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Original Article

XRCC1 Arg194Trp and Arg399Gln polymorphisms and risk of extrahepatic cholangiocarcinoma: a hospital-based case-control study in China

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Abstract: Background: Extrahepatic cholangiocarcinoma (ECCA) is a rare but devastating malignancy. Up to 90% of patients presenting with ECCA have no identifiable risk factors. The base excision repair (BER) pathway has a principal role in the repair of mutations caused by oxidized or reduced bases. The XRCC1 is one of the key proteins in the BER pathway. In this study, we investigated the influence of XRCC1 Arg194Trp and Arg399Gln polymorphisms on ECCA incidence. Methods: The study included 189 ECCA patients and 216 controls. Genotypes were detected by polymerase chain reaction restriction fragment length polymorphism (PCR-RFLP) method. Results: For codon 194, the genotype frequencies of C/C, T/C and T/T were 51.3, 43.4 and 5.3%, respectively, in the ECCA cases compared with 54.2, 38.9 and 6.9%, respectively, in the controls. No statistically significant differences were observed in the genotype frequencies of codon 194 between the two groups compared to the control (TC, OR: 0.85, 95% CI: 0.57-1.28, TT, OR: 1.24, 95% CI: 0.54-2.89, TC+TT, OR: 0.89, 95% CI: 0.60-1.32). For codon 399, the genotype frequencies of G/G, G/A and A/A were 54.0, 37.0 and 9.0%, respectively, in the ECCA cases compared with 56.1, 39.8 and 4.1%, respectively, in the controls. No statistically significant differences were observed in the genotype frequencies codon 399 between the two groups compared to the control (GA, OR: 1.04, 95% CI: 0.69-1.56, AA, OR: 0.45, 95% CI: 0.19-1.04, GA+AA, OR: 0.92, 95% CI: 0.62-1.36). Meanwhile, no statistically significant differences were found in the haplotype and risk of developing ECCA compared to the control (CA, OR: 0.83, 95% CI: 0.49-1.39, TG, OR: 0.96, 95% CI: 0.58-1.60, TA, OR: 0.83, 95% CI: 0.38-1.82).Conclusion: The present study suggested that Arg194Trp and Arg399Gln polymorphism in the DNA repair gene XRCC1 was not statistically associated with risk of ECCA. It would be necessary to confirm these findings in a large sample size and multiethnic population study in future.

Keywords: XRCC1, polymorphism, cholangiocarcinoma, risk, susceptibility

Introduction

Extrahepatic cholangiocarcinoma (ECCA), originating from the epithelial cells lining the biliary duct, is a rare but devastating malignancy [1, 2]. ECCA is clinically silent in the majority of cases. Radical resection of the tumor is applicable only in a minority of patients due to late clinical presentation and diagnosis. Moreover, the recurrence rate following resection is extremely high. Although advanced ECCA may respond to chemotherapy, there are no standard treatments for the palliation of advanced disease. The overall survival rate of the disease is poor. Although a number of risk factors have been identified, including primary sclerosing cholangitis (PSC), liver flukes infestion, toxic compounds, congenital disorders, cholelithiasis, viral hepatitis, alcohol abuse, smoking, obesity and diabetes [3, 4], only a minority of ECCA patients have known risk factors. Up to 90% of patients presenting with ECCA have no identifiable risk factors.

ECCA, in common with other cancers, is caused by gene-environment interactions. Carcinogens induce tumorigenesis in genetically susceptible individuals [5, 6]. Genomic DNA is continuously attacked by a large number of agents that damage DNA. However, cancers only occur in a small proportion of people since DNA damage is normally repaired by genome surveil-

Table 1. Primer sequences and restriction endonucleases of two SNPs in XRCC1 gene

SNPs	Location	Position	Primers	Enzymes	Digested fragments
Codon 194	exon 6	C26304T	F: GCCAGGGCCCCTCCTTCAA R: TACCCTCAGACCCACGAGT	PvuII	CC (485) CT (485, 396, 89) TT (396, 89)
Codon 399	exon 10	G28152A	F: TTGTGCTTTCTCTGTGTCCA R: TCCTCCAGCCTTTTCTGATA	MspI	GG (374, 241) GA (615, 374, 241) AA (615)

lance mechanisms and DNA repair pathways, including homologous recombination (HR), base excision repair (BER), nucleotide excision repair (NER) and mismatch repair (MMR) [7]. Polymorphisms of DNA repair genes may affect the quantity and activity of the resulting protein and the DNA repair capacity. The possession of specific alleles of polymorphic genes may increase susceptibility to cancers and facilitate cancer development in normal or exposed individuals [8].

X-ray repair cross complementing group 1 (*XRCC1*) protein encoded by *XRCC1* gene plays a critical role involved in the BER pathway, which interacts with enzymatic components of each stage of DNA strand break repair, including DNA polymerase beta, APE1 (apurinic/apyrimidinic endonuclease 1), PARP-1 (poly [ADP-ribose] polymerase 1), and DNA ligase III [9-12]. There are more than 60 validated single nucleotide polymorphisms (SNPs) in the *XRCC1* gene containing 17 exons and 16 introns on chromosome 19q13.2-13.3, among which two polymorphisms in the *XRCC1* gene at the codon 194 (exon 6, Arg to Trp), and codon 399 (exon 10, Arg to Gln) have been studied widely.

The genetic polymorphism of XRCC1 codon 194 results in an arginine to tryptophan amino acid substitution and occurs at a conserved residue in humans, hamsters, and mice, and this evolutionary conservation suggests that this site is functionally important [13, 14]. The genetic polymorphism in the XRCC1 gene at codon 399 results in an arginine to glutamine amino acid substitution. A report of Lunn and colleagues measured the prevalence of aflatoxin B1 adducts in placental DNA from 120 Taiwanese women and suggested that the XRCC1 codon 399 polymorphism may result in deficient DNA repair capacity [15]. Because amino acid residues at the protein-protein interfaces of multi-protein complexes and residues involved in the active sites play a role in enzyme function, it is possible that XRCC1 polymorphisms lead to alteration of DNA repair capacity.

Thus, we conducted this case-control study to comprehensively investigate the role of the polymorphisms (codon 194, and codon 399) in XRCC1 gene in the development of ECCA in a Chinese population.

Materials and methods

Subjects

This hospital-based case-control study included 189 newly diagnosed ECCA patients recruited at the Affiliated Cancer Hospital of Guangzhou Medical University and the Shandong Provincial Hospital between March 2009 and January 2015. The study was approved by the Ethics Committee of the Hospital. The patients were diagnosed with ECCA according to clinical presentations and imaging, including computerized tomography (CT), magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP) and endoscopic retrograde cholangiopancreatography (ERCP). All ECCA patients had no prior history of other types of cancer and were not previously treated with chemotherapy or radiotherapy. 216 normal controls were frequently matched by age (5-year intervals) and gender to permit assessment of unique and shared risk factors. Controls were required to be free of any digestion diseases with written informed consent, having no history and related clinical signs. All the subjects were ethnic Han Chinese without immediate family relations.

Blood samples and DNA isolation

The 5 mL venous blood samples obtained from the subjects were collected in an EDTA tube and stored at -70°C for extraction of DNA genome. Genomic DNA was extracted from the

Table 2. Characteristics of extrahepatic cholangiocarcinoma cases and controls

Variables	Case (%) N = 189	Control (%) N = 216	χ^2	P
Age				
≤ 65	116 (61.4)	128 (59.3)	0.19	0.66
> 65	73 (38.6)	88 (40.7)		
Gender				
Male	101 (53.4)	126 (58.3)	0.98	0.32
Female	88 (46.6)	90 (41.7)		
Smoking				
No	139 (73.5)	162 (75.0)	0.11	0.73
Yes	50 (26.5)	54 (25.0)		
Alcohol consumption				
No	156 (82.5)	181 (83.8)	0.11	0.74
Yes	33 (17.5)	35 (16.2)		
BMI (kg/m^2)				
≤ 18.5	15 (7.9)	14 (6.5)	0.95	0.81
18.5-22.9	74 (39.2)	90 (41.7)		
23.0-24.9	68 (36.0)	81 (37.5)		
> 25	32 (16.9)	31 (14.4)		

blood samples by a routine phenol-chloroform method.

XRCC1 genotyping

The genotypes of XRCC1 polymorphisms were determined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique. Primers and restriction endonucleases are shown in **Table 1**.

The PCR reaction started with a total volume of 15 μL for each mixture containing the following reagents: 7.5 μL 2 × Taq PCR MasterMix, 0.5 μM each primer, 1.0 μL (50 ng) DNA, and 5.6 μL deionized water.

PCR conditions were as follows: codon 194: 95°C for 2 min, followed by 35 cycles of 94°C for 30 s, 60°C for 30 s, 72°C for 45 s, and a final elongation step at 72°C for 7 min, codon 399: 94°C for 5 min, followed by 35 cycles of 94°C for 30 s, 57°C for 30 s, 72°C for 45 s, and a final elongation step at 72°C for 5 min, The digested products were resolved on 2% agarose gels (for codons 194 and 399) and stained with 0.5 μg/mL ethidium bromide.

All assays were repeated at least once by the same individual it is not relevant to verify the genotyping results. All experiments included positive and negative controls. Genotypes were validated by sequencing through biological technology company.

Statistical analysis

Mean and standard deviations are presented in cases of continuous variables. Differences between the means of the two continuous variables were evaluated by the student's t test. To determine whether the frequencies between cases and controls were significantly different ($\alpha = 0.05$), the χ^2 test was used. And χ^2 test was also used to compare distribution differences of haplotype, combined genotype, the number of mutation sites, and the number of mutation alleles among two genetic polymorphisms. Online software http://www.had2know.com/academics/hardy-weinberg-equilibrium-calculator-2-alleles.html was used to assess Hardy-Weinberg equilibrium for genotype frequency in controls by a Pearson's goodness-of-fit χ^2 test to compare the observed genotype frequencies to the expected ones, with one degree of freedom. Odds ratios (ORs) and 95% confidence intervals (95% CI) were used to detect the associations between these two polymorphisms and ECCA risk. Haplotypes for each individual were inferred using the SNPHAP 2.0 software. Statistical tests were two sided and were considered statistically significant whenever $P < 0.05$. All analyses were conducted by SPSS version 16.0 software (SPSS, Chicago, IL, USA).

Results

The case and control groups were not statistically different with respect to age ($\chi^2 = 0.19$, $P = 0.66$) and gender ($\chi^2 = 0.98$, $P = 0.32$). Other confirmed risk factors were also matched well between two groups (smoking, $\chi^2 = 0.11$, $P = 0.73$, alcohol, $\chi^2 = 0.11$, $P = 0.74$, BMI, $\chi^2 = 0.95$, $P = 0.81$) (**Table 2**). The association between XRCC1 genotypes and risk of ECCA are shown in **Table 3**. For codon 194, the genotype frequencies of C/C, T/C and T/T were 51.3, 43.4 and 5.3%, respectively, in the ECCA cases compared with 54.2, 38.9 and 6.9%, respectively, in the controls. The genotype distribution in the controls was within the Hardy-Weinberg equilibrium ($\chi^2 = 1.21$, $P > 0.05$). The frequency of the codon 194 C allele was 73.0% in the

Table 3. Association of XRCC1 genotypes with extrahepatic cholangiocarcinoma

Genotypes	Case (%) N = 189	Control (%) N = 216	OR (95% CI)	P
Codon 194				
CC	97 (51.3)	117 (54.2)	1.00	-
TC	82 (43.4)	84 (38.9)	0.85 (0.57-1.28)	0.43
TT	10 (5.3)	15 (6.9)	1.24 (0.54-2.89)	0.61
TC+TT	92 (48.7)	99 (45.8)	0.89 (0.60-1.32)	0.57
C	276 (73.0)	318 (73.6)	1.00	-
T	102 (27.0)	114 (26.4)	0.97 (0.71-1.33)	0.85
Codon 399				
GG	102 (54.0)	121 (56.1)	1.00	-
GA	70 (37.0)	86 (39.8)	1.04 (0.69-1.56)	0.87
AA	17 (9.0)	9 (4.1)	0.45 (0.19-1.04)	0.06
GA+AA	87 (46.0)	95 (43.9)	0.92 (0.62-1.36)	0.68
G	274 (72.5)	328 (75.9)	1.00	-
A	104 (27.5)	104 (24.1)	0.84 (0.61-1.15)	0.26

Table 4. XRCC1 haplotype analysis of two polymorphisms in XRCC1 gene

Haplotypes	Case *N* (%)	Control *N* (%)	OR (95% CI)	P
CG	100 (52.9)	121 (56.0)	1.00	-
CA	38 (20.1)	38 (17.6)	0.83 (0.49-1.39)	0.47
TG	37 (19.6)	43 (19.9)	0.96 (0.58-1.60)	0.88
TA	14 (7.4)	14 (6.5)	0.83 (0.38-1.82)	0.64

Table 5. Combination genotypes analysis of XRCC1 codons 194, 399

Combined genotypes	Case *N* (%)	Control *N* (%)	OR (95% CI)	P
CC/GG	52 (27.5)	66 (30.6)	1	-
CT/GA	30 (15.9)	33 (15.3)	0.87 (0.47-1.60)	0.65
CT/GG	44 (23.3)	47 (21.8)	0.84 (0.49-1.46)	0.54
CC/GA	36 (19.0)	46 (21.3)	1.01 (0.57-1.78)	0.98
TT/GG	5 (2.6)	8 (3.7)	1.26 (0.39-4.08)	0.70
CC/AA	9 (4.8)	5 (2.3)	0.44 (0.14-1.39)	0.15
CT/AA	7 (3.7)	4 (1.9)	0.45 (0.13-1.62)	0.35

ECCA group and 73.6% in the control group. No statistically significant differences were observed in the genotype frequencies compared to the control (TC, OR: 0.85, 95% CI: 0.57-1.28, TT, OR: 1.24, 95% CI: 0.54-2.89, TC+TT, OR: 0.89, 95% CI: 0.60-1.32) or the allele frequencies of codon 194 between the two groups (C, 1.00, T, OR: 0.97, 95% CI: 0.71-1.33) (**Table 3**). As shown in **Table 3**, for codon 399, the genotype frequencies of G/G, G/A and A/A were 54.0, 37.0 and 9.0%, respectively, in the ECCA cases compared with 56.1, 39.8 and 4.1%, respectively, in the controls. The genotype distribution in the controls was within the Hardy-Weinberg equilibrium (χ^2 = 2.65, P > 0.05). The frequency of the codon 399 G allele was 72.5% in the ECCA group and 75.9% in the control group. No statistically significant differences were observed in the genotype frequencies compared to the control (GA, OR: 1.04, 95% CI: 0.69-1.56, AA, OR: 0.45, 95% CI: 0.19-1.04, GA+AA, OR: 0.92, 95% CI: 0.62-1.36) or the allele frequencies (G, 1.00, A, OR: 0.84, 95% CI: 0.61-1.15) of codon 399 between the two groups (**Table 3**).

Table 4 shows the frequencies of the estimated haplotypes among patients and controls. For every susceptibility analysis of a haplotype, the haplotype CG (codon 194, codon 399) containing major allele was taken as control. The data of **Table 4** showed that no statistically significant differences were observed in the haplotype and risk of developing ECCA compared to the control (CA, OR: 0.83, 95% CI: 0.49-1.39, TG, OR: 0.96, 95% CI: 0.58-1.60, TA, OR: 0.83, 95% CI: 0.38-1.82).

Using combined wild genotype CC/GG as control, no statistically significant differences were observed in the combined mutation genotype and the risk of ECCA compared to the control (CT/GA, OR: 0.87, 95% CI: 0.47-1.60, CT/GG, OR: 0.84, 95% CI: 0.49-1.46, CC/GA, OR: 1.01, 95% CI: 0.57-1.78, TT/GG, OR: 1.26, 95% CI: 0.39-4.08, CC/AA, OR: 0.44, 95% CI: 0.14-1.39, CT/AA, OR: 0.45, 95% CI: 0.13-1.62) (**Table 5**).

Discussion

Radical surgical resection is the only therapeutic option for ECCA. Neither radiotherapy nor chemotherapy has been proven to be effective in randomized controlled trials [16]. However, patients with positive margins are no better than those who receive only palliative therapy [17]. The development of diagnostic and prognostic modalities (tumor markers and patho-

logical change) may be an important way of identifying patients who can benefit from R0 resection [3]. The mechanism of risk factors' role in the development of ECCA remains unclear. Environmental and genetic factors are considered to have a significant contribution in the development of cancer. Some studies have found that environmental factors including such as primary sclerosing cholangitis, liver fluke infection, HBV/HCV infection, biliary malformations, and cholelithiasis have been identified as risk factors [18-20]. However, not all individuals who have been exposed to the environmental risk factors actually develop ECCA, suggesting that genetic susceptibility might contribute to the individual risk of ECCA.

Base excision repair (BER) is the predominant DNA damage repair pathway for the processing of small base lesions, and some genetic variants in BER genes can increase the risk of cancer as a result of the defined biochemical alterations caused by those polymorphisms. It is widely accepted that functional variants in the XRCC1 gene may play a crucial role in the facilitation of human cancer development because of the alteration of base excision repair functions. Polymorphism in XRCC1 could affect DNA repair capability by altering the structure of the BRCT1 domain and thus the ability of XRCC1 to coordinate BER [21]. Previous meta-analyses have indicated that XRCC1 polymorphisms were associated with the risk of different kinds of cancers, including head and neck cancer [22], hepatocellular carcinoma [23], lung cancer [24]. However, the polymorphisms are not significantly associated with increased risk of pancreatic cancer [25], breast cancer [26].

Our data showed that there was no significant association between polymorphism of XRCC1 (codon 194, codon 399) and ECCA risk. To date, only a few studies about the contribution of genetic variants of so called 'susceptibility' genes to ECCA risk have been published, mainly in Asian cohorts. The most extensively studied genes in ECCA are those encoding enzymes involved in the phase I and II metabolism of carcinogens [27]. To our knowledge, this study is the second study which providing data on XRCC1 genetic variant and ECCA risk, and the first one using hospital-base control. The results partially supported previous study that codon 399 variant was not associated with ECCA risk, but compared with subjects carry ing the XRCC1 codon 194 CC genotype, those with homozygous genotype TT had a 1.9-fold risk of bile duct cancer (OR: 1.9, 95% CI 1.1-3.5) [12]. Possible explanation for the different result of two studies was that our study also revealed a trend of 1.24-fold risk but didn't reach a statistical significance because of small sample size and source of control. Second, Gallbladder stones and bile duct stones were more common among the cancer cases (68%) than the population controls (25%) in previous studies; however, our studies didn't take bile duct stones into consideration in statistical analysis. The relationship between XRCC1 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 two SNPs duplicated and verified them by DNA sequencing making the results credible. We are aware that our findings are based on a small number of cases and, therefore, the biologic significance of the results may be limited. However, considering the low incidence of ECCA, well-characterized cohorts are difficult to obtain.

Limitations and sources of bias should be considered. Like all other case-control studies, inherent biases like selection bias and recall bias in the present study may have led to some spurious results. The present study only investigated the XRCC1 gene polymorphism and ECCA risk. Many popular gene variant of other cancers did not evaluate in ECCA. Third, the present study only adjusted age, gender, smoking and BMI. Other risk factors, such as liver fluke infection, HBV/HCV infection, and cholelithiasis were not controlled which could present a bias in the obtained results. Although the relatively small sample size of our study didn't show statistical significance, a more comprehensive approach including environmental factors may improve the results.

In conclusion, the present study suggested that Arg194Trp and Arg399Gln polymorphism in the DNA repair gene XRCC1 was not statistically associated with risk of ECCA. It would be necessary to confirm these findings in a large sam-

ple 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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Disclosure of conflict of interest

None.

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