Original Article

Interaction between *XRCC1* Polymorphisms and Intake of Long-Term Stored Rice in the Risk of Esophageal Squamous Cell Carcinoma: A Case-Control Study*

YU HongJie[1], FU ChaoWei[1,#], WANG JianMing[2], XUE HengChuan[3], and XU Biao[1]

1.Department of Epidemiology, School of Public Health, Fudan University, Shanghai 200032, China; 2.Department of Epidemiology, School of Public Health, Nanjing Medical University, Nanjing 210029, Jiangsu, China; 3.Yangzhong People's Hospital, Yangzhong 212200, Jiangsu, China

Abstract

Objective This study aimed to explore the roles of three common single nucleotide polymorphisms in the X-ray repair cross-complementing group-1 gene (*XRCC1*) and of life style factors and their possible interactions in the risk of esophageal squamous cell carcinoma (ESCC) in China.

Methods A population-based case-control study of 432 cases and 915 controls was conducted in Yangzhong County, Jiangsu Province, China. Subjects were interviewed by trained interviewers using a structured questionnaire that included questions on demographics and life style. *XRCC1* genotypes were analyzed using a polymerase chain reaction based restriction fragment length polymorphism (PCR-RFLP) assay. Unconditional logistic regression analysis was used to calculate adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for associations of ESCC with *XRCC1* polymorphisms and lifestyle-related factors.

Results Both the drinking of river water and alcohol intake history were significantly associated with an increased risk of ESCC among men with aORs of 4.20 (95% CI: 2.90-6.07) and 2.03 (95% CI: 1.43-2.89), respectively. For women, the corresponding odds ratios were 8.37 (95% CI: 5.09-13.75) for river water drinking and 12.78 (95% CI: 2.69-60.69) for long-term stored rice intake. After the *XRCC1* G28152A polymorphism was adjusted for potential confounders, subjects with GA and AA genotypes had an increased risk for ESCC (aOR: 1.21, 95% CI: 0.93-1.56), compared with subjects with a GG genotype, and a positive multiplicative interaction between intake of long-term stored rice and the *XRCC1* G28152A polymorphism was observed (*P*=0.009).

Conclusions Our findings suggest that both lifestyle-related factors, including drinking river water, long-term stored rice and alcohol intake, and the *XRCC1* G28152A polymorphism were possible risk factors for ESCC, and that the *XRCC1* G28152A polymorphism modified the effect of long-term stored rice intake on the risk of ESCC among Chinese people.

Key words: *XRCC1*; Polymorphism; Lifestyle-related factors; Esophageal squamous cell carcinoma; Chinese people

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#Correspondence should be addressed to FU ChaoWei. Tel: 86-21-54237811. E-mail: cwfu@shmu.edu.cn

Biographical note of the first author: YU HongJie, male, born in 1982, graduate, School of Public Health, Fudan University, majoring in genetic and molecular epidemiology.

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INTRODUCTION

Esophageal cancer is one of the most common malignancies in the world, responsible for 3.8% of all new cancer cases and for 5.4% of cancer related deaths each year[1-3]. There are mainly two types of esophageal cancer: adenocarcinoma and esophageal squamous cell carcinoma (ESCC)[4-5]. In 2008, about 482 000 new cases occurred and 406 000 patients died from esophageal cancer worldwide, over 83% of which were in developing countries[2].

The X-ray repair cross-complementing group-1 gene (*XRCC1*) is involved in the DNA repair pathway and plays a critical role in the repair of single-strand DNA breaks and in DNA base excision repair (BER) by complexing with DNA ligase III, DNA polymerase and poly (ADP-ribose) polymerase (PARP). Many polymorphisms *XRCC1* have been found, and C26304T (rs1799782), G27466A (rs25489) and G28152A (rs25487) are three common single nucleotide polymorphisms (SNP) that result in the amino acid changes, Arg194Trp, Arg280His and Arg399Gln, respectively[6-9]. *XRCC1* polymorphisms may be associated with the risk of environmentally induced cancers, including gastric cancer, colorectal cancer, lung cancer and breast cancer[10-13]. There may also be an association between *XRCC1* polymorphisms and ESCC in Chinese populations[14-17].

Yangzhong County in Jiangsu Province has a high incidence of esophageal cancer (106.58 cases/100 000 subjects in 2004)[18-19]. Yangzhong consists of a group of small islands in the Yangtze River, with a special geographical environment and regional life style. There are numerous dams in Yangzhong that block natural water exchange between inland rivers and the Yangtze River to prevent potential flooding. The staple food in Yangzhong County is rice that has usually been stored for several years and eating rice that has been stored long-term is common among local people. To explore the roles of *XRCC1* polymorphisms and of lifestyle-related factors, such as the source of drinking water, long-term stored rice intake, tobacco smoking and alcohol intake, in the risk of ESCC, we carried out a population-based case-control study in Yangzhong County.

MATERIALS AND METHODS

Participants and Data Collection

This case-control study included 432 ESCC cases and 915 cancer-free controls. All cases were identified from the Yangzhong Cancer Registry between 1 January 2004 and 14 May 2008. Participants had been living in Yangzhong County for at least 5 years prior to the study. The ESCC cases were newly diagnosed and all patients were 30 years of age or above. The controls were randomly sampled from a pool of individuals participating in a community-based health examination program and they were cancer free and aged 30 years or above. The response rates were 89% for cases and 90% for controls.

After informed consent was obtained, subjects were interviewed by trained interviewers using a structured questionnaire that included questions on demographics, education, marital status, family history of ESCC, life style factors such as diet, source of drinking water, alcohol and tobacco consumption. After the interview, a 5 mL venous blood sample was collected. Tobacco smoking was defined as anyone who smoked at least one cigarette per day for at least the past six months. Alcohol drinking was defined as those who drank alcohol at least once per week for at least the past 6 months. Long-term Stored Rice Intake (LTSRI) was defined as those who had eaten rice that had been stored for more than 1 year for no less than 5 years.

Genotyping Methods

Genomic DNA was extracted using a phenol-chloroform method and SNPs of *XRCC1* were detected by analyzing polymerase chain reaction restriction fragment length polymorphisms (PCR-RFLPs). The primers for *XRCC1* C26304T were: forward 5'-GCC AGG GCC CCT CCT TCA A-3' and reverse 5'-TAC CCT CAG ACC CAC GAG T-3', which produced a 485 bp fragment[18]. The primers for *XRCC1* G27466A were: forward 5'-CCA GTG GTG CTA ACC TAA TC-3' and reverse 5'-CAC TCA GCA CCA CTA CCA CA-3', which produced a 201 bp fragment[16]. The primers for *XRCC1* G28152A were: forward 5'-TCC TCC ACC TTG TGC TTT CT-3' and reverse 5'-AGT AGT CTG CTG GCT CTG GG-3', which produced a 517 bp fragment[17]. A 20 μL PCR reaction contained 0.1 μg template DNA, 10 μL 2×Taq PCR MasterMix containing 0.1 U Taq polymerase/μL, 500 μmol/L each dNTP, 20 μmol/L Tris-HCl (pH 8.3), 100 mmol/L KCl, 3 mmol/L $MgCl_2$ (Tiangen, China) and 0.5 μL (10 μmol/L) of each primer. PCR conditions for C26304T included a denaturation step of 5 min at 94 °C, followed by 35 cycles of 30 s denaturation at 94 °C, 30 s annealing at 61 °C, 45 sec extension at 72 °C, and then a final extension step of 7 min at 72 °C. PCR conditions for G27466A and G28152A were the same as those for

C26304T except that their annealing temperatures were 54 °C and 56 °C, respectively.

Restriction enzymes PvuII, RsaI, and BcnI (Fermentas, MBI, Burlington, Canada) were used to detect C26304T, G27466A, and G28152A polymorphisms, respectively. 10μL of PCR products mixed with 5 U of restriction enzyme were digested at 37 °C overnight. The digestion products were resolved on 2% agarose gels (Biowest, Spain) stained with ethidium bromide and then observed using a UV imaging system (Imagemaster, Pharmacia Biotech, New Jersey, USA). All genotyping work was completed without knowing the disease outcome.

The digestion product of the 26304C allele produced a single fragment (585 bp), that of the 26304TT genotype produced 2 different fragments (396 bp and 89 bp), whereas the heterozygous genotype with both 26304C and 26304T alleles produced 3 fragments (585 bp, 396 bp, and 89 bp). The digestion product of the 27466G allele produced 2 fragments (145 bp and 56 bp) and that of the 27466AA genotype produced a single fragment (201 bp), while the heterozygous genotype produced 3 fragments (201 bp, 145 bp, and 56 bp). The digestion product of the 28152G allele produced 2 fragments (384 bp and 133 bp) and that of the 28152AA genotype produced a single fragment (517 bp), but the heterozygous genotype produced 3 fragments (517 bp, 383 bp, and 133 bp). To ensure the accuracy of genotyping, 10% (135/1 347) of samples were randomly selected to be sequenced, and the concordance rate of genotyping between PCR-RLFP and sequencing was 100%.

Statistical Analysis

Student's *t*-test (for continuous variables) and the chi-square test (for categorical variables) were used to determine differences in distributions of demographic characteristics, lifestyle variables, and *XRCC1* genotypes between cases and controls. The chi-square test was employed to test controls for conformity of genotype distributions according to the genetic equilibrium law of Hardy-Weinberg. To explore associations among lifestyle-related factors and *XRCC1* polymorphisms with the risk of ESCC, crude and adjusted odds ratios (ORs) and their 95% confidence intervals (95% CI) were calculated using an unconditional logistic regression model. The gene-environment interaction was evaluated by both stratified analysis and unconditional logistic regression analysis. The interactions between genes and environmental factors were assessed on a multiplicative scale by including related interaction terms in the unconditional logistic regression model, and then ORs of interaction and their 95% CIs were estimated. Stratum specific aORs and their 95% CIs were calculated when there was a significant interaction. All statistical tests were performed using SPSS 11.0 software (Chicago, Illinois).

RESULTS

Characteristics of Participants

As shown in Table 1 432 cases and 915 controls were recruited in this study, and the average age was 61.5±7.8 y for cases and 57.1±9.1 y for controls (t=-9.154, P<0.001). There were also significant differences in gender (χ^2=18.468, P<0.001) and in education level (χ^2=19.720, P<0.001) between cases and controls.

Table 1. General Demographic Characteristics of the Cases and Controls

Variables	Cases (%) (n=432)	Controls (%)(n=915)	χ^2	P
Gender				
Men	267 (61.8)	451 (49.3)	18.468	<0.001
Women	165 (38.2)	464 (50.7)		
Age[a]				
$\chi\pm s$	61.5±7.8	57.1±9.1	-9.154	<0.001
Education Level (Years)				
0	147 (34.0)	215 (23.5)	19.659	<0.001
1~6	191 (44.2)	426 (46.6)		
7~	94 (21.8)	274 (29.9)		

Note. [a]: Student's *t*-test.

Lifestyle-related Factors, XRCC1 Polymorphisms and Risk of ESCC

In controls, *XRCC1* C26304T, G27466A, and G28152A genotype distributions were all consistent with the law of Hardy-Weinberg (P>0.05). As shown in Table 2, after stratification by gender (which was considered an important factor influencing life styles) and adjustment for age and education level, drinking of river water and alcohol intake were significantly associated with an increased risk of ESCC for men with adjusted ORs being 4.20 (95% CI: 2.90-6.07) and 2.03 (95% CI: 1.43-2.89) respectively. The association between river water drinking and ESCC tended to be stronger in women and the corresponding adjusted OR was 8.37 (95% CI: 5.09-13.75). For women, LTSRI

significantly increased the risk of ESCC (aOR=12.78, 95% CI: 2.69-60.69).

The results for associations between *XRCC1* polymorphisms and ESCC are presented in Table 3. For the G27466A SNP, people with an AA genotype had a decreased risk of ESCC compared with those with a GG genotype (crude OR=0.70, 95% CI: 0.52-0.92). When AA and GA genotypes were combined, the OR was 0.70 (95% CI: 0.53-0.92). For G28152A, the GA genotype was associated with an increased risk of ESCC compared with the GG genotype (crude OR=1.84, 95% CI: 1.17-2.88). For C26304T, no significant difference was found between cases and controls. For the G28152A SNP, after potential confounding factors, including gender, age, education level, tobacco smoking, alcohol intake, LTSRI and river water drinking were adjusted, subjects with GA or AA genotypes had an adjusted OR of 1.21 (95% CI: 0.93-1.56) compared with subjects with the GG genotype, but there were no significant differences in the distribution of *XRCC1* polymorphisms between cases and controls.

Table 2. Risk of ESCC Associated with Lifestyle-related Factors, Stratified by Gender

Variables	Men					Women				
	Cases	Controls	OR[a]	95% CI[a]	*P*[a]	Cases	Controls	OR[a]	95% CI[a]	*P*[a]
River Water Drinking										
No	151	385	1.00			92	429	1.00		
Yes	116	66	4.20	2.90-6.07	<0.001	73	35	8.37	5.09-13.75	<0.001
LTSRI										
No	250	432	1.00			156	461	1.00		
Yes	17	19	1.31	0.63-2.70	0.468	9	3	12.78	2.69-60.69	0.001
Tobacco Smoker										
No	72	175	1.00			163	462	1.00		
Yes	195	276	1.37	0.94-1.99	0.105	2	2	6.49	0.68-62.42	0.105
Alcohol Drinker										
No	92	249	1.00			157	454	1.00		
Yes	175	202	2.03	1.43-2.89	<0.001	8	10	2.23	0.76-6.60	0.147

Note. [a]: Adjusted for age (continuous) and education level.

Table 3. Risk of ESCC Associated with *XRCC1* Polymorphisms

Genotypes	Case	Control	OR (95%CI)	OR (95%CI)[a]
C26304T				
CC	196	434	1.00	1.00
CT	187	389	1.18(0.80-1.73)	1.19(0.76-1.84)
TT	49	92	1.06(0.84-1.36)	1.06(0.81-1.39)
CT+TT	236	48	1.09(0.86-1.37)	1.08(0.84-1.40)
G27466A				
GG		670		
GA	344	227	1.00	1.00
AA	81	18	0.76(0.31-1.83)	0.94(0.36-2.48)
GA+AA	7	245	0.70(0.52-0.92)	0.80(0.58-1.10)
G28152A	88			
GG		536	0.70(0.53-0.92)	0.81(0.60-1.11)
GA	237	331		
AA	156	48	1.00	1.00
GA+AA	39	379	1.84(1.17-2.88)	1.48(0.89-2.48)
	195		1.07(0.84-1.36)	1.16(0.88-1.53)
			1.16(0.92-1.47)	1.21(0.93-1.56)

Note. [a]: Adjusted for gender, age (continuous), education level, tobacco smoking, alcohol intake, LTSRI and river water drinking.

Interaction between Lifestyle-related Factors and XRCC1 Polymorphisms

For the *XRCC1* G28152A SNP, after gender, age, education level, tobacco smoking, alcohol intake and river water drinking were adjusted, a positive multiplicative interaction between GA or AA genotypes and LTSRI on the risk of ESCC was observed (*P*=0.009) (Table 4). The adjusted OR for LTSRI associated with the risk of ESCC was 1.12 (95% CI: 0.50-2.50, *P*=0.778) for subjects with the GG genotype and 8.08 (95% CI: 2.45-26.64, *P*=0.001) for subjects with GA or AA genotypes.

DISCUSSION

Lifestyle-related factors, such as tobacco smoking, drinking alcohol, high salt or nitrosamine diets, spicy food intake and infections have been found to be risk factors for the incidence of ESCC[20-27]. In our study, alcohol intake was an important determinant of ESCC in men, but tobacco

Table 4. Interactions between *XRCC1* Polymorphisms and Lifestyle-related Factors on the Risk of ESCC

Variables	C26304T	Case/ Control	OR (95% CI)[a]	OR_{int} (95% CI)[a]	P_{int}[a]	G27466A	Case/ Control	OR (95% CI)[a]	OR_{int} (95% CI)[a]	P_{int}[a]	G28152A	Case/ Control	OR (95% I)[a]	OR_{int} (95% CI)[a]	P_{int}[a]
River Water Drinking															
-	CC	111/387	1.00	0.90 (0.50-1.62)	0.720	GG	191/594	1.00	0.84 (0.42-1.69)	0.628	GG	134/469	1.00	1.50 (0.82-2.74)	0.187
-	CT+ TT	132/427	1.11 (0.82-1.51)			GA+ AA	52/220	0.85 (0.59-1.21)			GA+ AA	109/345	1.09 (0.80-1.47)		
+	CC	85/47	5.91 (3.84-9.10)			GG	153/76	5.79 (4.14-8.09)			GG	103/67	4.77 (3.26-6.97)		
+	CT+ TT	104/54	5.91 (3.93-8.90)			GA+ AA	36/25	4.13 (2.37-7.20)			GA+ AA	86/34	7.78(4.92-12.30)		
LTSRI															
-	CC	187/426	1.00	0.76 (0.20-2.86)	0.684	GG	322/653	1.00	1.11 (0.22-5.63)	0.897	GG	224/519	1.00	6.58	0.009
-	CT+ TT	219/467	1.09 (0.84-1.43)			GA+ AA	84/240	0.81 (0.59-1.11)			GA+ AA	182/374	1.12 (0.86-1.46)	(1.60-27.11)	
+	CC	9/8	2.35 (0.83-6.71)			GG	22/17	1.95 (0.95-4.01)			GG	13/17	1.03 (0.45-2.34)		
+	CT+ TT	17/14	1.96 (0.86-4.44)			GA+ AA	4/5	1.75 (0.42-7.33)			GA+ AA	13/5	7.61(2.41-23.99)		
Tobacco Smoking															
-	CC	107/298	1.00	0.96 (0.57-1.62)	0.874	GG	185/461	1.00	1.23 (0.65-2.32)	0.530	GG	131/375	1.00		0.955
-	CT+ TT	128/339	1.10 (0.79-1.54)			GA+ AA	50/176	0.75 (0.51-1.11)			GA+ AA	104/262	1.20 (0.86-1.68)	1.02 (0.60-1.73)	
+	CC	89/136	1.56 (0.98-2.49)			GG	159/209	1.45 (0.97-2.17)			GG	106/161	1.50 (0.96-2.33)		
+	CT+ TT	108/142	1.64 (1.04-2.60)			GA+ AA	38/69	1.34 (0.77-2.31)			GA+ AA	91/117	1.82 (1.15-2.89)		
Alcohol Intake															
-	CC	105/331	1.00	0.68 (0.39-1.16)	0.157	GG	194/509	1.00	0.96 (0.50-1.85)	0.895	GG	140/402	1.00		0.175
-	CT+ TT	144/372	1.24 (0.90-1.72)			GA+ AA	55/194	0.82 (0.57-1.20)			GA+ AA	109/301	1.06 (0.77-1.46)	1.46 (0.85-2.53)	
+	CC	91/103	2.70 (1.74-4.18)			GG	150/161	2.20 (1.53-3.18)			GG	97/134	1.87 (1.24-2.82)		
+	CT+ TT	92/109	2.26 (1.45-3.53)			GA+ AA	33/51	1.74 (1.00-3.00)			GA+ AA	86/78	2.89(1.85-4.51)		

Note. [a]: Adjusted for gender, age (continuous), education level, tobacco smoking, alcohol intake, long-term stored rice intake (LTSRI) and river water drinking (excluding the analysis variable). OR_{int}: OR of interaction. P_{int}: *P* value of interaction.

smoking was not significantly associated with the risk of ESCC, which is not consistent with previous results[20, 22, 27]. In this study, we found that drinking river water was a risk factor of ESCC for people living in Yangzhong County. In recent years, increased attention has been paid to the relationship between drinking water and ESCC, although results have been inconsistent concerning water sources and the drinking of unboiled water[24, 28-29]. With the special geographical location of Yangzhong County, the river water of most inlands has been heavily polluted by metal ions and bacteria, and some previous studies have suggested that heavy metals, including Pb, As and Hg are closely related to the incidence of ESCC[30-32], which may partly explain the relationships between river water drinking and ESCC in Yangzhong County. Intake of long-term stored rice was a risk factor of ESCC among women in our study. Yangzhong County has an average humidity of over 80%, which makes rice susceptible to mildew and to be contaminated by fungi. Fungal toxins, such as aflatoxin B1 (AFB1) and nivalenol (NIV), are carcinogenic and mutagenic factors and are strongly associated with cancers of the digestive system[33-34]. There is a possibility that fungal toxins in long-term stored rice increase the risk of ESCC in women. However, it is not known why the association was only significant in women but not in men (aOR=1.31, 95% CI: 0.63-2.70), although the relatively small sample size may be one reason.

There is evidence that *XRCC1* polymorphisms are associated with susceptibility to environmentally induced cancers, such as lung cancer, breast cancer and ESCC[7-17, 35-40]. In China, Yu et al. found that the AA genotype of G28152A was associated with an increased risk of ESCC (OR=5.15, 95% CI: 2.42-10.93)[14]. Lee et al. reported similar results among alcohol drinkers (OR=2.78, 95% CI: 1.15-6.67)[15]. In this study, no significant differences among *XRCC1* polymorphisms between cases and controls were observed after possible confounders were adjusted. However, we observed a trend of lower ESCC risk in subjects with the AA genotype of G27466A compared with subjects with the GG genotype, and a trend of higher risk in subjects with the GA genotype of G28152A compared with subjects with the GG genotype. This finding was similar to results reported by Miao et al[39].

We tested the interaction between *XRCC1* G28152A polymorphisms and LTSRI and found a positive multiplicative interaction. People with both GA or AA genotypes and a history of LTSRI had a marked increase in ESCC risk compared with people with only GA or AA genotypes or LTSRI. LTSRI significantly increased the risk of ESCC for subjects with the GA or AA genotype, (aOR=8.08, 95% CI: 2.45-26.64, *P*=0.001) but not for subjects with the GG genotype (aOR=1.12, 95% CI: 0.50-2.50, *P*=0.778). Previous studies have reported interactive effects of *XRCC1* polymorphisms with tobacco smoking or alcohol intake on ESCC[15], but they were not observed in the current study.

This study was a community-based case-control study and selection bias would be small compared with a hospital-based design. The study included various important risk factors and potential confounders (gender, age, education level, tobacco smoking, alcohol intake, LTSRI and drinking of river water), which were carefully examined in the analysis. However, results from this study might be subject to some information biases, such as recall bias of participants. For some risk factors, there was a substantial amount of missing data, such as for LTSRI.

In conclusion, the findings from this study suggest that drinking river water, intake of long-term stored rice and alcohol intake might be risk factors for ESCC, and that there might be a modification effect between *XRCC1* G28152A polymorphisms and LTSRI on the risk of ESCC.

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