RESEARCH COMMUNICATION

Genetic Polymorphisms of DNA Repair Genes XRCC1 and XRCC3 and Risk of Colorectal Cancer in Chinese Population

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Abstract

Aim: The distribution of DNA repair gene XRCC1 and XRCC3 genotypes was used to assess the potential influence of genetic polymorphisms on risk of colorectal cancer, and interactions with other factors. Methods: a 1:2 matched case-control study was conducted with 485 cases and 970 controls. XRCC1 and XRCC2 genotype polymorphisms were based upon duplex polymerase-chain-reaction with the confronting-two-pairprimer (PCR-CTPP) method. Results:The XRCC1 399Cln allele polymorphism was found to be associated with an increased colorectal cancer risk, while an non-significant inversely association was noted for XRCC3 241Thr/Thr genotype. We also found that individuals with the XRCC1 399 Gln and XRCC3 241Met alleles had an elevated risk, while XRCC3241Thr/Thr was proctective. Conclusion: This study is the first to provide evidence of importance of XRCC1 and XRCC3 gene polymorphisms for risk of colorectal cancer in the Chinese population.

Keywords: XRCC1 - XRCC3 - genetic polymorphisms - colorectal cancer - Chinese population

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Introduction

Colorectal cancer is the third most common cancer in men (663,000 cases, 10.0% of the total) and the second in women (571,000 cases, 9.4% of the total) worldwide. Almost 60% of the cases occur in developed regions. Incidence rates vary 10-fold in both sexes worldwide, the highest rates being estimated in Australia/New Zealand and Western Europe, the lowest in Africa and South-Central Asia, and are intermediate in Latin America. Incidence rates are substantially higher in men than in women (overall sex ratio of the ASRs 1.4:1) (IARC, 2008). The wide geographic variation at an international levels of colorectal cancer in terms of incidence and mortality suggested the role of genetic and environmental factors in the pathogenesis of this cancer.

The development of colorectal cancer cancer has mainly been attributed to environmental factors, including diet, lifestyle and environmental pollution (Doll and Peto, 1981; Thomas, 1993), inter-individual differences in susceptibility to colorectal cancer may be due to genetic alterations, including those involved in DNA repair (Potter, 1999; De Jone et al., 2002). In recent years, it has been shown that genetic polymorphisms in DNA repair genes, X-ray repair cross-complementing groups 1, 3 (XRCC1 and XRCC3), play a role as a modifier of cancer risk. The XRCC1 gene (located at chromosome 19q13.2) produces an enzyme involved in the base excision repair (BER) pathway, amending small lesions such as singlestrand breaks (SSBs), non-bulky adducts, oxidative damage, alkylation, and methylation. Recently, the XRCC1 complex has also been described as part of an alternative route of DNA double-strand break (DSB) nonhomologous end-rejoining, i.e., PARP1–dependent end-joining of DSBs (Audebert et al., 2004). The XRCC1 protein is essential for mammalian viability and XRCC1-deficient cells are genetically unstable and sensitive to DNA damaging agents. Three common polymorphisms occurring at conserved sequences in XRCC1 gene have been reported, and amino acid substitutionsin XRCC1 were at codons 194 (exon 6, C→ T, Arg→ Trp), 280 (exon 9, G→ A, Arg→ His), and 399 (exon 10, G→ A, Arg→ Gln) (Shen et al., 1998). These mutations could alter XRCC1 function, diminish repair kinetics, influence susceptibility to adverse health effect, such as cancer.

The XRCC3 protein, involved in the homologous recombinational repair (HRR) of DNA double-strand break repair and cross-links, is a member of an emerging family of Rad-51-related proteins that likely participate in HR to maintain genomic stability and repair DNA damage (Brenneman et al., 2000). XRCC3 has been shown to interact directly with HsRa 51, and XRCC3 deficient cell lines display reduced HR (Pierce, 1999) and they are hypersensitive to ionizing radiation, UV radiation, genotoxic alkylating agents, and cross-linking agents (Caldecott, 1991). The main SNP in the XRCC3 gene leads to an amino acid substitution at codon 241 (exon 8, C→ T, Thr→ Met) (Shen, 1998).

Despite the fact that XRCC1 and XRCC3 have been widely examined and related to several types of

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cancer, their role in colorectal carcinogenesis in Chinese population has not been established. Therefore, we conducted this case-control study in an Chinese population to detect the distribution of DNA repair genes XRCC1 and XRCC3 genotypes and to assess the potential role of these genetic polymorphism on the risk of colorectal cancer, and the modification from potential factors.

Materials and Methods

Subjects and methods

The 1:2 matched case-control study was conducted with 485 cases (including 253 colon and 232 rectal cancer patients) and 970 controls. The controls were matched with cases by sex and age (±5 years). All cases were firstly diagnosed as primary colorectal carcinoma between January, 2007 and May, 2011. Controls were cancer-free healthy individuals, and they were selected people who requested general health examinations in the same hospital during the same period as the case collection.

A uniform questionnaire was used for all subjects regarding sociodemographic characteristics, dietary habits, alcohol consumption, smoking and other potential confounding factors by face to face interviewers. The trained interviewers were not aware of the study hypothesis. Cancer patients were asked to refer about the dietary habit a year before disease diagnosed. Information was collected on known or potential risk factors including education level, annual income, BMI, alcohol consumption, cigarette use, vegetable and fruit consumption, physical activity and family history of colorectal cancer.

Alcohol consumption were divided into never and moderate and heavy drinkers. Individuals who drank 100 -250 g alcohol (400 ml beers, 250 wine ml and 100 ml white spirit) per month and continued for 6 months were regarded as moderate drinkers, and those who drank more than 250 g alcohol per month were as heavy drinkers. Tobacco smoking was categorized into never and current drinking. Individuals who smoked 20-50 packets of cigarettes per year, or smoked more than one cigarette per day and continued for 6 months were regarded as moderate smokers, and those who smoked more than 50 packets of cigarettes per years were as heavy smokers. Height, current body weight and body weight 10 years before the study were recorded to analyze the body mass index (BMI, kg/m^2).

Genotyping of XRCC1 and XRCC3

XRCC1 and XRCC2 Genotype polymorphisms was based upon duplex polymerase-chain-reaction with the confronting-two-pairprimer (PCR-CTPP) method. PCR was performed in a reaction mixture of 10 μL containing 0.5 units of Taq biocatalysts, 1.8 mmol/L Mg2+, 2.4μL dNTPs, 8 primers, 15 pmol of each primer and 5-8 μL template. The XRCC1 Arg399Gln genotyped were determined according to the methods described in prious studies (Lunn et al., 1999). Primers for the Arg399Gln gene were 5'-GAACTCCCTGAAAAGCTAAAGC-3' and 5'-GTTGGGCTCAAATATACGGTGG-3'. The primers for the XRCC3 Thr241Met gene were 5'-GGTCGAGTGACAGTCCAAAC-3' and 5'-TGCAACGGCTGAGGGTCTT-3'. The PCR conditions were as follows: initial denaturation at 94°C for 5 min, followed by 35 cycles at 94°C for 30 s, at 62°C for 30 s, at 72°C for 30 s, and a final extension at 72°C for 5 min. After transient centrifugation, agarose electrophoresis was conducted.

Statistical analysis

All analysis was performed by using the STATA statistical package (version 10.0, STATA, College Station, TX). Hardy-Weinberg equilibrium of alleles at controls was assessed by using exact tests. Categorical variables were compared with use of the chi-square test or Fisher's exact test (when one expected value was <5). Conditional logistic regression was undertaken to estimate odds ratios (ORs) and their 95% confidence intervals (95% CIs) after controlling for potential confounding factors, including age, sex, education level, annual income, BMI, cigarette smoking, alcohol consumption, vegetable consumption, fruit consumption and family history of cancer. Statistical significance for the interaction was tested by the likelihood ratio test, which compared logistic models with and without interaction terms. Statistical significance was

Table 1. Characteristics of the Cases and Control in the Study

Characteristics	Cases n=485(%)	Controls n=970(%)	P value
Sex			
Male	327(67.4)	654(67.4)	0.52
Female	158 (32.6)	316(32.6)	
Age	59.3±7.4	58.8±7.7	0.11
Education level			
None/ Elementary	171(35.3)	257(26.5)	<0.001
Middle or high	202(41.6)	492(50.7)	
College or higher	112(23.1)	211(22.8)	
Annual income			
<5000	189(38.9)	266(27.4)	<0.001
5000-10000	214(44.2)	337(34.7)	
≥10000	82(16.9)	368(37.9)	
BMI(kg/m2) 10 years previously			
<18.5	153(31.6)	332(34.2)	0.23
18.5-23.9	177(36.5)	370(38.1)	
≥24	155(31.9)	269(27.7)	
Alcohol consumption(g alcohol/ per month)			
Never	239(49.2)	696(72.1)	<0.001
20-50	135(27.8)	179(18.5)	
>50	112(23.0)	91(9.4)	
Cigarette smoking(packets of cigarettes / year)			
Never	268(55.3)	696(71.8)	<0.001
100-250	104(21.4)	125(12.9)	
>250	113(23.3)	148(15.3)	
First degree relatives history of cancer			
Yes	93(19.2)	57(5.9)	<0.001
No	392(80.8)	913(94.1)	
Vegetable consumption(times / week)			
<3	176(36.3)	217(22.4)	<0.001
4~6	206(42.5)	356(36.7)	
>6	103(21.2)	397(40.9)	
Fruit consumption(times / week)			
<3	351(72.3)	566(58.4)	<0.001
4~6	73(15.0)	219(22.6)	
>6	57(11.7)	184(19.0)	

Table 2. Frequencies of the Studies XRCC1 and XRCC2 Polymorphisms on Colorectal Cancer Risk

Gene	Cases n=485(%)	Controls n=970(%)	OR[1](95% CI)	OR[2](95% CI)
XRCC1 Arg399Gln				
Arg/Arg	239(49.2)	556(57.3)	1.0(reference)	1.0(reference)
Arg/Gln	188(38.7)	354(36.5)	1.24(0.97-1.57)	1.33(1.02-1.68)
Gln/Gln	59(12.1)	60(6.2)	2.28(1.52-3.44)	2.47(1.63-3.50)
P for trend			0.04	0.03
XRCC3 Thr241Met				
Thr/Thr	357(73.7)	846(87.2)	1.0(reference)	1.0(reference)
Thr/Met	89(18.4)	81(8.4)	2.60(1.85-3.65)	1.82(1.24-2.93)
Met/Met	38(7.9)	43(4.4)	2.09(1.23-3.38)	1.84(1.15-3.12)
P for trend			0.17	0.45

[1]Unadjusted odds ratio; [2]Odds ratio after adjusted for age, sex, education level, annual income, BMI, cigarette smoking, alcohol consumption, vegetable consumption, fruit consumption and family history of cancer

defined as a 2-sided P-value of less than 0.05.

Results

The characteristics of the study subjects were summarized in Table 1. Case subjects seemed to have lower education level, lower annual income, heavy alcohol consumption, more cigarette smoking, having cancer history of the first degree relatives and fewer vegetable and fruit consumption would have higher risk of colorectal cancer. In contrast, sex, age and BMI did not substantially differ between cases and controls.

Genotype distributions of the XRCC1 Arg399Gln and XRCC3 Thr241Met polymorphisms in controls were in agreement with the Hardy-Weinberg equilibrium (p=0.19 for Arg399Gln and p=0.26 for Thr241Met). The XRCC1 399 Arg/Gln and Gln/Gln genotypes were significantly more frequently in cases than controls, and XRCC3 241 Thr/Met and Met/Met genotypes were also more in cases (Table 2). An high increased OR of colorectal cancer was found in individual with XRCC1 399 Gln/Gln genotype (OR=2.47, 95% CI=1.63-3.50). An increased trend of OR was found in XRCC1 Arg399Gln genotypes (p for trend =0.03). Moreover, a positive association was also found in individual with XRCC3 241 Thr/Met and Met/Met genotypes and colorectal cancer (OR=1.82, 95%CI=1.24-2.93 for 241 Thr/Met; OR=1.84, 95%CI=1.15-3.12 for 241 Met/Met).

Gene-gene interactions of the XRCC1 Arg399Gln and XRCC3 Thr241Met polymorphisms were also estimated (Table 3). Using the comined low-risk genotypes (XRCC1 399Arg/Arg and XRCC3 241Thr/Thr) as the referent group, the combination of XRCC1 399 Gln allele and XRCC3 241Met allele showed a significantly strong positive association with colorectal cancer (OR=3.06, 95%CI=2.04-3.85). Moreover, individual with XRCC1 399Arg/Arg and XRCC2 Met allele demonstrated a moderate risk of colorectal cancer.

Table 3. Combined Genotype Analysis of XRCC1 Arg399Gln and XRCC3 Thr24Met Genotype on Colorectal Cancer Risk

XRCC1 Arg399Gln	XRCC3 Thr241Met	Cases n=485(%)	Controls n=970(%)	OR[1](95% CI)
Arg/Arg	Thr/Thr	103(21.1)	319(32.9)	1.0(Reference)
Gln allele	Met allele	168(34.6)	194(20.0)	3.06(2.04-3.85)
Gln allele	Thr/Thr	79(16.3)	237(24.4)	1.41(0.85-1.78)
Arg/Arg	Met allele	136(28.0)	220(22.7)	2.16(1.52-2.85)

[1]Odds ratio after adjusted for age, sex, education level, annual income, BMI, cigarette smoking, alcohol consumption, vegetable consumption, fruit consumption and family history of cancer

We also analyze the frequencies of XRCC1 and XRCC2 polymorphisms on colorectal cancer risk by tumor site(Table 4). Individual with XRCC1 Gln/Gln and XRCC3 Met/Met showed higher cancer risk of rectum compared with colon cancer (OR=3.25, 95%CI=2.02-5.11 for 399Gln/Gln; OR=3.07, 95%CI=1.46-4.87 for 241Met/Met).

Discussion

In this study, we investigated the associations between genetic polymorphisms in the DNA repair gene XRCC1 and XRCC3 and colorectal cancer risk. Our results showed that the XRCC1 399Cln allele polymorphism is associated with increased colorectal cancer risk, while an non-significantly inversely association was found in XRCC3 241Thr/Thr genotype. We also found that individuals with the XRCC1 399 Gln allele and XRCC3 241Met allele had a heavy risk of colorectal cancer. In additional, we found the higher risk of XRCC1 399 Gln allele in rectum cancer and a lower risk of XRCC3241Thr/Thr in colon cancer.

An increased evidence showed that the genetic variation in DNA repair genes lead to different DNA repair capacity, variations in DNA repair capacity result in different biological responses to DNA damage and thus different susceptibility for developing cancers (Hu et al., 2002). Cumulating information on the DNA repair gene polymorphisms may be important in clarifying the causes

Table 4. Frequencies of XRCC1 and XRCC2 Polymorphisms on Colorectal Cancer Risk by Tumor Site

Gene		Controls n=750	Colon Cases n=40%	Colon OR[1](95% CI)	Rectum Cases n=60%	Rectum OR[1](95% CI)
XRCC1 Arg399Gln	Arg/Arg	556(57.3)	124(25.6)	1.0(Reference)	114(23.6)	1.0(Reference)
	Arg/Gln	354(36.5)	108(22.2)	1.47(0.93-1.97)	80(6.5)	1.56(1.05-2.16)
	Gln/Gln	60(6.2)	21(4.3)	2.21(1.18-2.92)	38(7.8)	3.25(2.02-5.11)
XRCC3 Thr241Met	Thr/Thr	846(87.2)	201(41.4)	1.0(Reference)	157(32.3)	1.0(Reference)
	Thr/Met	81(8.4)	51(10.5)	2.36(1.46-4.02)	38(7.9)	2.38(1.74-4.03)
	Met/Met	43(4.4)	18(3.7)	1.91(1.13-3.36)	20(4.2)	3.07(1.46-4.87)

[1]Odds ratio after adjusted for age, sex, education level, annual income, BMI, cigarette smoking, alcohol consumption, vegetable consumption, fruit consumption and family history of cancer

and mechanisms of cancers, and therefore DNA repair gene polymorphisms may act as genetic susceptibility factors and thus identify high-risk groups of exposed individuals. Number of previous studies which conducted in India, German, American, Singapores and Korea showed the association between DNA repair genes and the risk of colorectal cancer, but their results are inconsistent (Egger et al., 1997; Mort et al., 2003; Tranah et al., 2004; Hong et al., 2005; Stern et al., 2005). In our study, we showed the XRCC1 399 Gln allele significantly increased the colorectal cancer risk, which is in line with the study conducted in Japan (Yin et al., 2012), while different from the studies in Caucasian population and American (Mort et al., 2003; Stern et al., 2005). The variation association between DNA repair genes and colorectal cancer risk showed difference in the gene variation in ethnicities.

As we known, DNA damage may result in genetic instability, mutagenesis and cell death. DNA repair mechanisms are important for maintaining genome integrity and preventing carcinogenesis. Base excision repair XRCC1 is the predominant DNA damage repair pathway for the processing of small base lesions, derived from oxidation and alkylation's damage. XRCC1 gene is regarded an important proteins in the multistep BER pathway, and it is the first mammalian gene isolated that affects cellular sensitivity to ionizing radiation (Thompson et al., 1990). Mutations of XRCC1 may increase the risk of cancers by impairing the interaction of XRCC1 with other enzymatic proteins and consequently altering DNA repair activity (Basso et al., 2007; Tudek, 2007), and subsequently induce the carcinogenesis (Yu et al., 2003; Han et al., 2004). There were three reported polymorphisms at codons 194, 280 and 399 of XRCC1, codon 194 and 280 do not locate in the important domain, but codon 399 locates in the BRCT1 domain. Previous experimental study showed the amino acid replacement of codon 399 could injury the DNA repair captivities and increase the susceptibility to ionizing radiation. Our study showed the XRCC1 399 Gln allele could significantly increase the risk of colorectal cancer.

XRCC3 is one of the Rad51-related proteins and functions through complex interactions with other relevant proteins to repair double-strand breaks and to maintain genome integrity in multiple phases of a homologous recombination (Brenneman et al., 2000). Although previous studies showed polymorphisms of this gene may reduce the DNA repair capacity, the evidence is limited, and the epidemiologic studies in terms of the associations with colorectal cancer are conflict (Whitehouse et al., 2001; Mort et al., 2005; Improta et al., 2008). The Italian population showed XRCC3 241Met allele showed an moderate increased risk of colon cancer (Improta et al., 2008), while the Mort reported higher colorectal cancer risk among individual with XRCC3 241Thr/Thr (Mort et al., 2005). Moreover, study conducted in Norway showed no association between XRCC3 and colorectal cancer (Whitehouse et al., 2001). Our study showed individuals with XRCC3 241Thr allele are moderate associated with colorectal cancer risk, and heavy cancer risk was found in rectum cancer. The variation among studies with XRCC3 may be due to study sample or different DNA repair mechanism of XRCC3 in different ethnicities.

In our study, we also found the combine effect of XRCC1 399 Gln allele and XRCC3 241Thr allele had a higher risk of colorectal cancer. It is showed that the presence of deficient DNA repair capacity for each specific DNA-repair pathway may contribute to increased colorectal cancer risk. The multiplicative effects of combined genetic variants for different DNA-repair pathways have been previously reported for lung cancer, breast cancer and glioma cancer (Chen et al., 2002; Smith et al., 2003; Kiuru et al., 2008). Previous study showed the combined effect of XRCC1 and XPD genes could increase the risk of lung cancer (Zhou et al., 2003). Another study showed that the prolonged cell-cycle delay was significantly associated with variant alleles of the APE1 and XRCC1 genes (Hu et al., 2001). Therefore, it is reasonable to infer that the multiplicative effect of genetic polymorphism for DNA repair genes may simultaneously contribute to colorectal carcinogenesis.

In conclusion, this study is the first time to reported the XRCC1 and XRCC3 gene polymorphisms and their combination effect on the risk of colorectal cancer in Chinese population. Our results showed that the XRCC1 and XRCC3 gene polymorphisms are associated with the risk of colorectal cancer. However, the gene susceptibility showed variable in different ethnicity, therefore, further large sample multicenter studies are needed to confirm

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