GMR Genetics and Molecular Research
Online Journal
ISSN:1676-5680

Association between *ERCC1* and *XPF* polymorphisms and risk of colorectal cancer

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Genet. Mol. Res. 14 (1): 700-705 (2015)
Received November 26, 2013
Accepted October 1, 2014
Published January 30, 2015
DOI http://dx.doi.org/10.4238/2015.January.30.13

ABSTRACT. We conducted a hospital-based case-control study to evaluate the association between polymorphisms in excision repair cross-complementing group 1-xeroderma pigmentosum group F (*ERCC1-XPF*) variants and the risk of colorectal cancer in a Chinese population. Genotyping of the *ERCC1* rs2298881 and rs11615 and *XPF* rs2276466 polymorphisms were detected by polymerase chain reaction-restriction fragment length polymorphism. Colorectal cancer cases were more likely to be smokers, consume alcohol, have higher energy intake, and have a family history of cancer. Using conditional regression analysis, subjects carrying the *ERCC1* rs2298881CC genotype and C allele showed a significantly increased risk of colorectal cancer compared with those carrying the AA genotype. However, we found no association between the rs11615 and rs2276466 polymorphisms and the risk of colorectal cancer. In conclusion, the *ERCC1* rs2298881 polymorphism may be used as a predictive factor for determining the risk of colorectal cancer in a Chinese population. This finding may be

useful for identifying the genetic characteristics of colorectal cancer and developing more efficient strategies for prevention and treatment.

Key words: Colorectal cancer; Xeroderma pigmentosum group F; Genetic polymorphisms; Excision repair cross-complementing group 1

INTRODUCTION

Colorectal cancer is the third most common cancer in men and the second most common cancer in women worldwide (IARC, 2012). There were an estimated 746,000 cases in men and 614,000 cases in women in 2008. In China, colorectal cancer is the fifth leading cause of cancer-related deaths (IARC, 2012), and the morbidity and mortality of this cancer is increasing (Ballinger and Anggiansah, 2007; Cunningham et al., 2010). Colorectal cancer is caused by both genetic and environmental factors; tobacco smoking, obesity, meat and alcohol consumption, and host genetic background all play a role in its pathogenesis (Foulkes, 2008; Markowitz and Bertagnolli, 2009). Chromosomal instability, aberrant DNA methylation, and defects in DNA repair may also play an important role in the development of colorectal cancer. A previous study indicated that polymorphisms in DNA repair genes altered the efficacy of DNA repair, influencing the susceptibility to colorectal cancer (Huang et al., 2013; Ni et al., 2014). Excision repair cross-complementing group 1 (ERCC1) is an important protein during nucleotide excision repair (NER), and ERCC1 variants may influence genomic stability, increasing the susceptibility to cancer (Wood, 1997; Wang et al., 2011). Xeroderma pigmentosum group F (XPF) forms a heterodimer with ERCC1 to catalyze 5'-incision during excision of the DNA lesion (Wang et al., 2011). However, few studies have evaluated the association between polymorphisms in *ERCC1* and *XPF* and the risk of colorectal cancer in a Chinese population.

In this study, we conducted a hospital-based case-control study to evaluate the association between polymorphisms in *ERCC1-XPF* variants and the risk of colorectal cancer in a Chinese population.

MATERIAL AND METHODS

Subjects

The patient group included 279 individuals diagnosed with colorectal cancer at Wenzhou Medical University between May 2010 and October 2012. The average age of cases was 61.3 years (range 28-83 years), and 41.2% were females. The control group included 316 healthy subjects randomly selected during health check-ups at our hospital. Control subjects with a history of cancer or a digestive system disease were excluded. All subjects provided written informed consent before the collection of blood samples. Our study protocol was approved by the Ethics Committee of First Hospital, Wenzhou Medical University.

A self-designed questionnaire was used to collect demographic and clinical characteristics of colorectal cases and control subjects, including smoking status, drinking status, history of cancer, physical activity, vegetable intake, and energy intake.

Genotype analysis

All study participants provided 5 mL venous blood after enrolling in the study; blood samples were stored at -20°C until use. For genotype determination, DNA samples were obtained from the peripheral blood sample using the TIANamp blood DNA kit (Tiangen Biotech, Beijing, China). Genotyping for the *ERCC1* rs2298881 and rs11615 and *XPF* rs2276466 polymorphisms were detected using the polymerase chain reaction-restriction fragment length polymorphism method. Primer sequences for the *ERCC1* rs2298881 and rs11615 and *XPF* rs2276466 polymorphisms were designed using the Sequenom® Assay Design version 3.1 software (San Diego, CA, USA). The cycling program involved preliminary denaturation at 94°C for 5 min, followed by 35 cycles of denaturation at 94°C for 30 s and annealing at 55°C for 30 s, with a final extension at 72°C for 5 min. For quality control, a randomly chosen subgroup of 10% of the cases and control subjects was selected to repeat analysis. These results of the quality control analysis confirmed 100% concordance.

Statistical analysis

Continuous variables are reported as means ± standard deviation, while categorical variables are reported as frequencies and percentages. Continuous variables between case and control subjects were compared by the Student *t*-test, while categorical variables between groups were compared by the χ^2 test. Hardy-Weinberg equilibrium was compared in controls using the χ^2 test. Unconditional logistic regression was performed to evaluate the association between *ERCC1* and *XPF* polymorphisms and colorectal cancer risk. Odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were used to evaluate the effect of *ERCC1* and *XPF* polymorphisms on colorectal cancer risk. Statistical significance was defined as a P value <0.05, and all comparisons were two-sided. All statistical analyses were conducted using the SPSS 16.0 software (SPSS Inc., Chicago, IL, USA).

RESULTS

A total of 279 colorectal cancer cases and 316 healthy controls were included in this analysis (Table 1). There was no significant difference between the 2 groups in terms of gender, age, physical activity, and vegetable intake (P > 0.05). Colorectal cancer cases were more likely to be smokers, drinkers, have higher energy intake, and have a family history of cancer.

Genotype distributions of *ERCC1* rs2298881 and rs11615 and *XPF* rs2276466 are shown in Table 2. The distributions of *ERCC1* and *XPF* among controls were in accordance with Hardy-Weinberg equilibrium, while the distribution of rs2276466 was not (Table 2). The minor allele frequencies of the *ERCC1* rs2298881 and rs11615 and *XPF* rs2276466 polymorphisms among the controls were 0.220, 0.366, and 0.229, respectively, which were similar to those in in the NCBI dbSNP databases.

Unconditional regression analysis showed that subjects carrying the *ERCC1* rs2298881 CC genotype and C allele had a significantly increased risk of colorectal cancer compared with those carrying the AA genotype (CC *vs* AA, OR = 2.68, 95%CI = 1.47-4.75; C allele *vs* A allele, OR = 1.58, 95%CI = 1.25-2.03) (Table 3). However, we did not find an association between the rs11615 and rs2276466 polymorphisms and colorectal cancer risk.

Table 1. Comparison of selected characteristics of colorectal cases and controls.

Variables	Cases (N = 279)	%	Controls (N = 316)	%	χ^2	P value
Age (years)						
<60	119	42.6	141	44.7		
≥60	160	57.4	175	55.3	0.23	0.63
Gender						
Female	115	41.2	137	43.5		
Male	164	58.8	179	56.5	0.28	0.60
Cigarette smoking						
Never	174	62.3	222	70.4		
Ever	105	37.7	94	29.6	4.14	0.04
Alcohol drinking						
Never	157	56.3	208	65.6		
Ever	122	43.7	109	34.4	5.46	0.02
Physical activity						
Sedentary	160	57.4	200	63.2		
Intermediate	68	24.3	71	22.5		
Active	51	18.3	45	14.3	2.59	0.27
Energy intake (kcal/day)		1823.3 ± 453.4		1912.3 ± 641.3	1.93	0.03
Vegetable intake (g/day)		7.3 ± 2.4		7.6 ± 2.7	1.42	0.08
Cancer history in the first-degree relatives						
No	261	93.4	314	99.51		
Yes	18	6.6	2	0.49	15.40	<0.001

Table 2. Genotype characteristics of the three single nucleotide polymorphisms.

	Gene	Alleles	MAF		HWE (P value) in controls
			Control group	From dbSNP	
ERCC1	rs2298881	A/C	0.220	0.193	0.14
	rs11615	C/T	0.366	0.363	0.11
XPF	rs2276466	C/G	0.229	0.225	0.04

MAF = minor allele frequency; HWE = Hardy-Weinberg equilibrium.

Table 3. Logistic regression analysis of association between *ERCC1-XPF* polymorphisms and colorectal cancer risk.

Variants	Genotypes	Cases	%	Controls	%	Crude OR (95%CI)	P value	Crude OR (95%CI)[1]	P value
rs2298881	AA	149	53.4	197	62.3	1.0 (Ref.)	-	1.0 (Ref.)	-
	AC	92	33.0	99	31.3	1.23 (0.85-1.78)	0.26	1.37 (0.91-1.92)	0.13
	CC	37	13.6	20	6.3	2.45 (1.32-4.63)	0.002	2.68 (1.47-4.75)	<0.001
	A allele	390	139.8	493	156.0	1.0 (Ref.)	-	1.0 (Ref.)	-
	C allele	166	60.2	139	44.0	1.51 (1.15-1.98)	0.002	1.58 (1.25-2.03)	<0.001
rs11615	CC	108	38.7	134	42.4	1.0 (Ref.)	-	1.0 (Ref.)	-
	CT	121	43.4	133	42.1	1.23 (0.78-1.63)	0.5	1.34 (0.85-2.28)	0.31
	TT	50	17.9	49	15.5	1.12 (0.69-1.83)	0.63	1.37 (0.75-2.16)	0.51
	C allele	337	120.8	401	126.9	1.0 (Ref.)	-	1.0 (Ref.)	-
	T allele	221	79.2	231	73.1	1.28 (0.84-1.95)	0.22	1.42 (0.94-2.16)	0.12
rs2276466	CC	163	58.4	197	62.3	1.0 (Ref.)	-	1.0 (Ref.)	-
	CG	88	31.5	93	29.4	1.14 (0.79-1.66)	0.46	1.27 (0.85-1.83)	0.24
	GG	28	10.0	26	8.2	1.30 (0.70-2.41)	0.37	1.42 (0.74-2.62)	0.24
	C allele	414	148.4	487	154.1	1.0 (Ref.)	-	1.0 (Ref.)	-
	G allele	144	51.6	145	45.9	1.17 (0.89-1.54)	0.25	1.23 (0.92-1.63)	0.17

[1]Adjusted for gender, age, cigarette smoking, and cancer history in the first-degree relatives.

DISCUSSION

In this study, we found that a polymorphism in *ERCC1* rs2298881 was associated with a moderately increased risk of colorectal cancer, but polymorphisms in *ERCC1* rs11615 and rs2276466 were not associated with colorectal cancer risk. This is the first study demonstrating that the *ERCC1* rs2298881 polymorphism is related to an increased risk of colorectal cancer. Our findings suggest that *ERCC1* rs2298881 may be useful as a genetic susceptibility marker for colorectal cancer, which can be used for identifying high-risk individuals.

ERCC1 plays a critical role in the NER mechanism by encoding a subunit for the NER complex used during the incision step of the NER pathway (van Duin et al., 1986; Reed, 1998). Previous studies indicated that *ERCC1* polymorphisms are associated with an increased risk of various cancers, including lung cancer, prostate cancer, breast cancer, and gastric cancer (Yin et al., 2011; Barry et al., 2012; He et al., 2012; Yang et al., 2013). Yin et al. (2011) reported that rs2298881 polymorphisms may increase the risk of smoking-related lung cancer. He et al. (2012) suggested that *ERCC1* rs2298881C and rs11615A contribute to the risk of gastric cancer. Barry et al. (2012) reported that men carrying the variant A allele at *ERCC1* rs2298881 exhibited an increased prostate cancer risk. For colorectal cancer, a previous study showed that the *ERCC1* C8092A polymorphism may contribute to colorectal cancer susceptibility in the Chinese population (Ni et al., 2014). Another study indicated that a haplotype of *ERCC1* was associated with an increased risk of colorectal cancer (Moreno et al., 2006). In this study, we found that subjects carrying the *ERCC1* rs2298881CC genotype and C allele showed a significantly increased risk of colorectal cancer, which agreed with the results of previous studies (Moreno et al., 2006; Ni et al., 2014). Therefore, our study showed that *ERCC1* polymorphisms may be important in the genetic susceptibility to colorectal cancer and can thus be used to identify high-risk groups of individuals.

XPF, also known as ERCC4, is involved in the NER pathway and in removing DNA interstrand cross-links and DNA double-strand breaks; thus, XPF is associated with the susceptibility to malignant tumors (Zhu et al., 2003; Niedernhofer et al., 2004). Previous studies showed that polymorphisms in *XPF* may be associated with an increased risk of various cancers, including breast cancer, gastric cancer, and glioma (He et al., 2012; Yang et al., 2013; Cheng et al., 2013; Zhang et al., 2013; Wang et al., 2013). However, the results are inconsistent between these studies. Two previous studies reported an association between *XPF* polymorphisms and colorectal cancer risk (Huang et al., 2006; Joshi et al., 2009), and no significant association was found, which is similar to the results of our study.

There were several limitations to our study. First, the study was conducted in one hospital in China, and this population may not be representative of the entire population of China. Second, colorectal cancer is a disease induced by multiple genes and environmental factors, and other genetic and environmental factors should be examined in future studies. Third, the number of cases and controls was relatively small. Additional studies including a large sample size study are required to confirm the association between *ERCC1* and *XPF* polymorphisms and colorectal cancer risk.

In conclusion, we found that subjects carrying the *ERCC1* rs2298881CC genotype and C allele were associated with an increased risk of colorectal cancer in a Chinese population. However, no association was found between polymorphisms in rs11615 and rs2276466 and colorectal cancer risk. Further large-scale studies are required to determine whether *ERCC1* and *XPF* polymorphisms play a role in the development of colorectal cancer.

REFERENCES

Ballinger AB and Anggiansah C (2007). Colorectal cancer. *BMJ* 335: 715-718.

Barry KH, Koutros S, Andreotti G, Sandler DP, et al. (2012). Genetic variation in nucleotide excision repair pathway genes, pesticide exposure and prostate cancer risk. *Carcinogenesis* 33: 331-337.

Cheng HB, Xie C, Zhang RY, Hu SS, et al. (2013). Xeroderma pigmentosum complementation group F polymorphisms influence risk of glioma. *Asian Pac. J. Cancer Prev*. 14: 4083-4087.

Cunningham D, Atkin W, Lenz HJ, Lynch HT, et al. (2010). Colorectal cancer. *Lancet* 375: 1030-1047.

Foulkes WD (2008). Inherited susceptibility to common cancers. *N. Engl. J. Med*. 359: 2143-2153.

He J, Xu Y, Qiu LX, Li J, et al. (2012). Polymorphisms in ERCC1 and XPF genes and risk of gastric cancer in an eastern Chinese population. *PLoS One* 7: e49308.

Huang WY, Berndt SI, Kang D, Chatterjee N, et al. (2006). Nucleotide excision repair gene polymorphisms and risk of advanced colorectal adenoma: XPC polymorphisms modify smoking-related risk. *Cancer Epidemiol. Biomarkers Prev*. 15: 306-311.

Huang MY, Wang JY, Huang ML, Chang HJ, et al. (2013). Polymorphisms in XPD and ERCC1 Associated with Colorectal Cancer Outcome. *Int. J. Mol. Sci*. 14: 4121-4134.

International Agency for Research on Cancer (IARC) (2012). GLOBOCAN 2012: Estimated Cancer incidence, mortality and prevalence worldwide in 2012. [http://globocan.iarc.fr]. Accessed January 16, 2014.

Joshi AD, Corral R, Siegmund KD, Haile RW, et al. (2009). Red meat and poultry intake, polymorphisms in the nucleotide excision repair and mismatch repair pathways and colorectal cancer risk. *Carcinogenesis* 30: 472-479.

Markowitz SD and Bertagnolli MM (2009). Molecular origins of cancer: Molecular basis of colorectal cancer. *N. Engl. J. Med*. 361: 2449-2460.

Moreno V, Gemignani F, Landi S, Gioia-Patricola L, et al. (2006). Polymorphisms in genes of nucleotide and base excision repair: risk and prognosis of colorectal cancer. *Clin. Cancer Res*. 12: 2101-2108.

Ni M, Zhang WZ, Qiu JR, Liu F, et al. (2014). Association of ERCC1 and ERCC2 polymorphisms with colorectal cancer risk in a Chinese population. *Sci. Rep*. 4: 4112.

Niedernhofer LJ, Odijk H, Budzowska M, van Drunen E, et al. (2004). The structure-specific endonuclease Ercc1-Xpf is required to resolve DNA interstrand cross-link-induced double-strand breaks. *Mol. Cell. Biol*. 24: 5776-5787.

Reed E (1998). Platinum-DNA adduct, nucleotide excision repair and platinum based anti-cancer chemotherapy. *Cancer Treat. Rev*. 24: 331-344.

van Duin M, de Wit J, Odijk H, Westerveld A, et al. (1986). Molecular characterization of the human excision repair gene ERCC-1: cDNA cloning and amino acid homology with the yeast DNA repair gene RAD10. *Cell* 44: 913-923.

Wang AT, Sengerova B, Cattell E, Inagawa T, et al. (2011). Human SNM1A and XPF-ERCC1 collaborate to initiate DNA interstrand cross-link repair. *Genes Dev*. 25: 1859-1870.

Wang XF, Liu S and Shao ZK (2013). Effects of polymorphisms in nucleotide excision repair genes on glioma risk in a Chinese population. *Gene* 529: 317-320.

Wood RD (1997). Nucleotide excision repair in mammalian cells. *J. Biol. Chem*. 272: 23465-23468.

Yang Z, Fang X, Pei X and Li H (2013). Polymorphisms in the ERCC1 and XPF genes and risk of breast cancer in a Chinese population. *Genet. Test. Mol. Biomarkers* 17: 700-706.

Yin J, Vogel U, Ma Y, Qi R, et al. (2011). HapMap-based study of a region encompassing ERCC1 and ERCC2 related to lung cancer susceptibility in a Chinese population. *Mutat. Res*. 713: 1-7.

Zhang JS, Zhang C, Yan XY, Yuan ZF, et al. (2013). Effect of Xeroderma pigmentosum complementation group F polymorphisms on gastric cancer risk and associations with *H. pylori* infection. *Asian Pac. J. Cancer Prev*. 14: 1847-1850.

Zhu XD, Niedernhofer L, Kuster B, Mann M, et al. (2003). ERCC1/XPF removes the 3' overhang from uncapped telomeres and represses formation of telomeric DNA-containing double minute chromosomes. *Mol. Cell* 12: 1489-1498.