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Original Article

Association between ERCC1 and XPF polymorphisms and risk of extrahepatic cholangiocarcinoma

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Abstract: Background: Several risk factors, including primary sclerosing cholangitis, liver fluke infection, HBV/HCV infection, biliary malformations, and hepatolithiasis have been identified for developing cholangiocarcinoma (CCA). However, more than 85% of patients with extrahepatic cholangiocarcinoma (ECCA) have no explicit risk factors. Polymorphisms in excision repair cross-complementing group 1 (ERCC1) and xeroderma pigmentosum group F (XPF) could affect DNA repair capability. In this study, we studied the influence of ERCC1-XPF polymorphisms on ECCA incidence. Methods: The present study included 127 patients diagnosed of ECCA and 145 normal controls. The Genotypes of ERCC1-XPF were detected by polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) method, and then the products were sent for sequencing. Results: The ERCC1 rs3212986 C > A genotype AC+AA frequency was significantly different between the cases and controls (AC+AA, OR: 1.68, 95% CI: 1.04-2.72) comparing with genotype CC. The ERCC1 rs2298881 A > C genotype CC frequency was significantly different between the cases and controls (CC, OR: 2.15, 95% CI: 1.01-4.56) comparing with genotype AA. No associations with risk of ECCA were found for other three SNPs (ERCC1 rs11615, XPF rs6498486 and XPF rs2276466). Subgroup analysis showed that an extra increased risk in smokers was observed both in ERCC1 rs3212986 AC+AA genotype (OR: 2.75, 95% CI: 1.04-7.30) and rs229888 AC+CC genotype in smokers (OR: 3.22, 95% CI: 1.19-8.71). Conclusions: The present study indicated that rs3212986 C > A and rs2298881 A > C polymorphisms of ERCC1 were associated with an increased risk of ECCA, especially in smokers. It would be necessary to confirm these findings in a large sample size and multiethnic population study in future.

Keywords: Excision repair cross complementing group 1, xeroderma pigmentosum group F, polymorphism, cholangiocarcinoma, risk

Introduction

Extrahepatic cholangiocarcinoma (ECCA) is a rare but vicious tumor which originates from the epithelial cells of bile duct [1, 2]. Most patients usually present late and are often difficult to diagnose in most cases, so radical resection, the only curative option, is applicable in few patients. However, the recurrence rate after resection is extremely high. Even though chemotherapy regiment of gemcitabine and cisplatin is often used for advanced ECCA, the 5-year survival rate is very low [3, 4]. Several potential risk factors have been clarified, which include primary sclerosing cholangitis (PSC), parasitic infection, cholelithiasis, viral hepatitis, smoking, obesity and diabetes mellitus [5, 6], only a small percentage of patients have explicit risk factors. More than 85% of patients have no identifiable risk factors. Understanding of ECCA biology, oncogenic landscape and its complex interactions with tumor environment [7, 8] could lead to early diagnose and optimum therapies of this disease.

Human genomic DNA is continuously under attack by endogenous and exogenous mutagens. However, tumors only occur in a few people because DNA damage is spontaneously repaired by highly effective DNA repair pathways, which include base excision repair (BER), mismatch repair (MMR) and nucleotide excision repair (NER) [9]. Single-nucleotide polymorphisms (SNP) in DNA repair pathways might affect the quantity and quality of the encoding protein and the DNA repair capacity, conse-

Table 1. Characteristics of extrahepatic cholangiocarcinoma cases and controls

Variables	Case (%) N = 127	Control (%) N = 145	X^2	*P*
Age				
≤ 65	77 (60.6)	84 (57.9)	0.20	0.65
> 65	50 (39.4)	61 (42.1)		
Gender				
Male	68 (53.5)	85 (58.6)	0.71	0.40
Female	59 (46.5)	60 (41.4)		
Smoking				
No	91 (71.7)	112 (77.2)	1.12	0.29
Yes	36 (28.3)	33 (22.8)		
Alcohol consumption				
No	102 (80.3)	126 (86.9)	2.16	0.14
Yes	25 (19.7)	19 (13.1)		
BMI (kg/m^2)				
≤ 18.5	10 (7.9)	9 (6.2)	0.73	0.87
18.5-22.9	51 (40.2)	60 (41.4)		
23.0-24.9	46 (36.2)	49 (33.8)		
> 25	20 (15.7)	27 (18.6)		
Family history of cancer				
No	103 (81.1)	129 (89.0)	3.34	0.07
Yes	24 (18.9)	16 (11.0)		

quently increasing the susceptibility to carcinogens [10]. Excision repair cross-complementing group 1 (ERCC1) is located in chromosome 19q13.2-13.3, and takes part in the significant step of NER. Together with xeroderma pigmentosum group F (XPF), ERCC1 forms the ERCC1-XPF enzyme complex that participates in DNA repair and DNA recombination [11].

Previously, a lot of studies have investigated the association between ERCC1-XPF polymorphisms and the risk of breast cancer [12, 13], colorectal cancer [14-16], gastric cancer [17] and glioma [18], except cholangiocarcinoma. We here carried out a hospital-based case-control study to comprehensively investigate the association between ERCC1-XPF polymorphisms and the risk of developing ECCA in a Chinese population.

Materials and methods

Ethics

The present study was approved by the Ethics Committee of Qianfoshan Hospital of Shandong University (ethics approval number 2015013). All participants signed the informed consent.

Materials

A hospital-based case-control study was performed. 127 patients newly diagnosed of ECCA were recruited at Qianfoshan Hospital of Shandong University between March 2009 and January 2015. We included subjects that met the following criterion: (1) patients newly diagnosed with ECCA according to the clinical presentation and image examination, including computerized tomography (CT), magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP) and endoscopic retrograde cholangiopancreatography (ERCP); (2) those with no previous history of other cancers or precancerous lesions; (3) those did not receive chemotherapy or radiotherapy previously; (4) those with their signed informed consent for the use of human blood and the current study protocol. 145 normal controls were randomly selected from healthy volunteers who visited the hospital for general health check-up. We excluded subjects that met the following criterion: (1) patients diagnosed with malignancy within one year after blood draw in controls; (2) no blood specimens were available for analysis. After written informed consent was obtained, demographic data and environmental exposure history were obtained from the past digital records. All the subjects were the Han nationality without immediate family relations. This manuscript did not contain any individual person's data in any form.

Biochemical analysis

A total 5 ml venous blood samples were collected in an EDTA tube and stored at 4°C within 24 hours before DNA genome extracted. The genomic DNA was extracted by a routine phenol-chloroform method.

ERCC1 and XPF genotyping

The genotypes of ERCC1 and XPF polymorphisms were detected by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique. We selected ERCC1 SNP rs2298881 A > C which might affect the binding site activity of transcription factor, and other two widely investigated functional SNPs (rs3212986 C > A and rs11615 G > A).

Table 2. Association of ERCC1 and XPF polymorphisms with risk of extrahepatic cholangiocarcinoma

Genotypes	Case (%) N = 127	Control (%) N = 145	OR (95% CI)	*P*
ERCC1 rs3212986				
CC	59 (46.5)	86 (59.3)	1.00 (Ref.)	-
AC	52 (40.9)	49 (33.8)	1.55 (0.93-2.58)	0.09
AA	16 (12.6)	10 (6.9)	2.33 (0.99-5.49)	0.05
AC+AA	68 (53.5)	59 (40.7)	1.68 (1.04-2.72)	0.03
C	170 (66.9)	221 (76.2)	1.00 (Ref.)	-
A	84 (33.1)	69 (23.8)	1.58 (1.09-2.31)	0.02
ERCC1 rs2298881				
AA	57 (44.9)	78 (53.8)	1.00 (Ref.)	-
AC	48 (37.8)	53 (36.6)	1.24 (0.74-2.08)	0.42
CC	22 (17.3)	14 (9.6)	2.15 (1.01-4.56)	0.05
AC+CC	70 (55.1)	67 (46.2)	1.43 (0.89-2.31)	0.14
A	162 (63.8)	209 (72.1)	1.00 (Ref.)	-
C	92 (36.2)	81 (27.9)	1.47 (1.02-2.11)	0.04
ERCC1 rs11615				
GG	68 (53.5)	83 (57.2)	1.00 (Ref.)	-
AG	50 (39.4)	52 (35.9)	1.17 (0.71-1.94)	0.53
AA	9 (7.1)	10 (6.9)	1.10 (0.42-2.86)	0.85
AG+AA	59 (46.5)	62 (42.8)	1.16 (0.72-1.88)	0.54
G	186 (73.0)	218 (75.2)	1.00 (Ref.)	-
A	68 (27.0)	72 (24.8)	1.11 (0.75-1.63)	0.60
XPF rs6498486				
AA	70 (55.1)	84 (57.9)	1.00 (Ref.)	-
AC	44 (34.7)	52 (35.9)	1.02 (0.61-1.69)	0.95
CC	13 (10.2)	9 (6.2)	1.73 (0.70-4.29)	0.23
AC+CC	57 (44.9)	61 (42.1)	1.12 (0.69-1.81)	0.64
A	184 (72.4)	220 (75.9)	1.00 (Ref.)	-
C	70 (27.6)	70 (24.1)	1.20 (0.81-1.76)	0.36
XPF rs2276466				
CC	73 (57.5)	82 (56.6)	1.00 (Ref.)	-
CG	43 (33.9)	49 (33.8)	0.99 (0.59-1.65)	0.96
GG	11 (8.6)	14 (9.6)	0.88 (0.38-2.07)	0.77
CG+GG	54 (42.5)	63 (43.4)	0.96 (0.60-1.56)	0.88
C	189 (74.4)	213 (73.4)	1.00 (Ref.)	-
G	65 (25.6)	77 (26.6)	0.95 (0.65-1.40)	0.80

Meanwhile, we selected XPF SNP rs2276466 C > G and rs6498486 A > C, the former one might affect the miRNA binding site activity, while the latter one might affect the binding site activity of transcription factor.

After the PCR finished, the amplified fragments were identified by electrophoresis on 2% agarose gels and the PCR products were sent for sequencing by the Shanghai Sangon Biotech Corp (Shanghai, China). All assays were repeated at least once by the same individual. 10% of all samples were randomly selected to verify the results by repeating the tests.

Statistical analysis

Mean and standard deviations were used to summarize the continuous variables. Differences (α = 0.05) between two continuous variables were evaluated by the student's *t* test, while the χ^2 test was used to determine whether the frequencies between cases and controls were significantly different (α = 0.05). The χ^2 test was also used to compare distribution differences in haplotype and genotype. The Pearson's goodness-of-fit χ^2 test was used to assess Hardy-Weinberg equilibrium for genotype frequency in controls with one degree of freedom. Odds ratios (ORs) with 95% confidence intervals (CI) were used to detect the associations between these ERCC1-XPF polymorphisms and ECCA risk. Furthermore, we calculated crude ORs with 95% CIs by univariate logistic regression models to access the associations between the ERCC1-XPF genotypes and ECCA risk with and without adjustment for age, gender, smoking, alcohol consumption, body mass index (BMI) and family history of cancer. All statistical tests were two sided, considered statistically significant with $P < 0.05$. All analyses were conducted by SPSS version 16.0 software (SPSS, Chicago, IL, USA).

Results

Population characteristics

The distributions of demographic characteristics of the subjects were presented in **Table 1**. The case and control groups were not statistically different with respect to age (χ^2 = 0.20, *P* = 0.65) and gender (χ^2 = 0.71, *P* = 0.40). Other confirmed risk factors were also matched well between two groups (smoking, χ^2 = 1.12, *P* =

Table 3. ERCC1 and XPF genotype distribution within the Hardy-Weinberg equilibrium

SNPs	χ^2	*P*
ERCC1 rs3212986	0.673	0.412
ERCC1 rs2298881	1.230	0.267
ERCC1 rs11615	0.223	0.637
XPF rs6498486	0.063	0.802
XPF rs2276466	2.588	0.108

SNPs: single-nucleotide polymorphisms.

0.29, alcohol consumption, $\chi^2 = 2.16$, $P = 0.14$, BMI, $\chi^2 = 0.73$, $P = 0.87$, and family history of cancer, $\chi^2 = 3.34$, $P = 0.07$).

Association of ERCC1 and XPF polymorphisms with the risk of ECCA

The result of ERCC1 polymorphisms with the risk of ECCA was shown in **Table 2**. For ERCC1 rs3212986, the genotype frequencies of CC, AC and AA were 46.5, 40.9 and 12.6%, respectively, in the ECCA cases compared with 59.3, 33.8 and 6.9%, respectively, in the controls. The genotype distribution in the controls was within the Hardy-Weinberg equilibrium (χ^2 = 0.67, $P = 0.41$) (**Table 3**). The genotype AC+AA frequency was significantly different between the cases and controls (AC+AA, OR: 1.68, 95% CI: 1.04-2.72) comparing with genotype CC, but not for individual genotype AC and AA frequencies (AC, OR: 1.55, 95% CI: 0.93-2.58, AA, OR: 2.33, 95% CI: 0.99-5.49). The allele frequencies of rs3212986 C > A between the two groups (OR: 1.58, 95% CI: 1.09-2.31) was also significantly different. For ERCC1 rs2298881, the genotype frequencies of AA, AC and CC were 44.9, 37.8 and 17.3%, respectively, in the ECCA cases compared with 53.8, 36.6 and 9.6%, respectively, in the controls. The genotype distribution in the controls was within the Hardy-Weinberg equilibrium (χ^2 = 1.23, P = 0.27) (**Table 3**). The genotype CC frequency was significantly different between the cases and controls (CC, OR: 2.15, 95% CI: 1.01-4.56), but not for genotype AC and AC+CC frequencies (AC, OR: 1.24, 95% CI: 0.74-2.08, AC+CC, OR: 1.43, 95% CI: 0.89-2.31). The allele frequencies of rs2298881 A > C between the two groups (OR: 1.47, 95% CI: 1.02-2.11) was also significantly different. No association with risk of ECCA was found for other three SNPs (ERCC1 rs11615, XPF rs6498486 and XPF rs2276466).

Subgroup analysis for associations between ERCC1 variant genotypes with the risk of ECCA

Table 4 showed the association between variant genotypes of two selected SNPs of ERCC1 and risk of ECCA by subgroup analysis considering age, gender, smoking, alcohol consumption, BMI and family history of cancer. The ERCC1 rs3212986 variant AC+AA genotype was associated with an extra increased risk in smokers (OR: 2.75, 95% CI: 1.04-7.30). Quite similar result was observed for ERCC1 rs229888 variant AC+CC genotype in smokers (OR: 3.22, 95% CI: 1.19-8.71). However the other common risk factors, such as alcohol consumption status, BMI and family history of cancer, did not show an extra increased risk.

Discussion

Radical surgical resection is the only curative treatment for ECCA. Although chemotherapy regiment of gemcitabine and cisplatin is often used for advanced ECCA, the 5-year survival rate is very low [19]. Patients with positive margins are no better than those who receive only palliative therapy [20]. The development of diagnostic tools (genetic change and tumor markers) may be an important way of identifying early patients who can benefit from R0 resection [5]. The mechanism of cholangiocarcinogenesis is not yet clear. Environmental and genetic factors are thought to play an important role in the development of cancer. Previous studies showed that several environmental factors were identified as risk factors, including primary sclerosing cholangitis, liver fluke infection, HBV/HCV infection, biliary malformations, and cholelithiasis [21-23]. However, not all individuals who have been exposed to the environmental risk factors actually develop ECCA, and up to 90% of patients presenting with ECCA have no identifiable risk factors, suggesting that genetic susceptibility might contribute to the individual risk of ECCA. It is widely accepted that ERCC1-XPF enzyme complex was required for the nucleotide excision repair [24], DNA double-strand break repair [25, 26] and interstrand crosslink repair [27-29] pathways. Polymorphisms in ERCC1 and XPF could affect DNA repair capability. Previous meta-analyses have indicated that ERCC1 polymorphisms were associated with the risk of different kinds of cancers [30].

Table 4. Subgroup analysis for associations between ERCC1 variant genotypes and risk of extrahepatic cholangiocarcinom

Variables	rs3212986 (Cases/Controls)		OR (95% CI)	*P*	rs2298881 (Cases/Controls)		OR (95% CI)	*P*
	CC	AC+AA			AA	AC+CC		
Age								
≤ 65	36/49	41/35	1.59 (0.85-2.97)	0.14	35/45	42/39	1.38 (0.74-2.58)	0.30
> 65	23/37	27/24	1.81 (0.85-3.86)	0.12	22/33	28/28	1.50 (0.71-3.18)	0.29
Gender								
Male	33/53	35/32	1.76 (0.92-3.36)	0.09	32/47	36/38	1.39 (0.73-2.64)	0.31
Female	26/33	33/27	1.55 (0.75-3.20)	0.23	25/31	34/29	1.45 (0.71-3.00)	0.31
Smoking								
No	45/65	46/47	1.41 (0.81-2.47)	0.22	42/55	49/57	1.13 (0.65-1.96)	0.68
Yes	14/21	22/12	2.75 (1.04-7.30)	0.04	15/23	21/10	3.22 (1.19-8.71)	0.02
Alcohol								
No	48/74	54/52	1.60 (0.95-2.71)	0.08	47/68	55/58	1.37 (0.81-2.32)	0.24
Yes	11/12	14/7	2.18 (0.64-7.40)	0.21	10/10	15/9	1.67 (0.50-5.56)	0.41
BMI (kg/m^2)								
≤ 18.5	4/4	6/5	1.20 (0.19-7.44)	0.84	6/6	4/3	1.33 (0.20-8.71)	0.76
18.5-22.9	27/38	24/22	1.54 (0.72-3.28)	0.27	18/31	33/29	1.96 (0.91-4.21)	0.09
23.0-24.9	21/29	25/20	1.73 (0.77-3.89)	0.19	24/28	22/21	1.22 (0.54-2.75)	0.63
> 25	7/15	13/12	2.32 (0.70-7.64)	0.17	9/13	11/14	1.13 (0.36-3.62)	0.83
Family history of cancer								
No	50/76	53/53	1.52 (0.90-2.56)	0.12	46/71	57/58	1.52 (0.90-2.55)	0.12
Yes	9/10	15/6	2.78 (0.75-10.26)	0.13	11/7	13/9	0.92 (0.26-3.28)	0.90

Our data showed that ERCC1 rs3212986 genotype AC+AA frequency and rs2298881 genotype CC frequency were significant association with increased risk of ECCA, especially in smokers. To date, only a few studies have addressed the contribution of genetic variants of so called 'susceptibility' genes to ECCA risk. Glutathione S-transferase omega 1 (GSTO1) [31], 5, 10-methylenetetrahydrofolate reductase (MTHFR) plus thymidylate synthase enhancer region (TSER) [32], X-ray repair cross-complementing group 1 (XRCC1), apurinic/apyrimidinic endonuclease (APEX1) [33] and MutY homolog (MYH) polymorphisms were reported with an increased susceptibility to CCA, while N-acetyltransferase 2 [34] might significantly decrease the cancer risk. To our knowledge, this study is the first one which providing data on ERCC1 and XPF genetic variant and ECCA risk. Compared with subjects carrying the ERCC1 rs3212986 genotype CC, those with dominant model AC+AA had a 1.68-fold risk of ECCA (OR: 1.68, 95% CI: 1.04-2.72), while in smokers an extra increased risk was observed with a 2.75-fold risk (OR: 2.75, 95% CI: 1.04-7.30). Similarly, the ERCC1 rs2298881 genotype CC was associated with a 2.15-fold risk of ECCA (OR: 2.15, 95% CI: 1.01-4.56) comparing with genotype AA and an extra 3.22-fold increased risk of AC+CC genotype in smokers (OR: 3.22, 95% CI: 1.19-8.71). The relationship between ERCC1 polymorphism and ECCA risk needs to be clarified by more large size studies.

In this study, all our control subjects were under Hardy-Weinberg equilibrium minimizing population stratification. We conducted quality control strictly throughout the whole study. The controls were frequency matched and the investigators were unified-trained rigorously. Moreover, we sequenced the five SNPs duplicated and verified them by repeated 10% of randomly selected samples, making the results credible. We entirely noticed that our findings were based on a small number of cases and, therefore, the biologic significance of the results might be limited. However, considering the low incidence of ECCA, well-characterized cohorts are difficult to obtain.

Several limitations and sources of bias of this study should be addressed. Firstly, like all other case-control studies, inherent biases like selection bias and recall bias in the present study might have led to some spurious results. Secondly, the present study only investigated the ERCC1 and XPF gene polymorphism and ECCA risk. Many popular gene variants reported in other cancers were not investigated here. Thirdly, the present study only adjusted age, gender, smoking, BMI and family history of cancer. Other known risk factors, such as liver fluke infection, HBV/HCV infection, and cholelithiasis were not controlled which might present a bias in the results. Although the relatively small sample size of our study showed significant results, a more comprehensive approach including environmental factors might improve the results.

Conclusions

The present study suggested that rs3212986 C > A and rs2298881 A > C polymorphisms of ERCC1 were associated with an increased risk of ECCA, especially in smokers. It would be necessary to confirm these findings in a large sample size and multiethnic population study in future, because of the relatively small sample size in this study and limited gene-environment interaction analysis. The underlying mechanism of cholangiocarcinogenesis needs to be further investigated.

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All participants signed the informed consent. This study did not involve the use of any animal.

Disclosure of conflict of interest

None.

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