

RESEARCH COMMUNICATION

ADPRT Val762Ala and XRCC1 Arg194Trp Polymorphisms and Risk of Gastric Cancer in Sichuan of China

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Abstract

Objective: Gastric cancer remains a major health problem in China. We hypothesized that XRCC1 Arg194Trp and ADPRT Val762Ala may be associated with risk. **Methods:** We designed a multicenter 1:1 matched case-control study of 307 pairs of gastric cancers and controls between October 2010 and August 2011. XRCC1 Arg194Trp and ADPRT Val762Ala were sequenced, and demographic data as well as lifestyle factors were collected using a self-designed questionnaire. **Results:** Individuals carrying XRCC1 Trp/Trp or Arg/Trp variant genotype had a significantly increased risk of gastric cancer (OR, 1.718; 95% CI, 1.190-2.479), while the OR for ADPRT Val762Ala variant genotype (Ala/Ala or Val/Ala) was 1.175 (95% CI, 0.796-1.737). No gene-gene or gene-environment interactions were found. In addition, family history of cancer and drinkers proportion were higher among cases than among controls ($P < 0.05$). **Conclusions:** XRCC1 194 Arg/Trp or Trp/Trp genotype, family history of cancer, and drinking are suspected risk factors of gastric cancer from our study. Our findings may offer insight into further similar large gene-environment and gene-gene studies in this region.

Keywords: Gastric cancer - XRCC1 - ADPRT - polymorphisms - risk - China

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Introduction

Cancer has been one of the leading causes of death among Chinese adults (He et al., 2005). According to GLOBOCAN 2008, gastric cancer with an estimated age standardized rate of 29.9 per 100,000 (315,843 cases) ranks the second in terms of incidence among all cancer types in China, behind only lung cancer, and the estimated age standardized mortality rate reaches up to 22.3 per 100,000 (231,193 deaths), only lower than that for lung and liver cancers (Ferlay et al., 2010). Due to dramatic improvements in the social-economic environment, lifestyle, nutrition, education and health care system, there are remarkable declines in the incidence and especially mortality of gastric cancer in the last thirty years (Yang 2006). However, despite the declining incidence and mortality of gastric cancer in China, it remains a major health problem because of its poor prognosis and the aging of the population (Schottenfeld et al., 2006; Yang 2006).

DNA bears indispensable inheritance information in human beings and its damage is critical to carcinogenesis (Hoeijmakers, 2001). At least four major pathways of DNA repair have been described that operate on specific types of damaged DNA, including base excision repair (BER), mismatch repair, nucleotide excision repair, and

double-strand break repair. BER operates on small lesions including oxidized or reduced bases, fragmented or nonbulky adducts, or those produced by methylating agents (Goode et al., 2002). Of the multiple proteins involved in the BER pathway, X-ray repair cross-complementing group 1 (XRCC1) and adenosine diphosphate ribosyl transferase (ADPRT) are two important ones (Lindahl et al., 1999; Hoeijmakers, 2001). ADPRT specifically binds to DNA strand breaks where it is autoactivated and recruits the XRCC1-Ligase III α complex to stimulate BER, and as a result, XRCC1 interacts with ADPRT to recruit other partner proteins such as DNA polymerase β (Pol β) to execute BER (Masson et al., 1998; Keith, 2003). In this regard, functional variants of XRCC1 and ADPRT may alter BER functions and thus play an essential role in the evolution of gastric lesions (Li et al., 2009).

Host genetic susceptibility to carcinogenesis can be partially explained by genetic variations like single nucleotide polymorphisms in susceptible genes (Xue et al., 2011). XRCC1 Arg194Trp (C26304T) and ADPRT Val762Ala (T2446C) are two common candidate single-nucleotide polymorphisms that cause an amino acid change (Li et al., 2009). The XRCC1 Arg194Trp polymorphism with C to T transition at codon 194 is located at a conserved residue in humans (Lamerdin et

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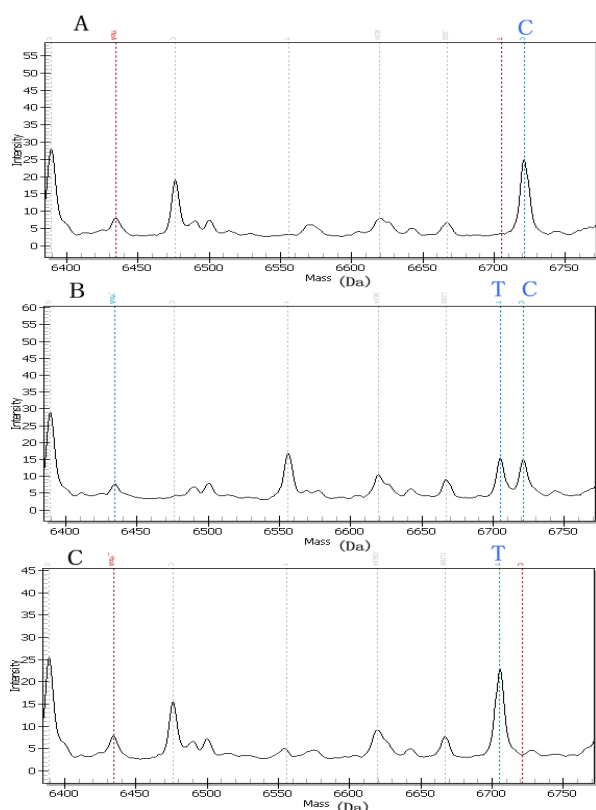


Figure 1. Spectra for Three Genotypes of XRCC1 Arg194Trp (C26304T) of an Anonymous DNA Sample: A for Arg/Arg, B for Arg/Trp, and C for Trp/Trp

al., 1995; Shen et al., 1998), and individuals with Arg/Arg genotype exhibited highly increased chromosomal breaks (Vodicka et al., 2007). Since Shen et al. (2000) suggested that XRCC1 Arg194Trp may be associated with risk of developing gastric cancer in a Chinese population, the association between XRCC1 Arg194Trp and gastric cancer (cardia and/or non-cardia cancers) has been investigated in different ethnicities (Shen et al., 2000; Lee et al., 2002; Ratnasinghe et al., 2004; Duarte et al., 2005; Hong et al., 2009; Liu et al., 2009; Shen et al., 2009; Yan et al., 2009; Palli et al., 2010; Yuan et al., 2010), though the results are conflicting. The ADPRT Val762Ala polymorphism with T to C transition at codon 762 is located in the sixth helix of catalytic domain that causes Val-to-Ala amino acid substitution. One study has shown that the 762Ala polymorphism is associated with altered ADPRT function, with the Ala allele contributing to significantly low activities in an allele dosage-dependent manner (Lockett et al., 2004). However, there is not much research regarding the association between ADPRT Val762Ala polymorphism and gastric cancer in Chinese population. In a meta-analysis summarizing risk of genetic polymorphisms for gastric cancer (Loh et al., 2009) concludes that XRCC1 Arg194Trp and ADPRT Val762Ala are separately associated with gastric cancer in Asians.

A recent study in China has reported that the interaction between ADPRT and XRCC1 polymorphisms confer possible host susceptibility to gastric cardia cancer (Miao et al., 2006). Based on the interactive role of ADPRT and XRCC1 in BER activities and functional relevance of their variants, we aimed to analyze the contribution of genetic polymorphisms of XRCC1 Arg194Trp and ADPRT

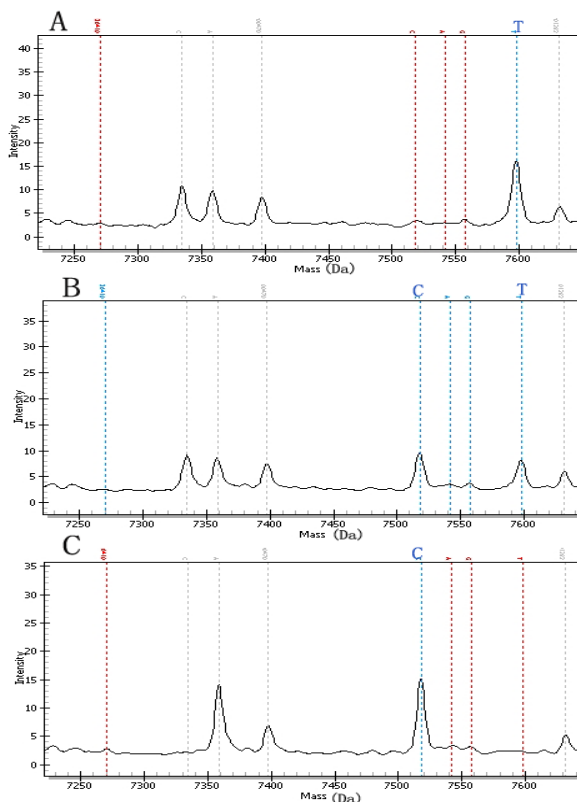


Figure 2. Spectra for Three Genotypes of ADPRT Val762Ala (T2446C) of an Anonymous DNA Sample: A for Val/Val, B for Val/Ala, and C for Ala/Ala

Val762Ala to host susceptibility to gastric cancer in a multicenter case-control study in Han Chinese population.

Materials and Methods

Subjects

The cases were 307 patients who were histologically diagnosed as having gastric cancer between October 2010 and August 2011 from Yanting Cancer Hospital & Institute in Yanting County, Sichuan University West China Hospital and Sichuan Cancer Hospital in Sichuan Province. Controls were selected from Sichuan University West China Fourth Hospital and a peri-urban community in Chengdu and matched to the cases by age (± 3 years) and sex (1:1). The controls who were relatives of cases, or had digestive diseases or a prior history of cancer were excluded.

A self-designed questionnaire was used to collect demographic data and potential risk factors, including smoking, alcohol drinking and family history of cancer. Approximately 2-5 ml of whole blood was collected from each subject after interview.

The research protocol was approved by the ethics committees of four participating hospitals, and informed consent was obtained from all recruited subjects.

XRCC1 Arg194Trp and ADPRT Val762Ala genotyping

DNA was extracted from the buffy-coat fractions with TIANamp blood DNA kit (Tiangen Biotech, Beijing, China). SNP genotyping was performed in a 384-well plate format on the Sequenom MassARRAY platform (Sequenom, San Diego, USA). Primers for

Table 1. Sequences of Primers and Masses of Extension Products of MALDI-TOF MS Assays

Single nucleotide polymorphism	Primer	Sequence	Mass (Da)
XRCC1 Arg194Trp (C26304T)	PCR Primer 1	ACGTTGGATGGCTCACCTGGTGATGTCTTG	
	PCR Primer 2	ACGTTGGATGTGAAGGAGGAGGATGAGAGC	
	Extension Primer	CTGGTGATGTCTTGTGATCC	6434.2
	Analyte C	CTGGTGATGTCTTGTGATCCG	6721.4
	Analyte T	CTGGTGATGTCTTGTGATCCA	6705.4
ADPRT Val762Ala (T2446C)	PCR Primer 1	ACGTTGGATGGCTTCTTTTGCTCCTCCAG	
	PCR Primer 2	ACGTTGGATGTGCTATCATCAGACCCTCCC	
	Extension Primer	TTCTTTTGCTCCTCCAGGCAAGG	7270.7
	Analyte T	TTCTTTTGCTCCTCCAGGCAAGGT	7597.8
	Analyte C	TTCTTTTGCTCCTCCAGGCAAGGC	7517.9

polymerase chain reaction (PCR) amplification and single base extension (SBE) assays were designed by the Translational Interface Core Facility at the National University of Singapore using Sequenom Assay Design 3.1 software (Table 1). ADPRT Val762Ala and XRCC1 Arg194Trp genotypes were analyzed using MALDI-TOF MS according to Justenhoven et al. (2004). Briefly, the initial PCR was carried out with 5 ng of genomic DNA in a reaction volume of 5 µl using GeneAmp® PCR System 9700 with Dual 384-Well Sample Block Module (Applied Biosystems, Carlsbad, USA). Following removal of excess dNTPs with shrimp alkaline phosphatase enzyme solution (Sequenom), base extension reaction using iPLEX® Gold SBE chemistry (Sequenom) was carried out. The final base extension products were treated with CLEAN resin (Sequenom) to remove salts (Table 1). A total of 10 nl of reaction solution was dispensed onto a 384 format SpectroCHIP microarray (Sequenom). The MassARRAY Analyzer Compact with ACQUAIRE Module (Sequenom) acquired spectra from the SpectroCHIP, and spectral data were automatically processed and saved to the MassARRAY database (Figure 1 and 2).

Statistical analysis

Stata 8.0 (StataCorp, College Station, USA) was used to perform statistical analyses. Demographic characteristics were compared between cases and controls by means of chi-square test and Student's t test. Hardy-Weinberg equilibrium (HWE) was checked for controls with the Chi-square test. Conditional logistic regression was used to calculate the odd ratio (OR) and 95% confidence interval (CI). Because of the low allele frequencies and relative rarity of the homozygous variant genotypes, we combined the homozygous variant and heterozygous groups for analysis.

Results

Subject characteristics

307 pairs of gastric cancer and control subjects were enrolled in this study, including 223 (72.6%) men and 84 (27.4%) women in each of the case and control groups. The average age was 57.7±10.6 (mean ±SD) years for cases and 57.6±11.1 years for controls. Baseline characteristics of cases and controls are summarized in Table 2. There were no statistically significant differences between cases and controls in terms of smoking status and education background. The proportion of subjects with a family

Table 2. Characteristics of Case and Control Subjects

Variables	Cases (n=307)	Controls (n=307)	P value ^a
Education, n (%)			
Primary school or below	139(45.6)	143(46.6)	0.38
Middle school	93(30.5)	93(30.3)	
High school or equivalent	47(15.4)	55(17.9)	
College or above	26(8.50)	16(5.20)	
Family history of cancer, n (%)			
No	215(70.0)	274(89.3)	<0.01
Yes	92(30.0)	33(10.7)	
Smoking			
Non-smokers	128 (41.7)	132 (43.0)	0.77
Smokers	179 (58.3)	175 (57.0)	
Drinking			
Non-drinkers	140 (45.6)	175 (57.0)	0.01
Drinkers	167 (54.4)	132 (43.0)	

^aP value by the chi-square test

history of cancer among patients was significantly higher than that among controls (30.0% vs. 10.7%, $P<0.05$). Statistically significant difference with regard to alcohol drinking ($P<0.05$) was also noted between the cases and controls.

Genotype distributions and their association with gastric cancer

The genotype distributions of XRCC1 Arg194Trp and ADPRT Val762Ala and their association with gastric cancer risk are summarized in Table 3. Genotyping results showed that the allele frequencies for XRCC1 194Trp and ADPRT 762Ala variants were 34.4% and 43.6% for cases and 27.4% and 44.3% for controls, respectively. The frequencies of XRCC1 194Arg/Arg, Arg/Trp, and Trp/Trp genotypes among controls were 52.1%, 41.0%, and 6.9%, respectively, which conformed to the Hardy-Weinberg equilibrium ($\chi^2=0.324$, $P=0.569$) but significantly differed from those among patients (42.0% Arg/Arg, 47.2% Arg/Trp, and 10.8% Trp/Trp, respectively) ($\chi^2=7.324$, $P=0.026$). Individuals carrying XRCC1 Trp/Trp or Arg/Trp variant genotype had a significantly increased risk of gastric cancer (adjusted OR, 1.718; 95%CI, 1.190-2.479). The frequencies of ADPRT 762Val/Val, -Val/Ala, and -Ala/Ala among controls were 34.20%, 43.00%, and 22.80%, respectively, and 31.3%, 50.1% and 18.6% among cases, which showed no significant difference between the cases and controls ($\chi^2=3.426$, $P=0.180$). OR (95% CI) for ADPRT Val762Ala variant genotype (Ala/Ala or Val/Ala) was 1.175 (95% CI, 0.796-1.737).

Table 3. XRCC1 Arg194Trp and ADPRT Val762Ala Genotypes in Cases and Controls and Their Association with Gastric Cancer Risk

Genotypes	Cases (n=307)	Controls (n=307)	OR (95% CI) ^a	
			Crude	Adjusted ^b
XRCC1 Arg194Trp				
Arg/Arg	129 (42.0)	160 (52.1)	1.0 (reference)	1.0 (reference)
Arg/Trp	145 (47.2)	126 (41.0)	1.45 (1.04-2.04)*	1.66 (1.14-2.43)*
Trp/Trp	33 (10.8)	21 (6.90)	2.01 (1.10-3.70)*	2.06 (1.05-4.02)*
Arg/Arg	129 (42.0)	160 (52.1)	1.0 (reference)	1.0 (reference)
Trp/Trp+Arg/Trp	178 (58.0)	147 (47.9)	1.53 (1.10-2.12)*	1.72 (1.19-2.48)*
ADPRT Val762Ala				
Val/ Val	96 (31.3)	105 (34.2)	1.0 (reference)	1.0 (reference)
Val/Ala	154 (50.1)	132 (43.0)	1.30 (0.89-1.90)	1.31 (0.86-1.99)
Ala/Ala	57 (18.6)	70 (22.8)	0.88 (0.56-1.40)	0.92 (0.55-1.54)
Val/ Val	96 (31.3)	105 (34.2)	1.0 (reference)	1.0 (reference)
Ala/Ala +Val/Ala	211 (68.7)	202 (65.8)	1.15 (0.81-1.63)	1.18 (0.80-1.74)
Combined effect				
XRCC1 Arg/Arg + ADPRT Val/ Val	37 (12.0)	58 (18.9)	1.0 (reference)	1.0 (reference)
XRCC1 Arg/Arg + ADPRT Ala/Ala or Val/Ala	92 (30.0)	102 (33.2)	1.51 (0.90-2.55)	1.29 (0.73-2.30)
XRCC1 Trp/Trp or Arg/Trp + ADPRT Val/ Val	59 (19.2)	47 (15.3)	2.05 (1.16-3.63)*	1.86 (1.00-3.48)
XRCC1 Trp/Trp or Arg/Trp + ADPRT Ala/Ala or Val/Ala	119 (38.8)	100 (32.6)	2.06 (1.20-3.54)*	2.18 (1.22-3.93)*

^aORs and 95% CIs were calculated using conditional logistic regression; ^bORs were adjusted for family history of cancer, education background, drinking and smoking; * $P < 0.05$

Gene-gene and gene-environment interaction on risk of gastric cancer

We further analyzed the combination effect of XRCC1 Arg194Trp and ADPRT Val762Ala genotypes on the risk of gastric cancer (Table 3). The results showed that individuals with both XRCC1 Arg194Trp and ADPRT Val762Ala variant genotypes (XRCC1 Trp/Trp or Arg/Trp + ADPRT Ala/Ala or Val/Ala) had a significantly increased risk of gastric cancer (OR, 2.063; 95%CI, 1.202-3.540), compared to subjects who were wild type for both polymorphisms. This risk for gastric cancer remained after adjusting potential risk factors (OR, 2.176; 95%CI, 1.206-3.925). In our tentative analysis, no interaction was noted between the XRCC1 genotype and drinking (OR, 0.869; 95%CI, 0.550-1.374) and smoking (OR, 1.261, 95%CI, 0.646-2.461).

Discussion

Genetic variation in DNA repair genes has been postulated as an important component for the etiology of gastric cancer (Gonzalez et al., 2002; Goode et al., 2002; Capella et al., 2008; Palli et al., 2010). Reliable understanding of which sequence variants on the gastric cancer risk may help in identifying individuals at high risk and elucidate its etiology. In addition, the host-environment interaction is currently a major concern in epidemiological studies for gastric cancer (Wu et al., 2005). Increasing reviews have assessed ADPRT and XRCC1 polymorphisms for risk of gastric cancer in different populations, but no consensus has yet been concluded (Goode et al., 2002; Hu et al., 2005; Hung et al., 2005; Qu et al., 2005; Jiang et al., 2009). As the first case-control study in West China showed individuals carrying XRCC1 Trp/Trp or Arg/Trp variant genotype had a significantly increased risk of gastric cancer, and no association was found between ADPRT Val762Ala variant genotype and gastric cancer.

In our study, we found that family history of cancer was noted more among patients than among controls. The positive association between gastric cancer risk and family history of cancer in the current study is consistent with previous reports in the Chinese population (Li et al., 1989; Tran et al., 2005; Gao et al., 2009). A study in Iran also showed that family history of gastric cancer, especially in first-degree relatives, increases the risk of development of the disease (Safaei et al., 2011). Our data also showed that a higher percentage of former or current drinkers developed gastric cancer than non-drinkers. Munoz et al. (2001) observed substantially higher risk of gastric cancer for current drinkers (OR, 2.9; 95% CI, 1.9-4.3) and former drinkers (OR, 3.5; 95% CI, 2.0-6.0) compared with non-drinkers, which is fairly consistent with our results. There was no statistically significant difference in smoking in our study ($P=0.774$), which may be because smoking might be more prevalent among general population in Sichuan province than in other provinces.

We observed that XRCC1 194Trp was a hazard allele and the XRCC1 Arg194Trp variant genotype was associated with moderate increased risk of gastric cancer (OR, 1.718; 95% CI, 1.190-2.479). Wang YG et al found that individuals with XRCC1-77C variant have a significantly higher cancer risk, particularly in the Asian population (Wang et al., 2012). Two recent studies in Western and Southeastern China reported moderate association between XRCC1 194Arg allele and gastric cancer risk (Shen et al., 2009; Yuan et al., 2010), while researchers in Northern China has limited this association only among the elderly (≥ 60 years old) (Liu et al., 2009). Since people in different parts of China have apparent different living standards and lifestyles, we consider that geographic variation may confound the relationship between XRCC1 Arg194Trp polymorphism and gastric cancer if not properly controlled in analysis. It should also be considered that the apparent inconsistency of these reports may underlie differences in ethnicity (Palli et al.,

2010), which is corroborated by the fact that conflicting findings arise between Italians (Palli et al., 2010), Koreans (Hong et al., 2009) and Brazilians (Duarte et al., 2005). When individual patients with gastric cardia cancer were examined separately in the Chinese population, no evidence was reported for association between XRCC1 Arg194Trp and cancer of the gastric cardia (Shen et al., 2000; Ratnasinghe et al., 2004; Yan et al., 2009). However, in two other studies (Liu et al., 2009; Yuan et al., 2010), XRCC1 194Trp allele significantly added risk to the development of gastric cardia cancer. XRCC1 gene also affects the occurrence of other cancers, Li Q W et al observed that XRCC1-Arg399Cln polymorphism is associated with susceptibility to HCC (Li et al., 2012). Given the small size of cardia cancer cases in these two studies (<35), the statistical power is limited to test for the mentioned association, thus further studies need to be investigated the association between gastric cancer at this subsite.

In the current study, no association between ADPRT Val762Ala polymorphism and risk of gastric cancer was detected (OR, 1.175; 95% CI, 0.796-1.737; Ala/Ala or Val/Ala vs. Val/Val), which appears to be contradictory to two association studies in Northwestern China (OR, 1.942; 95% CI, 1.157-3.257; Ala/Ala vs. Val/Val) (Zhang et al., 2009) and Northern China (OR, 2.07; 95% CI, 1.33-3.21; Ala/Ala vs. Val/Val) (Zhang et al., 2006), as both suggest that ADPRT 762 Ala/Ala could be a risk factor for gastric cancer in Han Chinese population. In another study that examined the contribution of ADPRT Val762Ala polymorphism to gastric cardia cancer in Northern China, it is concluded that the ADPRT polymorphism confers host susceptibility to the cancer (OR, 2.17; 95% CI, 1.55-3.04; Ala/Ala or Val/Ala vs. Val/Val) (Miao et al., 2006). The difference in studies may be due to sample size, inevitable information bias or by chance.

When we tried to assess interaction between the XRCC1 Arg194Trp and ADPRT Val762Ala polymorphisms, we found that subjects carrying both XRCC1 Arg194Trp and ADPRT Val762Ala variant genotypes had an OR of 2.176 for gastric cancer, as compared to 1.718 for those with XRCC1 194Trp/Trp+Arg/Trp alone. This finding demonstrates that there may be no interaction between these two genetic polymorphisms. Inconsistently, a recent study reported that the XRCC1 and XRCC3 gene polymorphisms and their combination effect on the risk of colorectal cancer in Chinese population (Zhao et al., 2012). Another study in China showed that joint effect between the ADPRT Ala/Ala and XRCC1 399 Gln/Gln genotypes may exist in increasing the risk for the development of gastric cardia cancer (Miao et al., 2006). Since ADPRT is identified as a partner of XRCC1 (Masson et al., 1998), and the low ADPRT activity is expected to reduce its ability to recruit XRCC1 and other related proteins in BER (Zhang et al., 2005), our results need to be validated in future research on structural and functional connection between these two polymorphism in gastric carcinogenesis.

We did not find significant gene-environment interaction between the XRCC1 Arg194Trp variant genotype and drinking as well as smoking, suggesting

that the XRCC1 194Trp allele has no excess risk for gastric cancer in drinkers and smokers. Chronic alcohol consumption can lead to DNA damage through the production of certain molecules during the ethanol metabolism, such as reactive oxygen species, lipid peroxidation products, and acetaldehyde (Brooks 1997). The frequency of DNA single-strand breaks also increases with prolonged exposure to alcohol. As a major component of BER, the XRCC1 variant genotype is supposed to increase risk associated with excessive alcohol consumption for development of gastric cancer. Moreover, tobacco may induce the DNA damage and thus to increase the process of carcinogenesis of gastric cancer. Tobacco may have an interactive role with the DNA repair gene. However, the magnitudes of associations with drinking and smoking may vary across different subsites of gastric cancer, and the modification of effects on sequence variants might also be different. Consequently, further study on interaction between XRCC1 Arg194Trp polymorphism and drinking for gastric cancer of different subsites (cardia or noncardia cancer) is warranted.

In conclusion, several genetic and environmental factors are suspected candidates accounting for risk of gastric cancer in the present cancer case-control study, including XRCC1 194 Arg/Trp or Trp/Trp genotype, family history of cancer, and drinking. There is no significant association between ADPRT Val762Ala polymorphism and gastric cancer. Our findings may offer insight into risk associated with the development of gastric cancer and serve as a reference for further similar large gene-environment and gene-gene studies in this region.

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