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WJG mainly publishes articles reporting research results and findings obtained in the field of gastroenterology and hepatology and covering a wide range of topics including gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, gastrointestinal oncology, and pediatric gastroenterology.

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ORIGINAL ARTICLE

Case Control Study

Nucleotide excision repair pathway gene polymorphisms are associated with risk and prognosis of colorectal cancer

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Author contributions: Yuan Y designed the study and revised the manuscript; Xing CZ recruited the patients; Sun LP collected the data; Xu Q, Gong YH, and Jing JJ performed the experiments; Li YK analyzed the data and drafted the manuscript.

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Abstract

BACKGROUND

Single nucleotide polymorphisms (SNPs) are universally present in nucleotide excision repair (NER) pathway genes, which could make impacts on colorectal carcinogenesis and prognosis.

AIM

To explore the association of all tagSNPs in NER pathway genes with colorectal cancer (CRC) risk and prognosis in a northern Chinese population by a two-stage case-control design composed of a discovery and validation stage.

METHODS

Genotyping for NER SNPs was performed using kompetitive allele specific PCR. In the discovery stage, 39 tagSNPs in eight genes were genotyped in 368 subjects, including 184 CRC cases and 184 individual-matched controls. In the validation stage, 13 SNPs in six genes were analyzed in a total of 1712 subjects, including 854 CRC cases and 858 CRC-free controls.

RESULTS

Two SNPs (XPA rs10817938 and XPC rs2607775) were associated with an increased CRC risk in overall and stratification analyses. Significant cumulative and interaction effects were also demonstrated in the studied SNPs on CRC risk. Another two SNPs (ERCC2 rs1052555 and ERCC5 rs2228959) were newly found to be associated with a poor overall survival of CRC patients.

CONCLUSION

Our findings suggest novel SNPs in NER pathway genes that can be predictive

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for CRC risk and prognosis in a large-scale Chinese population. The present study has referential values for the identification of all-round NER-based genetic biomarkers in predicting the susceptibility and clinical outcome of CRC.

Key words: Nucleotide excision repair; Polymorphism; Colorectal cancer; Susceptibility; Prognosis

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Core tip: We conducted a two-stage case-control study to explore the association of all tag-single nucleotide polymorphisms (SNPs) in eight nucleotide excision repair pathway genes with colorectal cancer (CRC) risk and prognosis in a northern Chinese population, including a discovery and validation stage. We newly found that two SNPs (XPA rs10817938 and XPC rs2607775) contributed to an increased CRC risk in overall and stratification analyses. Another two SNPs (ERCC2 rs1052555 and ERCC5 rs2228959) were also first reported to be associated with a poor CRC prognosis.

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INTRODUCTION

Colorectal cancer (CRC) is the third common malignant neoplasm and the fifth leading cause of cancer-related death in China. The incidence has been continuously rising in the past decades, which has exceeded the average levels both in developed and developing countries[1,2]. Genetic factors are thought to play a critical role in the susceptibility to CRC with hereditable factors estimated to account for 35% of the risk[3]. The identification of genetic biomarkers associated with CRC is quite crucial for its early diagnosis and treatment.

Nucleotide excision repair (NER) is one of the most versatile DNA repair pathways, which can protect cellular DNA against ultraviolet-induced cyclobutane pyrimidine dimers, DNA crosslinks, and bulky adducts[4]. It involves damage recognition, damage demarcation and unwinding, damage incision, and new strand ligation. All the stages are completed by eight key proteins, comprising DDB2, ERCC1, ERCC2, ERCC3, ERCC4, ERCC5, XPA, and XPC[5,6], which respond to a wide range of DNA damage but are particularly important for the removal of bulky adducts caused by environmental carcinogens, such as heterocyclic amines and polycyclic aromatic hydrocarbons. They are putative environmental risk factors for colorectal neoplasia, found in tobacco smoke and red meat cooked at high temperature[7,8]. Therefore, the dysfunction of NER system may interfere with DNA damage repair from these exogenous carcinogens, and contribute to CRC development.

Genetic variation of genes can lead to the dysfunction of their encoding proteins. As the most common genetic variants in human genomes, single nucleotide polymorphisms (SNPs) are universally present in NER pathway genes. It has been suggested that NER SNPs could influence the expression or function of corresponding proteins, leading to the aberration of DNA reparative process and thus making impacts on colorectal carcinogenesis and prognosis[9,10]. Accumulating studies have investigated the association of NER SNPs with CRC risk or prognosis in various regions. For instance, Paszkowska-Szczur *et al*[11] assessed the association between SNPs in seven XP genes (XPA-XPG) and CRC risk in the Polish population, and their results confirmed that polymorphisms in XPC (rs2228000) and XPD (rs1799793 and rs238406) might be associated with CRC risk. Another study reported by Dai *et al*[12] showed that the AA genotype of ERCC1 rs2336219 had a significantly increased CRC risk and the CC genotype of ERCC1 rs735482 was associated with a lower response to oxaliplatin-based chemotherapy, shorter survival, and higher risk of relapse or metastasis. Currently, however, most researches in this field are only focused on a few SNPs in partial NER genes. A comprehensive investigation for the association of NER pathway gene polymorphisms with CRC risk and prognosis based on a large-scale

Chinese population remains lacking.

In the present study, we intend to explore the association of all tagSNPs in NER pathway genes with CRC risk and prognosis in a northern Chinese population by a two-stage case-control design composed of a discovery and validation stage. Our study aimed to identify all-round NER-based genetic biomarkers for prediction of the susceptibility to CRC and the clinical outcome of CRC patients, particularly applicable for China region.

MATERIALS AND METHODS

Study subjects and study design

The Ethics Committee of the First Hospital of China Medical University approved this project. All subjects provided written informed consent. A two-stage case-control study was designed. As an exploratory evaluation of selected candidate tagSNPs for disease risk, the first-stage study was carried out in a screening population of 184 CRC cases and 184 individual-matched controls (1:1) who were recruited between 2012 and 2014. Based on the initial results from these subjects, the secondary-stage study was subsequently performed in an enlarged population to validate the association of those SNPs who showed some hints in the discovery stage, consisting of 854 CRC cases and 858 frequency-matched controls in total. All the cases were selected from histopathologically confirmed CRC patients admitted to the Department of Anorectal Surgery of the First Hospital of China Medical University between September 2012 and March 2018. The controls were recruited from the healthy subjects seeking for physical examination at the hospital and the inpatients diagnosed with benign anal diseases by digital rectal examination or other approaches during the same period. The control group was matched to the case group based on gender and age (± 5 years). Fasting venous blood sample (5 mL) was collected from each participant.

Information collection

The epidemiological information of study participants was collected by a questionnaire survey or from the medical records of inpatients, including smoking history, drinking history, and *Helicobacter pylori* (*H. pylori*) infection status. The clinicopathological data were obtained from the pathological reports of surgical patients. Clinical staging for CRC was performed according to the UICC/AJCC TNM staging system (2002). Regular follow-up was conducted for CRC patients after radical surgery until October 2018. A total of 565 cases with available survival information were involved in the prognosis study, including survival status and overall survival (OS).

SNP screening

A two-step strategy was adopted for SNP selection in this association study. First, we extracted all the eight NER pathway genes encompassing 5 kb of upstream and downstream flanking sequences from the HapMap Chinese Han Beijing population (http://www.HapMap.org)[6]. Then, the genome sequences were imported into Haploview 4.2 software to select all the tagSNPs in NER pathway genes according to the following criteria: (1) Minor allele frequency (MAF) in CHB > 0.05; and (2) Linkage disequilibrium (LD) $r^2 < 0.8$. Consequently, a total of 39 candidate tagSNPs were enrolled in the discovery stage. Second, we evaluated the association between all of them and CRC risk in a small sample size. And SNP function prediction was performed using SNPinfo Web Server (https://snpinfo.niehs.nih.gov). Based on the analyses from the two aspects, we further screened out several SNPs for the next large-scale exploration. The screening principles were set as follows: (1) Showing a significant or borderline association with CRC risk; or (2) Having potential biological function; and (3) Having two alleles that suited for batch genotyping. Finally, 13 SNPs in six NER pathway genes were selected as research targets in the validation stage, including DDB2 rs2029298; ERCC1 rs11615 and rs735482; ERCC2 rs1052555 and rs50871; ERCC5 rs1047768, rs2094258, rs2228959, rs2296147, and rs873601; XPA rs10817938 and rs3176629; and XPC rs2607775.

SNP genotyping

Genomic DNA was isolated from each blood sample using the phenol-chloroform method. Genotyping was conducted using kompetitive allele specific PCR with the SNPLine platform (LGC Genomics, Hoddesdon, United Kingdom) by Shanghai Baygene Biotechnology Company Limited (China)[13]. Additionally, 10% of samples were randomly chosen to be repeatedly assayed for quality control, and the results of duplicated samples reached a 100% consistency.

Statistical analysis

χ^2 test was used to calculate the Hardy-Weinberg equilibrium (HWE) for studied SNPs in the control group and evaluate the differences in the baseline characteristics between case and control groups. The association of each SNP with CRC risk was estimated using multiple logistic regression by calculating odds ratio (OR) and 95% confidence interval (95%CI) adjusted by gender and age. Linear regression was applied to assess the cumulative effect of increasing SNP genotypes associated with CRC risk. Haplotype analysis was performed employing SHEsis online software (http://analysis.bio-x.cn/myAnalysis.php). Log likelihood ratio test was used to evaluate the interaction between each SNP and environmental factors on CRC risk. Kaplan-Meier method was applied to figure out median survival time (MST) and mean survival time was adopted when MST could not be calculated. Log rank test was used to judge the differences in the survival distribution between groups. The association of each SNP with CRC prognosis was estimated using Cox regression both in univariate and multivariate modes by calculating hazard ratio with 95%CI. The dominant and recessive genetic models were, respectively, defined as variant homozygote + heterozygote *vs* wild homozygote and variant homozygote *vs* heterozygote + wild homozygote. All statistical analyses mentioned above were performed with SPSS 22.0 software (Chicago, IL, United States). All the *P*-values were two-sided and statistical significance was regarded at $P < 0.05$, except the risk study in the discovery stage ($P < 0.1$).

RESULTS

Characteristics of study participants

In the discovery stage, 39 tagSNPs in eight NER pathway genes were genotyped in 368 subjects. The case and control groups were exactly matched (Table S1). In the validation stage, 13 SNPs in six genes were analyzed in a total of 1712 subjects, including 854 CRC cases and 858 CRC-free controls, which were also successfully matched by gender and age. Notably, the *H. pylori* infection rate was significantly higher in CRC patients than in the controls ($P < 0.001$). No significant difference was shown in the distribution of individuals with smoking or drinking history between the two groups (Table S2).

Basic information and function prediction results of NER SNPs

The basic information and function prediction results of all tagSNPs in NER pathway genes are presented in Table 1. The assessment items for SNP function mainly contained non-synonymous SNP (nsSNP), splicing site, splicing abolish domain, exon splicing enhancer (ESE) or exon splicing silencer (ESS), stop codon, Polyphen, and transcription factor binding site.

Association of NER SNPs with CRC risk

In the discovery stage, the association between all tagSNPs in NER pathway genes and CRC risk was initially investigated. The results showed that seven SNPs were associated with CRC risk in a screening population ($P < 0.1$, Table S3). Combined with the findings in SNP function prediction, 13 NER SNPs were chosen in the next association study with an enlarged population.

In the validation stage, we first evaluated the association between each SNP and CRC risk in overall subjects. The genotype frequency of three SNPs in the control group did not meet the HWE ($P_{HWE} < 0.05$), including ERCC2 rs50871, ERCC5 rs2228959, and XPA rs3176629. On this account, they were excluded from subsequent risk study. The validated results showed that two NER SNPs were found to be associated with CRC risk. The XPA rs10817938 polymorphism conferred to an increased CRC risk in its variant homozygote and recessive model (CC *vs* TT: $P = 0.021$, OR = 1.70, 95%CI = 1.08-2.66; CC *vs* TC + TT: $P = 0.033$, OR = 1.62, 95%CI = 1.04-2.52). The variant genotypes of XPC rs2607775 polymorphism could also enhance disease risk when compared with the wild type (CG *vs* CC: $P = 0.027$, OR = 1.49, 95%CI = 1.05-2.13; CG + GG *vs* CC: $P = 0.016$, OR = 1.54, 95%CI = 1.09-2.18, Table 2).

A stratification analysis was further performed based on host characteristics, including gender and age. The associations of XPA rs10817938 and XPC rs2607775 polymorphisms with CRC risk were both demonstrated in the subgroups of male and age ≤ 60 years, while no hint was shown in the opposite groups. All related variant genotypes of them were linked to an increased CRC risk in the specific subgroups. Similar to the overall analysis, no association was observed in other NER SNPs with CRC risk either (Table S4).

Table 1 Function prediction of nucleotide excision repair polymorphisms in the discovery stage

SNP	Chro-moso-me	Near-by gene	Allele	Posi-tion	ns-SNP	Spli-cing (site)	Spli-cing (abo-lish do-main)	Spli-cing (ESE or ESS)	Stop Co-don	Poly-phen	SNPs 3D (svm pro-file)	SNPs 3D (svm struc-ture)	TFBS	mi-RNA (mi-Randa)	mi-RNA (San-ger)	Reg Poten-tial	Conse rva-tion
rs2029298	11	*DDB2*	A/G	Promo-ter	--	--	--	--	--	--	--	--	Y	--	--	0	0.001
rs326222	11	*DDB2*	C/T	Intron	--	--	--	--	--	--	--	--	--	--	--	0	0.001
rs3781619	11	*DDB2*	A/G	Intron	--	--	--	--	--	--	--	--	--	--	--	NA	0
rs830083	11	*DDB2*	A/C/G/T	Intron	--	--	--	--	--	--	--	--	--	--	--	NA	0
rs11615	19	*ERCC1*	C/T	Exon	--	--	--	Y	--	--	--	--	--	--	--	0.26724	0.989
rs2298881	19	*ERCC1*	A/C/T	Intron	--	--	--	--	--	--	--	--	Y	--	--	0.252611	0
rs3212955	19	*ERCC1*	A/G	Intron	--	--	--	--	--	--	--	--	--	--	--	0.246701	0
rs3212961	19	*ERCC1*	A/C/T	Intron	--	--	--	--	--	--	--	--	--	--	--	0	0
rs3212986	19	*ERCC1*	A/C/G/T	Exon	Y	--	--	--	--	Benign	--	--	--	--	--	0.305187	0
rs735482	19	*ERCC1*	A/C	Exon	Y	--	--	--	--	Benign	--	--	--	--	--	0	0
rs1052555	19	*ERCC2*	C/T	Exon	--	--	Y	Y	--	--	--	--	--	--	--	0.478925	1
rs13181	19	*ERCC2*	A/G/T	Exon	Y	--	Y	Y	--	Benign	--	--	--	--	--	0.585468	0.999
rs238406	19	*ERCC2*	G/T	Exon	--	--	Y	Y	--	--	--	--	--	--	--	0.36557	0.996
rs238417	19	*ERCC2*	A/C/G	Intron	--	--	--	--	--	--	--	--	--	--	--	0.037099	0
rs50871	19	*ERCC2*	G/T	Intron	--	--	--	--	--	--	--	--	--	--	--	0	0.001
rs50872	19	*ERCC2*	A/C/T	Intron	--	--	--	--	--	--	--	--	--	--	--	0.137364	0.001
rs4150441	2	*ERCC3*	A/G	Intron	--	--	--	--	--	--	--	--	--	--	--	0	0
rs4150448	2	*ERCC3*	A/G	Intron	--	--	--	--	--	--	--	--	--	--	--	0	0
rs4150506	2	*ERCC3*	C/T	Intron	--	--	--	--	--	--	--	--	--	--	--	NA	0
rs1799801	16	*ERCC4*	C/T	Exon	--	--	--	--	--	--	--	--	--	--	--	0.205381	0.326
rs2276464	16	*ERCC4*	A/C/G	3'-UTR	--	--	--	--	--	--	--	--	--	Y	Y	0	0
rs254942	16	*ERCC4*	A/C/G/T	Intron	--	--	--	--	--	--	--	--	--	--	--	0.168034	0.005
rs1047768	13	*ERCC5*	C/T	Exon	--	--	Y	Y	--	--	--	--	--	--	--	0.24405	0.914
rs2094258	13	*ERCC5*	A/G	Promo-ter	--	--	--	--	--	--	--	--	Y	--	--	0	0.001
rs2228959	13	*ERCC5*	A/C	Exon	--	--	--	--	--	--	--	--	--	--	--	0.181402	0.509
rs2296147	13	*ERCC5*	C/T	Promo-ter	--	--	--	--	--	--	--	--	Y	--	--	0.175993	0
rs4150291	13	*ERCC5*	A/T	Intron	--	--	--	--	--	--	--	--	--	--	--	0	0
rs4150383	13	*ERCC5*	A/G	Intron	--	--	--	--	--	--	--	--	--	--	--	0	0

rs751402	13	*ERCC5*	C/T	Promo-ter	--	--	Y	Y	--	--	--	--	Y	--	--	0.256130	0
rs873601	13	*ERCC5*	A/G	Exon	--	--	Y	Y	--	--	--	--	--	Y	Y	0	0.005
rs10817938	9	*XPA*	C/T	Promo-ter	--	--	--	Y	--	--	--	--	--	--	--	NA	0.94
rs2808668	9	*XPA*	C/G/T	Intron	--	--	--	--	--	--	--	--	--	--	--	0	0.004
rs3176629	9	*XPA*	C/T	Promo-ter	--	--	--	--	--	--	--	--	Y	--	--	0	0
rs1870134	3	*XPC*	C/G/T	Exon	Y	--	--	Y	--	--	--	--	--	--	--	0.272801	0
rs2228000	3	*XPC*	C/T	Exon	Y	--	--	--	--	--	--	--	--	--	--	0.136701	0
rs2228001	3	*XPC*	A/C	Exon	Y	--	--	--	--	--	--	--	--	--	--	0.189938	1
rs2470352	3	*XPC*	A/G/T	Exon	--	--	--	--	--	--	--	--	--	--	--	0	0
rs2607775	3	*XPC*	C/G	Exon	--	--	--	Y	--	--	--	--	Y	--	--	0.282058	0

SNP: Single nucleotide polymorphism; nsSNP: Non-synonymous SNP; ESE: Exon splicing enhancer; ESS: Exon splicing silencer; TFBS: Transcription factor binding site.

Cumulative effect of risk-related NER SNPs

Based on the findings shown in the last part, we explored the cumulative effect of NER SNPs on CRC risk. The best genetic models were identified for each polymorphism: XPA rs10817938 CC *vs* TC + TT and XPC rs2607775 CG + GG *vs* CC. According to the number of risk genotypes that individuals carried with, all the subjects were categorized into three groups (0, 1, and 2). Then, we analyzed the linear trend in CRC risk. The disease risk was found to be significantly enhanced with the increasing number of risk genotypes of studied SNPs (P_{trend} = 0.001, Table 3).

Association of NER SNP haplotypes with CRC risk

A haplotype analysis was conducted for the SNPs in the same NER pathway gene, including ERCC1 rs11615-rs735482 and ERCC5 rs1047768-rs2094258-rs2296147-rs873601. The association between each haplotype and CRC risk was evaluated. It was suggested that one haplotype of ERCC5, C-G-C-G, demonstrated borderline significance in the association with CRC risk (P = 0.051, OR = 1.47, 95%CI = 1.00-2.17, Table S5).

Interaction of NER SNPs with environmental factors

We further investigated the interaction effects of NER SNPs with environmental factors on CRC risk, including smoking, drinking, and *H. pylori* infection. The DDB2 rs2029298 polymorphism could be negatively interacted with drinking. Its GG genotype could reduce CRC risk by 0.52-fold in the population with drinking history when compared with GA + AA genotype ($P_{interaction}$ = 0.019, OR = 0.52, 95%CI = 0.30-0.90). No interaction was shown between NER SNPs and smoking or *H. pylori* infection (Table 4).

Association of NER SNPs with CRC prognosis

Before the prognosis study, an assessment was made at first for the association between host factors and the OS of CRC patients, including all the epidemiological and clinicopathological characteristics. We found the OS could be affected by TNM stage, macroscopic type, histological type, depth of invasion, growth mode, and lymphatic metastasis (P < 0.001). Therefore, these factors were treated as adjustment parameters in the subsequent multivariate survival analysis (Table 5).

The association between NER SNPs and CRC prognosis was evaluated next. Two SNPs showed a significant association with prognosis in both univariate and multivariate analyses. The variant homozygote of ERCC2 rs1052555 polymorphism suggested a worse OS in CRC patients (TT *vs* CC: P = 0.010, OR = 14.99, 95%CI = 1.90-118.10; TT *vs* CT + CC: P = 0.009, OR = 15.89, 95%CI = 2.20-125.16). A similar trend was also indicated in the ERCC5 rs2228959 polymorphism, which conferred to a poor CRC prognosis as well (AA *vs* CC: P = 0.046, OR = 4.32, 95%CI = 1.03-18.17; AA *vs* CA + CC: P = 0.049, OR = 4.20, 95%CI = 1.00-17.60, Table 6).

Table 2 Association between nucleotide excision repair polymorphisms and colorectal cancer risk in the validation stage[1], *n* (%)

SNP genotype	NCBI Ref	CRC	CON	*P* value	OR (95%CI)
DDB2					
rs2029298		*n* = 849	*n* = 849		
GG	32 (37.2)	393 (46.3)	385 (45.3)		1 (Ref)
GA	38 (44.2)	359 (42.3)	368 (43.3)	0.650	0.95 (0.78-1.17)
AA	16 (18.6)	97 (11.4)	96 (11.3)	0.919	0.98 (0.72-1.35)
GA + AA *vs* GG				0.677	0.96 (0.79-1.16)
AA *vs* GA + GG				0.980	1.00 (0.74-1.36)
P_{HWE}	0.584		0.570		
ERCC1					
rs11615		*n* = 850	*n* = 847		
CC	54 (62.8)	518 (60.9)	494 (58.3)		1 (Ref)
CT	24 (27.9)	293 (34.5)	305 (36.0)	0.355	0.91 (0.74-1.11)
TT	8 (9.3)	39 (4.6)	48 (5.7)	0.248	0.77 (0.50-1.20)
CT + TT *vs* CC				0.244	0.89 (0.73-1.08)
TT *vs* CT + CC				0.321	0.80 (0.52-1.24)
P_{HWE}	0.200		0.919		
rs735482		*n* = 836	*n* = 838		
CC	18 (20.9)	169 (20.2)	168 (20.0)		1 (Ref)
CA	40 (46.5)	405 (48.4)	403 (48.1)	0.966	1.00 (0.77-1.28)
AA	28 (32.6)	262 (31.3)	267 (31.9)	0.856	0.98 (0.74-1.28)
CA + AA *vs* CC				0.920	0.99 (0.78-1.26)
AA *vs* CA + CC				0.812	0.98 (0.79-1.20)
P_{HWE}	0.752		0.477		
ERCC2					
rs1052555		*n* = 852	*n* = 851		
CC	NA	767 (90.0)	759 (89.2)		1 (Ref)
CT	NA	84 (9.9)	91 (10.7)	0.605	0.92 (0.67-1.26)
TT	NA	1 (0.1)	1 (0.1)	0.970	0.95 (0.06-15.21)
CT + TT *vs* CC				0.602	0.92 (0.67-1.26)
TT *vs* CT + CC				0.971	0.95 (0.06-15.22)
P_{HWE}	NA		0.307		
rs50871		*n* = 838	*n* = 845		
TT	40 (46.5)	429 (51.2)	451 (53.4)		1 (Ref)
TG	36 (41.9)	337 (40.2)	358 (42.4)	0.922	0.99 (0.81-1.21)
GG	10 (11.6)	72 (8.6)	36 (4.3)	0.001	2.09 (1.37-3.19)
TG + GG *vs* TT				0.374	1.09 (0.90-1.32)
GG *vs* TG + TT				< 0.001	2.08 (1.38-3.15)
P_{HWE}	1.000		0.001		
ERCC5					
rs1047768		*n* = 839	*n* = 845		
CC	8 (9.3)	75 (8.9)	71 (8.4)		1 (Ref)
CT	30 (34.9)	348 (41.5)	351 (41.5)	0.735	0.94 (0.66-1.35)
TT	48 (55.8)	416 (49.6)	423 (50.1)	0.708	0.94 (0.66-1.33)
CT + TT *vs* CC				0.717	0.94 (0.67-1.32)
TT *vs* CT + CC				0.822	0.98 (0.81-1.19)
P_{HWE}	0.480		0.880		
rs2094258		*n* = 843	*n* = 841		
GG	38 (44.2)	307 (36.4)	326 (38.8)		1 (Ref)
GA	42 (48.8)	409 (48.5)	392 (46.6)	0.389	1.10 (0.89-1.35)
AA	6 (7.0)	127 (15.1)	123 (14.6)	0.615	1.08 (0.80-1.45)
GA + AA *vs* GG				0.370	1.10 (0.90-1.33)
AA *vs* GA + GG				0.837	1.03 (0.79-1.35)

P_{HWE}	0.403		0.770		
rs2228959		*n* = 841	*n* = 851		
CC	74 (86.0)	754 (89.7)	782 (91.9)		1 (Ref)
CA	12 (14.0)	83 (9.9)	62 (7.3)	0.051	1.41 (1.00-1.99)
AA	0 (0.0)	4 (0.5)	7 (0.8)	0.408	0.59 (0.17-2.04)
CA + AA *vs* CC				0.095	1.33 (0.95-1.85)
AA *vs* CA + CC				0.383	0.58 (0.17-1.98)
P_{HWE}	1.000		< 0.001		
rs2296147		*n* = 844	*n* = 847		
TT	52 (60.5)	508 (60.2)	517 (61.0)		1 (Ref)
TC	32 (37.2)	294 (34.8)	289 (34.1)	0.684	1.04 (0.85-1.28)
CC	2 (2.3)	42 (5.0)	41 (4.8)	0.904	1.03 (0.66-1.61)
TC + CC *vs* TT				0.679	1.04 (0.86-1.27)
CC *vs* TC + TT				0.952	1.01 (0.65-1.58)
P_{HWE}	0.439		0.940		
rs873601		*n* = 842	*n* = 837		
GG	16 (18.6)	230 (27.3)	223 (26.6)		1 (Ref)
GA	48 (55.8)	435 (51.7)	413 (49.3)	0.807	1.03 (0.82-1.29)
AA	22 (25.6)	177 (21.0)	201 (24.0)	0.310	0.87 (0.66-1.14)
GA + AA *vs* GG				0.849	0.98 (0.79-1.22)
AA *vs* GA + GG				0.155	0.85 (0.67-1.07)
P_{HWE}	0.439		0.719		
XPA					
rs10817938		*n* = 823	*n* = 822		
TT	58 (67.4)	511 (62.1)	547 (66.5)		1(Ref)
TC	24 (27.9)	259 (31.5)	241 (29.3)	0.231	1.14 (0.92-1.41)
CC	4 (4.7)	53 (6.4)	34 (4.1)	0.021	1.70 (1.08-2.66)
TC + CC *vs* TT				0.071	1.21 (0.98-1.48)
CC *vs* TC + TT				0.033	1.62 (1.04-2.52)
P_{HWE}	0.655		0.257		
rs3176629		*n* = 847	*n* = 852		
CC	68 (79.1)	689 (81.3)	706 (82.9)		1 (Ref)
CT	18 (20.9)	151 (17.8)	133 (15.6)	0.240	1.17 (0.90-1.51)
TT	0 (0.0)	7 (0.8)	13 (1.5)	0.225	0.56 (0.22-1.42)
CT + TT *vs* CC				0.399	1.11 (0.87-1.43)
TT *vs* CT + CC				0.205	0.55 (0.22-1.39)
P_{HWE}	0.752		0.024		
XPC					
rs2607775		*n* = 840	*n* = 850		
CC	76 (84.5)	755 (89.9)	792 (93.2)		1(Ref)
CG	12 (13.3)	80 (9.5)	56 (6.6)	0.027	1.49 (1.05-2.13)
GG	2 (2.2)	5 (0.6)	2 (0.2)	0.219	2.81 (0.54-14.56)
CG + GG *vs* CC				0.016	1.54 (1.09-2.18)
GG *vs* CG + CC				0.238	2.69 (0.52-13.95)
P_{HWE}	0.251		0.343		

[1]*P* was adjusted by gender and age. Statistically significant associations are in bold ($P < 0.05$). SNP: Single nucleotide polymorphism; NCBI Ref: Reference frequency of the SNPs in healthy controls (Beijing Han, China, NCBI database); CRC: Colorectal cancer; CON: Control; OR: Odds ratio; CI: Confidence interval; P_{HWE}: Hardy-Weinberg Equilibrium in control group; NA: Not available.

DISCUSSION

In the present study, we explored the association of all tagSNPs in eight NER pathway genes with CRC risk and prognosis in a total of 1712 northern Chinese. In the discovery stage, 39 tagSNPs were analyzed for their association and potential biological function, and 13 SNPs were enrolled in the validation stage. Among them,

Table 3 Cumulative effect of nucleotide excision repair polymorphisms associated with colorectal cancer risk[1], *n* (%)

Number of SNP risk genotypes	CRC	CON	*P* value	OR (95%CI)
	n = 841	*n* = 847		
0	706 (83.9)	755 (89.1)		1 (Ref)
1	131 (15.6)	92 (10.9)	0.004	1.53 (1.15-2.04)
2	4 (0.5)	0 (0.0)	NA	NA
			P_{trend} = 0.001	

[1]*P* was adjusted by gender and age. Statistically significant associations are in bold ($P < 0.05$). SNP: Single nucleotide polymorphism; CRC: Colorectal cancer; CON: Control; OR: Odds ratio; CI: Confidence interval; NA: Not available.

the XPA rs10817938 and XPC rs2607775 polymorphisms were found to be associated with CRC risk both in overall and stratified analyses. They also demonstrated cumulative effects on disease risk with the increasing number of risk genotypes. Moreover, the DDB2 rs2029298 polymorphism had a negative interaction effect with drinking on CRC risk. In the prognosis study, the ERCC2 rs1052555 and ERCC5 rs2228959 polymorphisms were associated with the OS of CRC cases. To our knowledge, this is the first comprehensive report on the association of NER SNPs with CRC risk and prognosis based on a large-scale Chinese population.

In our research, the XPA rs10817938 and XPC rs2607775 polymorphisms showed a significant association with an increased CRC risk. The XPA (xeroderma pigmentosum group A) gene, located in chromosome 9q22.3 containing 9 exons and 8 introns, encodes a zinc finger DNA-binding protein involved in NER to maintain genomic integrity[14]. It was suggested that the XPA protein was significantly decreased in CRC tissue than in adjacent non-tumor tissue, and its high expression showed an association with better survival of CRC cases[15]. Therefore, XPA is a CRC-related protein marker. The gene polymorphisms in XPA were also revealed to be associated with CRC risk, such as 23Gly/Ala (rs1800975)[16-19]. However, rare studies have focused on the rs10817938 polymorphism, which has been only reported by Hu *et al*[20] that rs10817938 CT/TT genotype retains a significant association with a longer OS ($P = 0.008$) in CRC patients receiving oxaliplatin-based chemotherapy. Thus, our study first referred to it as a CRC risk-related SNP. Similar to XPA, the XPC (xeroderma pigmentosum group C) gene is also a well-accepted marker related to CRC, which is located in chromosome 3p25 with 16 exons and 15 introns[21]. It encodes a 940-amino acid protein involved in DNA damage recognition and DNA repair initiation in the NER pathway, and the binding of XPC to damaged DNA is the rate-limiting step for NER[22-24]. The XPC gene is highly polymorphic and its SNPs have been foci of interest for the association with CRC risk, such as 939Lys/Gln (rs2228001) and 499Ala/Val (rs2228000)[25-29]. In our study, we newly found that the rs2607775 polymorphism could modulate CRC risk. In a word, the XPA rs10817938 and XPC rs2607775 polymorphisms could be potential genetic markers applicable for the prediction of CRC susceptibility in the future.

In the stratified analysis, it was noteworthy that the two meaningful SNPs for CRC risk in the overall population only demonstrated their association in the male and age ≤ 60 years subgroups, while no significance was found in the female and age > 60 years subgroups. The risk effects of NER SNPs seemed to change with gender and age. The morbidity and mortality of CRC are higher in men than in women both in China and worldwide[1,30]. That could be attributed to a subset of X-chromosome genes escaping X-inactivation, named "escape from X-inactivation tumor-suppressor" (EXITS) genes, which would protect females from complete functional loss by a single mutation and thus result in sex bias in a variety of tumor types[31]. In addition, it is well acknowledged that CRC incidence strongly increases with age, probably due to the weakened immunity and accumulated carcinogens with people aging[30,32]. As a result, the association of NER SNPs could be masked by gender and age but manifested when the two factors are considered as stratification items to eliminate their effects on CRC risk. These findings suggested the XPA rs10817938 and XPC rs2607775 polymorphisms might also be predictive biomarkers for the susceptibility to CRC in some specific populations like males or youngsters.

Owing to the multiple elements involved in carcinogenesis, the efficacy of single polymorphism for risk detection is relatively limited. And the combination of multi-variants usually has more advantages[33,34]. In our study, a significant cumulative trend was shown in NER SNPs for the association with CRC risk, which could be enhanced

Table 4 Effect of interaction between nucleotide excision repair polymorphisms and environmental factors on colorectal cancer risk[1]

SNP genotype	Smoking		Drinking		*Helicobacter pylori* infection	
	No	Yes	No	Yes	Negative	Positive
DDB2						
rs2029298	n = 981	n = 468	n = 1190	n = 257	n = 810	n = 443
GA + AA						
Case/Control	312/220	142/104	367/274	87/49	164/286	189/44
OR (95%CI)	1 (Ref)	0.96 (0.71-1.31)	1 (Ref)	1.33 (0.90-1.95)	1 (Ref)	7.49 (5.12-10.96)
GG						
Case/Control	267/182	124/98	330/219	61/60	140/220	158/52
OR (95%CI)	1.03 (0.80-1.34)	0.89 (0.65-1.22)	1.13 (0.89-1.42)	0.76 (0.51-1.12)	1.11 (0.83-1.48)	5.30 (3.67-7.65)
	$P_{interaction}$ = 0.618		$P_{interaction}$ = 0.019 OR (95%CI) = 0.52 (0.30-0.90)		$P_{interaction}$ = 0.095	
ERCC1						
rs11615	n = 982	n = 467	n = 1190	n = 257	n = 812	n = 444
CT + TT						
Case/Control	231/160	101/88	278/205	54/40	110/210	146/42
OR (95%CI)	1 (Ref)	0.80 (0.56-1.13)	1 (Ref)	1.00 (0.64-1.56)	1 (Ref)	6.64 (4.39-10.04)
CC						
Case/Control	349/242	165/113	421/286	93/70	194/298	203/53
OR (95%CI)	1.00 (0.77-1.30)	1.01 (0.74-1.38)	1.09 (0.86-1.37)	0.98 (0.68-1.40)	1.24 (0.93-1.67)	7.31 (5.00-10.70)
	$P_{interaction}$ = 0.309		$P_{interaction}$ = 0.749		$P_{interaction}$ = 0.642	
rs735482	n = 968	n = 461	n = 1171	n = 256	n = 803	n = 434
AA						
Case/Control	175/124	87/64	213/148	49/40	89/161	115/24
OR (95%CI)	1 (Ref)	0.96 (0.65-1.43)	1 (Ref)	0.85 (0.53-1.36)	1 (Ref)	8.67 (5.20-14.44)
CA + CC						
Case/Control	396/273	174/136	471/339	99/68	212/341	224/71
OR (95%CI)	1.03 (0.78-1.36)	0.91 (0.66-1.25)	0.97 (0.75-1.24)	1.01 (0.70-1.47)	1.13 (0.82-1.53)	5.71 (3.94-8.28)
	$P_{interaction}$ = 0.638		$P_{interaction}$ = 0.446		$P_{interaction}$ = 0.082	
ERCC2						
rs1052555	n = 986	n = 468	n = 1193	n = 259	n = 811	n = 447
CT + TT						
Case/Control	55/39	30/27	68/56	17/10	27/54	39/11
OR (95%CI)	1 (Ref)	0.79 (0.41-1.53)	1 (Ref)	1.40 (0.59-3.30)	1 (Ref)	7.09 (3.15-15.99)
CC						
Case/Control	527/365	236/175	632/437	131/101	277/453	312/85
OR (95%CI)	1.02 (0.67-1.58)	0.96 (0.61-1.51)	1.19 (0.82-1.73)	1.07 (0.69-1.66)	1.22 (0.75-1.99)	7.34 (4.36-12.35)
	$P_{interaction}$ = 0.624		$P_{interaction}$ = 0.319		$P_{interaction}$ = 0.712	
ERCC5						
rs1047768	n = 973	n = 464	n = 1177	n = 258	n = 808	n = 437
CT + TT						
Case/Control	524/368	236/190	622/452	138/103	272/460	317/88
OR (95%CI)	1 (Ref)	0.87 (0.69-1.10)	1 (Ref)	0.97 (0.73-1.29)	1 (Ref)	6.09 (4.61-8.06)
CC						
Case/Control	49/32	26/12	66/37	9/8	29/47	26/6
OR (95%CI)	1.08 (0.68-1.71)	1.52 (0.76-3.06)	1.30 (0.85-1.97)	0.82 (0.31-2.14)	1.04 (0.64-1.70)	7.33 (2.98-18.03)
	$P_{interaction}$ = 0.241		$P_{interaction}$ = 0.491		$P_{interaction}$ = 0.843	
rs2094258	n = 973	n = 464	n = 1180	n = 255	n = 805	n = 443
GG						
Case/Control	209/150	97/70	251/180	55/40	119/203	116/38
OR (95%CI)	1 (Ref)	1.00 (0.69-1.44)	1 (Ref)	0.99 (0.63-1.55)	1 (Ref)	5.21 (3.39-8.01)
GA + AA						
Case/Control	364/250	169/128	442/307	91/69	181/302	233/56

OR (95%CI)	1.05 (0.80-1.36)	0.95 (0.69-1.29)	1.03 (0.81-1.31)	0.95 (0.66-1.37)	1.02 (0.76-1.37)	7.10 (4.91-10.27)
	$P_{interaction}$ = 0.587		$P_{interaction}$ = 0.685		$P_{interaction}$ = 0.314	
rs2296147	*n* = 979	*n* = 466	*n* = 1185	*n* = 258	*n* = 807	*n* = 440
TT						
Case/Control	356/251	151/126	426/301	81/75	184/298	207/59
OR (95%CI)	1 (Ref)	0.85 (0.64-1.13)	1 (Ref)	0.76 (0.54-1.08)	1 (Ref)	5.68 (4.03-8.01)
TC+CC						
Case/Control	221/151	112/77	268/190	65/37	118/207	138/36
OR (95%CI)	1.03 (0.79-1.34)	1.03 (0.74-1.43)	1.00 (0.79-1.26)	1.24 (0.81-1.91)	0.92 (0.69-1.24)	6.21 (4.12-9.36)
	$P_{interaction}$ = 0.506		$P_{interaction}$ = 0.089		$P_{interaction}$ = 0.562	
rs873601	*n* = 974	*n* = 462	*n* = 1179	*n* = 255	*n* = 798	*n* = 439
AA						
Case/Control	130/94	47/51	148/116	29/28	69/126	75/25
OR (95%CI)	1 (Ref)	0.67 (0.41-1.07)	1 (Ref)	0.81 (0.46-1.44)	1 (Ref)	5.48 (3.19-9.40)
GA + GG						
Case/Control	446/304	215/149	543/372	118/80	234/369	269/70
OR (95%CI)	1.06 (0.78-1.44)	1.04 (0.74-1.46)	1.14 (0.87-1.51)	1.16 (0.80-1.68)	1.16 (0.83-1.62)	7.02 (4.73-10.41)
	$P_{interaction}$ = 0.202		$P_{interaction}$ = 0.550		$P_{interaction}$ = 0.764	
XPA						
rs10817938	*n* = 952	*n* = 453	*n* = 1152	*n* = 252	*n* = 785	*n* = 429
TC + TT						
Case/Control	527/380	239/183	631/459	135/103	281/470	311/88
OR (95%CI)	1 (Ref)	0.94 (0.75-1.19)	1 (Ref)	0.95 (0.72-1.27)	1 (Ref)	5.91 (4.47-7.81)
CC						
Case/Control	33/12	20/11	45/17	8/6	14/20	25/5
OR (95%CI)	1.98 (1.01-3.89)	1.31 (0.62-2.77)	1.93 (1.09-3.41)	0.97 (0.33-2.81)	1.17 (0.58-2.36)	8.36 (3.17-22.09)
	$P_{interaction}$ = 0.516		$P_{interaction}$ = 0.299		$P_{interaction}$ = 0.738	
XPC						
rs2607775	*n* = 979	*n* = 463	*n* = 1184	*n* = 256	*n* = 809	*n* = 439
CC						
Case/Control	513/369	238/195	617/458	134/103	273/475	314/88
OR (95%CI)	1 (Ref)	0.88 (0.70-1.11)	1 (Ref)	0.97 (0.73-1.28)	1 (Ref)	6.21 (4.70-8.21)
CG + GG						
Case/Control	61/36	24/6	73/36	12/7	28/33	30/7
OR (95%CI)	1.22 (0.79-1.88)	2.88 (1.16-7.11)	1.51 (0.99-2.28)	1.27 (0.50-3.26)	1.48 (0.87-2.50)	7.46 (3.23-17.21)
	$P_{interaction}$=0.066		$P_{interaction}$=0.728		$P_{interaction}$=0.766	

[1]*P* for interaction was adjusted by gender and age. Statistically significant associations are in bold ($P < 0.05$). SNP: Single nucleotide polymorphism; CRC: Colorectal cancer; CON: Control; OR: Odds ratio; CI: Confidence interval.

with the increasing number of risk genotypes (XPA rs10817938 CC and XPC rs2607775 CG + GG). That indicated a dosage effect of risk-related NER SNPs that an individual carried with. Moreover, borderline significance linked to CRC risk was observed in a haplotype of ERCC5 rs1047768-rs2094258-rs2296147-rs873601 (C-G-C-G). Therefore, better diagnostic capacity for the susceptibility to CRC could be obtained when combining multiple SNPs in NER pathway genes.

Except for genetic factors, environmental factors also play a vital role in CRC development such as tobacco smoking, alcohol consumption, and dietary constituents especially red meat[35-37]. Knowledge of gene-environment interactions may help to elucidate substantial hidden heritability within the architecture of cancer initiation[38]. The effects of interaction between SNPs in NER pathway genes and environmental factors on CRC risk has been preliminarily explored[39]. Here, we newly found that the DDB2 rs2029298 polymorphism could be negatively interacted with drinking-related CRC risk. In contrast to this, no association was found in any DDB2 SNP in the main effect analysis. Alcohol consumption is a well-recognized carcinogen of CRC due to DNA lesion caused by the exposure of DNA to acetaldehyde produced by ethanol[40]. However, the effect of DDB2 rs2029298 polymorphism was modified in the population with drinking history and its GG genotype decreased CRC risk by 0.52-fold, suggesting that an antagonism existed between DDB2 SNPs with drinking.

Table 5 Association between host factors and the overall survival of colorectal cancer patients

Factor	CRC patients	Death	MST (M)	*P* value
Total	*n* = 565	*n* = 95		
Gender				0.862
Male	384	63	46.6[1]	
Female	181	32	47.1[1]	
Age (yr)				0.127
≤ 60	322	46	47.9[1]	
> 60	243	49	44.7[1]	
Smoking				0.111
Ever Smoker	180	23	48.7[1]	
Never Smoker	383	72	45.9[1]	
Drinking				0.157
Drinker	107	14	49.3[1]	
Non-drinker	456	81	46.1[1]	
TNM stage				< 0.001
I + II	336	23	52.1[1]	
III + IV	223	69	48	
Macroscopic type				< 0.001
Protrude type	104	5	53.4[1]	
Ulcerative/Invasive type	458	90	45.2[1]	
Histological type				< 0.001
High/Middle differentiation	367	40	50.2[1]	
Low differentiation	196	55	39.3[1]	
Depth of invasion				< 0.001
T1 + T2	114	6	53.4[1]	
T3 + T4	450	89	44.9[1]	
Growth mode				< 0.001
Nest	236	18	52.1[1]	
Invasion	326	77	42.6[1]	
Lymphatic metastasis				< 0.001
Positive	217	68	47	
Negative	342	24	52.0[1]	

CRC: Colorectal cancer; MST (M): Median survival time (mo).
[1]Mean survival time was provided when MST could not be calculated. Statistically significant associations are in bold ($P < 0.05$).

Hence, the interactions between NER SNPs and environmental factors may also benefit the risk prediction of CRC. The possible mechanism concerned with our findings needs to be clarified by further researches.

In addition to CRC susceptibility, the influence of SNPs in NER pathway genes on CRC prognosis cannot be ignored either. The present study showed that the ERCC2 rs1052555 and ERCC5 rs2228959 polymorphisms were associated with a poor OS in CRC patients. The ERCC2 (excision repair cross-complementing group 2) gene, also known as XPD (xeroderma pigmentosum group D) with 24 exons and 23 introns, encodes a helicase, which is a component of transcription factor TFIIH participating in the opening of damaged DNA during NER[41]. Mounting evidence has demonstrated that the SNPs in ERCC2 have predictive values for the clinical outcome of CRC patients treated with various chemotherapy, such as 751Lys/Gln (13181)[42-46]. However, no report has referred to the rs1052555 polymorphism yet, which is located in exon 24 of ERCC2. According to the SNP function prediction, it may affect the splicing pattern of mRNA after transcription as a result of the formation of splicing abolish domain or ESE/ESS. And both the RegPotential and Conservation scores were relatively high, suggesting that it might be a highly conserved variant in the course of evolution with regulatory roles. Therefore, the ERCC2 rs1052555 polymorphism is very likely to be a functional SNP and should be paid more attention in the future. The other highly polymorphic NER gene, ERCC5 (excision repair cross-

Table 6 Association between nucleotide excision repair polymorphisms and colorectal cancer prognosis

SNP genotype	CRC patients	Death	MST (M)	Univariate		Multivariate	
				P value	HR (95%CI)	*P* value	HR (95%CI)
DDB2							
rs2029298	*n* = 560	*n* = 94					
GG	262	50	44.4[1]		1(Ref)		1 (Ref)
GA	230	35	47.4[1]	0.368	0.82 (0.53-1.26)	0.393	0.82 (0.53-1.29)
AA	68	9	48.6[1]	0.265	0.67 (0.33-1.36)	0.467	0.77 (0.37-1.57)
GA + AA *vs* GG				0.235	0.78 (0.52-1.17)	0.307	0.81 (0.53-1.22)
AA *vs* GA + GG				0.370	0.73 (0.37-1.45)	0.581	0.82 (0.41-1.65)
ERCC1							
rs11615	*n* = 561	*n* = 95					
CC	345	62	46.4[1]		1 (Ref)		1 (Ref)
CT	188	29	47.2[1]	0.647	0.90 (0.58-1.40)	0.947	1.02 (0.65-1.59)
TT	28	4	45.8[1]	0.955	0.97 (0.35-2.67)	0.975	0.98 (0.35-2.76)
CT + TT *vs* CC				0.662	0.91 (0.60-1.39)	0.974	0.99 (0.65-1.53)
TT *vs* CT + CC				0.999	1.00 (0.37-2.73)	0.911	0.94 (0.34-2.60)
rs735482	*n* = 552	*n* = 91					
CC	123	23	46.8[1]		1 (Ref)		1 (Ref)
CA	258	38	47.3[1]	0.982	0.99 (0.59-1.67)	0.582	1.16 (0.69-1.96)
AA	171	30	45.5[1]	0.603	1.16 (0.67-1.99)	0.774	0.92 (0.53-1.61)
CA + AA *vs* CC				0.829	1.05 (0.66-1.69)	0.923	1.02 (0.64-1.65)
AA *vs* CA + CC				0.517	1.16 (0.75-1.79)	0.521	0.86 (0.55-1.35)
ERCC2							
rs1052555	*n* = 563	*n* = 95					
CC	506	86	46.6[1]		1 (Ref)		1 (Ref)
CT	56	8	48.3[1]	0.377	0.72 (0.35-1.49)	0.998	1.00 (0.48-2.09)
TT	1	1	2	< 0.001	49.73 (6.37-388.47)	0.010	14.99 (1.90-118.10)
CT + TT *vs* CC				0.551	0.81 (0.41-1.61)	0.744	1.12 (0.56-2.26)
TT *vs* CT + CC				< 0.001	55.22 (7.07-431.35)	0.009	15.89 (2.02-125.16)
rs50871	*n* = 551	*n* = 92					
TT	294	43	47.0[1]		1 (Ref)		1 (Ref)
TG	210	40	45.7[1]	0.256	1.28 (0.83-1.98)	0.446	1.19 (0.77-1.84)
GG	47	9	45.8[1]	0.541	1.25 (0.61-2.57)	0.576	0.80 (0.37-1.74)
TG + GG *vs* TT				0.239	1.28 (0.85-1.93)	0.646	1.10 (0.73-1.68)
GG *vs* TG + TT				0.749	1.12 (0.56-2.23)	0.354	0.71 (0.34-1.47)
ERCC5							
rs1047768	*n* = 553	*n* = 92					
CC	55	9	46.7[1]		1 (Ref)		1 (Ref)
CT	233	44	46.5[1]	0.785	1.11 (0.54-2.26)	0.945	0.97 (0.45-2.09)
TT	265	39	47.0[1]	0.933	1.03 (0.50-2.13)	0.542	0.78 (0.36-1.72)
CT + TT *vs* CC				0.851	1.07 (0.54-2.13)	0.768	0.90 (0.43-1.87)
TT *vs* CT + CC				0.799	0.95 (0.63-1.43)	0.387	0.83 (0.54-1.27)
rs2094258	*n* = 555	*n* = 93					
GG	207	38	46.6[1]		1 (Ref)		1 (Ref)
GA	269	42	47.0[1]	0.721	0.92 (0.60-1.43)	0.400	0.82 (0.53-1.29)
AA	79	13	44.3[1]	0.973	0.99 (0.53-1.86)	0.588	0.84 (0.44-1.59)
GA + AA *vs* GG				0.773	0.94 (0.62-1.42)	0.424	0.84 (0.55-1.29)
AA *vs* GA + GG				0.869	1.05 (0.59-1.89)	0.916	1.03 (0.57-1.87)
rs2228959	*n* = 558	*n* = 93					
CC	501	82	47.1[1]		1 (Ref)		1 (Ref)
CA	53	9	45.4[1]	0.768	1.11 (0.56-2.21)	0.811	0.92 (0.46-1.85)
AA	4	2	13.8[1]	0.006	7.18 (1.75-29.50)	0.046	4.32 (1.03-18.17)
CA + AA *vs* CC				0.402	1.31 (0.70-2.46)	0.847	1.07 (0.56-2.02)

AA *vs* CA + CC				0.006	7.16 (1.75-29.32)	0.049	4.20 (1.00-17.60)
rs2296147	*n* = 556	*n* = 92					
TT	318	46	47.4[1]		1 (Ref)		1 (Ref)
TC	207	42	45.4[1]	0.384	1.21 (0.79-1.83)	0.194	1.32 (0.87-2.02)
CC	31	4	48.1[1]	0.691	0.81 (0.29-2.26)	0.658	1.32 (0.38-4.57)
TC + CC *vs* TT				0.484	1.16 (0.77-1.74)	0.184	1.33 (0.87-2.02)
CC *vs* TC + TT				0.573	0.75 (0.28-2.04)	0.978	1.02 (0.31-3.32)
rs873601	*n* = 558	*n* = 95					
GG	140	21	47.5[1]		1 (Ref)		1 (Ref)
GA	301	49	46.9[1]	0.745	1.09 (0.65-1.82)	0.923	0.98 (0.58-1.64)
AA	117	25	44.5[1]	0.293	1.37 (0.76-2.44)	0.713	1.12 (0.62-2.03)
GA + AA *vs* GG				0.526	1.17 (0.72-1.90)	0.951	1.02 (0.62-1.66)
AA *vs* GA + GG				0.275	1.29 (0.82-2.04)	0.473	1.19 (0.74-1.90)
XPA							
rs10817938	*n* = 545	*n* = 93					
TT	351	61	46.6[1]		1 (Ref)		1 (Ref)
TC	163	29	46.2[1]	0.815	1.05 (0.68-1.64)	0.472	1.18 (0.75-1.88)
CC	31	3	49.5[1]	0.429	0.63 (0.20-2.00)	0.903	0.93 (0.29-3.02)
TC + CC *vs* TT				0.968	0.99 (0.65-1.52)	0.489	1.17 (0.75-1.83)
CC *vs* TC+TT				0.414	0.62 (0.20-1.96)	0.863	0.90 (0.28-2.89)
rs3176629	*n* = 558	*n* = 94					
CC	450	74	47.0[1]		1 (Ref)		1 (Ref)
CT	103	19	44.8[1]	0.470	1.20 (0.73-1.99)	0.420	0.81 (0.48-1.36)
TT	5	1	49.3[1]	0.824	0.80 (0.11-5.76)	0.660	0.64 (0.09-4.64)
CT + TT *vs* CC				0.521	1.18 (0.72-1.93)	0.375	0.79 (0.47-1.33)
TT *vs* CT + CC				0.787	0.76 (0.11-5.47)	0.690	0.67 (0.09-4.82)
XPC							
rs2607775	*n* = 556	*n* = 92					
CC	494	84	46.8[1]		1 (Ref)		1 (Ref)
CG	57	8	46.3[1]	0.739	0.88 (0.43-1.83)	0.842	0.93 (0.44-1.94)
GG	5	0	NA	0.525	NA	0.969	NA
CG + GG *vs* CC				0.555	0.80 (0.39-1.66)	0.604	0.82 (0.40-1.72)
GG *vs* CG + CC				0.528	NA	0.970	NA

SNP: Single nucleotide polymorphism; CRC: Colorectal cancer; MST (M): Median survival time (mo); HR: Hazard ratio; CI: Confidence interval; NA: Not available.
[1]mean survival time was provided when MST could not be calculated. Statistically significant associations are in bold ($P < 0.05$).

complementing group 5) or XPG (xeroderma pigmentosum group G), is located in chromosome 13q22-123, consisting of 15 exons and 14 introns[47]. The protein of 1186 amino acids encoded by ERCC5 is a member of the flap structure-specific endonuclease (FEN1) family and plays an essential role in the two incision steps of NER[48,49]. A few SNPs in ERCC5 have been reported to be associated with CRC prognosis although the rs2228959 polymorphism is not covered, which belongs to exon 8 of the gene[50-53]. Interestingly, the SNP function prediction showed no special hint for its potential biological function. A reasonable interpretation for the phenomenon could be that the observation on CRC prognosis might not result from the focused polymorphism rs2228959, instead, another undiscovered variant in strong LD with it located in ERCC5 or neighbor genes[54]. Anyway, the ERCC2 rs1052555 and ERCC5 rs2228959 polymorphisms could be novel genetic biomarkers with predictive values for the clinical outcome of CRC patients. Further investigations are needed to validate all the assumptions.

Some limitations in our study should be acknowledged. First, the design of a retrospective case-control study had its inherent limitations. Second, a small percentage of data missing may influence the statistical efficacy to some extent. Additionally, only association study was emphasized in our research. All involved mechanisms need to be investigated by in-depth molecular experiments in the future.

In summary, a two-stage case-control study was performed to explore the association of all tagSNPs in eight NER pathway genes with CRC risk and prognosis in a northern Chinese population, including a discovery and validation stage. Two

SNPs (XPA rs10817938 and XPC rs2607775) were found to contribute to an increased CRC risk in overall and stratification analyses. Another two SNPs (ERCC2 rs1052555 and ERCC5 rs2228959) were found to be associated with a poor CRC prognosis. The present study has referential values for the identification of NER-based genetic biomarkers in predicting the susceptibility and clinical outcome of CRC, and may also provide clues for the access to individualized early diagnosis and therapy of CRC patients.

ARTICLE HIGHLIGHTS

Research background

Single nucleotide polymorphisms (SNPs) are universally present in nucleotide excision repair (NER) pathway genes. Previous studies have suggested that NER SNPs could make impacts on colorectal cancer (CRC) risk and prognosis.

Research motivation

Currently, most researches in this field are only focused on a few SNPs in partial NER genes. A comprehensive investigation based on a large-scale Chinese population remains lacking.

Research objectives

The study aimed to explore the association of all tagSNPs in NER pathway genes with CRC risk and prognosis in a northern Chinese population by a two-stage case-control design composed of a discovery and validation stage.

Research methods

Genotyping for NER SNPs was performed using kompetitive allele specific PCR. In the discovery stage, 39 tagSNPs in eight genes were genotyped in 368 subjects, including 184 CRC cases and 184 individual-matched controls. In the validation stage, 13 SNPs in six genes were analyzed in a total of 1712 subjects, including 854 CRC cases and 858 CRC-free controls.

Research results

We found that two SNPs (XPA rs10817938 and XPC rs2607775) were associated with an increased CRC risk in overall and stratification analyses. Significant cumulative and interaction effects were also demonstrated in the studied SNPs on CRC risk. Another two SNPs (ERCC2 rs1052555 and ERCC5 rs2228959) were newly found to be associated with a poor overall survival in CRC patients.

Research conclusions

Our findings suggested novel predictive SNPs in NER pathway genes for CRC risk and prognosis in a large-scale Chinese population.

Research perspectives

The present study has referential values for the identification of NER-based genetic biomarkers in predicting the susceptibility and clinical outcome of CRC, and may also provide clues for the access to individualized early diagnosis and therapy of CRC patients.

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