RESEARCH ARTICLE

Polymorphisms in *XRCC1* Gene, Alcohol drinking, and Risk of Colorectal Cancer: a Case-control Study in Jiangsu Province of China

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Abstract

To evaluate the relationship between alcohol drinking, *XRCC1* codon 194 and 399 polymorphisms and risk of colorectal cancer, we conducted a case-control study with 315 colorectal cancer cases (105 colon, 210 rectal) and 439 population-based controls in Jiangsu Province of China. The *XRCC1* codon 194 and 399 genotypes were identified using polymerase chain reaction and restrictrion fragment length polymorphism methods (PCR–RFLP). A structured questionnaire was used to elicit detailed information. Odds ratios (ORs) were estimated with an unconditional logistic model. In this study no significant differences were observed among the studied groups with regard to the genotype distribution of the *XRCC1* codons 194 and 399 and the risk of colorectal cancer did not appear to be significantly influenced by genotype alone, whereas alcohol consumption showed a positive association (*P* for trend <0.01). When combined effects of *XRCC1* polymorphisms and alcohol consumption were analyzed, we found that the 194Trp or 399Gln alleles further increased the colorectal cancer risk due to high alcohol intake. These findings support the conclusion that colorectal cancer susceptibility may be altered by gene-environment interactions.

Keywords: Colorectal cancer - *XRCC1* - gene polymorphisms - alcohol drinking - susceptibility

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Introduction

The x-ray cross-complementig group 1 (*XRCC1*) is a DNA repair gene. This gene code for protein involved in the repair of single-strand breaks (SSB) and in base excision repair (BER) of damaged DNA bases caused by endogenous and exogenous oxidants. The *XRCC1* protein is a scaffolding protein directly associated with polymerase and functions in a complex to facilitate the BER and SSB processes. Genetic polymorphisms in *XRCC1* gene may influence individual variation in DNA repair capacity, which may be associated with a higher risk of developing cancer. The polymorphisms occurring at conserved sequences in the *XRCC1* gene were reported by Shen et al (1998).. These coding polymorphisms, resulting in amino acid substitutions, were detected at codons 194 (Arg-Trp, rs1799782), 399 (Arg-Gln, rs25487) and 280 (Arg-His). Many authors have analysed relationship between the *XRCC1* polymorphisms and the risk of several cancers, including colorectal cancer, however study findings have been inconsistent (Abdel-Rahman et al., 2000; Yeh et al., 2005; Stern et al., 2007; Jin et al., 2007, 2008; Improta et al., 2008; Curtin et al., 2009; Wang et al., 2010; Canbay et al., 2011; Gsur et al., 2011; Reeves et al., 2012; Jelonek et al., 2012; Karahalil et al., 2012). Hong et al. (2005) in South Korean and Yin et al. (2012) in Japanese observed an increased risk of colorectal cancer associated with the *XRCC1* Arg399Gln polymorphism and high alcohol intake. Whereas in another study in Japanese, Kasahara et al. (2008) found *XRCC1* Arg399Gln was not associated with a colorectal cancer risk. To evaluate possible relationship between the *XRCC1* codons 194 and 399 polymorphisms and the risk of colorectal cancer in the Jiangsu Province of China, we conducted a population-based case-control study.

Materials and Methods

Study Subjects

We recruited colorectal cancer cases using data of the Cancer Registries in Huian and Jintan Cities of the Jiangsu Province of China, and also recruited cases who visited Jiangsu Province Cancer Hospital from these cities from August 2000 to September 2002. All were histopathologically diagnosed as having a primary colorectal cancer, and have never been other cancers.

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Physicians at the hospital or families of patients asked eligible cases to participate in our study, and doctors or nurses interviewed the subjects and collected their blood samples from a peripheral vein after obtaining informed consent. Population-based controls were selected from healthy residents in eight villages or towns of Huian and Jintan Cities. They must be not any cancers. Doctors of the public health center randomly selected one or two controls for each case, after matching for ethnicity, sex and age within 2 years using the records of residents at the local governmental office, and then asked eligible residents for their participation, and conducted interviews and collected blood samples in the same manner. A total of 10 patients and 33 residents refused to participate in our study, but the response rates was 97% for cases and 93% for controls. The ethics committee of the Jiangsu Province Institute of Cancer Research approved this study.

Background Data and environmental factors

All participants completed an in-person interview that used a structured questionnaire. The items of our questionnaire covered demographic background, height, body weight, alcohol drinking and smoking habits. In this study, smoking status was categorized as never and ever-smokers (including both current and former smokers) and drinking status as drinkers/non-drinkers (the latter including individuals whose average alcohol consumption <1 g/day). Alcohol consumption was calculated according to 40g/100g of hot wine, 3.5g/100 g of beer and 12g/100g of grape wine. The body mass index (BMI) was calculated based on body weights and heights, and stratified into three categories (<23, 23-29.9,≥30).

DNA extraction and genotyping

Whole blood was collected into EDTA-coated tubes and centrifuged for 15 min, and the buffy coat layer was isolated. Genomic DNA was extracted from 200 μL of buffy coat using a Qiagen QIAamp DNA Blood Mini Kit (QIAGEN Inc, Valencia, CA).

The *XRCC1* genotypes were determined by polymerase chain reaction and restriction fragment length polymorphism methods (PCR-RFLP). The sequences of primers used in this study are forward (F): 5'-GCCCCGTCCCAGGTA-3' and reverse (R): 5'-AGCCCCAAGACCCTTTCACT-3' for codon 194, and F: 5'-TTGTGCTTTCTCTGTGTCCA-3' and R: 5'-TCCTCCAGCCTTTTCTGATA-3' for codon 399. PCR reactions for codon 194 were carried out in a total volume of 25 μL containing 10 pmol of each primer, 2.5μL 4 × dNTP, 1.5 μL $MgCl_2$, 2.5 μL 10× buffer, 1 IU Tag polymerase and 0.5 μL genomic DNA. PCR conditions were 94°C for 5 min, followed by 35 cycles of 94°C for 30 s, 58°C for 30 s, 72°C for 30 s, with a final extension at 72°C for 7 min. PCR reactions for codon 399 were carried out in a total volume of 25 μL containing 10 pmol of each primer, 2.5μL 4 × dNTP, 2 μL $MgCl_2$, 2.5 μL 10× buffer, 1 IU Tag polymerase and 0.5 μL genomic DNA. PCR conditions were 95°C for 5 min, followed by 35 cycles of 95°C for 30 s, 52°C for 30 s, 72°C for 30 s, with a final extension at 72°C for 7 min. The PCR products were subjected to MspI restriction enzyme digestion at 37°C for 2 hr and samples were then analyzed by electrophoresis in 2% (for codon194) and 3.5% (for codon 399) agarose gel. Three genotypes of codon 194 were Arg/Arg (292 bp), Arg/Trp (292 and 313bp) and Trp/Trp (313 bp), respectively. Three genotypes of codon 399 were Arg/Arg (615 bp), Arg/Gln (615bp, 374 and 221bp) and Gln/Gln (374 and 211 bp), respectively. Among 754 examined samples, PCR products for the *XRCC1* codon 399 could not be visualized for 2 cases and 4 controls.

Statistical analysis

Associations between the *XRCC1* codon 194 and codon 399 polymorphisms and colorectal cancer risk were estimated by odds ratio (OR), using the unconditional logistic regression model. We calculated adjusted ORs for age (continuous), sex, body mass index (BMI), smoking and drinking habits. The procedure LOGISTIC from the statistical package SAS was employed for the calculations. The probability of Hardy-Weinberg equilibrium was assessed by the χ^2 test.

Table 1. Background Characteristics and Genotype Distributions in Colorectal Cancer Cases and Their Controls

	Controls n (%)	Colorectum n (%)	Colon n (%)	Rectum n (%)
All subjects	439 (100)	315 (100)	105 (100)	210 (100)
Mean age ±SD	55.7±11.0	55.3±12.7	56.4±13.4	54.7±12.3
t test P		0.6172	0.6325	0.3159
BMI				
<23	228 (50.9)	166 (52.7)	59 (56.2)	107 (50.9)
23-29.9	200 (45.6)	140 (44.4)	42 (40.0)	98 (46.7)
≥30	11 (2.5)	9 (2.9)	4 3.8)	5 (2.4)
χ^2 (*P*)		0.16 (0.925)	1.40 (0.50)	0.07 (0.964)
Smoking				
Never	283 (64.5)	176 (55.9)	61 (58.1)	115 (54.8)
Current and former	156 (35.5)	139 (44.1)	44 (41.9)	95 (45.2)
χ^2 (*P*)		5.68 (0.017)	1.48 (0.224)	5.63 (0.018)
Alcohol drinking				
Never	327 (74.5)	190 (60.3)	66 (62.9)	124 (59.0)
Current and former	112 (25.5)	125 (39.7)	39 (37.1)	86 (41.0)
χ^2 (*P*)		17.06 (0.001)	5.71 (0.017)	15.95 (>0.001)
XRCC1 194				
Arg/Arg	223 (50.8)	145 (46.0)	48 (45.7)	97 (46.2)
Arg/Trp	174 (39.6)	141 (44.8)	51 (48.6)	90 (42.9)
Trp/Trp	42 (9.6)	29 (9.2)	6 (5.7)	23 (10.9)
χ^2 (*P*)		2.030 (0.363)	3.495 (0.174)	1.244 (0.537)
XRCC1 399				
Arg/Arg	218 (50.1)	153 (48.9)	53 (50.5)	100 (48.1)
Arg/Gln	185 (42.5)	133 (42.5)	47 (44.8)	86 (41.3)
Gln/Gln	32 (7.4)	27 (8.6)	5 (4.7)	22 (10.6)
χ^2 (*P*)		0.427 (0.808)	0.930 (0.628)	1.900 (0.387)
Genotype distributions in males				
XRCC1 194				
Arg/Arg	120 (53.8)	90 (47.4)	28 (43.1)	62 (49.6)
Arg/Trp	85 (38.1)	85 (44.7)	33 (50.8)	52 (41.6)
Trp/Trp	18 (8.1)	15 (7.9)	4 (6.1)	11 (8.8)
χ^2 (*P*)		1.929 (0.381)	3.326 (0.190)	0.568 (0.753)
XRCC1 399				
Arg/Arg	98 (44.3)	84 (44.4)	33 (50.8)	51 (41.1)
Arg/Gln	104 (47.1)	88 (46.6)	31 (47.7)	57 (46.0)
Gln/Gln	19 (8.6)	17 (9.0)	1 (1.5)	16 (12.9)
χ^2 (*P*)		0.024 (0.988)	4.022 (0.134)	1.657 (0.437)
Genotype distributions in females				
XRCC1 194				
Arg/Arg	103 (47.7)	55 (44.0)	20 (50.0)	35 (41.2)
Arg/Trp	89 (42.2)	56 (44.8)	18 (45.0)	38 (44.7)
Trp/Trp	24 (11.1)	14 (11.2)	2 (5.0)	12 (14.1)
χ^2 (*P*)		0.472 (0.790)	1.390)	1.198 (0.549)
XRCC1 399				
Arg/Arg	120 (56.1)	69 (55.6)	20 (50.0)	49 (58.3)
Arg/Gln	81 (37.8)	45 (36.3)	16 (40.0)	29 (34.5)
Gln/Gln	13 (6.1)	10 (8.1)	4 (10.0)	6 (7.1)
χ^2 (*P*)		0.509 (0.775)	1.038 (0.595)	0.342 (0.843)

Table 2. Polymorphisms in XRCC1 Gene and Risk of Colorectal Cancer

Genotypes	Colorectum OR (95%CI)	Colon OR (95%CI)	Rectum OR (95%CI)
Total			
XRCC1 194			
Arg/Arg	1.00	1.00	1.00
Arg/Trp	1.27 (0.93-1.73)	1.37 (0.88-2.14)	1.22 (0.86-1.74)
Trp/Trp	1.14 (0.67-1.93)	0.69 (0.28-1.74)	1.39 (0.78-2.49)
XRCC1 399			
Arg/Arg	1.00	1.00	1.00
Arg/Gln	0.95 (0.70-1.30)	0.98 (0.63-1.53)	0.93 (0.65-1.33)
Gln/Gln	1.21 (0.69-2.13)	0.68 (0.25-1.87)	1.49 (0.81-2.75)
Male			
XRCC1 194			
Arg/Arg	1.00	1.00	1.00
Arg/Trp	1.30 (0.86-1.96)	1.64 (0.92-2.95)	1.15 (0.72-1.85)
Trp/Trp	1.14 (0.54-2.44)	1.09 (0.33-3.66)	1.22 (0.52-2.82)
XRCC1 399			
Arg/Arg	1.00	1.00	1.00
Arg/Gln	0.95 (0.63-1.43)	0.85 (0.48-1.51)	1.02 (0.63-1.64)
Gln/Gln	1.03 (0.49-2.14)	0.17 (0.02-1.30)	1.62 (0.75-3.50)
Female			
XRCC1 194			
Arg/Arg	1.00	1.00	1.00
Arg/Trp	1.18 (0.73-1.89)	1.09 (0.53-2.25)	1.23 (0.71-2.13)
Trp/Trp	1.03 (0.48-2.21)	0.42 (0.09-1.98)	1.38 (0.60-3.17)
XRCC1 399			
Arg/Arg	1.00	1.00	1.00
Arg/Gln	0.95 (0.59-1.52)	1.22 (0.59-2.53)	0.81 (0.47-1.40)
Gln/Gln	1.52 (0.61-3.77)	2.39 (0.65-8.83)	1.32 (0.46-3.79)

ORs are adjusted for age, sex, smoking, alcohol drinking and BMI

Results

A total of 190 male and 125 female cases with colorectal cancer, and 223 male and 216 female controls, were included in this study. The background characteristics of cases and controls have been described in previous articles (Cao et al., 2008; Gao et al., 2010). The proportional distribution of females in controls was higher than that in colorectal cases. The mean age and BMI did not significantly differ between cases and controls. The proportional distributions of smokers and alcohol drinkers were higher in colorectal cancer cases than in controls (Table 1).

The genotype distributions of the *XRCC1* codon 194 and 399 are presented Table 1. The proportional distributions of the *XRCC1* codon 194 Arg/Arg, Arg/Trp and Trp/Trp genotypes were 50.8%, 39.6% and 9.6% in controls, 46.0%, 44.8% and 9.2% in colorectal cancer case, respectively. The genotype distributions were in Hardy-Weinberg Equilibrium in controls (P value > 0.05). It shows that subjects from population are representative. The proportional distributions of the *XRCC1* codon 399 Arg/Arg, Arg/Gln and Gln/Gln genotypes were 50.1%, 42.5% and 7.4% in controls, and 48.9%, 42.5% and 8.6% in colorectal cancer cases, respectively. The genotype distributions of the *XRCC1* codon 399 also were in Hardy-Weinberg Equilibrium in controls (P value > 0.05). No significant differences were observed among the studied groups with regard to the genotype distributions of the *XRCC1* codons 194 and 399 (all P value > 0.05).

Data for associations between the *XRCC1* codons 194 and 399 polymorphisms and the colorectal cancer risk are presented Table 2. The *XRCC1* polymorphisms were not associated significantly with risk of the colorectal cancer. Similar results also were observed in subgroup analyses based on gender and cancer locations (Table 1, Table 2). The data were further analyzed to examine the combined effects of *XRCC1* codon 194 and 399 genotypes on risk of the colorectal, colon and rectal cancers (Table 3), however, no significant combined effects were observed. Among controls with the 194Trp allele, the frequencies of the 399Arg and Gln alleles were 0.80 and 0.20, respectively, were not in Hardy-Weinberg Equilibrium (χ^2=5.939, P value <0.02), suggesting that the *XRCC1* 194 and 399 polymorphisms were in linkage disequilibrium.

Table 4 shows the relationship of alcohol drinking and colorectal cancer risk. Alcohol drinkers showed increased ORs for colorectal, colon and rectal cancers. The ORs were increased along with an increase in alcohol intake, the trend being significant for colorectal (p<0.0001), colon (P=0.0020) and rectal (P<0.0001) cancers.

Table 5 summarizes the combined effects of the *XRCC1* polymorphisms and alcohol consumption on colorectal cancer risk. As compared with non-drinkers (average alcohol consumption <1 g/day) who had the 194 Arg/Arg genotype, individuals who had high alcohol intake (average consumption >20 g/day) and with same genotype had an increased OR for colorectal cancer (2.40, 95%CI: 1.26-4.57), whereas individuals who had high alcohol intake and with the 194 Trp allele had a further increased OR for colorectal cancer (3.18, 95%CI: 1.68-5.99). As compared with nondrinkers who had the 399 Arg/Arg genotype, individuals who had high alcohol intake and with same genotype had an increased OR

Table 3. Combined Effects of XRCC1 194 and 399 Polymorphisms on Risk of Colorectal Cancer

XRCC1		Controls	Colorectal cancer		Colon cancer		Rectal cancer	
194 genotypes	399 genotypes	n	n	OR (95%CI)	n	OR (95%CI)	n	OR (95%CI)
Arg/Arg	Arg/Arg	86	56	1.00	20	1.00	36	1.00
Arg/Arg	Arg/Gln	97	75	1.26 (0.79-2.00)	28	1.34 (0.69-2.60)	47	1.21 (0.71-2.06)
Arg/Arg	Gln/Gln	35	22	1.00 (0.52-1.92)	5	0.62 (0.21-1.83)	17	1.24 (0.60-2.59)
Arg/Trp	Arg/Arg	104	66	0.93 (0.58-1.49)	23	0.95 (0.48-1.88)	43	0.94 (0.55-1.62)
Arg/Trp	Arg/Gln	74	63	1.21 (0.74-1.97)	23	1.28 (0.64-2.54)	40	1.15 (0.65-2.04)
Arg/Trp	Gln/Gln	7	4	1.00 (0.27-3.68)	1	0.57 (0.06-5.26)	3	1.15 (0.27-4.96)
Trp/Trp	Arg/Arg	29	23	1.35 (0.68-2.66)	5	0.81 (0.27-2.41)	18	1.74 (0.80-3.76)
Trp/Trp	Arg/Gln	3	3	1.19 (0.22-6.40)	0	……	3	1.72 (0.31-9.55)
Trp/Trp	Gln/Gln	0	1	……	0	……	1	……

ORs are adjusted for age, sex, smoking, alcohol drinking and BMI

Table 4. Alcohol Drinking and Colorectal Cancer Risk

Alcohol drinking	Controls	Colorectal cancer		Colon cancer		Rectal cancer	
	n	n	OR (95%CI)	n	OR (95%CI)	n	OR (95%CI)
Drinking status							
Non dinkers	330	190	1.00	66	1.00	124	1.00
Drinkers	109	125	1.87 (1.28-2.74)	39	1.65 (0.95-2.85)	86	2.02 (1.32-3.09)
Alcohol intake (g/day)							
0`	330	190	1.00	66	1.00	124	1.00
1-20`	52	43	1.35 (0.83-2.20)	12	1.11 (0.52-2.34)	31	1.51 (0.88-2.60)
>20	57	82	2.38 (1.51-3.74)	27	2.22 (1.17-4.19)	55	2.52 (1.51-4.19)
P for trend			<0.0001		0.0020		<0.0001

ORs are adjusted for age, sex, smoking and BMI

Table 5. Combined Effects of *XRCC1* Polymorphisms and Alcohol Intake on Risk of Colorectal Cancer

XRCC1	Alcohol intake	Controls	Colorectal cancer		Colon cancer		Rectal cancer	
genotypes	g/day	n	n	OR (95%CI)	n	OR (95%CI)	n	OR (95%CI)
194 genotypes								
Arg/Arg	0`	166	86	1.00	31	1.00	55	1.00
Arg/Trp+Trp/Trp	0`	164	104	1.23 (0.86-1.77)	35	1.18 (0.69-2.01)	69	1.27 (0.83-1.92)
Arg/Arg	1-20`	27	21	1.47 (0.74-2.89)	5	1.11 (0.37-3.35)	16	1.66 (0.79-3.52)
Arg/Trp+Trp/Trp	1-20`	25	22	1.70 (0.85-3.40)	7	1.56 (0.55-4.37)	15	1.74 (0.79-3.81)
Arg/Arg	>20	30	38	2.40 (1.26-4.57)	12	2.37 (0.93-6.04)	26	2.43 (1.18-5.02)
Arg/Trp+Trp/Trp	>20	27	44	3.18 (1.68-5.99)	15	3.30 (1.35-8.06)	29	3.29 (1.62-6.66)
Arg/Arg	>20	30	38	1.00	12	1.00	26	1.00
Arg/Trp+Trp/Trp	>20	27	44	1.27 (0.64-2.54)	15	1.64 (0.62-4.38)	29	1.22 (0.57-2.59)
399 genotypes								
Arg/Arg	0`	169	101	1.00	34	1.00	67	1.00
Arg/Gln+Gln/Gln	0`	158	88	0.93 (0.65-1.34)	32	1.04 (0.61-1.78)	56	0.87 (0.57-1.33)
Arg/Arg	1-20`	22	15	0.94 (0.43-2.04)	7	1.31 (0.45-3.83)	8	0.76 (0.30-1.94)
Arg/Gln+Gln/Gln	1-20`	30	28	1.35 (0.71-2.57)	5	0.79 (0.26-2.42)	23	1.66 (0.82-3.34)
Arg/Arg	>20	27	37	1.93 (1.00-3.70)	12	1.70 (0.67-4.32)	25	2.11 (1.02-4.37)
Arg/Gln+Gln/Gln	>20	29	44	2.17 (1.13-4.17)	15	2.31 (0.92-5.78)	29	2.07 (0.99-4.35)
Arg/Arg	>20	27	37	1.00	12	1.00	25	1.00
Arg/Gln+Gln/Gln	>20	29	44	1.07 (0.53-2.15)	15	1.26 (0.47-3.34)	29	1.02 (0.47-2.23)

ORs are adjusted for age, sex, smoking and BMI

for colorectal cancer (1.93, 95%CI: 1.00-3.70), whereas individuals who had high alcohol intake and with the 399 Gln allele also had a further increased OR for colorectal cancer (2.17, 95%CI: 1.13-4.17). However, among the subjects with highest alcohol intake, the increased OR by 194Trp or 399Gln allele had not statistics significance. Similar combined effects also were observed in subgroup analyses based on cancer locations (colon, rectum, Table 5).

The combined effects of the *XRCC1* polymorphisms and smoking on colorectal cancer risk also were examined, but no significant combined effect was observed (data not shown).

Discussion

In this study, we investigated the associations between genetic polymorphisms in the DNA repair gene *XRCC1* and colorectal cancer risk. The results showed that the *XRCC1* codons 194 and 399 polymorphisms themselves no significant associate with the risk of colorectal cancer, and that no significant combined effect between *XRCC1* codon 194 and 399 polymorphisms on colorectal cancer risk.

There have been a lot of papers on the relation between *XRCC1* gene polymorphism and cancer risk, including colorectal cancer. However, results in these papers have been inconsistent. In a larger case-control study of Taiwan of China, Yeh et al. (2005) found the risk for colorectal cancer did not appear to differ significantly amongst individuals featuring the *XRCC1* 399Arg/Arg genotype. Stern et al. (2007) in the Singapore Chinese Health Study found that no significant association between the *XRCC1* codon 194 and 399 polymorphisms and the colorectal cancer risk. Two studies in Han people of China (Jin et al., 2007; 2008) and seven studies in various countries (Improta et al., 2008; Kasahara et al., 2008; Curtin et al., 2009; Canbay et al., 2011; Gsur et al., 2011; Muñiz-Mendoza et al., 2012; Reeves et al., 2012) also discovered that single *XRCC1* gene polymorphisms have not correlations to the colorectal cancer susceptibility. Our present findings are consistent with these previous studies. Although some studies suggested the *XRCC1* 399Gln/Gln genotype was associated with colorectal (Abdel-Rahman et al., 2000; Hong et al., 2005; Karahalil et al., 2012; Yin et al., 2012), colon (Jelonek et al., 2012) or rectal (Wang et al., 2010) cancer risk.

Hsieh et al. (2003) reported linkage disequilibrium between Arg194Trp and Arg399Gln, by showing that all carrying the 194Trp allele also carried the 399Arg allele.

Three studies (Hong et al., 2005; Jin et al., 2007; Yin et al., 2012) also observed a close linkage among Arg194Trp, Arg280His and Arg399Gln. In this study, we found that among controls with the 194Trp allele, frequencies of the 399Arg and Gln alleles were 0.80 and 0.20, respectively, were not in Hardy-Weinberg Equilibrium. Our results also suggesting that the *XRCC1* 194 and 399 polymorphisms were in linkage disequilibrium.

The environment factors are important in development of colorectal cancer. The gene-environment interactions also have been noted for colorectal cancer risk. In the present study, we found that high alcohol consumption is associated with increased risk of colorectal cancer. We also found that the effect of high alcohol intake in elevate the risk of colorectal cancer was more notable in carriers of the *XRCC1* codons 194 Trp allele or 399 Gln allele. This finding is similar to the study results in Korea (Hong et al., 2005) and in Fukuoka of Japan (Yin et al., 2012). However, we also found the increased OR by 194Trp or 399Gln allele among the subjects with highest alcohol intake had not statistics significance. These results suggesting that *XRCC1* polymorphisms themselves only has a little or no biological impact on colorectal cancer susceptibility. An interaction effect between *XRCC1* polymorphisms and alcohol intake on colorectal cancer risk is biologically plausible. The *XRCC1* is a gene of the DNA base-excision repair and radiation-induced damage repair. *XRCC1* polymorphisms affect DNA repair capacity. High alcohol intake is an important risk factor for colorectal cancer, may induce carcinogenesis through DNA damage caused by the toxic effects of alcohol or its metabolites (Brooks, 1997; Blasiac, 2001). Alcohol is converted to acetaldehyde in the colonic lumen, which induces the formation of DNA adducts and produces oxidative DNA damage (Brooks et al., 2005). Alcohol intake also is associated with the production of reactive oxygen species, including oxygen free radicals, which may generate DNA base lesions (Hoek et al., 2002).

Smoking is an important environmental risk factor in human cancers, but in previous study (Gao et al., 2010), we found no relationship between cigarette smoking and colorectal cancer risk. In the present study, we also found no interaction between smoking and *XRCC1* polymorphisms on the risk of colorectal cancer. This finding is consistent with the study results in Japanese population (Kasahara et al., 2008; Yin et al., 2012).

Finally, some limitations in this study require further discussion. In this study, we did not deal with some reported risk factors for colorectal cancer such as dietary habits, physical activity and family history. These risk factors could be potential confounder of *XRCC1* polymorphisms or could interact with *XRCC1* polymorphisms, therefore influence the effects. The sample size in this study was not sufficient for stratified subgroup analyses, with consequent reduction in the magnitude of statistical power and increase in the potential for random error. Another possible problem is selection bias for controls, these being recruited by local health staff, although from the general population with a high response rate. The proportional distribution of females in controls was higher than that in colorectal cases, which may have caused a lower prevalence of smokers and alcohol drinkers in the present controls, although we adjusted for sex, smoking and drinking in all statistical analyses.

In summary, this study showed that the *XRCC1* codon 194 and 399 polymorphisms themselves were not associated with colorectal cancer risk, but there is a cooperative action between the 194Trp allele or the 399Gln allele and high alcohol intake on increasing colorectal cancer risk. These results support the fact that colorectal cancer susceptibility may be altered by interaction of gene-environment. However, the genetic susceptibility showed variable in different ethnicity, therefore, further large sample multicenter studies are needed to confirmation.

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