Role of *ERCC5* polymorphisms in non-small cell lung cancer risk and responsiveness/toxicity to cisplatin-based chemotherapy in the Chinese population

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Abstract. Non-small cell lung cancer (NSCLC) is the leading cause of cancer-related deaths worldwide. Cisplatin-based chemotherapy currently represents the main treatment option for patients with NSCLC. The aim of the present study was to evaluate effect of single nucleotide polymorphisms (SNPs) within the excision repair cross-complementing group 5 (*ERCC5*) gene on susceptibility to NSCLC, as well as the responsiveness to and toxicity of cisplatin chemotherapy. A total of 506 patients with NSCLC and 510 healthy controls were recruited for the present study. All DNA samples were genotyped by the Agena MassARRAY platform. Logistic regression analysis was carried out to assess the relationship between *ERCC5* polymorphisms with NSCLC susceptibility and responsiveness to chemotherapy. The rs4771436 TG-GG genotype was associated with increased NSCLC risk. When the data were stratified according to age, sex, tobacco smoking, body mass index and histological type, *ERCC5* polymorphisms (rs2016073, rs4771436, rs11069498 and rs4150330) were associated with NSCLC risk. Furthermore, the A allele and GA-AA genotype of rs11069498 were related to the response to chemotherapy. *ERCC5* (rs11069498 and rs4150330) polymorphisms were associated with the increased risk of toxicity. However, rs4771436 in *ERCC5* gene was significantly correlated with the reduced risk of toxicity. These results suggested a potential relationship between *ERCC5* polymorphisms, the risk of NSCLC and the sensitivity to cisplatin-based chemotherapy among Chinese populations.

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Introduction

Non-small cell lung cancer (NSCLC) is one of the most common malignancies, with a high morbidity and mortality rate both in men and women worldwide (1). In China, the prevalence of NSCLC has been increasing rapidly in the past few decades, and it is reported that 652,842 new patients were diagnosed in 2012 (2). A large number of epidemiological studies have confirmed that environmental factors, especially tobacco smoking and heavy alcohol drinking are associated with the risk of NSCLC (3,4). Recently, an increasing amount of studies have revealed that hereditary factors play a crucial role in susceptibility to NSCLC (5,6).

Except for a few who are eligible for surgical treatment, most patients with NSCLC are diagnosed at an advanced stage and can only receive platinum-based chemotherapy for treatment (7,8). Both the effectiveness and toxicity of chemotherapy vary between patients. Recent studies have suggested that genetic factors play an important role in inter-individual differences in response to chemotherapy, such as the *XRCC1*, *GSTP1* and *ERCC1* genes (9-11). Cheng *et al* (9) reported that polymorphism in the *ERCC1* gene was associated with the response of late-stage patients with NSCLC to cisplatin-based chemotherapy. A recent meta-analysis demonstrated that *GSTP1* GG genotype was associated with the response to cisplatin-based chemotherapy in patients with NSCLC (12).

In the present study, five polymorphisms (rs2016073, rs4771436, rs11069498, rs4150330 and rs873601) in the excision repair cross-complementing group 5 (*ERCC5*) gene were selected in order to evaluate the relationship between *ERCC5* polymorphism and NSCLC susceptibility and to examine the effect of *ERCC5* variants on the response to cisplatin-based chemotherapy in Chinese patients with NSCLC.

Materials and methods

Study populations. For the present study, 506 patients with NSCLC were recruited from the Fifth People's Hospital of Qinghai Province from June 2017 to December 2018. The present study was approved by the Institutional Review Board of the Fifth People's Hospital of Qinghai Province and was carried out in accordance with the 1964 Declaration of Helsinki. All participants were aware of the purpose of the study and signed an informed consent form. NSCLC diagnosis was established and histologically confirmed by histopathological examination according to the International Classification of Diseases for Oncology (13). Patients with a prior history of other cancer, acute and chronic infectious diseases, liver and renal dysfunction or serious concomitant systemic disorder who could not receive chemotherapy were excluded from the present study. A total of 510 healthy controls were randomly enrolled from the physical examination center of the same hospital from June 2017 to December 2018. The control subjects had no history of any type of cancer. Demographic and clinical information of all participants, including age, sex, tobacco smoking, alcohol drinking, body mass index (BMI), carcinoembryonic antigen (CEA), serum ferritin (SF), tumor necrosis factor (TNF), carbohydrate antigen 50 (CA50), α-fetoprotein (AFP), neuron-specific enolase (NSE), cytokeratin-19-fragment CYFRA21-1 (CF211) and pro-gastrin releasing peptides (Pro-GRP) were collected from questionnaires or medical records at the time of recruitment.

Evaluation of cisplatin-based chemotherapeutic effect. In total, 189 patients with NSCLC underwent cisplatin-based combination chemotherapy based on the following criteria: i) Eastern Cooperative Oncology Group (ECOG) performance status (PS) ≤1; ii) age >18 years; and iii) satisfactory liver and renal function (14). The chemotherapy was repeated every 3 weeks for up to six cycles until disease relapse or unacceptable toxicity occurred. Patients who displayed a complete response or partial remission were considered good responders. By contrast, patients with stable disease or progressive disease were considered poor responders (15). Patients with chemotherapy-related toxicity were evaluated. Toxicity associated with treatment, such as nausea, vomiting and renal toxic effects were recorded.

DNA extraction and genotyping. Peripheral whole blood (5 ml) was obtained from each participant and stored in vacutainer tubes containing EDTA anticoagulant. Genomic DNA was isolated from all samples using GoldMag whole blood genomic DNA purification kit (cat. no. GMag-LJ0210; GoldMag Nanobiotech Co., Ltd.). DNA concentration was measured using a NanoDrop™ 2000 spectrophotometer (NanoDrop™ Technologies; Thermo Fisher Scientific, Inc.). Single nucleotide polymorphisms (SNPs) in the *ERCC5* gene were selected based on minor allele frequency (MAF) >0.05 in the Chinese or Asian population from the 1,000 Genomes Project data (http://www.internationalgenome.org/), in accordance with the Hardy-Weinberg equilibrium (HWE; P>0.05) and a genotyping call rate >95%. As a result, five SNPs (rs2016073, rs4771436, rs11069498, rs4150330 and rs873601) were selected in the present study. Primers for amplification were designed using the Assay Design Suite V2.0 software (Agena Bioscience, Inc.). Subsequently, the MassARRAY iPLEX platform (Agena Bioscience, Inc.) was used to genotype the SNPs following the manufacturer's protocol. Data management was conducted using the Agena Bioscience 4.0 software (Agena Bioscience, Inc.). For quality control, approximately 10% of samples were randomly selected to repeat genotyping, and the reproducibility was 100%.

Statistical analysis. SPSS 20.0 software (IBM Corp.) was used for statistical analysis. The P-values for HWE were obtained using Fisher's exact test. Genotype and allele frequencies were compared between NSCLC cases and controls using χ^2 tests. The association between *ERCC5* polymorphisms and NSCLC risk, responsiveness to and toxicity of chemotherapy was assessed by logistic regression analysis, and the results are presented as an odds ratio (OR) and 95% confidence interval (CI). Four genetic models were used to evaluate the association of *ERCC5* SNPs with NSCLC risk using PLINK software (http://zzz.bwh.harvard.edu/plink/). Linkage disequilibrium (LD) of *ERCC5* SNPs was analyzed using Haploview 4.2 software (https://haploview.software.informer.com/), in which the haplotype frequencies <0.01 were omitted. All P-values were two-sided, and P<0.05 was considered to indicate a statistically significant difference. Considering Bonferroni multiple testing correction for evaluating the association of five SNPs with a specified disease in the same population, the significance level of the P-value was <0.01 (0.05 divided by 5).

Results

Characteristics of the participants. A total of 506 patients with NSCLC, including 350 males and 156 females were recruited. In addition, 510 unrelated healthy individuals, 353 males and 157 females, were recruited. The average age of patients and controls were 59.80±9.08 years and 59.80±10.63 years, respectively. No significant difference in age or sex distribution was observed among the two groups (P=0.992 and P=0.987, respectively, Table I). In total, 242 patients were tobacco smokers. In addition, 133 patients had a BMI ≤24 kg/m^2, and 81 patients had a BMI >24 kg/m^2. Moreover, 174 patients had squamous carcinoma, 212 patients had adenocarcinoma, and 286 patients had stage III-IV. Lastly, 42 patients exhibited good response (complete or partial remission) to chemotherapy, and 37 patients displayed toxicity to chemotherapy. The 37 patients who suffered from toxicity included 19 patients with nausea, 12 patients with myelosuppression, 5 patients with nausea and myelosuppression, and 1 patient with liver injury.

Association between ERCC5 SNPs and the risk of NSCLC. A total of five SNPs (rs2016073, rs4771436, rs11069498, rs4150330 and rs873601) were selected for the present study. *ERCC5* SNPs were genotyped in patients with NSCLC and healthy controls. Information regarding position, allele, MAF, HWE, OR and 95% CI for these SNPs are presented in Table II. All five SNPs were in HWE (P≥0.05), indicating good sample selection.

No relationship was observed between the minor allele of *ERCC5* SNPs and NSCLC risk (all P>0.05). A total of

Table I. Characteristics of cases and controls.

A, General characteristics

Variables	Cases (n=506)	Controls (n=510)	P-value
Age, years (mean ± SD)	59.80 ± 9.08	59.80 ± 10.63	0.992
≤59	235 (46%)	235 (46%)	
>59	271 (54%)	275 (54%)	
Sex			0.987
Male	350 (69%)	353 (69%)	
Female	156 (31%)	157 (31%)	
Tobacco smoking			
Yes	242 (48%)	108 (21%)	
No	161 (32%)	180 (35%)	
Information loss	103 (20%)	222 (44%)	
Alcohol drinking			
Yes	109 (22%)	103 (20%)	
No	267 (53%)	156 (31%)	
Information loss	130 (25%)	251 (49%)	
BMI, kg/m^2			
≤24	133 (26%)	138 (27%)	
>24	81 (16%)	181 (36%)	
Information loss	292 (58%)	191 (37%)	
Histological types			
Squamous carcinoma	174 (34%)		
Adenocarcinoma	212 (42%)		
Information loss	37 (7%)		
Tumor location			
Left	218 (43%)		
Right	264 (52%)		
Information loss	24 (5%)		
Lymph node metastasis			
Yes	269 (53%)		
No	103 (20%)		
Information loss	50 (10%)		
Tumor stage			
III-IV	286 (57%)		
I-II	93 (18%)		
Information loss	78 (15%)		

B, Cisplatin-based chemotherapy

Variables	Cases (n=189)
Response to chemotherapy	
Good response	42 (22%)
Poor response	100 (53%)
Unavailable	47 (25%)
Toxicity to chemotherapy	
Yes	37 (20%)
No	152 (80%)

P-values were calculated from χ^2 test. P<0.05 indicates statistical significance. SD, standard deviation; BMI, body mass index.

Table II. Basic characteristics and allele frequencies among *ERCC5* SNPs.

SNP	Chr	Allele	MAF		HWE P-value	OR (95% CI)	P-value
			Case	Control			
rs2016073	13	G/A	0.30	0.30	0.458	1.02 (0.84-1.23)	0.847
rs4771436	13	G/T	0.28	0.27	0.263	1.05 (0.86-1.28)	0.624
rs11069498	13	A/G	0.29	0.29	0.669	0.99 (0.81-1.20)	0.885
rs4150330	13	G/A	0.22	0.23	0.999	0.95 (0.77-1.17)	0.626
rs873601	13	A/G	0.47	0.49	0.376	0.93 (0.78-1.11)	0.420

P-values were calculated with two-sided χ^2 test; P<0.05 indicates statistical significance. *ERCC5*, excision repair cross-complementing group 5; SNP, single nucleotide polymorphism; Chr, chromosome; MAF, minor allele frequency, HWE, Hardy-Weinberg equilibrium; OR, odds ratio; CI, confidence interval.

four genetic models were carried out to analyze the correlation between SNP genotypes and NSCLC susceptibility. The results indicated that the TG-GG genotype of rs4771436 was associated with a higher risk of NSCLC in the dominant model (OR=1.61; 95% CI, 1.02-2.57; P=0.043), however, the significance did not exist after multiple testing correction. In addition, no significant association between any genotypes of other SNPs and NSCLC risk was observed (Table III). In addition, the relationship between *ERCC5* polymorphisms and clinicopathological parameters, such as CEA, SF, TNF, CA50, AFP, NSE, CF211 and ProGRP was analyzed (Table SI).

The data were then stratified according to the characteristics of participants and clinical parameters, including age, sex, tobacco smoking, alcohol drinking, BMI, tumor location, histological types, lymph node metastasis and tumor stage (Table IV). The GG genotype of rs4771436 increased the risk of NSCLC in the subjects aged ≤59 years (GG vs. TT, OR=2.25, P=0.036; GG vs. TG-TT, OR=2.41, P=0.020). The AA genotype of rs11069498 was associated with an increased NSCLC risk in patients aged >59 years (OR=2.03, P=0.039). In men, the rs2016073 GG genotype was associated with increased NSCLC risk (GG vs. AA, OR=1.77, P=0.045; GG vs. GA-AA, OR=1.75, P=0.043). Compared with the TT genotype, the GG genotype of rs4771436 was also related to NSCLC risk (OR=1.88, P=0.044). The heterozygous genotype GA of rs4150330 reduced the risk of NSCLC (OR=0.71, P=0.035). However, these significances did not exist after multiple testing correction.

In women, GA, GA-GG genotypes of rs2016073 and the TG genotype of rs4771436 decreased NSCLC risk (GA vs. AA, OR=0.55, P=0.014; GA-GG vs. AA, OR=0.58, P=0.017; TG vs. TT, OR=0.61, P=0.044, respectively). Stratified by tobacco smoking, the GA and GA-GG genotypes of rs4150330 were associated with a reduced risk of NSCLC (GA vs. AA, OR=0.58, P=0.028; GA-GG vs. AA, OR=0.61, P=0.039). In addition, the GG genotype of rs4771436 decreased the risk of NSCLC in subjects with a BMI >24 kg/m^2 (OR=2.87, P=0.037). By contrast, compared with the GG genotype, rs11069498 GA genotype was associated with reduced risk of squamous carcinoma (OR=0.65, P=0.029). However, these significances did not exist after multiple testing correction. No significant association was observed for alcohol drinking, tumor location, lymph node metastasis and tumor stage (data not shown).

Association between ERCC5 SNPs and cisplatin-based chemotherapy response. In total, 189 patients who received cisplatin-based chemotherapy were evaluated, of which 42 patients were good responders, 100 patients were poor responders and 47 patients were unavailable (Table I). Association between *ERCC5* polymorphisms and response to chemotherapy was analyzed (Table V). Using logistic regression analysis, the A allele of rs11069498 was found to be associated with a lower response rate to chemotherapy, compared with the G allele (OR=0.52, P=0.031). *ERCC5* rs11069498 polymorphism was also related to lower response rates to chemotherapy under the dominant genetic model (OR=0.44, P=0.033) and the log-additive model (OR=0.50, P=0.031). However, these significances did not exist after multiple testing correction. In addition, no statistically significant relationship was observed between the remaining SNPs and the response to chemotherapy under multiple genetic models (all P>0.05).

Association between ERCC5 SNPs and chemotherapy toxicity. Subsequently, 189 patients with treatment-related toxicity were recorded, of which 37 patients suffered chemotherapy-related toxicity, and 152 patients expressed no toxicity (Table I). By analyzing *ERCC5* polymorphisms with the risk of chemotherapy-related toxicity, it was revealed that *ERCC5* rs4771436, rs11069498 and rs4150330 polymorphisms were associated with chemotherapy-related toxicity. *ERCC5* rs11069498 polymorphism was related to the increased risk of toxicity in the co-dominant model (OR=3.87, P=0.025 and OR=3.24, P=0.006), the dominant model (OR=3.37, P=0.003), the log-additive model (OR=2.20, P=0.004) and the allele model (OR=2.28, P=0.002). For rs4150330, compared with the A allele, the G allele was associated with the higher risk of toxicity (OR=2.16, P=0.006). The GG and GA-GG genotypes of rs4150330 were also associated with higher toxicity risk (GG vs. AA, OR=3.15, P=0.006; GA-GG vs. AA, OR=2.93, P=0.006). The significance for *ERCC5* rs11069498 and rs4150330 still existed after multiple testing correction. Nevertheless, the G allele,

Table III. Association between five SNPs within the *ERCC5* gene and the risk of lung cancer.

SNP	Model	Genotype	Cases	Controls	OR (95% CI)	P-value
rs2016073	Co-dominant	A/A	256	248	1	
		G/A	194	221	0.85 (0.66-1.10)	0.223
		G/G	55	41	1.30 (0.84-2.02)	0.244
	Dominant	A/A	256	248	1	
		G/A-G/G	249	262	0.92 (0.72-1.18)	0.511
	Recessive	A/A-G/A	450	469	1	
		G/G	55	41	1.40 (0.91-2.14)	0.121
	Log-additive	-	-	-	1.02 (0.84-1.23)	0.847
rs4771436	Co-dominant	T/T	270	266	1	
		T/G	184	212	0.86 (0.66-1.11)	0.239
		G/G	49	32	1.51 (0.94-2.43)	0.091
	Dominant	T/T	270	266	1	
		T/G-G/G	233	244	**1.61 (1.02-2.57)**	**0.043**[a]
	Recessive	T/T-T/G	454	478	1	
		G/G	49	32	0.79 (0.31-2.01)	0.617
	Log-additive	-	-	-	1.05 (0.86-1.27)	0.627
rs11069498	Co-dominant	G/G	262	254	1	
		G/A	192	215	0.87 (0.67-1.12)	0.280
		A/A	49	41	1.16 (0.74-1.82)	0.520
	Dominant	G/G	262	254	1	
		G/A-A/A	241	256	0.91 (0.71-1.17)	0.471
	Recessive	G/G-G/A	454	469	1	
		A/A	49	41	1.24 (0.80-1.91)	0.341
	Log-additive	-	-	-	0.99 (0.82-1.19)	0.891
rs4150330	Co-dominant	A/A	315	302	1	
		G/A	158	181	0.84 (0.64-1.09)	0.189
		G/G	33	27	1.17 (0.69-2.00)	0.560
	Dominant	A/A	315	302	1	
		G/A-G/G	191	208	0.88 (0.68-1.13)	0.322
	Recessive	A/A-G/A	473	483	1	
		G/G	33	27	1.25 (0.74-2.11)	0.407
	Log-additive	-	-	-	0.95 (0.78-1.17)	0.634
rs873601	Co-dominant	G/G	142	127	1	
		G/A	250	266	0.84 (0.63-1.13)	0.249
		A/A	114	117	0.87 (0.61-1.24)	0.443
	Dominant	G/G	142	127		
		G/A-A/A	364	383	0.85 (0.64-1.12)	0.254
	Recessive	G/G-G/A	392	393		
		A/A	114	117	0.98 (0.73-1.31)	0.875
	Log-additive				0.93 (0.78-1.11)	0.416

Bold and [a]P<0.05 indicate statistical significance. SNP, single nucleotide polymorphism; *ERCC5*, excision repair cross-complementing group 5; OR, odds ratio; CI, confidence interval.

GG genotype, and TG-GG genotype of rs4771436 were associated with reduced risk of toxicity (G vs. T, OR=0.51, P=0.032, GG vs. TT, OR=0.38, P=0.034; TG-GG vs. TT, OR=0.41, P=0.027). However, these significances did not exist after multiple testing correction. In addition, no statistically significant relationship between *ERCC5* polymorphisms (rs2016073 and rs873601) and chemotherapy toxicity were observed (Table VI).

Discussion

Numerous studies have demonstrated that both environmental and genetic factors are involved in the occurrence and progression of NSCLC (10,16). Increasing evidence suggests that genetic polymorphisms are associated with the risk of NSCLC, as well as inter-individual differences in responses to and toxicity of chemotherapy (17,18). In the present study,

Table IV. Association between *ERCC5* polymorphisms and clinical features of lung cancer.

SNP	Variables	OR (95% CI), P-value					
		Allele	Homozygote	Heterozygote	Dominant	Recessive	Log-additive
rs2016073		G/A	G/G	G/A	G/A-G/G	G/G	
	Age, years						
	≤59	1.10 (0.83-1.45), 0.523	1.43 (0.74-2.73), 0.286	0.94 (0.64-1.39), 0.771	1.02 (0.71-1.47), 0.918	1.46 (0.78-2.74), 0.234	1.09 (0.83-1.44), 0.539
	>59	0.96 (0.74-1.24), 0.738	1.24 (0.68-2.27), 0.487	0.75 (0.52-1.07), 0.113	0.82 (0.59-1.16), 0.260	1.41 (0.79-2.53), 0.250	0.96 (0.74-1.24), 0.730
	Sex						
	Male	1.20 (0.95-1.51), 0.129	**1.77 (1.01-3.09), 0.045**[a]	1.02 (0.75-1.40), 0.882	1.13 (0.84-1.52), 0.43	**1.75 (1.02-3.00), 0.043**[a]	1.19 (0.95-1.50), 0.134
	Female	0.73 (0.52-1.02), 0.065	0.71 (0.34-1.49), 0.363	**0.55 (0.34-0.88), 0.014**[a]	**0.58 (0.37-0.91), 0.017**[a]	0.95 (0.47-1.92), 0.889	0.73 (0.52-1.02), 0.067
	Smoking						
	Yes	1.21 (0.84-1.74), 0.301	1.23 (0.55-2.74), 0.607	1.32 (0.80-2.15), 0.274	1.30 (0.82-2.05), 0.265	1.11 (0.51-2.4), 0.801	1.18 (0.84-1.68), 0.343
	No	0.92 (0.67-1.28), 0.639	0.97 (0.44-2.11), 0.930	0.62 (0.38-0.99), 0.050	0.67 (0.43-1.05), 0.083	1.22 (0.58-2.56), 0.606	0.83 (0.59-1.17), 0.280
	BMI, kg/m^2						
	≤24	0.89 (0.19-1.29), 0.544	1.10 (0.48-2.5), 0.817	0.73 (0.44-1.23), 0.237	0.80 (0.49-1.3), 0.363	1.26 (0.57-2.78), 0.567	0.93 (0.65-1.33), 0.678
	>24	1.07 (0.71-1.61), 0.744	1.75 (0.68-4.5), 0.245	0.65 (0.36-1.16), 0.143	0.78 (0.46-1.34), 0.374	2.11 (0.85-5.25), 0.108	1.00 (0.66-1.52), 0.991
	Tumor types						
	Squamous carcinoma	1.07 (0.82-1.39), 0.641	1.71 (0.94-3.12), 0.079	0.93 (0.64-1.35), 0.684	1.04 (0.73-1.48), 0.828	1.77 (1.00-3.15), 0.051	1.15 (0.88-1.51), 0.304
	Adenocarcinoma	1.01 (0.79-1.29), 0.954	1.13 (0.63-2.01), 0.688	0.87 (0.62-1.22), 0.413	0.91 (0.66-1.26), 0.560	1.20 (0.69-2.10), 0.516	0.98 (0.76-1.26), 0.867
rs4771436		T/G	G/G	T/G	T/G-G/G	G/G	
	Age, years						
	≤59	1.17 (0.88-1.57), 0.272	**2.25 (1.06-4.79), 0.036**[a]	0.85 (0.58-1.25), 0.420	0.99 (0.69-1.43), 0.968	**2.41 (1.15-5.03), 0.020**[a]	1.15 (0.87-1.54), 0.330
	>59	0.95 (0.73-1.25), 0.729	1.10 (0.58-2.07), 0.772	0.81 0.57-1.17), 0.262	0.86 (0.61-1.21), 0.379	1.20 (0.65-2.22), 0.565	0.94 (0.72-1.23), 0.663
	Sex						
	Male	1.17 (0.92-1.49), 0.19	**1.88 (1.02-3.46), 0.044**[a]	0.99 (0.72-1.35), 0.933	1.09 (0.81-1.47), 0.579	1.89 (1.04-3.43), 0.038	1.17 (0.92-1.49), 0.191
	Female	0.83 (0.59-1.18), 0.302	1.01 (0.47-2.2), 0.973	**0.61 (0.38-0.99), 0.044**[a]	0.68 (0.43-1.06), 0.089	1.26 (0.60-2.65), 0.546	0.84 (0.60-1.18), 0.313
	Smoking						
	Yes	1.14 (0.79-1.65), 0.488	1.44 (0.58-3.55), 0.431	1.04 (0.64-1.69), 0.887	1.10 (0.69-1.74), 0.689	1.42 (0.59-3.44), 0.439	1.12 (0.79-1.61), 0.522
	No	1.02 (0.73-1.42), 0.911	1.27 (0.57-2.86), 0.558	0.73 (0.46-1.17), 0.193	0.81 (0.52-1.27), 0.353	1.47 (0.67-3.19), 0.336	0.95 (0.68-1.34), 0.776
	BMI, kg/m^2						
	≤24	0.91 (0.19-1.33), 0.622	1.06 (0.44-2.56), 0.906	0.8 (0.48-1.34), 0.406	0.85 (0.52-1.37), 0.499	1.16 (0.49-2.73), 0.743	0.93 (0.64-1.35), 0.705
	>24	1.28 (0.84-1.93), 0.250	2.6 (0.94-7.23), 0.066	0.79 (0.44-1.41), 0.425	0.97 (0.56-1.66), 0.904	**2.87 (1.07-7.75), 0.037**[a]	1.19 (0.78-1.82), 0.429
	Tumor types						
	Squamous carcinoma	1.07 (0.82-1.41), 0.607	1.51 (0.75-3.01), 0.248	1.05 (0.73-1.52), 0.782	1.11 (0.78-1.58), 0.567	1.47 (0.75-2.88), 0.261	1.14 (0.86-1.52), 0.359
	Adenocarcinoma	1.05 (0.81-1.35), 0.726	1.45 (0.8-2.63), 0.225	0.83 (0.59-1.17), 0.279	0.91 (0.66-1.26), 0.569	1.57 (0.88-2.81), 0.128	1.03 (0.79-1.32), 0.851

Table IV. Continued.

SNP	Variables	OR (95% CI), P-value					
		Allele	Homozygote	Heterozygote	Dominant	Recessive	Log-additive
rs1106		G/A	A/A	G/A	G/A-A/A	A/A	
9498	Age, years						
	≤59	0.84 (0.64-1.12), 0.230	0.76 (0.41-1.41), 0.377	0.80 (0.54-1.19), 0.272	0.79 (0.55-1.14), 0.214	0.83 (0.46-1.51), 0.543	0.85 (0.64-1.11), 0.230
	>59	1.13 (0.87-1.48), 0.352	1.95 (0.98-3.88), 0.058	0.91 (0.64-1.3), 0.609	1.02 (0.73-1.43), 0.898	**2.03 (1.04-3.97), 0.039**[a]	1.14 (0.87-1.50), 0.327
	Sex						
	Male	0.88 (0.70-1.11), 0.279	0.94 (0.54-1.62), 0.817	0.77 (0.56-1.05), 0.099	0.8 (0.59-1.07), 0.131	1.06 (0.62-1.79), 0.835	0.88 (0.70-1.11), 0.281
	Female	1.28 (0.90-1.82), 0.166	1.82 (0.81-4.1), 0.146	1.13 (0.71-1.82), 0.605	1.24 (0.80-1.94), 0.338	1.73 (0.79-3.81), 0.171	1.26 (0.90-1.77), 0.182
	Smoking						
	Yes	0.74 (0.53-1.05), 0.090	0.55 (0.27-1.15), 0.111	0.84 (0.51-1.38), 0.490	0.76 (0.48-1.2), 0.244	0.60 (0.30-1.20), 0.145	0.77 (0.55-1.08), 0.126
	No	1.02 (0.73-1.43), 0.902	1.23 (0.52-2.91), 0.643	1.01 (0.63-1.61), 0.982	1.04 (0.66-1.63), 0.869	1.22 (0.53-2.84), 0.638	1.06 (0.75-1.51), 0.743
	BMI, kg/m^2						
	≤24	1.08 (0.19-1.59), 0.682	1.3 (0.53-3.21), 0.569	1.08 (0.64-1.81), 0.771	1.12 (0.69-1.82), 0.655	1.26 (0.52-3.04), 0.605	1.12 (0.77-1.62), 0.571
	>24	0.97 (0.65-1.45), 0.865	0.82 (0.29-2.27), 0.696	1.16 (0.66-2.04), 0.605	1.10 (0.64-1.88), 0.742	0.76 (0.28-2.03), 0.583	1.00 (0.66-1.52), 0.993
	Tumor types						
	Squamous carcinoma	0.87 (0.66-1.14), 0.315	1.05 (0.56-1.96), 0.874	**0.65 (0.45-0.96), 0.029**[a]	0.72 (0.5-1.02), 0.066	1.26 (0.69-2.3), 0.458	0.85 (0.65-1.13), 0.268
	Adenocarcinoma	1.12 (0.88-1.43), 0.365	1.41 (0.8-2.49), 0.229	1.05 (0.75-1.48), 0.772	1.11 (0.8-1.54), 0.523	1.38 (0.80-2.38), 0.242	1.14 (0.89-1.46), 0.313
rs4150330		G/A	G/G	G/A	G/A-G/G	G/G	
	Age, years						
	≤59	0.86 (0.63-1.16), 0.317	0.85 (0.42-1.75), 0.666	0.8 (0.54-1.19), 0.266	0.81 (0.56-1.17), 0.262	0.92 (0.46-1.86), 0.822	0.87 (0.65-1.16), 0.335
	>59	1.04 (0.78-1.39), 0.784	1.82 (0.79-4.21), 0.162	0.86 (0.60-1.24), 0.422	0.94 (0.67-1.33), 0.741	1.92 (0.84-4.39), 0.124	1.04 (0.78-1.39), 0.769
	Sex						
	Male	0.87 (0.68-1.11), 0.264	1.16 (0.61-2.2), 0.662	**0.71 (0.52-0.98), 0.035**[a]	0.76 (0.56-1.03), 0.079	1.31 (0.69-2.47), 0.407	0.87 (0.68-1.11), 0.270
	Female	1.17 (0.8-1.71), 0.414	1.21 (0.47-3.1), 0.698	1.23 (0.75-1.99), 0.410	1.22 (0.77-1.94), 0.390	1.13 (0.44-2.85), 0.802	1.16 (0.8-1.67), 0.432
	Smoking						
	Yes	0.71 (0.49-1.03), 0.070	0.81 (0.33-1.99), 0.640	**0.58 (0.35-0.94), 0.028**[a]	**0.61 (0.39-0.97), 0.039**[a]	0.99 (0.41-2.39), 0.983	0.74 (0.52-1.06), 0.105
	No	1 (0.7-1.45),0.982	1.02 (0.35-2.93), 0.977	1.07 (0.66-1.72), 0.783	1.06 (0.67-1.68), 0.795	0.99 (0.35-2.82), 0.989	1.04 (0.71-1.52), 0.832
	BMI, kg/m^2						
	≤24	0.98 (0.21-1.49), 0.916	1.45 (0.44-4.80), 0.539	0.88 (0.52-1.49), 0.634	0.94 (0.57-1.55), 0.80	1.52 (0.46-4.94), 0.491	1.01 (0.66-1.53), 0.97
	>24	0.93 (0.60-1.43), 0.743	0.58 (0.16-2.15), 0.414	1.23 (0.70-2.15), 0.466	1.12 (0.66-1.93), 0.673	0.53 (0.15-1.93), 0.337	0.99 (0.64-1.54), 0.969
	Tumor types						
	Squamous carcinoma	0.92 (0.68-1.23), 0.567	1.35 (0.66-2.74), 0.411	0.7 (0.47-1.03), 0.068	0.78 (0.54-1.12), 0.171	1.53 (0.76-3.07), 0.237	0.91 (0.68-1.22), 0.514
	Adenocarcinoma	1.03 (0.79-1.35), 0.823	1.24 (0.63-2.46), 0.539	0.98 (0.70-1.39), 0.924	1.02 (0.73-1.41), 0.919	1.25 (0.64-2.44), 0.520	1.05 (0.8-1.37), 0.740

Bold and [a]P<0.05 indicate statistical significance. *ERCC5*, excision repair cross-complementing group 5; SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval; BMI, body mass index.

Table V. Gene polymorphism and cisplatin-based chemotherapy response (n=142) in lung cancer patients.

SNP	Model	Genotype	Good response (n=42)	Poor response (n=100)	OR (95% CI)	P-value
rs2016073	Allele	A	52	148	1	
		G	29	55	1.50 (0.87-2.60)	0.147
	Co-dominant	A/A	17	54	1	
		G/A	21	40	1.66 (0.78-3.56)	0.189
		G/G	4	6	2.15 (0.54-8.57)	0.277
	Dominant	A/A	17	54	1	
		G/A-G/G	25	46	1.73 (0.83-3.59)	0.143
	Recessive	A/A-G/A	38	94	1	
		G/G	4	6	1.68 (0.45-6.32)	0.443
	Log-additive	-			1.55 (0.87-2.75)	0.136
rs4771436	Allele	T	49	151	1	
		G	28	56	1.54 (0.88-2.69)	0.126
	Co-dominant	T/T	18	57	1	
		T/G	20	37	1.72 (0.80-3.69)	0.164
		G/G	4	6	2.17 (0.55-8.59)	0.272
	Dominant	T/T	18	57	1	
		T/G-G/G	24	43	1.78 (0.86-3.70)	0.122
	Recessive	T/T-T/G	38	94	1	
		G/G	4	6	1.69 (0.45-6.36)	0.439
	Log-additive	-			1.57 (0.89-2.79)	0.121
rs11069498	Allele	G	66	134	1	
		A	17	67	**0.52 (0.31-0.95)**	**0.031**[a]
	Co-dominant	G/G	27	45	1	
		G/A	13	44	0.28 (0.06-1.4)	0.121
		A/A	2	11	0.48 (0.22-1.05)	0.066
	Dominant	G/G	27	45	1	
		G/A-A/A	15	55	**0.44 (0.21-0.93)**	**0.033**[a]
	Recessive	G/G-G/A	40	89	1	
		A/A	2	11	0.39 (0.08-1.86)	0.239
	Log-additive	-	-	-	**0.50 (0.27-0.94)**	**0.031**[a]
rs4150330	Allele	A	50	150	1	
		G	15	69	0.65 (0.34-1.24)	0.191
	Co-dominant	A/A	29	57	1	
		G/A	11	36	0.60 (0.26-1.34)	0.211
		G/G	2	7	0.53 (0.1-2.77)	0.454
	Dominant	A/A	29	57	1	
		G/A-G/G	13	43	0.59 (0.27-1.26)	0.172
	Recessive	A/A-G/A	40	93	1	
		G/G	2	7	0.64 (0.12-3.24)	0.585
	Log-additive	-			0.66 (0.35-1.24)	0.191
rs873601	Allele	G	91	109	1	
		A	41	43	1.14 (0.69-1.9)	0.610
	Co-dominant	G/G	10	29	1	
		G/A	23	51	1.31 (0.55-3.12)	0.549
		A/A	9	20	1.30 (0.45-3.77)	0.635
	Dominant	G/G	10	29	1	
		G/A-A/A	32	71	1.30 (0.57-2.99)	0.534
	Recessive	G/G-G/A	33	80	1	
		A/A	9	20	1.08 (0.45-2.63)	0.859
	Log-additive				1.15 (0.68-1.94)	0.611

P-values were calculated using χ^2 test. Bold and [a]P<0.05 indicate statistical significance. SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

Table VI. Gene polymorphisms and chemotherapy toxicity (n=189) in lung cancer patients.

SNP	Model	Genotype	Toxicity to chemotherapy		OR (95% CI)	P-value
			Yes (n=37)	No (n=152)		
rs2016073	Allele	A	105	199	1	
		G	17	57	0.57 (0.31-1.02)	0.056
	Co-dominant	A/A	23	65	1	
		G/A	11	69	0.46 (0.2-1.04)	0.061
		G/G	3	18	0.48 (0.13-1.83)	0.282
	Dominant	A/A	23	65	1	
		G/A-G/G	14	87	0.46 (0.22-0.99)	0.056
	Recessive	A/A-G/A	34	134	1	
		G/G	3	18	0.66 (0.18-2.43)	0.533
	Log-additive	-			0.58 (0.32-1.06)	0.077
rs4771436	Allele	T	60	208	1	
		G	14	96	**0.51 (0.27-0.95)**	**0.032[a]**
	Co-dominant	T/T	26	74	1	
		T/G	8	60	0.50 (0.13-1.86)	0.301
		G/G	3	18	**0.38 (0.16-0.93)**	**0.034[a]**
	Dominant	T/T	26	74	1	
		T/G-G/G	11	78	**0.41 (0.19-0.91)**	**0.027[a]**
	Recessive	T/T-T/G	34	134	1	
		G/G	3	18	0.68 (0.19-2.49)	0.561
	Log-additive	-	-	-	0.55 (0.30-1.03)	0.061
rs11069498	Allele	G	43	231	1	
		A	31	73	**2.28 (1.34-3.88)**	**0.002[a]**
	Co-dominant	G/G	12	91	1	
		G/A	19	49	**3.87 (1.19-12.61)**	**0.025[a]**
		A/A	6	12	**3.24 (1.41-7.45)**	**0.006[a]**
	Dominant	G/G	12	91	1	
		G/A-A/A	25	61	**3.37 (1.53-7.43)**	**0.003[a]**
	Recessive	G/G-G/A	31	140	1	
		A/A	6	12	2.20 (0.75-6.47)	0.150
	Log-additive	-	-	-	**2.20 (1.29-3.76)**	**0.004[a]**
rs4150330	Allele	A	49	246	1	
		G	25	58	**2.16 (1.24-3.79)**	**0.006[a]**
	Co-dominant	A/A	16	105	1	
		G/A	17	36	2.25 (0.62-8.19)	0.218
		G/G	4	11	**3.15 (1.40-7.07)**	**0.006[a]**
	Dominant	A/A	16	105	1	
		G/A-G/G	21	47	**2.93 (1.37-6.27)**	**0.006[a]**
	Recessive	A/A-G/A	33	141	1	
		G/G	4	11	1.44 (0.42-4.95)	0.560
	Log-additive	-	-	-	**1.89 (1.10-3.24)**	**0.021[a]**
rs873601	Allele	G	138	166	1	
		A	40	34	1.42 (0.85-2.36)	0.181
	Co-dominant	G/G	8	44	1	
		G/A	18	78	1.27 (0.5-3.23)	0.619
		A/A	11	30	1.98 (0.69-5.64)	0.201
	Dominant	G/G	8	44	1	
		G/A-A/A	29	108	1.47 (0.61-3.54)	0.39
	Recessive	G/G-G/A	26	122	1	
		A/A	11	30	1.69 (0.74-3.88)	0.216
	Log-additive				1.41 (0.83-2.4)	0.201

Bold and [a]P<0.05 indicate statistical significance. SNP, single nucleotide polymorphism; OR, odds ratio; CI, confidence interval.

the rs4771436 TG-GG genotype of the *ERCC5* gene was associated with an increased risk of NSCLC. The present study also observed that rs11069498 polymorphism was associated with a lower response to chemotherapy. Furthermore, *ERCC5* rs4771436, rs11069498 and rs4150330 polymorphisms were associated with the risk of chemotherapy-related toxicity.

DNA base damage is commonly induced by environmental carcinogens, including chemical exposure (19). Efficient DNA repair is crucial for the maintenance of genomic integrity in response to DNA damage caused by environmental carcinogens. At present, four major DNA repair pathways have been identified, including double-strand break repair for double-stranded DNA damage, mismatch repair for replication errors, base-excision repair for small lesions, and nucleotide excision repair for bulk lesions (7). It has been revealed that DNA damage can lead to genetic mutations and carcinogenesis (20). The *ERCC5* gene, also known as *Xeroderma pigmentosum* complementation group G (*XPG*), is located on chromosome 13q22-33 and contains 15 exons. ERCC5 is a crucial DNA repair enzyme (21). A previous study has revealed that mutations in the *ERCC5* gene can lead to genomic instability, impaired DNA repair responses and abnormal gene transcription, indicating that *ERCC5* polymorphisms may modulate cancer risk (14).

Previous genetic studies have indicated that *ERCC5* gene variants are related to the risk of various cancer types, including gastric cancer, breast cancer, glioma and NSCLC (7,22,23). Na *et al* (22) reported that *ERCC5* rs2094258 was associated with the risk of breast cancer in Chinese patients. Guo *et al* (23) evaluated the association between *ERCC5* SNPs (rs17655 and rs751402) and susceptibility to gastric cancer and reported that, compared with the GG genotype, the AA genotype of rs751402 was associated with an increased risk of gastric cancer. Li *et al* (24) evaluated the role of *ERCC5* SNPs in the pathogenesis of lung cancer, and observed a relationship between rs17655 and lung cancer risk. Moreover, they observed an independent effect of the rs17655 GG genotype on lung cancer risk among female, elderly samples and non-smoker patients (24). In the present study, the rs4771436 TG-GG genotype in the *ERCC5* gene was associated with the highest risk of NSCLC after adjustment for sex and age. In addition, *ERCC5* SNPs (rs2016073, rs4771436, rs11069498 and rs4150330) and the risk of NSCLC were related to clinical parameters including age, sex, tobacco smoking, BMI and histological type.

Numerous studies have revealed that variations in *ERCC5* were related to severe toxicity in patients with NSCLC receiving chemotherapy (17,18). Liu *et al* (11) reported that *ERCC5* p.H46H was associated with a favorable response to platinum-based chemotherapy in patients with NSCLC. In a recent study of 228 Chinese patients with advanced NSCLC who received chemotherapy, He *et al* (25) demonstrated that the rs751402 AA genotype was correlated with a favorable response to cisplatin-based chemotherapy, compared with the AG-GG genotype. Rulli *et al* (18) reported that polymorphism in the 5' non-coding region of the *ERCC5* gene had no effect on responsiveness to therapy in Caucasian patients with NSCLC. Moreover, a recent meta-analysis involving five studies with 846 patients suggested that the TT genotype of rs1047768 in *ERCC5* was associated with a good response to chemotherapy (26). Additionally, no significant association of rs1047768 with chemotherapy toxicity was observed in Spanish patients with NSCLC (27). In the present study, the A allele of rs11069498 was associated with a lower response rate to chemotherapy, compared with the G allele. The GA-AA genotype of rs11069498 was also associated with a poorer response to chemotherapy. In addition, the GA and GA-AA genotypes of rs11069498 and the GG and GA-GG genotypes of rs4150330 were associated with the increased risk of toxicity. However, the G allele, GG genotype, and TG-GG genotype of rs4771436 were associated with reduced risk of toxicity. No statistically significant relationship was identified between rs873601 and the response to and toxicity of cisplatin-based chemotherapy. Although there was a small number of patients in the present study with toxicity the results can still be compared with previous studies from different populations. Zhang *et al* (28) reported that *ERCC5* D1104H was related with non-hematological toxicities (infection). Song *et al* (29) reported that in the subgroup of patients who were over 58 years old, *ERCC5* variants (rs4150339, rs2296147 and rs4150360) exhibited consecutive significant signals in gastrointestinal toxicity. Unfortunately, the association between *ERCC5* polymorphism and chemotherapy toxicity (gastrointestinal toxicity and hematological toxicities) was not analyzed in this study. Further studies with larger population and complete toxicological information are also required for further investigation.

Several potential limitations of the present study should also be considered. Firstly, the retrospective case-controlled design of this study may have resulted in sampling bias. However, age- and sex-matched cases and controls were recruited to reduce the bias. Secondly, the sample size of patients with cisplatin-based chemotherapy was relatively small. Therefore, the association between *ERCC5* polymorphism and various types of toxicity was not assessed. In the future we would like to expand the sample size, and attempt to compare these findings with previous studies in different populations. Thirdly, although *ERCC5* SNPs may be associated with NSCLC risk, the results were not significant after multiple testing correction. Thus, the present findings need to be confirmed in future studies with a larger sample size.

In summary, the present study indicated that *ERCC5* rs4771436 polymorphism increased the risk of NSCLC. In addition, *ERCC5* rs11069498 polymorphism may be associated with responsiveness to chemotherapy. *ERCC5* rs4771436, rs11069498 and rs4150330 polymorphisms were related to the risk of chemotherapy-related toxicity. To the best of our knowledge, the present study is the first to suggest that SNPs are associated with responsiveness to platinum-based chemotherapy and toxicity in Chinese patients with NSCLC. Thus, *ERCC5* SNPs may represent valuable biomarkers for improving personalized therapy for Chinese patients with NSCLC.

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Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available, as they contain information

that could compromise the privacy of the participants, but are available from the corresponding author on reasonable request.

Authors' contributions

ML drafted the manuscript. BJ and GW performed the DNA extraction and genotyping. RC and CF analyzed the data. CY collected samples and recorded information. ML and GJ conceived and supervised the study. All authors read and approved the manuscript and agree to be accountable for all aspects of the research in ensuring that the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Ethics approval and consent to participate

The present study was approved by the Institutional Review Board of the Fifth People's Hospital of Qinghai Province and was carried out in accordance with the 1964 Declaration of Helsinki. All participants were aware of the purpose of the study and signed an informed consent form.

Patient consent for publication

Not applicable.

Competing interests

The authors have declared that they have no competing interests.

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