Final extension	72	60 s	1	72	60 sec	1



studied in this study, of which 66 patients with an average age of 54.18 years had gastric cancer. Of these, 47 (71.21%) were men, and 19 (28.78%) were women. A total of 67 individuals with an average age of 52.12 were healthy individuals who were considered as controls. In the control group, 46 (69%) were men and 21 (31%) were women (Table 1).

Genomic DNA was extracted from all samples, and genotypes of individuals were determined by PCR-RFLP method. After determining the polymorphism of the control and patient groups, the genotype distribution of all three genotypes between the two groups was compared for two polymorphisms.

Following enzyme digestion of the 194 loci by the MspI enzyme, three forms were observed: TT homozygotes without polymorphism having two bands of 178 and 313 bp, CT heterozygotes with polymorphisms in one of the two DNA sequences with four bands of 313, 293, 178, 20 bp and CC homozygotes containing polymorphisms in both DNA sequences with three bands of 178, 20, 293 bp were observed on an agarose gel (Figure 1).

Allele and genotype frequencies of *XRCC1* (194 loci) polymorphism in the participants (patients and controls) are presented in Table 4. For 194 C/T locus, the frequen-

cies of CC, CT, and TT genotypes in the patient group were 62%, 18%, and 20%, respectively. However, the genotypic frequency of the control group was 78%, 10%, and 12%, respectively, for TT, CT, CC genotypes (Table 4). According to these results, no significant correlation was found between genotypes frequency at 194 loci between the patient and control groups ( $P=0.13$ ). As indicated in Table 4, the frequency of the C allele was 17% in the control group and 29% in the patient group ( $P=0.02$ ) which shows a positive association between allele frequency and gastric cancer.

Following enzyme digestion of the 399 loci by the MspI enzyme, three forms were observed: The 614 bp single band represents the genotype AA, the two bands of 376 and 238 bp represent the GG genotype, and the three bands of 614, 376, 238 bp represent the GA genotype (Figure 2).

The frequencies of the *XRCC1-399-GG*, *-GA*, and *-AA* genotypes in the healthy individuals were 44%, 44%, and 12%, respectively and the frequencies of GG (41%), GA (42%), and AA (17%) genotypes were seen in the patients (Table 4). Based on the results, no significant correlation was found between genotype frequencies at 399 loci between the patient and control groups ( $P=0.71$ ). Moreover, the frequency of A allele was 85.5% in the

**Table 4.** Distribution of allele and genotype frequencies of polymorphism Arg194Trp and Arg399Gln in gastric cancer patients and controls

Genotype/Allele	Patients (%)	Controls (%)	Chi-square	P	
194 Genotype	CC	62% (n=41)	78% (n=53)	4	0.13
	CT	18% (n=12)	10% (n=7)		
	TT	20% (n=13)	12% (n=8)		
Allele	C	71	83	5.37	0.02
	T	29	17		
399 Genotype	GG	41% (n=27)	44% (n=30)	0.67	0.71
	GA	42% (n=28)	44% (n=30)		
	AA	17% (n=11)	12% (n=8)		
Allele	G	62	66	0.47	0.48
	A	38	34		



control group and 84.6% in the patients that present no positive association between allele frequency and gastric cancer (P=0.48).

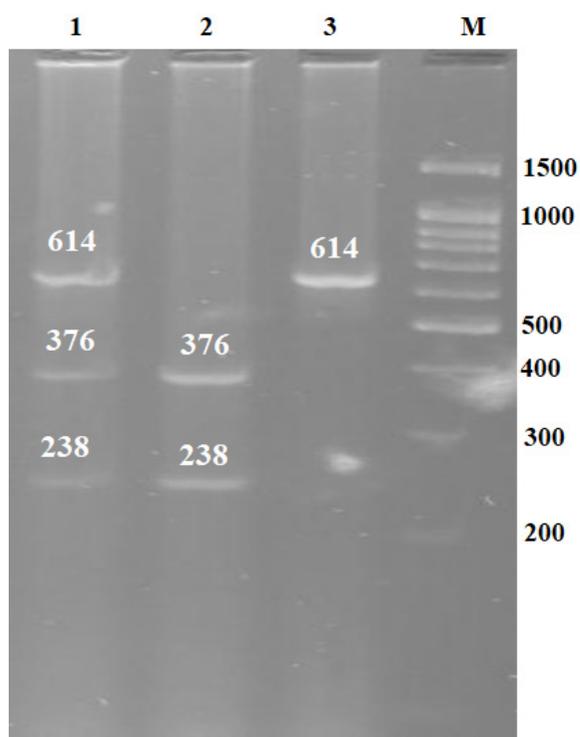
## Discussion

DNA damage such as oxidative DNA damage, single-stranded, and double-stranded DNA fractures can increase the risk of cancer. These damages may lead to errors in the DNA synthesis process and will continue to cause DNA mutations and increase the risk of cancer development. These damages may be repaired by DNA repairing genes through various repairing pathways [26, 27]. In humans, more than 70 genes are involved in the DNA repair pathway that the polymorphisms of these DNA repair genes in the human population play an important role in the genetic ability of individuals to develop cancer [9]. One of the important genes in the BER and SSBR is the *XRCC1* gene, and it has been shown that the polymorphisms of this gene affect various cancers [28]. It has been demonstrated that Arg194Trp polymorphism on exon 10 and Arg399Gln polymorphisms on exon 6 of the *XRCC1* gene have a high impact on various cancers [29, 30]. Therefore, the role of Arg194Trp and Arg399Gln polymorphisms of *XRCC1* gene in gastric cancer in a Western Iranian population was investigated.

The results of this study indicated the association between Arg194Trp polymorphism of the *XRCC1* gene in terms of allele frequency and gastric cancer. There was a significant difference between T-alleles in two groups of

healthy and patients, indicating the association between Arg194Trp polymorphism and gastric cancer among the patients. T allele at the site of this polymorphism can be a risk factor for gastric cancer, and it may be possible to detect this allele as a prognostic and diagnostic biomarker in gastric cancer screening programs. High prevalence of CC genotype of *XRCC1* Arg194Trp polymorphism in the healthy (78%) compared with the patients (62%) suggests that this genotype may have a protective role and act as a protective genotype against gastric cancer. On the other hand, no significant difference was found between the frequency of CT and TT genotype in the patients. In the study of Arg399Gln polymorphism between the control and patient groups, no significant differences were found in genotypic and allelic abundance. Therefore, there is no effect on the increased risk of gastric cancer in the population under study.

There are different results for the association between these polymorphisms and the risk of cancer, regardless of the type of cancer. The results of a meta-analysis on the polymorphisms of the *XRCC1* gene showed that carriers of the TT genotype in Arg194Trp polymorphism might be at increased risk for gastric cancer [12]. Other similar studies have shown that CT, TT, and T alleles increase the risk of oral cancers [31]. Chien-I Chiang and colleagues showed that people with the *XRCC1* Arg399Gln and *XRCC1* Arg194Trp polymorphisms have a high probability of catching bladder cancer [32]. Investigation of the relationship between *XRCC1* polymorphisms and cancer, Huang showed that the presence of TT, CT,



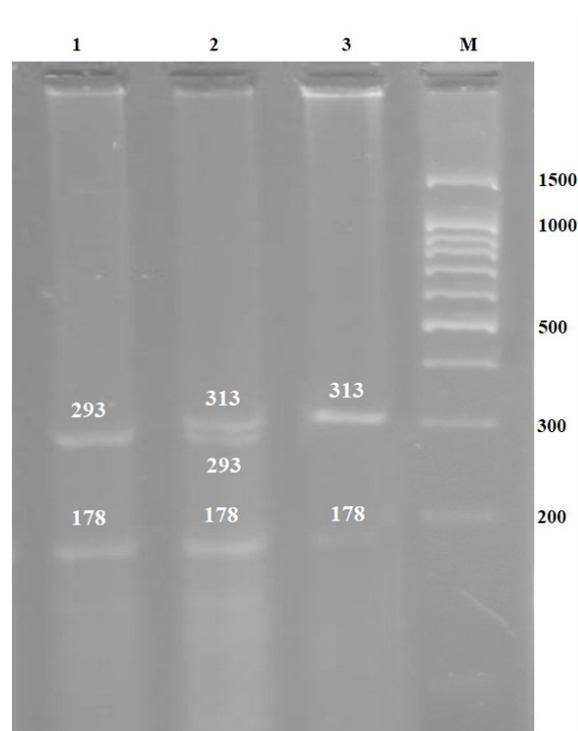
**Figure 2.** Enzymatic digestion of Arg 399Gln polymorphism by MspI (Hpa II) enzyme on Agarose gel 2%

1: Enzymatic digestion product with GA genotype (614, 376, 238 bp); 2: GG genotype (376, 238 bp); 3: AA genotype (614 bp), M: Marker 100 bp.

and T alleles increases the risk of gastric cancer [33]. In the study of Yuan-Yuan Wen et al. on the Sichuan population of China, it has been shown that carriers of the TT genotype in the Arg194Trp polymorphism may be at increased risk for gastric cancer [34]. They also concluded that polymorphism Arg (Trp194) has a significant effect on gastric cancer, while polymorphism Arg (Gln399) is less important [18].

In the study on the Sichuan population of China, it has been shown that carriers of the TT genotype in the Arg194Trp polymorphism may be at increased risk for gastric cancer [34]. In some other studies, no difference was found in the distribution of genotype, the frequency of the allele, and its association with the incidence of cancer. In a study in America, the results showed no relationship between the CT genotype and T allele with gastric cancer [35]. The results of another meta-analysis showed no association between Arg194Trp polymorphism and liver cancer [35].

Possible reasons for the difference in the results of various studies may be partly due to racial-ethnic differences, disease status, organs involved in the disease, sample size, genetic backgrounds, as well as the complexity of



**Figure 1.** Enzymatic digestion of Arg194Trp polymorphism by MspI (Hpa II) enzyme on 2% agarose gel

1: Enzymatic digestion product with CC genotype (178, 293 bp); 2: CT genotype (313, 293, 178, 20 bp); 3: TT genotype (313, 178 bp); M: marker 100 bp.

gene expression or the regulation of gene expression at various levels. The phenotypic effects of single nucleotide polymorphisms are influenced by genetic and environmental factors, which is an example of the interaction of the gene and the environment to create a phenotype. Hence, it seems that polymorphisms cause disease and disorder only in relation to a specific genetic context or environmental factors. Therefore, to investigate more precisely polymorphisms and their relation to diseases, patient and control samples should be selected from similar areas in addition to the same genetic background with related environmental factors.

## Conclusion

In this study, no polymorphism in codon 399 was found in terms of genotypic frequency and no allele frequency between the two groups of patients and control. Therefore, there is no relationship between codon 399 polymorphism and the risk of gastric cancer in the people living in the Western part of Iran. However, there was a significant correlation between the frequency of the T allele in the Arg194Trp polymorphism of the *XRCCI* gene and the risk of gastric cancer after comparing the control and patient group. Those with Arg/Trp and Trp/Trp gen-

otype in codon 194 were more at risk for gastric cancer than the rest of the population. This allele polymorphism is another testament to the role of this polymorphism in the development of cancers. The Arg194Trp polymorphism is located in the exon 6 of the *XRCC1* gene and in the protected *XRCC1* scaffold domain, which affects the formation and efficiency of the repairing complex. This polymorphism induces an amino acid change from arginine to tryptophan in codon 194, which may alter the structure or function of the protein and affect the effectiveness of the BER system, thus change the ability of individuals to develop gastric cancer.

## Ethical Considerations

### Compliance with ethical guidelines

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee. Informed consent was obtained from all individual participants involved in the study.

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The paper was extracted from the MSc. thesis of Maryam Sanaie, Cell and Molecular Biology, Hakim Sabzevari University.

### Authors' contributions

Conceptualization and Supervision: Jafar Vatandoost and Kheirollah Yari; Methodology: Maryam Sanaie; Writing – original draft and Writing – review & editing: All authors.

### Conflict of interest

All authors declare no conflict of interest.

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## References

- [1] Yousif Elemam IB, Mohammed Ali Elnour A, Alobaid AE, Elsheikh MA, Elhaleem A, Mohammed HM. Assessment of proliferation activity by using nucleolar organiser regions count among sudanese patients with prostate cancer and benign prostate hyperplasia. *J Pharm Biomed Sci.* 2015; 05: 863-6. <http://repository.ush.sd:8080/jspui/handle/123456789/436>
- [2] Geng J, Zhang Q, Zhu C, Wang J, Chen L. XRCC1 genetic polymorphism Arg399Gln and prostate cancer risk: A meta-analysis. *Urology.* 2009; 74(3):648-53. [DOI:10.1016/j.urolgy.2009.02.046] [PMID]
- [3] Brooks-Wilson AR, Kaurah P, Suriano G, Leach S, Senz J, Grehan N, Butterfield YS, Jeyes J, Schinas J, Bacani J, Kelsey M. Germline E-cadherin mutations in hereditary diffuse gastric cancer: assessment of 42 new families and review of genetic screening criteria. *J Med Genet.* 2004; 41(7):508-17. [DOI:10.1136/jmg.2004.018275] [PMID] [PMCID]
- [4] Dong LM, Potter JD, White E, Ulrich CM, Cardon LR, Peters U. Genetic susceptibility to cancer: The role of polymorphisms in candidate genes. *Jama.* 2008; 299(20):2423-36. [DOI:10.1001/jama.299.20.2423] [PMID] [PMCID]
- [5] Elmore S. Apoptosis: A review of programmed cell death. *Toxicol Pathol.* 2007; 35: 495-516. [DOI:10.1080/01926230701320337] [PMID] [PMCID]
- [6] Goode EL, Ulrich CM, Potter JD. Polymorphisms in DNA repair genes and associations with cancer risk. *Cancer Epidemiol Prev Biomarkers.* 2002; 11(12):1513-30.
- [7] Lowdon RF, Wang T. Epigenomic annotation of noncoding mutations identifies mutated pathways in primary liver cancer. *PLoS One.* 2017; 12:e0174032. [DOI:10.1371/journal.pone.0174032] [PMID] [PMCID]
- [8] Sugeran PB, Joseph BK, Savage NW. The role of oncogenes, tumour suppressor genes and growth factors in oral squamous cell carcinoma: A case of apoptosis versus proliferation. *Oral Dis.* 1995; 1(3):172-88. [DOI:10.1111/j.1601-0825.1995.tb00181.x] [PMID]
- [9] Setlow RB. Variations in DNA repair among people, in epidemiology and quantitation of environmental risk in humans from radiation and other agents. *NATO ASI Series (Series A: Life Sciences), vol 96.* Springer, Boston, MA. [DOI:10.1007/978-1-4615-9445-1\_13]
- [10] Bond GL, Hu W, Levine A. A single nucleotide polymorphism in the MDM2 gene: From a molecular and cellular explanation to clinical effect. *Cancer Res.* 2005; 65(13):5481-4. [DOI:10.1158/0008-5472.CAN-05-0825] [PMID]
- [11] Lichtenstein P, Holm NV, Verkasalo PK, Iliadou A, Kaprio J, Koskenvuo M, et al. Environmental and heritable factors in the causation of cancer – analyses of cohorts of twins from Sweden, Denmark, and Finland. *N Engl J Med.* 2000; 343(2):78-85. [DOI:10.1056/NEJM200007133430201] [PMID]
- [12] Gao L, Nieters A, Brenner H. Cell proliferation-related genetic polymorphisms and gastric cancer risk: Systematic review and meta-analysis. *Eur J Hum Genet.* 2009; 17(12):1658-67. [DOI:10.1038/ejhg.2009.102] [PMID] [PMCID]
- [13] Ryu RA, Tae K, Min HJ, Jeong JH, Cho SH, Lee SH, Ahn YH. XRCC1 polymorphisms and risk of papillary thyroid carcinoma in a Korean sample. *J Korean Med Sci.* 2011; 26(8):991-5. [DOI:10.3346/jkms.2011.26.8.991] [PMID] [PMCID]
- [14] Chacko P, Rajan B, Joseph T, Mathew BS, Pillai MR. Polymorphisms in DNA repair gene XRCC1 and increased genetic

- susceptibility to breast cancer. *Breast Cancer Res Treat.* 2005; 89(1):15-21. [DOI:10.1007/s10549-004-1004-x] [PMID]
- [15] Xing D, Qi J, Miao X, Lu W, Tan W, Lin D. Polymorphisms of DNA repair genes XRCC1 and XPD and their associations with risk of esophageal squamous cell carcinoma in a Chinese population. *Int J Cancer.* 2002; 100(5):600-5. [DOI:10.1002/ijc.10528] [PMID]
- [16] Przybylowska K, Kabzinski J, Sygut A, Dziki L, Dziki A, Majsterek I. An association selected polymorphisms of XRCC1, OGG1 and MUTYH gene and the level of efficiency oxidative DNA damage repair with a risk of colorectal cancer. *Mutat Res/Fundam Mol Mech Mutagen.* 2013; 745:6-15. [DOI:10.1016/j.mrfmmm.2013.04.002] [PMID]
- [17] Langsenlehner T, Renner W, Gerger A, Hofmann G, Thurner EM, Kapp KS, Langsenlehner U. Association between single nucleotide polymorphisms in the gene for XRCC1 and radiation-induced late toxicity in prostate cancer patients. *Radiother Oncol.* 2011; 98(3):387-93. [DOI:10.1016/j.radonc.2011.01.021] [PMID]
- [18] Putthanachote N, Promthet S, Suwanrungruan K, Chopjitt P, Wiangnon S, Chen LS, et al. XRCC1 gene polymorphism, clinicopathological characteristics and stomach cancer survival in Thailand. *Asian Pac J Cancer Prev.* 2015; 16(14):6111-6. [DOI:10.7314/APJCP.2015.16.14.6111] [PMID]
- [19] Hanssen-Bauer A, Solvang-Garten K, Gilljam KM, Torseth K, Wilson III DM, Akbari M, Otterlei M. The region of XRCC1 which harbours the three most common nonsynonymous polymorphic variants, is essential for the scaffolding function of XRCC1. *DNA Repair.* 2012; 11(4):357-66. [DOI:10.1016/j.dnarep.2012.01.001] [PMID] [PMCID]
- [20] Fortini P, Dogliotti E. Base damage and single-strand break repair: mechanisms and functional significance of short-and long-patch repair subpathways. *DNA Repair.* 2007;6(4):398-409. [DOI:10.1016/j.dnarep.2006.10.008] [PMID]
- [21] Thompson LH, Brookman KW, Dillehay LE, Carrano AV, Mazrimas JA, Mooney CL, et al. A CHO-cell strain having hypersensitivity to mutagens, a defect in DNA strand-break repair, and an extraordinary baseline frequency of sister-chromatid exchange. *Mutat Res/Fundam Mol Mech Mutagen.* 1982; 95(2-3):427-40. [DOI:10.1016/0027-5107(82)90276-7]
- [22] Zdzienicka MZ, Van Der Schans GP, Natarajan AT, Thompson LH, Neuteboom I, Simons JW. A Chinese hamster ovary cell mutant (EM-C11) with sensitivity to simple alkylating agents and a very high level of sister chromatid exchanges. *Mutagenesis.* 1992; 7(4):265-9. [DOI:10.1093/mutage/7.4.265] [PMID]
- [23] Mandal RK, Mittal RD. Genetic variant Arg399Gln G> A of XRCC1 DNA repair gene enhanced cancer risk among Indian Population: evidence from meta-analysis and trial sequence analyses. *Indi J Clin Biochem.* 2018; 33(3):262-72. [DOI:10.1007/s12291-017-0669-y] [PMID] [PMCID]
- [24] Duarte MC, Colombo J, Rossit AR, Caetano A, Borim AA, Wornrath D, Silva AE. Polymorphisms of DNA repair genes XRCC1 and XRCC3, interaction with environmental exposure and risk of chronic gastritis and gastric cancer. *World J Gastroenterol.* 2005; 11(42):6593. [DOI:10.3748/wjg.v11.i42.6593] [PMID] [PMCID]
- [25] Zhang Z, Wan J, Jin X, Jin T, Shen H, Lu D, et al. Genetic polymorphisms in XRCC1, APE1, ADPRT, XRCC2, and XRCC3 and risk of chronic benzene poisoning in a Chinese occupational population. *Cancer Epidemiol Prev Biomarkers.* 2005; 14(11):2614-9. [DOI:10.1158/1055-9965.EPI-05-0143] [PMID]
- [26] Curtin NJ. DNA repair dysregulation from cancer driver to therapeutic target. *Nat Rev Cancer.* 2012; 12(12):801-17. [DOI:10.1038/nrc3399] [PMID]
- [27] Hoeijmakers JH. Genome maintenance mechanisms for preventing cancer. *Nature.* 2001; 411(6835):366-74. [DOI:10.1038/35077232] [PMID]
- [28] Caldecott KW, McKeown CK, Tucker JD, Ljungquist S, Thompson LH. An interaction between the mammalian DNA repair protein XRCC1 and DNA ligase III. *Mol Cell Biol.* 1994; 14(1):68-76. [DOI:10.1128/MCB.14.1.68] [PMID] [PMCID]
- [29] Ginsberg G, Angle K, Guyton K, Sonawane B. Polymorphism in the DNA repair enzyme XRCC1: Utility of current database and implications for human health risk assessment. *Mutat Res/Rev Mutat Res.* 2011; 727(1-2):1-5. [DOI:10.1016/j.mrrev.2011.02.001] [PMID]
- [30] Thompson LH, Brookman KW, Jones NJ, Allen SA, Carrano AV. Molecular cloning of the human XRCC1 gene, which corrects defective DNA strand break repair and sister chromatid exchange. *Mol Cell Biol.* 1990; 10(12):6160-71. [DOI:10.1128/MCB.10.12.6160] [PMID] [PMCID]
- [31] Zhang Y, Wang Y, Wu J, Li LJ. XRCC1 Arg194Trp polymorphism is associated with oral cancer risk: Evidence from a meta-analysis. *Tumor Biol.* 2013; 34(4):2321-7. [DOI:10.1007/s13277-013-0888-7]
- [32] Chiang CI, Huang YL, Chen WJ, Shiue HS, Huang CY, Pu YS, Lin YC, Hsueh YM. XRCC1 Arg194Trp and Arg399Gln polymorphisms and arsenic methylation capacity are associated with urothelial carcinoma. *Toxicol Appl Pharmacol.* 2014; 279(3):373-9. [DOI:10.1016/j.taap.2014.06.027] [PMID]
- [33] Huang ZH, Hua D, Du X. Polymorphisms in p53, GSTP1 and XRCC1 predict relapse and survival of gastric cancer patients treated with oxaliplatin-based adjuvant chemotherapy. *Cancer Chemother Pharmacol.* 2009; 64(5):1001-7. [DOI:10.1007/s00280-009-0956-2] [PMID]
- [34] Wen YY, Pan XF, Loh M, Tian Z, Yang SJ, Lv SH, et al. ADPRT Val762Ala and XRCC1 Arg194Trp polymorphisms and risk of gastric cancer in Sichuan of China. *Asian Pac J Cancer Prev* 2012; 13(5):2139-44. [DOI:10.7314/APJCP.2012.13.5.2139] [PMID]
- [35] Ratnasinghe LD, Abnet C, Qiao YL, Modali R, Stolzenberg-Solomon R, Dong ZW, et al. Polymorphisms of XRCC1 and risk of esophageal and gastric cardia cancer. *Cancer Lett.* 2004; 216(2):157-64. [DOI:10.1016/j.canlet.2004.03.012] [PMID]