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Original Article

ERCC1 rs3212986 and *ERCC2* rs13181 gene polymorphisms contributes to the susceptibility to pancreatic cancer in a Chinese population

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Abstract: DNA repair is responsible for maintaining genomic stability in response to the assault of the environmental carcinogens that cause DNA damage. We carried out a case-control study to investigate the role of *ERCC1* (rs11615, rs2298881 and rs3212986) and *ERCC2* (rs13181) genetic variations in the risk of pancreatic cancer. This case-control study is comprised of 254 pancreatic cancer patients and 277 control subjects between January 2013 and March 2015. The *ERCC1* (rs11615, rs2298881 and rs3212986) and *ERCC2* (rs13181) polymorphisms were genotyped by polymerase chain reaction-restriction fragment length of polymorphism (PCR-RFLP). By unconditional logistic regression analysis, we found that the TT genotype (OR=2.20, 95% CI=1.14-4.35) and T allele (OR=1.39, 95% CI=1.06-1.82) of *ERCC1* rs3212986 were associated with an increased risk of pancreatic cancer when compared to the GG genotype. Moreover, the GG genotype and G allele of *ERCC2* rs13181 had a 2.31 and 1.31 fold risk of pancreatic cancer compared to the TT genotype. However, no significant relationship was observed between *ERCC1* rs11615 and rs2298881 genetic polymorphisms and the susceptibility to pancreatic cancer. In conclusion, our study suggests the *ERCC1* rs3212986 and *ERCC2* rs13181 genetic polymorphisms exposed higher risk to pancreatic cancer regardless of confounding factors.

Keywords: *ERCC1*, *ERCC2*, polymorphism, pancreatic cancer

Introduction

Pancreatic cancer is the fourth most common cause of cancer-related death worldwide [1]. It has been estimated that approximately 178,000 new cases (0.56% of the total) of pancreatic cancer occurred in 2012, making it the twelfth most common malignancy in the world [2]. In China, it is estimated that there were 39,299 new cases of pancreatic cancer and 37,775 fatalities in 2012, and it ranks as the tenth most common cancer [2]. Pancreatic cancer among the deadliest cancer in the world, it's 5-year survival rate is only 4% after patients diagnosed and patients with early found and by surgical radical resection is less than 20% [1]. The actual etiology of this cancer remains unclear. The development of pancreatic cancer involves various environmental and lifestyle factors, and previous epidemiologic studies have reported that smoking, drinking, diabetes, environmental chemicals, heavy metals, and obesity are risk factors for pancreatic cancer [3-5]. However, not all individuals develop pancreatic cancer, even when they are exposed to similar risk factors, which show that hereditary factors play an important role in its development.

It is well known that DNA repair is responsible for maintaining genomic stability in response to the assault of the environmental carcinogens that cause DNA damage. If DNA damage is not repaired, it can cause mutation fixation and initiation of carcinogenesis [6]. Nucleotide excision repair (NER) is a key DNA repair mechanisms that can influence gene-gene rearrangement, translocation, amplification, and deletion [7, 8]. Single nucleotide polymorphisms (SNPs) of genes in the NER pathway can alter the func-

Table 1. Primers and restriction enzymes of *ERCC1* (rs11615, rs2298881 and rs3212986) and *ERCC2* (rs13181) genes

SNPs	Primers (5'-3')		Restriction enzyme
ERCC1 rs11615	Forward	CCTTCGTCCCTCCCCAGA	BsrDI
	Reverse	CCCAGCACATAGTCGGGAAT	
ERCC1 rs2298881	Forward	TACAGGTCCACAAGTCCCATC	RsaI
	Reverse	ATCATTGCCGAGTCTGAGAGA	
ERCC1 rs3212986	Forward	CAGAGACAGTGCCCCAAGAG	MboII
	Reverse	GGGCACCTTCAGCTTTCTTT	
ERCC2 rs13181	Forward	GCCCGCTCTGGATTATACG	PstI
	Reverse	CTATCATCTCCTGGCCCCC	

tion and efficiency of DNA repair process, and thus plays an important role in the risk of cancer development. Excision repair cross complementation group 1 (*ERCC1*) and *ERCC2* are DNA repair genes with the chromosomal locus 19q13.3; the proteins they encode play an important role in NER [9]. Mutations of these genes have a major impact on cancer formation and/or progression. This condition happens because once these genes were mutated, they lost the ability to repair the mutated DNA suggesting the processes that repair DNA damage are fundamental importance in mutagenesis and carcinogenesis [10]. To date, only several studies reported the correlation between the *ERCC1* and *ERCC2* genetic polymorphisms and the susceptibility to pancreatic cancer, and the results are inconclusive [11-14]. We investigated whether the *ERCC1* (rs11615, rs2298881 and rs3212986) and *ERCC2* (rs13181) genetic variations could influence the risk of developing pancreatic cancer.

Materials and methods

Patients

This case-control study is comprised of 254 pancreatic cancer patients and 277 control subjects from the Affiliated Hospital of Inner Mongolia Medical University between January 2013 and March 2015. The patients were pathologically confirmed primary pancreatic cancer by two pathologists. Pancreatic cancer patients were excluded from this study if those had a history of malignant tumor except for pancreatic cancer, end-stage kidney and liver diseases, or nutritional diseases.

Between January 2013 and March 2015, healthy volunteers were recruited from individuals who received regular health check-ups in our hospital. These control subjects confirmed to be free from cancer and endocrine, metabolic, or nutritional diseases.

Information on demographic and clinical data of all study subjects were collected from medical records or personal interview with a structured questionnaire, including age, gender, cigarette smoking, alcohol consumption, body mass index (BMI), diabetes, and family history of cancer as well as other risk factors of pancreatic cancer. All the pancreatic cancer patients were ranged from 41 to 82 years old with mean age of 60.50±8.56 years. The control subjects were ranged from 35 to 76 years old, and their mean age was 59.65±9.47 years. The pancreatic cancer patients comprised 98 (38.58%) females and 156 (61.42%) females, and the control subjects were made up of 129 (46.57%) male and 148 (53.43%) female. The mean BMI values of pancreatic cancer patients and control subjects were 25.16±2.16 and 24.84±2.30, respectively. The written consent of the subjects was obtained by an informed consent. The protocol of this study got approval from the Ethics Committee of the Affiliated Hospital of Inner Mongolia Medical University.

DNA extraction and genotyping

Peripheral blood (5 mL) was obtained from each study subject, and DNA was extracted from the blood samples using TIANamp Blood DNA Kit (Tiangen, Beijing, China) following the manufacturer's recommendation. The *ERCC1* (rs11615, rs2298881 and rs3212986) and *ERCC2* (rs13181) polymorphisms were genotyped by polymerase chain reaction-restriction fragment length of polymorphism (PCR-RFLP). The forward and reverse primers for *ERCC1* (rs11615, rs2298881 and rs3212986) and *ERCC2* (rs13181) were designed using Sequenom Assay Design 3.1 software (**Table 1**). PCR was performed in a 25 μl reaction mixture containing 100 ng of DNA, 0.3 μM of each primer, 0.2 mM of dNTP mixtures, 2.0 mM of $MgCl_2$ solution, 1.0 unit of DNA polymerase. The PCR condition was set at: 95°C for 5 mins, followed by 35 cycles of 94°C for 60 s, 58°C for 30 s and 72°C for 45 s, and a final elongation of 10

Table 2. Demographic and clinical data of study groups

Variables	Patients N=254	%	Controls N=277	%	χ^2 test or t test	*P* value
Mean age, years		60.50±8.56		59.65±9.47	1.08	0.14
Gender						
Female	98	38.58	129	46.57		
Male	156	61.42	148	53.43	3.45	0.06
Family history of cancer						
No	225	88.58	261	94.22		
Yes	29	11.42	16	5.78	5.44	0.02
History of diabetes						
No	207	81.50	251	90.61		
Yes	47	18.50	26	9.39	9.26	0.002
Tobacco smoking						
No	139	54.72	178	64.26		
Yes	115	45.28	99	35.74	5.01	0.03
Alcohol consumption						
No	164	64.57	201	72.56		
Yes	90	35.43	76	27.44	3.94	0.04
Body mass index, kg/m^2						
<25	120	47.24	146	52.71		
≥25	134	52.76	131	47.29	1.58	0.21
Tumor stage						
I-II	157	61.81				
III-IV	97	38.19				

minutes at 72°C. The PCR products were stored at 4°C. The resulted fragments were electrophoresized on 2% agarose gel stained with ethidium bromide to determine the genotypes of the subjects for both polymorphic sites. Around 5% of the samples containing all genotypes for both SNPs were repeated for PCR-RFLP and all were matched to their genotype, which further confirmed using direct sequencing.

Statistical analysis

The differences of the demographic and clinical data between pancreatic cancer patients and control subjects are compared using the chi-square tests (χ^2 test) for the categorical data and student *t* test for continuous variables. The statistical difference between the allelic and genotypic frequencies of patients and controls were done using Pearson's χ^2 test. The unconditional logistic regression analysis was done to evaluate the relationship of *ERCC1* (rs11615, rs2298881 and rs3212986) and *ERCC2* (rs-13181) with pancreatic cancer polymorphisms, and the results was expressed using odds ratio (ORs) and 95% confidence interval (CI) with adjustment for possible confounders. Agreement with the Hardy-Weinberg equilibrium in both groups was evaluated using a goodness-of-fit chi-square test. Further to find out the high risk subgroups, the stratified association analysis, stratified analysis was carried out to identify the modulation in susceptibility for various stratified categories made on the basis of demographic and clinical data. All *P*-values were two-sided, and *P*-values <0.05 were considered as statistically significant. Version 16.0 of the SPSS® statistical package for Windows® (SPSS Inc., Chicago, IL, USA) was the software tool used to carry out all the statistical analysis.

Results

The demographic and clinical data of pancreatic cancer patients and control subjects were shown in **Table 2**. Using the chi-square tests or student *t* test, statistically significant differences were observed between pancreatic cancer patients and control subjects with respect to family history of cancer (χ^2 = 5.44, P = 0.02), history of diabetes (χ^2 = 9.26, P = 0.002), tobacco smoking (χ^2 = 5.01, P = 0.03) and alcohol consumption (χ^2 = 3.94, P = 0.04). The patients and control subjects were comparable in terms of mean age (*t* = 1.08, P = 0.14), gender (χ^2 = 3.45, P = 0.06) and body mass index (χ^2 = 1.58, P = 0.21). Of the 254 patients with pancreatic cancer, 157 (61.81%) cases were at

Table 3. Genotype distributions of *ERCC1* and *ERCC2* genetic polymorphisms and their association with pancreatic cancer risk

Variables	Patients	%	Controls	%	χ^2 test	*P* value	P for HWE		OR (95% CI)[1]	*P* value
							Patients	Controls		
ERCC1 rs11615										
CC	93	36.61	110	39.71		-			1.0 (Ref.)	
CT	131	51.57	138	49.82					1.12 (0.77-1.65)	0.53
TT	30	11.81	29	10.47	0.62	0.73	0.11	0.14	1.22 (0.66-2.28)	0.50
C allele	317	62.40	358	64.62					1.0 (Ref.)	
T allele	191	37.60	196	35.38	0.56	0.45			1.10 (0.85-1.42)	0.45
ERCC1 rs2298881										
CC	123	48.43	146	52.71					1.0 (Ref.)	
CA	113	44.49	118	42.60					1.14 (0.79-1.64)	0.48
AA	18	7.09	13	4.69	1.89	0.39	0.24	0.07	1.64 (0.73-3.80)	0.19
C allele	359	70.67	410	74.01					1.0 (Ref.)	
A allele	149	29.33	144	25.99	1.48	0.22			1.18 (0.89-1.56)	0.22
ERCC1 rs3212986										
GG	107	42.13	140	50.54					1.0 (Ref.)	
GT	115	45.28	118	42.60					1.28 (0.88-1.86)	0.18
TT	32	12.60	19	6.86	6.78	0.03	0.89	0.38	2.20 (1.14-4.35)	0.01
G allele	329	64.76	398	71.84					1.0 (Ref.)	
T allele	179	35.24	156	28.16	6.15	0.01			1.39 (1.06-1.82)	0.01
ERCC2 rs13181										
TT	116	45.67	138	49.82		-			1.0 (Ref.)	
TG	103	40.55	121	43.68					1.01 (0.69-1.48)	0.95
GG	35	13.78	18	6.50	7.82	0.02	0.12	0.21	2.31 (1.20-4.57)	0.01
T allele	335	65.94	397	71.66					1.0 (Ref.)	
G allele	173	34.06	157	28.34	4.04	0.04			1.31 (1.01-1.71)	0.04

[1]Adjusted for age, gender, family history of cancer, history of diabetes, tobacco smoking and alcohol consumption.

I-II tumor stage and 97 (38.19%) cases were at III-IV tumor stage.

The genotype distributions of *ERCC1* and *ERCC2* genetic polymorphisms were shown in **Table 3**. We observed that the *ERCC1* rs11615, rs2298881 and rs3212986 and *ERCC2* rs13181 genetic polymorphisms agreed with the Hardy-Weinberg equilibrium in the patients with pancreatic cancer and the controls. By Chi-square test, the genetic distributions of *ERCC1* rs3212986 (χ^2 = 6.78, P = 0.03) and *ERCC2* rs13181 (χ^2 = 7.82, P = 0.02) showed statistically significant difference between pancreatic cancer patients and control subjects. However, no significant differences were observed between pancreatic cancer patients and control subjects in terms of genetic distributions of *ERCC1* rs11615 (χ^2 = 0.56, P = 0.45) and *ERCC1* rs2298881 (χ^2 = 1.89, P = 0.39).

By unconditional logistic regression analysis, we found that the TT genotype (OR=2.20, 95% CI = 1.14-4.35) and T allele (OR = 1.39, 95% CI = 1.06-1.82) of *ERCC1* rs3212986 were associated with an increased risk of pancreatic cancer when compared to the GG genotype. Moreover, the GG genotype and G allele of *ERCC2* rs13181 had a 2.31 and 1.31 fold risk of pancreatic cancer compared to the TT genotype. However, no significant relationship was observed between *ERCC1* rs11615 and rs2298881 genetic polymorphisms and the susceptibility to pancreatic cancer.

We further evaluate the relationship between *ERCC1* rs3212986 and *ERCC2* rs13181 genetic polymorphisms and pancreatic cancer risk stratified analysis based on family history of cancer, history of diabetes, tobacco smoking and alcohol consumption (**Table 4**). However,

Table 4. Relationship between *ERCC1* rs3212986 and *ERCC2* rs13181 and pancreatic cancer risk stratification based on the demographic characteristics

Variable	*ERCC1* rs3212986				OR (95% CI)	*P* value	*ERCC2* rs13181				OR (95% CI)	*P* value
	GG	GT+TT	GG	GT+TT			TT	TG+GG	TT	TG+GG		
	Patients		Controls				Patients		Controls			
Family history of cancer												
No	96	129	130	131	1.33 (0.92-1.94)	0.12	103	122	127	134	1.22 (0.77-1.63)	0.53
Yes	11	18	10	6	2.73 (0.66-11.75)	0.11	13	16	11	5	2.71 (0.64-12.39)	0.12
History of diabetes												
No	88	119	128	123	1.41 (0.96-2.07)	0.07	95	112	124	127	1.15 (0.78-1.69)	0.45
Yes	19	28	12	14	1.26 (0.43-3.69)	0.64	21	26	14	12	1.44 (0.50-4.23)	0.45
Tobacco smoking												
No	51	88	83	95	1.51 (0.93-2.44)	0.08	64	75	87	91	1.12 (0.70-1.79)	0.62
Yes	56	59	57	42	1.43 (0.80-2.55)	0.19	52	63	51	48	1.29 (0.73-2.29)	0.36
Alcohol consumption												
No	61	103	94	107	1.48 (0.95-2.31)	0.07	78	86	102	99	1.14 (0.74-1.75)	0.54
Yes	46	44	46	30	1.47 (0.76-2.86)	0.52	38	52	36	40	1.23 (0.64-2.38)	0.51

no significant correlation was found between *ERCC1* rs3212986 and *ERCC2* rs13181 genetic variations and demographic and clinical characteristics in the development of pancreatic cancer.

Discussion

It is well known that DNA damage induced by several exogenous or endogenous factors requires efficient DNA repair to restore genomic integrity, and a number of DNA repair genes participate in DNA repair. Recently, several studies have reported that SNPs in DNA repair genes, such as *XRCC1*, *XRCC4*, and *MGMT*, are associated with susceptibility to pancreatic cancer [15, 16]. NER is a critical part of the DNA repair pathway, and it plays an important role in maintaining genomic integrity by removing DNA interstrand crosslinks [17, 18]. *ERCC1* and *ERCC2* produce two important rate-limiting enzymes that are involved in the NER process. In the present study, we observed that the TT and T allele of *ERCC1* rs3212986 and GG and G allele of *ERCC2* rs13181 genetic polymorphisms was correlated with the susceptibility to pancreatic cancer.

Previous experimental studies have reported that ERCC1 is a subunit of the NER complex, is associated with XPA, XPF, and/or RPA, and leads to 5' cleavage activity in the NER pathway [19, 20]. A previous study reported that cells from ERCC1-deficient mice present high gene variations, and a high rate of gene mutation is associated with an increased level of genomic instability and a decreased frequency of S-phase-dependent illegitimate chromosome exchange-a response adopted by rodent cells to prevent the accumulation of DNA double-strand breaks [21]. *ERCC2* has the chromosomal locus 19q13.3. It possesses both single-strand DNA-dependent ATPase and 5'-3' DNA helicase activities, and participates in DNA unwinding during NER [22, 23]. Genetic variations in *ERCC2* could decrease helicase activity, thereby inhibiting DNA repair [24, 25]. Therefore, genetic variations in *ERCC1* could influence the function of cellular DNA repair, and thus increase susceptibility to pancreatic cancer.

Many studies have revealed that the *ERCC1* and *ERCC2* genetic polymorphisms could influence the susceptibility of several kinds of cancers, such as colorectal cancer, lung cancer, glioma, laryngeal cancer, ovarian cancer and esophageal squamous cell carcinoma [26-31]. For the association between pancreatic cancer risk and genetic variation of *ERCC1* and *ERCC2*, only four previous studies have investigated their relationship and reported inconsistent results [11-14].

Currently, the authors of only three studies have reported an association between *ERCC1* and *ERCC2* gene polymorphisms and the development of pancreatic cancer [11-14]. Jiao et al.

carried out a study in American population, and reported that *ERCC2* rs13181 could be a genetic risk factor for smoking-related pancreatic cancer [11]. Duell et al. done a case-control study involving 308 patients and 964 controls, and demonstrated that *ERCC2* rs13181 may contribute to the smoking related pancreatic cancer [12]. Zhao et al. found that *ERCC1* rs3212986 and *ERCC2* rs13181 may play an important role in the development of pancreatic cancer in a Chinese population [14]. However, McWilliams et al. did not found a significant association between *ERCC1* rs3212986 and pancreatic cancer in an American population [13]. In our study, we revealed *ERCC1* rs3212986 and *ERCC2* rs13181 genetic polymorphism exposed higher risk to pancreatic cancer. The discrepancies of the above mentioned studies can be attributed to the differences in populations, selection of study subjects, and sample sizes.

However, our study had some limitations. First, the study subjects were recruited from one single hospital in China, which may induce selection bias in this study. However, the genotype distributions of *ERCC1* rs3212986 and *ERCC2* rs13181 agreed with the Hardy-Weinberg equilibrium in both patients and controls, which suggest the study subjects have representative of the general population. Second, subgroup analyses stratified by age and other factors were not done in the present study. Third, our analysis might overlook the possibility of gene-gene or SNP-SNP interactions. Further study with large sample size and more ethnicities are expected.

In conclusion, our study suggests the *ERCC1* rs3212986 and *ERCC2* rs13181 genetic polymorphisms exposed higher risk to pancreatic cancer regardless of confounding factors. Our study demonstrates that *ERCC1* rs3212986 and *ERCC2* rs13181 polymorphism can act as a biomarker and predictive tool for detection of pancreatic cancer. Further studies with larger sample size are greatly required to confirm the association between *ERCC1* and *ERCC2* genetic polymorphisms and development of pancreatic cancer.

Disclosure of conflict of interest

None.

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