

Polymorphisms in the *XPC* gene and gastric cancer susceptibility in a Southern Chinese population

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Abstract: Previous studies have reported that *XPC* gene polymorphisms may modify the individual susceptibility to gastric cancer. In this case-control study with a total of 1,142 cases and 1,173 controls, four potentially functional polymorphisms were genotyped in the *XPC* gene (rs2228001 A>C, rs2228000 C>T, rs2607775 C>G, and rs1870134 G>C) by Taqman assays and their associations were analyzed with the risk of gastric cancer in a Southern Chinese population. No significant association between any of *XPC* polymorphisms and gastric cancer risk was detected except for a borderline association with the rs2228000 CT/TT genotype (crude odds ratio =0.86, 95% confidence interval =0.73–1.02, *P*=0.088) when compared to the rs2228000 CC genotype. Further stratified analysis revealed that the protective effect of rs2228000 CT/TT on the risk of gastric cancer was only significant among subjects older than 58 years. In summary, results indicated that genetic variations in *XPC* gene may play a weak effect on gastric cancer susceptibility in Southern Chinese population, which warrants further confirmation in larger prospective studies with different ethnic populations.

Keywords: gastric cancer, *XPC*, polymorphism, DNA repair, genetic susceptibility

Introduction

Gastric cancer is the fifth most common cancer and the third leading cause of cancer-related deaths worldwide. Although a marked decrease in incidence and mortality rates has been observed in most industrialized countries, the incident rate remains high in Eastern Asia, Eastern Europe, and South America.¹ In People's Republic of China, the survival of gastric cancer is poor. Although remarkable achievements have been made in surgical treatments, targeted therapies, and chemotherapies, the overall 5-year survival rate for gastric cancer is relatively low, ~27.4%. As a result, People's Republic of China still carries a substantial burden of gastric cancer.² The initiation and development of gastric cancer is a multistep and multifactorial process influenced by environmental, genetic, and epigenetic factors.³ Epidemiological studies have revealed that *Helicobacter pylori* infection, nutritional deficiencies, low fresh vegetable and fruit intake, smoking, drinking, and high body mass index may contribute to the etiology of gastric cancer.^{4–7} However, most individuals exposed to these environmental risk factors actually never develop gastric cancer in their lifetime, suggesting the indispensable role of genetic factors in gastric carcinogenesis.^{8–12}

DNA repair system plays a vital role in maintaining the stability and integrity of human genome and normal cellular functions. To date, at least five known major DNA repair pathways consisting of >130 genes are validated.¹³ Nucleotide excision repair

(NER) pathway, one of the most versatile DNA repair mechanisms, is responsible for removing a wide variety of DNA lesions, such as alkylating damage, bulky adducts, cross-links, oxidative DNA damage, and thymidine dimers.^{13,14} In humans, defects in the NER pathway can result in a rare autosomal recessive disease, xeroderma pigmentosum (XP), which is characterized by extreme susceptibility to ultraviolet and a high predisposition to sunlight-induced skin cancer.¹⁵ Thus far, at least eight complementation groups (XPA to G and ERCC1), which limit the rate of NER mechanism, have been identified.¹⁶

The *XPC* gene is one of the eight key genes in the NER pathway. Its protein product plays an important role in global genomic NER, especially in damage recognition, open complex formation, and reparation.¹⁷ XPC tightly binds to HR23B (also known as ultraviolet excision repair protein RAD23 homolog B) to form the XPC–HR23B complex, which functions as an early damage detector and a molecular matchmaker for recruitment of the transcription factor IIIH (including two helicases: ERCC3/XPB and ERCC2/XPD) to the damaged DNA during the global genomic NER.^{17,18}

To date, ~2,582 polymorphic variants in the *XPC* gene have been identified (<http://www.ncbi.nlm.nih.gov/projects/SNP>). A multitude of studies have been performed to investigate the association between the *XPC* polymorphisms and cancer risk.^{19–22} However, the association between *XPC* gene polymorphisms and gastric cancer remains conflicting due to limited sample size and ethnic diversity. Therefore, it is essential to further assess the associations of potentially functional *XPC* polymorphisms with gastric cancer susceptibility. In this study, the current case–control study was conducted to better understand the associations between four functional single nucleotide polymorphisms (SNPs) of *XPC* gene and the risk of gastric cancer, consisting of 1,173 healthy controls and 1,142 gastric cancer patients.

Materials and methods

Study population

A total of 1,142 gastric cancer patients were enrolled between February 2002 and September 2013 from Sun Yat-sen University Cancer Center. Cases were eligible if they had newly diagnosed and histologically confirmed primary gastric cancer without undergoing radiotherapy and chemotherapy treatment. All 1,173 healthy controls without tumor and other diseases were randomly enrolled from Sihui city, Guangdong. All the research subjects were unrelated ethnic Han Chinese population from Southern China. They were interviewed face-to-face by specially trained professional interviewers

and provided signed informed consent forms. The questions included demographic characteristics (eg, age and sex) and lifestyle habits (eg, smoking habits and alcohol drinking). Individuals who smoked <1 package of cigarettes every day but no more than a year were defined as nonsmokers, while those who drank alcohol less than once a week but no more than a year were defined as nondrinkers, as described earlier.⁹ With the permission of the subjects, ~5 mL of venous blood sample was collected from each subject for genetic testing. In general, the response rates of both cases and controls were >85%. This study was approved by the institutional review board of Sun Yat-sen University Cancer Center.

Selection of candidate SNPs and genotyping

The potentially functional SNPs were selected by using the NCBI dbSNP database and SNPinfo (<http://snpinfo.niehs.nih.gov/snpinfo/snpfunc.htm>). The following criteria were applied: 1) the minor allele frequency reported in HapMap was >5% for Chinese Han subjects; 2) putative functional potential SNPs, which might affect transcription activity or binding capacity of the microRNA-binding site; and 3) SNPs in low linkage disequilibrium with each other ($R^2 < 0.8$). Based on the criteria, four potential functional SNPs (rs2228001 A>C, rs2228000 C>T, rs2607775 C>G, and rs1870134 G>C) were selected.

Genomic DNA was extracted from blood samples using the Qiagen Blood DNA Mini Kit (Qiagen Inc., Valencia, CA, USA) according to the instructions of the manufacturer. Genotype analyses of all SNPs were performed by the Taqman real-time polymerase chain reaction method using a 7900 Sequence Detection System (Thermo Fisher Scientific, Waltham, MA, USA) as described previously.⁹ To achieve more reliable genotyping results, four duplicated positive controls and four negative controls without DNA template were loaded in each of 384-well plates. Genotyping was repeated on a random 10% of the samples, and the results were 100% concordant.

Statistical analysis

Chi-square test was used to compare the differences between cases and controls regarding demographic characteristics, smoking and drinking status, and SNP genotypes. Goodness-of-fit χ^2 test was performed to test whether the genotype frequency distribution of each polymorphism in controls was in Hardy–Weinberg equilibrium. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the associations between each SNP and gastric cancer risk,

using univariate and multivariate logistic regression models. Further stratification analysis by age, sex, pack-years, smoking and drinking status, tumor sites, and TNM stages were also performed. All statistical analysis was performed using SAS software (version 9.1; SAS Institute Inc., Cary, NC, USA). A two-sided statistical significance level of 0.05 was chosen.

Results

Population characteristics

The clinical and demographic characteristics of the study population, consisting of 1,142 cases and 1,173 healthy controls, are summarized in Table 1. No significant differences were observed between the cases and controls in term of sex ($P=0.393$). However, the average age of cases were significantly higher than that of controls ($P<0.0001$). The controls were more likely to be smokers and drinkers than the cases (both $P<0.0001$). Moreover, there was significant difference in the distributions of pack-years between

Table 1 Clinical and demographic characteristics of gastric cancer patients and cancer-free controls

Variables	Case, n (%)	Control, n (%)	P-value ^a
All subjects	1,142 (100.0)	1,173 (100.0)	
Sex			0.393
Male	749 (65.6)	789 (67.3)	
Female	393 (34.4)	384 (32.7)	
Age, years	15–86	16–80	<0.0001
Mean	56.3±12.5	45.2±11.6	
≤50	334 (29.3)	789 (67.3)	
51–60	362 (31.7)	285 (24.3)	
61–70	312 (27.3)	73 (6.2)	
>70	134 (11.7)	26 (2.2)	
Smoking status			<0.0001
Never	735 (64.4)	662 (56.4)	
Ever	407 (35.6)	511 (43.6)	
Drinking status			<0.0001
No	934 (81.8)	600 (51.2)	
Yes	208 (18.2)	573 (48.8)	
Pack-years			<0.0001
0	735 (64.4)	662 (56.4)	
≤30	272 (23.8)	383 (32.7)	
>30	135 (11.8)	128 (10.9)	
Sites			
Cardia	240 (21.0)	–	
Non-cardia	902 (79.0)	–	
TNM stage			
I	140 (12.3)	–	
II	329 (28.8)	–	
III	456 (39.9)	–	
IV	217 (19.0)	–	

Note: ^aTwo-sided chi-square test for distributions between gastric cancer cases and cancer-free controls.

the cases and controls ($P<0.0001$). Among gastric cancer patients, 21% (240 cases) had gastric cardia adenocarcinoma, while 79% (902 cases) had nongastric cardia adenocarcinoma. Regarding tumor stage, 140 (12.3%), 329 (28.8%), 456 (39.9%), and 217 tumors (19%) were classified as TNM stages I, II, III, and IV, respectively, according to the 7th Edition of the American Joint Committee on Cancer.²³

Associations between XPC gene polymorphisms and gastric cancer risk

The genotype distributions of the selected XPC gene polymorphisms in cases and controls and their associations with gastric cancer risk are summarized in Table 2. The genotype frequency distributions of all SNPs in the control subjects were in agreement with Hardy–Weinberg equilibrium. Variables including age, smoking, drinking, and pack-years were adjusted for in the subsequent multivariate logistic regression analyses. The logistic regression analysis showed that none of the four SNPs was associated with gastric cancer risk in homozygotes or heterozygotes after being adjusted for age, sex, smoking, and drinking status. When compared with CC genotypes, the rs2228000 CT/TT genotypes were not associated with gastric cancer risk (crude OR = 0.86, 95% CI = 0.73–1.02, $P=0.088$), even after adjustment for age, sex, smoking, and drinking status (adjusted OR = 0.90, 95% CI = 0.74–1.09, $P=0.261$).

Stratification analysis

Further investigation was done on the potential association between XPC rs2228000 C>T polymorphism and the risk of gastric cancer in the stratified study by age, sex, smoking status, pack-year, drinking status, tumor sites, and TNM stages. The results of stratified analysis are shown in Table 3. The rs2228000 CT/TT genotypes were found to be associated with a significantly decreased risk of gastric cancer among individuals older than 58 (adjusted OR = 0.67, 95% CI = 0.46–0.97), when CC genotype served as a reference. Similarly, when compared with noncarriers, carriers of rs2228000 CT/TT genotypes had a significantly decreased risk of gastric cancer among nondrinkers (crude OR = 0.80, 95% CI = 0.65–0.99). Statistical significance of the association was reevaluated after adjustment for age, sex, smoking, and drinking status, and the protective effect of rs2228000 CT/TT genotypes against gastric cancer was not observed. Moreover, no significant association between gastric cancer risk and rs2228000 genotypes was observed in the stratified analyses by sex, smoking status, pack-year, tumor sites, and TNM stages.

Table 2 Association between XPC gene polymorphisms and gastric cancer risk

Genotypes	Cases, n (%)	Controls, n (%)	P-value ^a	OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value ^b
rs2228001 A>C							
AA	460 (40.3)	472 (40.2)		1.00		1.00	
AC	534 (46.8)	557 (47.5)		0.98 (0.83–1.17)	0.854	1.03 (0.85–1.26)	0.756
CC	148 (13.0)	144 (12.3)		1.06 (0.81–1.37)	0.692	1.06 (0.79–1.42)	0.712
Dominant	682 (59.7)	701 (59.8)	0.984	1.00 (0.85–1.18)	0.984	1.04 (0.86–1.25)	0.703
Additive model			0.870	1.01 (0.90–1.15)	0.818	1.03 (0.90–1.18)	0.679
Recessive	994 (87.0)	1,029 (87.7)	0.620	1.06 (0.83–1.36)	0.620	1.04 (0.79–1.37)	0.783
rs2228000 C>T							
CC	457 (40.0)	429 (36.6)		1.00		1.00	
CT	524 (45.9)	583 (49.7)		0.84 (0.71–1.01)	0.060	0.89 (0.72–1.08)	0.231
TT	161 (14.1)	161 (13.7)		0.94 (0.73–1.21)	0.627	0.94 (0.70–1.25)	0.666
Dominant	685 (60.0)	744 (63.4)	0.088	0.86 (0.73–1.02)	0.088	0.90 (0.74–1.09)	0.261
Additive model			0.164	0.94 (0.83–1.06)	0.278	0.95 (0.83–1.09)	0.431
Recessive	981 (85.9)	1,012 (86.3)	0.796	1.03 (0.82–1.31)	0.796	1.01 (0.77–1.31)	0.973
rs2607775 C>G							
CC	1,051 (92.0)	1,079 (92.0)		1.00		1.00	
CG	87 (7.6)	91 (7.8)		0.98 (0.72–1.33)	0.905	0.94 (0.66–1.33)	0.708
GG	4 (0.4)	3 (0.3)		1.37 (0.31–6.12)	0.683	0.57 (0.11–3.15)	0.508
Dominant	91 (8.0)	94 (8.0)	0.968	0.99 (0.74–1.34)	0.968	0.92 (0.65–1.30)	0.625
Additive model			0.911	1.01 (0.76–1.34)	0.967	0.91 (0.65–1.26)	0.558
Recessive	1,138 (99.6)	1,170 (99.7)	0.679	1.37 (0.31–6.13)	0.682	0.57 (0.11–3.17)	0.512
rs1870134 G>C							
GG	711 (62.3)	742 (63.3)		1.00		1.00	
GC	378 (33.1)	374 (31.9)		1.06 (0.88–1.26)	0.553	1.05 (0.86–1.29)	0.606
CC	53 (4.6)	57 (4.9)		0.97 (0.66–1.43)	0.879	0.95 (0.61–1.47)	0.819
Dominant	431 (37.7)	431 (36.7)	0.620	1.04 (0.88–1.24)	0.620	1.04 (0.86–1.26)	0.688
Additive model			0.813	1.02 (0.89–1.18)	0.747	1.02 (0.87–1.19)	0.828
Recessive	1,089 (95.4)	1,116 (95.1)	0.805	0.95 (0.65–1.40)	0.805	0.93 (0.61–1.44)	0.755

Notes: ^aChi-square test for genotype distributions between cases and controls; ^bAdjusted for age, sex, smoking, and drinking status.

Abbreviations: CI, confidence interval; OR, odds ratio.

Table 3 Stratification analysis for association between XPC rs2228000 C>T genotypes and gastric cancer risk

Variables	rs2228000 C>T (cases/controls)		OR (95% CI)	P-value	Adjusted OR (95% CI)	P-value ^a
	CC	CT/TT				
Median age, years						
≤58	224/377	377/639	0.99 (0.80–1.21)	0.888	0.98 (0.79–1.22)	0.841
>58	233/52	311/105	0.66 (0.46–0.96)	0.030	0.67 (0.46–0.97)	0.034
Sex						
Male	307/293	442/496	0.85 (0.69–1.04)	0.122	0.90 (0.71–1.14)	0.390
Female	150/136	243/248	0.89 (0.66–1.19)	0.427	0.88 (0.64–1.21)	0.433
Smoking status						
Never	293/238	442/424	0.85 (0.68–1.05)	0.133	0.86 (0.67–1.11)	0.240
Ever	164/191	243/320	0.88 (0.68–1.16)	0.367	0.93 (0.69–1.26)	0.646
Pack-year						
0	293/238	442/424	0.85 (0.68–1.05)	0.133	0.86 (0.67–1.11)	0.240
≤30	106/150	166/233	1.01 (0.73–1.39)	0.960	1.04 (0.71–1.51)	0.844
>30	58/41	77/87	0.63 (0.38–1.04)	0.068	0.73 (0.42–1.25)	0.245
Drinking status						
Never	375/210	559/390	0.80 (0.65–0.99)	0.043	0.85 (0.68–1.07)	0.171
Ever	82/219	126/354	0.95 (0.69–1.32)	0.760	0.92 (0.63–1.34)	0.649
Tumor sites						
Cardia	99/429	141/744	0.82 (0.62–1.09)	0.173	0.87 (0.63–1.20)	0.386
Non-cardia	358/429	544/744	0.88 (0.73–1.05)	0.147	0.88 (0.72–1.08)	0.216
TNM stages						
I/II	175/429	294/744	0.97 (0.78–1.21)	0.778	0.95 (0.74–1.22)	0.695
III/IV	282/429	391/744	0.80 (0.66–0.97)	0.024	0.83 (0.67–1.04)	0.101

Notes: ^aObtained in logistic regression models with adjustment for age, sex, smoking, and drinking status. Results in bold are significant findings.

Abbreviations: CI, confidence interval; OR, odds ratio.

Discussion

In this study, a large scale case–control study was performed to investigate the associations between four potentially functional SNPs in the *XPC* gene and the risk of gastric cancer in a Southern Chinese population. The results showed that none of the four polymorphisms in the *XPC* gene had a significant main effect on the risk of developing gastric cancer. However, compared with CC genotype, the rs2228000 CT/TT genotypes carriers were associated with a borderline decreased risk of gastric cancer and this protective effect against gastric cancer was more evident among individuals older than 58 years of age. It was worth noting that the increased protective effect in the older group might be ascribed to the reduction of sample sizes. To the best of the authors' knowledge, by far, this is the largest study to investigate the association of the four *XPC* SNPs with gastric cancer risk.

The *XPC* gene is located at chromosome 3p25 containing 16 exons and 15 introns. It encodes a 940-amino acid protein that can form a XPC–RAD23B complex through the interaction with RAD23B.²⁴ In the process of NER, the XPC–HR23B complex first recognizes the DNA damage site and then recruits the transcription factor IIIH helicases ERCC2/XPD and ERCC3/XPB to open the DNA strands surrounding the site of the lesion.^{18,25} The binding of XPC to damaged DNA is the rate-limiting step for NER.²⁶ Subsequently, a multiprotein factor composed of XPA and the single-strand DNA-binding protein replication protein A are then recruited to the opened structure near the lesion to verify the damage-specific localization of repair complexes or to assure the correct 3D assembly.²⁵ Finally, the open DNA complex creates the substrate for cleavage by two structure-specific endonucleases ERCC1–XPF²⁷ and XPG.²⁸ Many polymorphisms that were detected in *XPC* gene may change the DNA repair capacity, and thus contribute to cancer susceptibility.^{29,30} These variants may modulate susceptibility to gastric cancer through the complex gene–gene and gene–environment interactions.

Although a few studies have investigated the role of *XPC* polymorphisms in gastric cancer, inconsistent results have been reported. In a hospital-based case–control study consisting of 106 cases and 116 controls in Turkish population, no association between *XPC* Lys939Gln (rs2228001) polymorphism and susceptibility to gastric cancer was observed.³¹ Long et al also found the null association between *XPC* Lys939Gln and gastric cancer risk in a Chinese population.³² In contrast, other studies reported opposite results regarding the association. In a study of 496 Japanese gastric cancer patients, the *XPC* rs2228000 TT

genotype was associated with shorter overall survival and recurrence-free survival, compared with CC/CT genotypes.³³ Lately, Xue et al reported that *XPC* rs2228001 had no statistical association with response to chemotherapy in 410 gastric cancer patients recruited from People's Republic of China.³⁴ In a meta-analysis consisting of 1,355 gastric cancer cases and 2,753 controls from six studies, Peng et al found that there were no association between three *XPC* polymorphisms (Lys939Gln (rs2228001 A>C), Val499Arg (rs2228000 C>T), and PAT⁻⁴) and gastric cancer risk in the overall and subgroup analyses.³⁵ The discrepancies among studies might be partly due to tumor specificity, ethnic and demographic differences, or insufficient statistical power resulting from a small sample size. For example, the frequency of the rs2228001 C allele was 0.36 in Chinese populations in the current study, 0.38 in Swedish population,³⁶ and 0.55 in Turkish population in the study by Engin et al.³¹

Given the critical role of the *XPC* gene in the NER pathway, it is biologically plausible that functional *XPC* variants may alter the DNA repair capacity of NER, and thereby modify the risk of gastric cancer. In this study, no significant association was observed between variant genotypes of *XPC* polymorphisms and gastric cancer risk in the overall analysis. The following reasons may help to explain the negative observation. First, gastric cancer is a multifactorial disease resulting from complex interactions between environmental and genetic factors.³⁷ Variants at a single locus may moderately contribute to risk of cancer due to their weak penetrance. Second, the true associations of *XPC* gene polymorphisms with gastric cancer might be covered by the other seven core genes (ie, *XPA*, *XPB*, *XPD*, *XPE*, *XPF*, *XPG*, and *ERCC1*), because variants in these genes may interfere with each other while modifying the DNA repair capacity of NER.

Although four potentially functional SNPs were extensively analyzed in the *XPC* gene in a large case–control study, some limitations should be noted when interpreting the findings. First, frequency matching between cases and controls in this research was only performed on sex, but not on age, smoking, and drinking status. Multivariate logistic regression analysis was used to reduce the impact of these factors to some extent but not adequately. Second, other risk factors, such as dietary intake, occupational exposure, *H. pylori* infection status, and environmental factors, should be considered. Lack of these data might affect the reliability of the results as gastric cancer is a heterogeneous disease. Third, the selection of SNPs in this study is based on database searching. Although these four SNPs genotyped in this study can

represent all potentially functional SNPs with minor allele frequency >0.5 recorded in HapMap database, it should be noted that some SNPs not recorded in the database may be omitted. Future studies containing more SNPs in the *XPC* gene are needed. Fourth, survival data were not available for the present study, which limited the survival analysis in the current study. Finally, this study was a hospital-based case-control study with subjects from South China, which may not well represent other Chinese populations in a different region. As a result, selection bias is inevitable.

In conclusion, it was found that the *XPC* rs2228001 A>C, rs2228000 C>T, rs2607775 C>G, and rs1870134 G>C polymorphisms were not associated with gastric cancer susceptibility. Well designed, prospective studies with a larger sample size, involving different ethnicities, are warranted to clarify the role of these polymorphisms in the future.

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Disclosure

The authors report no conflicts of interest in this work.

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