RESEARCH ARTICLE

Polymorphisms of XRCC1 and ADPRT Genes and Risk of Noncardia Gastric Cancer in a Chinese Population: a Case-control Study

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Abstract

Objective: Gastric cancer (GC) is one of the most common malignancies and its mortality ranks third among all cancers in China. We previously noted that XRCC1 Arg194Trp was associated with GC risk in Western China in a study on XRCC1 Arg194Trp and ADPRT Val762Ala. We aimed to further explore the association of these polymorphisms with risk of the noncardia subtype. Methods: We enrolled 176 noncardia GC patients and 308 controls from four hospitals and a community between October 2010 and August 2011. Genotyping was performed in a 384-well plate format on the Sequenom MassARRAY platform. A self-designed questionnaire was utilized to collect epidemiological data from the subjects regarding demographic factors and potential risk factors. Results: Subjects were aged 56.8±11.8 (mean ± standard deviation) and 57.6±11.1 years in the case and control groups, respectively. Individuals carrying the XRCC1 Trp/Trp or Arg/Trp variant genotype were at significantly increased risk of noncardia GC (adjusted OR, 1.48; 95% CI, 1.00-2.17), after adjustment for family history of cancer, drinking, and smoking. The increased risk of XRCC1 Arg194Trp variant genotype was more pronounced among subjects below 60 years old (adjusted OR, 1.78; 95% CI, 1.07-2.96), compared to older individuals. ADPRT Val762Ala variants (Ala/Ala or Val/Ala) were not associated with noncardia GC (adjusted OR, 1.03; 95% CI, 0.69-1.54). Conclusions: Our study suggests that XRCC1 Arg194Trp is a genetic susceptibility factor for developing noncardia GC in Han Chinese in Western China. In particular, individuals with the XRCC1 Arg194Trp variant genotype are at increased risk for GC below 60 years old.

Keywords: Noncardia gastric cancer - ADPRT Val762Ala - XRCC1 Arg194Trp - polymorphisms - risk - China

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Introduction

Gastric cancer (GC) is the sixth most commonly diagnosed malignancy and the third leading cause of cancer deaths worldwide (Ferlay et al., 2010). The highest incidence rates are noted in Japan, Eastern Asia, Andean regions of South America and Eastern Europe, whereas the lowest are observed in North and East Africa, Northern Europe and North America (Ferlay et al., 2010). Incidence rates for GC have declined steadily in several western countries, and similar declining trends have been witnessed only in more recent years in countries with historically high GC incidence including Japan, China, Korea, Columbia, Ecuador, Ukraine, and Russia (Bertuccio et al., 2009). However, while the incidence of noncardia GC has declined in most countries, the rates of cardia GC has remained stable, or have risen in several European countries, Japan and North America (Gonzalez et al., 2012). In China, GC is one of the most common malignancies and its mortality ranks the third among all cancers (Ferlay et al., 2010), making it one of the top priorities in cancer prevention and control in this populous country.

Gastric carcinogenesis is a complex multistep and multifactorial process. Multiple lines of evidence have been documented for a model of gastric carcinogenesis with following sequential stages: chronic gastritis, atrophy, intestinal metaplasia, and dysplasia (Correa, 1992). Risk factors of GC identified so far include H. pylori (HP) infection, smoking, alcohol, diet and nutrition such as red and processed meat, genetics and epigenetic factors (Gonzalez et al., 2012). Host genetic susceptibility is assumed to be an important factor for development of GC, and can be partially explained by genetic variations like single nucleotide polymorphisms (SNPs) in susceptible genes (Xue et al., 2011). In addition, gene-gene and gene-environment interactions may add to the risk of GC in an additive or multiplicative model.

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Recent genetic association studies on cancer risk have focused on identifying effects of SNPs in candidate genes, among which DNA repair genes are increasingly studied because of their critical role in maintaining genome integrity (Hung et al., 2005). The base excision repair (BER) is a DNA repair mechanism that repairs small aberrations such as oxidized or reduced bases, fragmented or nonbulky adducts, or those produced by methylating agents (Goode et al., 2002). X-ray repair cross-complementing group 1 (XRCC1) and adenosine diphosphate ribosyl transferase (ADPRT) are two of many proteins involved in the BER pathway. Several genetic polymorphisms have been identified in both ADPRT and XRCC1 genes, of which XRCC1 Arg194Trp (C26304T) (Shen et al., 2000; Ratnasinghe et al., 2004; Liu et al., 2009; Shen et al., 2009; Yan et al., 2009; Yuan et al., 2010) and ADPRT Val762Ala (T2446C) (Miao et al., 2006; Zhang et al., 2006; Zhang et al., 2009) have been widely studied for association with cardia and/or noncardia GC in the Chinese population, albeit with conflicting results reported.

Cardia GC that arises from the cardia (proximal) portion of the stomach and the junction between the esophagus and stomach presents distinct epidemiologic features compared with noncardia GC of more distal parts of the stomach (i.e., fundus, body, and antrum) (Brown et al., 2002). Noncardia GC occurs often in patients with gastric atrophy and hypochlorhydria (McColl et al., 2000), which seem to protect against the more proximal cardia carcinoma (Blaser, 1999). These distinct patterns suggest that etiologic factors for noncardia GC may differ from those for cardia GC. In a recent study, we noted that XRCC1 Arg194Trp was associated with GC risk in Sichuan, a western province in China (Wen et al., 2012). This is consistent with findings in two other studies for overall GC risk in Southwestern and Southeastern China (Shen et al., 2009; Yuan et al., 2010). However, contradictory results have been obtained in three Chinese studies focusing on association of XRCC1 Arg194Trp with cardia GC. Overall, borderline risk (Ratnasinghe et al., 2004; Yan et al., 2009) or even decreased risk (Shen et al., 2000) was observed for the XRCC1 Arg194Trp genotype for cardia GC risk, leading us to suspect that XRCC1 Arg194Trp genotypes may implicate varied host susceptibility to GC at different anatomical subsites (Shen et al., 2000). Based on our previous results (Loh et al., 2009; Wen et al., 2012), we conducted additional investigation into association of XRCC1 Arg194Trp and ADPRT Val762Ala polymorphisms with risk of the noncardia subtype in Western China.

Materials and Methods

Research subjects

As reported in our previous study (Wen et al., 2012), we enrolled GC patients from three hospitals and control subjects from one hospital and a community between October 2010 and August 2011. Histologically confirmed GCs were defined to have a cardia location if they were found in the most proximal 3 cm of the stomach, and a noncardia location if they were observed outside this region. For research purposes in this article, we only selected the noncardia GC cases. The control subjects who were relatives of cases, or had digestive diseases or a prior history of cancer were excluded.

We utilized a self-designed questionnaire to collect epidemiological data from the subjects regarding demographic factors and potential risk factors. Individuals who smoked once a day for over one year prior to diagnosis for our recruited cases were defined as smokers, and individuals who consumed three or more alcoholic beverages a week for over one year prior to diagnosis for the cases were defined as drinkers. Family history of cancer was defined as any reported cancer in first three-degree relatives (parents, siblings, or children). Approximately 2-5ml of whole blood was collected on site after the interview and informed consent was obtained from all recruited subjects at recruitment. Research was approved by the ethics committees of four participating hospitals.

XRCC1 Arg194Trp and ADPRT Val762Ala genotyping

Genomic DNA was extracted using the TIANamp blood DNA kit (Tiangen Biotech, Beijing, China) as per the manufacturer's instructions. SNP genotyping was performed in a 384-well plate format on the Sequenom MassARRAY platform (Sequenom, San Diego, USA). Primers for polymerase chain reaction (PCR) amplification and single base extension assays were designed using Sequenom Assay Design 3.1 software (Wen et al., 2012) (Table 1). ADPRT Val762Ala and XRCC1 Arg194Trp genotypes were analyzed using MALDI-TOF MS according to Justenhoven et al. (Justenhoven et al., 2004) and procedures described in our previous article (Wen

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	CTGGTGATGTCTTGTTGATCC	6434.2
	Analyte C	CTGGTGATGTCTTGTTGATCCG	6721.4
	Analyte T	CTGGTGATGTCTTGTTGATCCA	6705.4
ADPRT Val762Ala (T2446C)	PCR Primer 1	ACGTTGGATGGCTTTCTTTTGCTCCTCCAG	
	PCR Primer 2	ACGTTGGATGTGCTATCATCAGACCCTCCC	
	Extension Primer	TTCTTTTGCTCCTCCAGGCCAAGG	7270.7
	Analyte T	TTCTTTTGCTCCTCCAGGCCAAGGT	7597.8
	Analyte C	TTCTTTTGCTCCTCCAGGCCAAGGC	7517.9

*Reproduced from Wen et al., 2012

et al., 2012). The MassARRAY Analyzer Compact with ACQUAIRE Module (Sequenom) acquired spectra from the SpectroCHIP, which were automatically processed and saved to the MassARRAY database (Wen et al., 2012).

Statistical analysis

Statistical analysis was performed by using the SPSS 11.0 software package (IBM, Armonk, USA). Demographic characteristics were compared between cases and controls by means of chi-square test. Hardy–Weinberg analysis was performed to compare the observed and expected frequencies of XRCC1 Arg194Trp and ADPRT Val762Ala genotypes using the chi-square test. The odd ratio (OR) and 95% confidence interval (CI) were calculated by unconditional logistic regression. In addition to the overall association analysis, we conducted stratified analyses by selecting epidemiologic factors to further explore the association XRCC1 Arg194Trp genotypes and risk of noncardia GC in subgroups. All *P* values were two-tailed and statistical significance was indicated by a value of $P<0.05$.

Table 2. Distribution of Characteristics of Noncardia GC Patients and Control Subjects

Variables	Cases (n=176, %)	Controls (n=308, %)	*P* value[a]
Sex			
Male	122 (69.3)	224 (72.7)	0.42
Female	54 (30.7)	84 (27.3)	
Age (years)			
<60	104 (59.1)	168 (54.6)	0.33
≥60	72 (41.0)	140 (45.5)	
Family history of cancer			
Yes	45 (25.6)	33 (10.7)	<0.01
No	131 (74.4)	275 (89.3)	
Smoking status			
Smokers	99 (56.3)	176 (57.1)	0.85
Non-smokers	77 (43.8)	132 (42.9)	
Drinking status			
Drinkers	95 (54.0)	133 (43.1)	0.02
Non-drinkers	81 (46.0)	175 (56.8)	

[a]*P* value by the chi-square test

Results

Subject characteristics

This study enrolled 176 patients with noncardia GC including 122 (69%) men and 54 (31%) women, and 308 control subjects including 224 (73%) men and 87 (27%) women. Baseline characteristics of patients with noncardia GC and control subjects are summarized in Table 2. Subjects were 56.8±11.8 (mean ± standard deviation) and 57.6±11.1 years in the case group and control group respectively. The distributions of sex and age were comparable in the patients and controls ($P=0.42$ and 0.33, respectively). There were no statistically significant differences in smoking status between noncardia GC patients and controls ($P=0.85$). The noncardia GC patients reported a significantly higher proportion of subjects with family history of cancer than the controls (26% versus 11%; $P<0.01$). The patients and controls were significantly different in terms of drinking status ($P=0.02$).

Genotype distributions and their association with noncardia GC

The genotype distribution of XRCC1 Arg194Trp and ADPRT Val762Ala and their association with developing noncardia GC are summarized in Table 3. The allele frequencies for XRCC1 194Trp and ADPRT 762Ala variants were 32.4% and 43.5% in patients, and 27.6% and 44.5% in controls, respectively. The frequencies of XRCC1 194Arg/Arg, Arg/Trp, and Trp/Trp genotypes among control subjects were 52.0%, 40.9%, and 7.14%, which conformed to the Hardy–Weinberg equilibrium ($\chi2=0.17$, $P=0.68$). Individuals carrying one or two copies of the XRCC1 Arg194Trp (Trp/Trp or Arg/Trp) variant genotype, were at significantly increased risk of noncardia GC (adjusted OR, 1.48; 95% CI, 1.00-2.17) after adjustment for family history of cancer, drinking, and smoking. The frequencies of three ADPRT genotypes, ie, 762Val/Val, -Val/Ala, and -Ala/Ala, were 34.1%, 42.9%, and 23.1%, respectively, among controls. The respective ADPRT genotype frequencies among patients were 34.1%,

Table 3. XRCC1 Arg194Trp and ADPRT Val762Ala Genotypes in Noncardia GC Patients and Controls and Association with Noncardia GC Risk

Genotypes	Cases (n=176, %)	Controls (n=308, %)	OR (95% CI)[a] Crude	Adjusted[b]
XRCC1 Arg194Trp				
Arg/Arg	76 (43.2)	160 (52.0)	1.00 (reference)	1.00 (reference)
Arg/Trp	86 (48.9)	126 (40.9)	1.44 (0.98-2.12)	1.50 (1.01-2.24)*
Trp/Trp	14 (7.95)	22 (7.14)	1.34 (0.65-2.76)	1.33 (0.66-2.80)
Trp/Trp+Arg/Trp	100 (56.8)	148 (48.1)	1.42 (0.98-2.07)	1.48 (1.00-2.17)*
ADPRT Val762Ala				
Val/ Val	60 (34.1)	105 (34.1)	1.00 (reference)	1.00 (reference)
Val/Ala	79 (44.9)	132 (42.9)	1.05 (0.69-1.60)	1.07 (0.69-1.65)
Ala/Ala	37 (21.0)	71 (23.1)	0.91 (0.55-1.52)	0.95 (0.56-1.61)
Ala/Ala +Val/Ala	116 (65.9)	203 (65.9)	1.00 (0.68-1.48)	1.03 (0.69-1.54)
Combined effect				
XRCC1 Arg/Arg + ADPRT Val/ Val	26 (14.8)	58 (18.8)	1.00 (reference)	1.00 (reference)
XRCC1 Arg/Arg + ADRRT Ala/Ala or Val/Ala	50 (28.4)	102 (33.1)	1.09 (0.62-1.94)	1.05 (0.58-1.90)
XRCC1 Trp/Trp or Arg/Trp + ADPRT Val/ Val	34 (19.3)	47 (15.3)	1.61 (0.85-3.06)	1.53 (0.79-2.96)
XRCC1 Trp/Trp or Arg/Trp + ADRRT Ala/Ala or Val/Ala	66 (37.5)	101 (32.8)	1.46 (0.84-2.54)	1.52 (0.85-2.69)

[a]ORs and 95% CIs were calculated by using unconditional logistic regression; [b]adjusted for family history of cancer, drinking and smoking; *$P<0.05$

Table 4. Stratified Analyses of XRCC1 Arg194Trp and Risk of Noncardia GC

Variables	Cases (n=176, %)		Controls (n=308, %)		Arg/Trp or Trp/Trp versus Arg/Arg[a]	
	Arg/Arg	Arg/Trp or Trp/Trp	Arg/Arg	Arg/Trp or Trp/Trp	OR(95% CI)	*P* Value[b]
Total	76 (43.2)	100 (56.8)	160 (52.0)	148 (48.1)	1.42 (0.98-2.08)	0.07
Sex						
Male	54 (44.3)	68 (55.7)	121 (54.0)	103 (46.0)	1.47 (0.94-2.31)	0.09
Female	22 (40.7)	32 (59.3)	39 (46.4)	45 (53.6)	1.33 (0.66-2.68)	0.43
Age						
<60 years	41 (39.4)	63 (60.6)	88 (52.4)	80 (47.6)	1.78 (1.07-2.96)	0.03
≥60 years	35 (48.6)	37 (51.4)	72 (51.4)	68 (48.6)	1.09 (0.61-1.94)	0.84
Smoking status						
Smokers	45 (45.5)	54 (54.6)	95 (54.0)	81 (46.0)	1.36 (0.82-2.26)	0.23
Nonsmokers	31 (40.3)	46 (59.7)	65 (49.2)	67 (50.8)	1.46 (0.82-2.59)	0.20
Drinking status						
Drinkers	44 (46.3)	51 (53.7)	71 (53.4)	62 (46.6)	1.33 (0.78-2.25)	0.30
Nondrinkers	32 (39.5)	49 (60.5)	89 (50.9)	86 (49.1)	1.49 (0.87-2.56)	0.15

[a]ORs and 95% CIs were adjusted for other variables for each stratum by using unconditional logistic regression; [b]*P* values from unconditional logistic regression analyses

44.9%, and 21.0%, which showed no significant difference compared with those among controls (χ^2=0.31, *P*=0.86) (Wen et al., 2012). There was no significant association between the ADPRT Val762Ala variant genotype (Ala/Ala or Val/Ala) and noncardia GC (adjusted OR, 1.03; 95% CI, 0.69-1.54). We further analyzed the combined effect of XRCC1 Arg194Trp and ADPRT Val762Ala genotypes on the risk of noncardia GC (Table 3). We showed the joint risk estimates when subjects were classified according to the four categories generated from XRCC1 Arg194Trp and ADPRT Val762Ala polymorphisms. Individuals carrying the ADPRT Val762Ala variant genotype did not increase the risk of XRCC1 Trp.

Stratified analysis for risk of noncardia GC

The dichotomized genotypes (XRCC1 194Trp/Trp or Arg/Trp versus Arg/Arg genotype) of XRCC1 Arg194Trp were further examined for subgroups of the variables listed in Table 1 and the adjusted ORs in the stratification analyses are presented in Table 4. Increased risk associated with XRCC1 Arg194Trp variant genotype seemed more pronounced among subjects below 60 years old (adjusted OR, 1.78; 95% CI, 1.07-2.96), compared to older individuals. The association of XRCC1 Arg194Trp variant genotype with noncardia GC was similar in subgroups stratified by sex, smoking and drinking, respectively.

Discussion

XRCC1 and ADPRT are important molecules involved in the restoration phase of BER. XRCC1 is a scaffolding protein that functions in the repair of single-strand breaks, the most common lesions in cellular DNA (Caldecott et al., 1995). ADPRT is an abundant nuclear protein that specifically recognizes and binds DNA strand breaks through two tandem-arrayed N-terminal zinc fingers, and recruits other DNA repair proteins to jointly perform the DNA damage repair (Zhang et al., 2009). In response to DNA damage, ADPRT specifically binds to DNA strand breaks, at which it is auto-activated and recruits the XRCC1-Ligase IIIα complex to stimulate BER, and XRCC1 subsequently interacts with ADPRT to recruit other partner proteins such as DNA polymerase β (Ploβ) to execute BER (Masson et al., 1998; Keith W 2003; Miao et al., 2006). Sequence variants in ADPRT and XRCC1 genes are thus hypothesized to modulate DNA repair capacity and be associated with altered GC risk. XRCC1 Arg194Trp and ADPRT Val762Ala are two of the most extensively studied SNPs of these two genes for cancer risk. In this study, we found that XRCC1 Trp/Trp or Arg/Trp variant genotype was associated with increased risk of noncardia GC, while ADPRT Val762Ala variant was not. In addition, stratified analyses indicated that the effect of XRCC1 Arg194Trp variant genotype was more pronounced in individuals below 60 years old.

Although XRCC1 gene polymorphisms have been widely studied for risk of cancer, our study is the first one to explore their risk for noncardia GC in Western China. We noted increased risk for noncardia GC in carriers of XRCC1 194Trp/Trp or Arg/Trp variant genotype in our study. Even higher risk was exhibited after controlling for possible confounders such as family history of cancer, drinking and smoking. This agrees well with our earlier finding in respect to risk for general GC in a matched case-control design (Wen et al., 2012), but contrasts the finding in three other Chinese studies that suggested decreased or only borderline risk for cardia GC (Shen et al., 2000; Ratnasinghe et al., 2004; Yan et al., 2009). The XRCC1 194 Trp variant allele seems to confer increased risk for noncardia GC, but tends to be protective for the cardia subtype. This variation supports our suspicion that XRCC1 Arg194Trp may function differently for developing GC at different subsites. In another study, XRCC1 194 Trp allele instead of Arg allele was closely associated to development of cardia GC (Yuan et al., 2010). This seems to be contradictory to findings in other similar studies for cardia GC in Chinese (Shen et al., 2000; Ratnasinghe et al., 2004; Yan et al., 2009). We found the frequency of XRCC1 194 Trp allele was only 7% in the control group of that study (Yuan et al., 2010), much lower than the range of 25%-35% (34.6%, 31.4%, and 26.8%, respectively) in other three studies. The effect of variability in genotype distribution, especially between China and distant European or American countries, also

explains the conflicting findings in different populations. Both studies in Brazil (Duarte et al., 2005) and Italy (Palli et al., 2010) found no evidence of a relationship between the XRCC1 Arg194Trp polymorphism and the development of GC, which may be due to much lower frequency of the 194Trp allele (generally lower than 15%) in these populations than those in China.

ADPRT Val762Ala polymorphism was not statistically associated with noncardia GC in our study, which was inconsistent with three other studies on risk of cardia GC (Miao et al., 2006) and GC in general (Zhang et al., 2006; Zhang et al., 2009) in Han Chinese. Reliable evidence exists for risk of prostate cancer (Lockett et al., 2004), lung cancer (Zhang et al., 2005) and esophageal cancer (Hao et al., 2004). We postulate that etiologic variation between cardia and noncardia cancers may explain in part this observation. For example, although HP infection is identified to increase risk for noncardia GC, the same does not hold true for cardia GC. HP infection is even postulated to protect against cardia GC, since this malignancy is clinically and epidemiologically closer to esophageal than to GC (Yang et al., 1988) and HP possibly protects against esophageal cancer (Henrik Siman et al., 2001). We consider that HP infection may have its role in confounding the risk of ADPRT Val762Ala genotype. Unfortunately, we were not able to analyze the risk of ADPRT Val762Ala polymorphisms after adjustment for HP infection status. This may signal a future direction for SNPs in the development of noncardia GC. In our study, the combined effect of XRCC1 Arg194Trp and ADPRT Val762Ala variant genotypes did not increase the risk of XRCC1 Arg194Trp for noncardia GC (ORs were 1.52 and 1.53, respectively), indicating a lack of interaction between the two polymorphisms.

Since a major determinant of cancer risk appears to be the interaction between genotype and environment (Wiseman, 2008), we continued a stratified analysis for noncardia GC risk. We only found that increased risk with XRCC1 Arg194Trp variant genotype was more pronounced among subjects below 60 years old, which seems contradictory to the finding in Northern China (Liu et al., 2009). We did not observe evidence of interaction between the XRCC1 genotype and sex, smoking, or drinking for risk of noncardia GC. The XRCC1 Arg194Trp variant genotype only seemingly conferred nonsignificant similar risk for noncardia GC between nonsmokers and smokers, and between nondrinkers and drinkers (1.46 versus 1.36; 1.49 versus 1.33). Putatively, smoking and drinking do not interact with XRCC1 Arg194Trp for risk of noncardia GC (Wen et al., 2012).

In conclusion, our study suggests that XRCC1 Arg194Trp is a genetic susceptibility factor for developing noncardia GC in Han Chinese in Western China. In particular, individuals with XRCC1 Arg194Trp variant genotype are at increased risk for noncardia GC below 60 years old. The ADPRT Val762Ala is not associated with increased noncardia GC risk. Since there are about 38 reported ADPRT variants and 17 XRCC1 variants (Zhang et al., 2005), we consider that future research may be warranted to incorporate several SNPs of each for haplotype analysis for noncardia GC. Research for their functional relevance may be also important, as relevant genetic polymorphisms do not necessarily translate into change in BER pathway activity.

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