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The Relationship of *XPA* and *XPC* Gene Polymorphisms with the Risk of Colorectal Cancer in Iran

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Abstract

Background: The objective of this study was to investigate the effect of several *XPA* and *XPC* polymorphisms on the risk of colorectal cancer (CRC) in northeastern Iran.

Method: 180 CRC patients and 160 healthy subjects participated in this case-control study. We determined the genotypes by RFLP-PCR and PIRA-PCR, and analyzed the results using logistic regression and χ^2-test.

Results: Our findings showed that only BMI could affect the risk of cancer among the studied demographic factors. Three of the four polymorphisms studied, namely *XPA* A23G, *XPC* rs2228000 C > T and *XPC* rs2228001 A > C, did not correlate with CRC (*P*-values > 0.05); however, the polymorphism of *XPC* poly AT (PAT) increased the risk of CRC (*P*= 0.024). The *XPC* rs2228000 C> T polymorphism increased the CRC risk only in patients aged 50 or more. The risk of CRC in heterozygote individuals (*XPC* PAT D/I) was higher than that of homozygous individuals (*XPC* PAT D/D); also, at least one PAT I variant allele increased the likelihood of CRC (for PAT D/I OR =2.168; 95% CI = 1.809-4.319: and for PAT D/I and PAT I/I OR = 1.810; 95% CI = 1.165-2.813). The *XPC* haplotypes were similar between the cases and controls, and *P*-values were >0.05.

Conclusion: In the whole population, *XPC* PAT polymorphism, overweightness, and *XPC* rs2228000 C>T polymorphism in elderly people are related to CRC. Therefore, they can probably be considered as markers of CRC in Iran.

Keywords: *XPA*, *XPC*, Polymorphism, Colorectal cancer

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Introduction

Colorectal cancer (CRC) is one of the most prevalent cancers in the world. Although this type of cancer is more common in western countries, it is growing in developing countries due to lifestyle changes and industrialization.[1] Fast food, environmental and workplace pollution, physical inactivity, and psychological stress can increase the risk of CRC. These factors damage

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the DNA and cause various mutations.[2] Many proteins are involved in the DNA repair mechanisms. One of the repair pathways for DNA damages is the nucleotide-excision repair (NER) which components are *XPA* and *XPC* proteins.

Xeroderma Pigmentosum, Complementation Group A (*XPA*) gene, encodes an essential scaffolding protein comprised of 273 amino acids and containing a zinc-finger motif.[3] Depending on the type of damage, *XPA* protein, with different affinities, binds to the DNA after the formation of the NER bubble.[4] Other proteins involved in the NER, such as replication protein A (RPA) and TFIIH, are attached to *XPA* to ensure the appropriate excision of lesions.[5] Animal studies have shown that the absence of *XPA* protein causes NER to not be performed.[6] It has recently been revealed that the expression of this protein in CRC tissues is significantly less than its adjacent healthy tissues.[7] Therefore, it is safe to say that *XPA* protein plays a highly important role in the risk of CRC. The presence of single nucleotide polymorphism (SNP) in the upstream of the *XPA* gene may reduce its expression, thereby contributing to cancer development. The relevance of the *XPA* (-4) G-to-A polymorphism (rs1800975, A23G), located in the 5`-untranslated region (5`-UTR), to cancer has been studied in different countries with contradictory results.[8,9] However, there has been no research on the association between this SNP and CRC in Iran; thus, we studied this relationship for the first time.

Xeroderma Pigmentosum, Complementation Group C (*XPC*) gene, encodes a 940 amino acid protein responsible for detecting DNA damages and initiating repairs.[10] To do this, *XPC* protein binds to the RAD23B, *XPA*, TFIIH, and several other proteins in the NER mechanism.[11] It is known that the C-terminal part of this protein (residues 492-940) interacts with damaged DNA, and its N-terminal portion (residues 156-325) connects to *XPA*.[12] Studies have shown that the lack of *XPC* in mice has caused NER defects and predisposition to various cancers.[13,14] Therefore, *XPC* gene polymorphisms are likely to contribute to the development of CRC either in the coding region, which may alter the conformation of the protein or in introns, which may reduce its expression. It has already been observed that a poly AT insertion (I)/deletion (D) polymorphism rs77907221 (*XPC* PAT) in intron 9 is associated with some cancers.[15,16] The relationship between cancers and the two common polymorphisms of the *XPC* gene, rs2228001 A > C (Lys939Gln) and rs2228000 C > T (Ala499Val), has also been investigated with contradictory results in different countries.[17-20] However, in Iran (Khorasan Razavi province, northeastern Iran), the relationship between the three mentioned polymorphisms has not been studied so far. Therefore, the present study aimed to determine the genetic linkages of CRC with different ethnic groups.

Materials and Methods

Study participants and blood collection

180 CRC patients (from Reza Radiotherapy and Oncology Center in Mashhad and 22 Bahman Hospital in Neyshabur) and 160 age- and sex-matched healthy volunteers participated in this case-control study. The mean (±SD) age of the patients and healthy subjects was 57.9±14.4 and 57.2±13.9 years, respectively. Peripheral blood samples were taken from each subject and kept at -20°C until DNA extraction. Research approval was obtained from the Ethics Committee of the Islamic Azad University (No: IR.IAU.NEYSHABUR.REC.1395.9). Also, written informed consent was obtained from the case and control subjects.

We collected the demographic characteristics of all participants via questionnaire, and their clinicopathological data were specified by the manual review of their pathology reports and hospital records.

Genotyping

We extracted the DNA samples according to the instructions of the Kit purchased from Korea's Bioneer Company. Genotyping of polymorphisms was carried out by restriction fragment length polymorphism (RFLP)-PCR for *XPA* A23G and *XPC* rs2228001 A > C, primer-introduced restriction analysis (PIRA)-PCR for *XPC* rs2228000 C > T, and PCR for *XPC* rs77907221

Table 1. Primers and PCR Conditions used to determine the polymorphisms in *XPA* and *XPC* genes

SNPs	Primers	Product Size (bp)	PCR Conditions/ Restriction Enzyme
XPA rs1800975 A23>G min/BspEI	F) CTAGGTCCTCGGAGTGGTCC R) GCCCAAACCTCCAGTAGCC	204 Wild: AA = 204 Variant: GG = 185 and 19	94°C 5 min, 30 cycles a94°C 30 s, 57°C 30 s 72°C 60 s, 72°C 7
XPC rs2228001 A>C	F) GGAGGTGGACTCTCTTCTGATG R) TAGATCCCAGCAGATGACC	765 Wild: AA=765 Variant: CC=582 and 183	95°C 5min 30 cycles. 95°C 30s, 64°C 45s, 72°C 30s 72°C 5min / PvuII
XPC rs2228000 C>T	F) TAAGGACCCAAGCTTGCCC*G R) CCCACTTTTCCTCCTGCTCACAG	152 Wild: TT=152 Variant: CC=131 and 21	95°C 5 min 30 cycles. 95°C 30s, 63°C 45s, 72°C 30s 72°C 5min / SacII
XPC PAT D/I	F) TAGCACCCAGCAGTCAAAG R) TGTGAATGTGCTTAATGCTG	Wild: PAT D/D (266) Variant: PAT I/I (344)	95°C 5min 30 cycles: 94°C 30s, 58°C 30s, 72°C 30s 72°C 5min

*mismatched base

PAT. RFLP-PCR and PIRA-PCR are two of the most widely utilized techniques in SNP detection. The first step in RFLP-PCR analysis is the amplification of a fragment containing the variation. This is followed by treatment of the amplified fragment with an appropriate restriction enzyme. The PIRA-PCR method introduces an artificial RFLP or a restriction site into a PCR product by the use of a primer with a single-base mismatch close to its 3`end.[21] The continuation of this method is similar to RFLP-PCR. Table 1 shows the forward (F) and reverse (R) primers, the cycle conditions, the restriction enzymes, and the size of products.[16,22] Regarding PCR in 25µl reaction, the employed reagents were 250 µm dNTPs, 1.5 mM MgCl2, 100 ng DNA, 12.5 pmol of each primer, and 1 U Taq DNA polymerase. We used water as a negative control in each PCR plate. To verify the genotyping, 10% of the samples were randomly selected and subjected to repeat analyses as a quality control measure

Statistical analysis

To compare the frequencies of observed genotype with the estimated values within control group, we tested the Hardy-Weinberg equilibrium by chi-square test, available at the http://www.oege.org/software/hwe-mr-calc.shtml;[23] the associated *P*-values were then calculated through the website available at the https://www.socscistatistics.com/pvalues/chidistribution.aspx. SNPStats (http://www.snpstats/.net.start.htm) was employed to construct the haplotypes, and we compared the demographic variables and genotype frequencies in different groups via the two-sided chi-squared test. A logistic regression model calculated the odds ratios (OR) and 95% confidence intervals (CI). To perform the statistical calculations, SPSS 20.0 (SPSS Inc, Chicago, Illinois) was used, and all *P*-values < 0.05 were considered as significant.

Results

The *XPA* A23>G (rs1800975), *XPC* rs2228001 A > C, *XPC* rs2228000 C > T, and *XPC* PAT genotypes in the control group were in Hardy-Weinberg equilibrium. This is demonstrated by the lack of any significant difference between their observed and expected frequencies (χ^2=0.63; *P*=0.427, χ^2=0.73; *P*=0.393, χ^2=3.04; *P*=0.080, χ^2=0.26; *P*=0.610, respectively). Therefore, we suggest that the control subjects may represent

Table 2. Frequency distributions of selected variables in the CRC patients and controls

Variables		Cases (n/%)	Controls (n/%)	*P*
Age(years)	≤50	49(27.2)	45(28.1)	1.000
	50-65	63(35.0)	59(36.9)	
	≥65	60(33.3)	56(35.0)	
Gender	male	77(42.8)	70(43.8)	0.931
	female	103(57.2)	90(56.2)	
Body mass index (kg/m2)	Under weight	13(10.6)	14(8.7)	0.001*
	Normal weight	60(48.8)	114(71.2)	
	Over weight	43(35.0)	28(17.5)	
	Obesity	7(5.7)	4(2.5)	
Smoking	Yes	35(19.4)	30(18.8)	0.900
	No	142(78.9)	130(81.2)	
Opioid addiction	Yes	16(8.9)	14(8.8)	1.000
	No	161(89.4)	146(91.2)	
Alcohol consumption	Yes	4(2.2)	5(3.1)	0.742
	No	172(95.6)	86.1(96.9)	

*Statistically significant, CRC: colorectal cancer

the general population.

Table 2 shows the frequency distribution of age, sex, and certain other demographic characteristics of the participants. The control and case groups had no significant differences in terms of smoking, alcohol consumption, and opioid addiction. Of the studied demographic variables, only the body mass index (BMI) was significantly different, such that cancer patients had more BMI compared with healthy subjects.

Table 3 shows the distribution of genotypes in regard to demographic and clinical variables. The results showed no interaction between most of these variables and the polymorphisms of the *XPA* and *XPC* genes. Only the *XPC* rs2228000 C>T polymorphism significantly influenced the risk of CRC due to age.

Regarding the distribution of *XPA* A23>G (rs1800975), *XPC* rs2228001 A>C, and *XPC* rs2228000 C>T polymorphisms, there was no difference between the cases and controls, with all *P*-values being higher than 0.05 (Table 4). Therefore, these polymorphisms did not have a role in the CRC people of Khorasan Razavi province, Iran. However, *XPC* rs77907221 PAT polymorphism was significantly different between the two groups. The frequency of *XPC*-PAT D/I heterozygote was significantly higher in CRC patients compared with healthy subjects (OR, 2.168 and 95% CI, 1.809-4.319). Furthermore, the control group had significantly more patients with *XPC*-PAT I (OR, 1.810 and 95% CI, 1.165-2.813).

As detailed in table 5, haplotyping of *XPC* rs2228001A>C, rs2228000 C > T, and rs77907221 PAT D/I polymorphisms generated eight different haplotypes. The frequencies of all heplotypes of the cases and the controls were almost the same, and the *P*- values were higher than 0.05.

Discussion

We found that three of the four studied polymorphisms, namely *XPA* A23G, *XPC* rs2228000 C>T, and *XPC* rs2228001 A>C, were not associated with CRC; however, the polymorphism of *XPC* poly AT (PAT) increased the risk of CRC. Based on previous studies, it can be expected that defects in any of the *XPA* and *XPC* proteins may lead to various cancers such as CRC.[7, 13, 14, 24] Genome-wide association studies (GWAS) have identified thousands of single-nucleotide polymorphisms (SNPs) associated with a variety of major human diseases.[25] It has been proposed that genetic polymorphisms may influence the amount or structure of proteins. This is the reason behind proteins not being able to properly perform their functions.[15,26]

Table 3. The association polymorphisms of *XPA* and *XPC* genes with clinicopathological and demographic variables in CRC patients

Variable (number)	XPA (rs1800975), -4G/A, A23>G			XPC rs2228001 A>C			XPC rs2228000 C>T			XPC PAT D/I		
	AA	AG+GG	*P*	AA	AC+CC	*P*	CC	CT+TT	*P*	D/D.	D/I+ I/I	*P*
Gender			0.30			0.31			0.55			0.75
Female (n=77)	23	54		33.	44		39	38		26	51	
Male (n=103)	23	80		52	51		48	55		32	71	
Age			0.24			0.32			0.04*			0.72
<50 (n=61)	21	40		32.	29		31.	30		22.	39	
50-65 (n=63)	12	41		21	32		18	34		18	35	
>65 (n=58)	13	45		30	28		24	34		17	41	
Tumor site			1.00			0.87			0.74			0.72
Colon (n=48)	12	36		22	26		25	23		17	31	
Rectum (n=130)	34	96		63	67		62	67		41	89	
Stage			0.46			0.85			0.69			0.97
I (n=1)	1	0		1	0		1	0		0	1	
II (n=27)	7	20		12	15		16	11		9	18	
III (n=36)	10	26		15	21		19	17		10	26	
IV (n=27)	6	21		11	16		12	14		8	19	
Grade			0.13			0.67			0.45			0.53
WD (n=65)	23	42		30	35		31	34		25	40	
MD (n=70)	13	57		34	36		38	32		19	51	
PD (n=5)	2	3		4	1		2	3		2	3	
UD (n=2)	1	1		1	1		0	2		1	1	
Tumor Size (cm)			0.70			0.63			0.89			0.05
<5 (n=53)	13	40		24	29		27	26		12	41	
5-10 (n=30)	10	20		15	15		13	17		14	16	
>10 (n=6)	2	4		4	2		3	3		3	3	
Local tumor			0.90			0.67			0.61			0.39
T1-T2 (n=14)	5	9		5	9		7	7		3	10	
T3-T4 (n=59)	17	42		28	31		24	25		18	41	
Lymph nodes			0.21			0.81			0.98			0.87
N0 (n=30)	8	22		13	17		17	13		19	21	
N1-N2 (n=42)	14	28		20	24		22	18		12	30	
Distant metastasis			0.67			0.92			0.70			0.49
M0 (n=12)	3	9		5	7		7	5		5	7	
M1-M2 (n=37)	7	30		18	19		18	19		9	28	

WD: well-differentiated; MD: moderately differentiated; PD: poorly differentiated; UD: undifferentiated, CRC: Colorectal cancer, *Statistically significant

Table 4. Distribution and correlation of polymorphisms of *XPA* and *XPC* genes in CRC patients and controls

Genotype	Cases (n = 180) Number (%)	Controls (n = 160) Number (%)	Cases versus controls OR (95% CI)	*P*
***XPA* (rs1800975), -4G/A, A23>G**				
AA	46(25.6)	35(21.9)	Reference	
AG	97(53.9)	87(54.4)	0.741(0.394-1.392)	0.351
GG	37(20.6)	38(23.8)	0.873(0.510-1.495)	0.621
AG+GG	134(74.4)	125(78.1)	0.816(0.493-1.348)	0.427
***XPC* rs2228001 A>C**				
AA	85(47.2)	88(55)	Reference	
AC	82(45.6)	65(40.6)	1.923(0.732-5.502)	0.185
CC	13(7.2)	7(4.4)	1.472(0.555-3.902)	0.437
AC+CC	95(52.8)	72(45)	1.366(0.891-2.904)	0.153
***XPC* rs2228000 C>T**				
CC	87(48.3)	90(56.2)	Reference	
CT	66(36.7)	50(31.3)	1.397(0.730-2.672)	0.313
TT	27(15.0)	20(12.5)	1.023(0.515-2.029)	0.949
CT+TT	93(51.7)	70(43.8)	0.728(0.474-1.116)	0.145
***XPC* PAT D/I**				
D/D	59(32.8)	75(46.9)	Reference	
D/I	92(51.1)	68(42.5)	2.168(1.809-4.319)	0.028*
I/I	29(16.1)	17(10.6)	1.261(0.641-2.478	0.501
D/I+ I/I	122(67.8)	85(53.1)	1.810(1.165-2.813)	0.008*

OR: Odds ratio; CI: Confidence interval; CRC: Colorectal cancer; *Statistically significant

The results of studies related to *XPA* A23>G polymorphism and cancers are very different.[8,9,27] For example, Zhu et al. reported that individuals with one 23G variant allele (AG+GG genotypes) were less likely to develop lung cancer compared with wild type genotypes (23AA).[27] Similarly, in the current study, as shown in table 4, the G allele in the control group was higher, though not significantly, in heterozygote AG and homozygous GG states compared with patients. Therefore, the mutant G allele has a low CRC-protecting effect. On the contrary, in a meta-analysis study and a research study, the relationship between this polymorphism and digestive system cancers and CRC were not elucidated.[9, 29] Similarly, in our study, there was no significant correlation between *XPA* A23>G polymorphism and CRC in Khorasan Razavi, Iran. In fact, A23>G polymorphism in the upstream gene was not able to affect the gene expression.

Unlike Iran, there exists a lot of research regarding the association of the rs2228001 A > C and rs2228000 C > T polymorphisms with CRC in different countries. Hua et al. found that none of these two polymorphisms were associated with CRC in southern China, and the *P*-value of each was 0.470 and 0.521, respectively.[17] χ^2-test revealed the similarity of the results of the current study, with the *P*-values of both polymorphisms being higher than 0.05. We further observed that *XPC* C (rs2228001) and *XPC* T (rs2228000) alleles in heterozygote and homozygous states were higher, though not significantly, in patients than in controls (Table 4). Therefore, minor alleles C and T did not affect CRC. Contrary to our findings, He et al. reported in a meta-analysis study that both polymorphisms were associated with an increased risk of CRC (Gln/Gln versus Lys/Lys: OR = 1.16, 95% CI = 1.07 -1.25, *P* <0.001; Val/Val vs. Ala/Ala: OR = 1.21, 95% CI = 1.07-1.36, *P* = 0.003).[29] Other previous studies on the relationship between these polymorphisms and other cancers are also inconsistent. For example, Zhu et al. observed that these polymorphisms did not correlate with Wilms Tumor Risk, and that *P*-values were more than 0.05.30 Sun et al., on the other hand, reported that *XPC* rs2228001 A>C polymorphism was effective in increasing the risk of bladder cancer (*P*=0.002).[18] A gene may simultaneously have

Table 5. Distribution of different haplotypes of *XPC* rs2228001A>C, rs2228000 C>T and rs77907221 PAT D/I polymorphisms in CRC patients and controls

Haplotypes	Cases (%)	Controls (%)	OR (95% CI)	*P*
ACD	27(15)	35(21)	Reference	-
ATD	19(10.6)	17(10.6)	1.000(0.478-2.094	1.000
CCD	14(7.8)	15(9.3)	0.862(0.370-2.008)	0.731
CTD	13(7.2)	12(7.5)	1.682(0.722-3.919)	0.228
ACI	34(18.9)	24(15)	1.836(0.890-3.790)	0.100
ATI	23(12.8)	14(8.7)	1.268(0.549-2.928)	0.579
CCI	16(8.8)	19(11.9)	1.518(0.619-3.720)	0.362
CTI	34(18.9)	24(15)	1.308(0.509-3.357)	0.577

OR: Odds ratio; CI: Confidence interval; CRC: Colorectal cancer; *P*: *P*-value

multiple polymorphisms, thereby exerting a significant impact. The simultaneous absence of polymorphisms is also expected in different human populations, hence the justifiability of all the mentioned differences. Therefore, although the Ala499Val polymorphism is present in an area of *XPC* that reacts with RAD23B protein and DNA damage, and Lys939Gln is located in a region linked to TFIIH, they did not affect our subjects. A stratified analysis reported that increased age led to *XPA* rs2228000 C>T polymorphism augmenting the risk of CRC. In fact, increase in age results in mutations in other genes and this polymorphism, possibly increasing the risk of CRC.

A number of studies have also been conducted on the impact of intronic Poly AT (PAT) polymorphism of the DNA repair gene *XPC* on the increased risk of CRC. In line with the results of the current study, most have determined that this polymorphism is involved in the development of CRC. Wu et al. reported that PAT I/I genotype was associated with increased risk of CRC (OR = 1.5; 95% CI = 1.0-2.3) compared with PAT D/D genotype.[31] Our results revealed that in subjects with at least one PAT I variant allele, the risk of CRC was higher than that of the PTA D/D genotype. As shown in table 4, there was a significant difference in the number of cancer patients and healthy individuals with only one minor PAT I allele. However, the difference in the number of patients with PAT I/I genotype and the control group was not significant. In fact, the PAT D and PAT I alleles were codominant in CRC. Because introns are involved in regulating tissue-specific gene expression, mRNA transcription and translation.[32] Therefore, the presence of a polymorphism in an intron may interfere with these actions and contribute to cancer. By examining the SNPs' haplotypes, we found no significant difference between the patients and the control group; in fact, the haplotypes of the *XPC* gene did not influence the risk of CRC.

Among the selected demographic factors, only BMI was associated with an increased risk of CRC. Cigarette smoking, alcohol consumption, and opioid addiction, did not have an impact on the risk of CRC in our study subjects. However, in most studies, alcohol consumption and smoking have been proven as CRC risk factors.[1,2] Therefore, the difference between the current results and these studies is probably due to the low number of studied subjects , particularly alcohol consumers and smokers (Table 2).

Conclusion

We examined the association between the polymorphisms of *XPA* and *XPC* genes and CRC, their interaction with demographic and clinico-pathological factors, and the difference between cancer patients and healthy individuals concerning these factors. We found that high body mass index, *XPC* rs2228000 C > T polymorphism in subjects over 50 years of age, heterozygosity (*XPC* PAT D/D), and *XPC* PAT I variant allele increased the risk of CRC. Accordingly, these factors can be conducive to screening for early prevention and early detection of CRC in the Khorasan Razavi province, and possibly similar provinces.

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Conflict of Interest

None declared.

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