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Original Article

Association between XRCC1 and XRCC3 gene polymorphisms and risk of thyroid cancer

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Abstract: We conducted a case-control study to examine the role of genetic polymorphisms in XRCC1 at codons 194 (Arg>Trp), 280 (Arg>His) and 399 (Arg>Gln) and XRCC3 at codon 241 (Thr>Met) in the risk of TC. This study included 276 consecutive primary TC patients and 552 control subjects. The genotypes of XRCC1 at codons 194 (Arg>Trp), 280 (Arg>His) and 399 (Arg>Gln) and XRCC3 at codon 241 (Thr>Met) were analyzed by PCR-RFLP. TT and CT+TT genotypes of XRCC1 194 (Arg>Trp) were significantly associated with increased risk of TC, and CC and TC+CC genotypes of XRCC3 241 (Thr>Met) revealed a significant associated with the TC risk. We only found that XRCC1 194 (Arg>Trp) and XRCC3 241 (Thr>Met) polymorphisms had interaction with smoking and drinking habits. In conclusion, the current study suggests that XRCC1 194 (Arg>Trp) and XRCC3 241 (Thr>Met) polymorphisms may be associated with TC risk in a Chinese population, especially in smokers and drinkers.

Keywords: XRCC1, XRCC3, polymorphism, thyroid cancer

Introduction

The thyroid cancer (TC) is one of the common cancers in all primary endocrine cancers worldwide, and this cancer showed an increased trend in recent years [1]. It is reported that the incidence of TC increased by 67% in females and 48% in males from 1973 to 2002 worldwide [2, 3]. TC is a kind of disease which caused by complex, multistep, and multifactorial process. The real etiology of thyroid cancer is not well understood, and exposure to radiation is a well-known risk factor for TC [4, 5]. However, most patients are without a history of radiation exposure, and genetic factors may be involved in the development of TC. Therefore, understanding the genetic etiology of TC may be helpful in revealing the mechanism of TC and provide new insight for the diagnosis and treatment.

Genetic polymorphisms in DNA repair genes which lead to amino acid substitution may lead to differential capacity to repair DNA damage. This effect has been found to be associated with increased genetic instability and carcinogenesis [6]. In mammalian cells four different DNA repair mechanisms have been identified: base excision repair (BER), nucleotide excision repair (NER), double-strand break repair and mismatch repair as well as homologous recombination repair (HRR) [7, 8]. All these DNA repair pathways are finely regulated for the maintenance of genomic integrity and modulation of repair capacity in response to DNA damage and thus susceptibility to TC.

X-ray repair cross-complementing group 1 (XRCC1) protein functions in a complex with many other components to facilitate BER and single-strand break-repair processes, and it plays an important role in base excision repair (BER) and single-strand breaks repair (SSBR), upon exposure to endogenous reactive oxygen species, ionising radiation or alkylating agents [9, 10]. The BER pathway mainly removes non-bulky base adducts produced by methylation, oxidation or reduction by ionizing radiation or oxidative damage [11]. Several SNPs in XRCC1 have been identified, and three coding polymorphisms were detected at codons 194 (Arg>Trp), 280 (Arg>His) and 399 (Arg>Gln) in several

Table 1. Characteristics of included subjects

Characteristics	Controls	%	TC cases	%	χ^2 value	*P* value
Age						
<50	217	39.31	115	41.67		
≥50	335	60.69	161	58.33	0.42	0.51
Sex						
Male	240	43.48	125	45.29		
Female	312	56.52	151	54.71	0.24	0.62
BMI						
<25	343	62.14	184	66.67		
≥25	209	37.86	92	33.33	1.63	0.2
Tobacco smoking						
Never	416	79.69	181	65.58		
Current or ex-smoker	106	20.31	95	34.42	19.09	<0.05
Alcohol drinking						
Never	399	76.44	145	52.54		
Current or ex-drinker	123	23.56	131	47.46	47.53	<0.05
TSH level						
>0.3 mIU/L	34	6.16	32	11.59		
0.3-3.0 mIU/L	460	83.33	183	66.30		
>3.0 mIU/L	58	10.51	62	22.46	31.8	<0.05
Family history of thyroid cancer						
No	541	98.01	258	93.48		
Yes	11	1.99	18	6.52	17.44	<0.05
History of thyroid disease						
No	537	97.28	247	89.49		
Yes	15	2.72	29	10.51	22.19	<0.05
TNM stage						
I/II			147	53.26		
III/IV			129	46.74		
Mass size, cm						
<1			156	56.52		
≥1			120	43.48		

kinds of cancers [12-14]. The X-ray cross-complementing group 3 (XRCC3) is an important protein in the HRR pathway, and is involving in repairing DNA double-strand breaks (DSBs) [15, 16]. The XRCC3 gene has a sequence variation in exon 7 (C-T), and an amino acid substitution at codon 241 (Thr>Met) could influence the function of this protein [17].

In this present study, we conducted a case-control study to examine the role of genetic polymorphisms in XRCC1 at codons 194 (Arg>Trp), 280 (Arg>His) and 399 (Arg>Gln) and XRCC3 at codon 241 (Thr>Met) in the risk of TC. Further we also investigated whether there is a link between the clinic-pathological variables with the XRCC1 and XRCC3 gene polymorphisms and its role in modulating the risk of TC.

Materials and methods

Study population

This study included 276 consecutive primary TC patients. All TC patients were recruited from the Affiliated Hospital of Qingdao University. Tumor types and stages were determined by two experienced pathologists. The cases who had not received any chemo or radiotherapy were chosen for this study. Blood samples of 552 age and sex matched individuals with no

Table 2. Association between XRCC1 and XRCC3 gene polymorphisms and TC risk

Genotypes	Controls	%	TC cases	%	OR (95% CI)	*P* value
XRCC1 194 (Arg>Trp)						
CC	411	74.46	181	65.58	1.00 (Ref)	-
CT	95	17.21	52	18.84	1.24 (0.83-1.85)	0.26
TT	46	8.33	43	15.58	2.12 (1.32-3.41)	<0.05
CT+TT	141	25.54	95	34.42	1.53 (1.10-2.12)	<0.05
XRCC1 280 (Arg>His)						
GG	322	58.33	153	55.43	1.00 (Ref)	-
GA	174	31.52	91	32.97	1.10 (0.89-1.53)	0.55
AA	56	10.14	32	11.59	1.20 (0.72-1.98)	0.45
GA+AA	230	41.67	123	44.57	1.13 (0.84-1.53)	0.40
XRCC1 399 (Arg>Gln)						
GG	290	52.54	138	50.00	1.00 (Ref)	-
GA	206	37.32	105	38.04	1.07 (0.77-1.48)	0.66
AA	56	10.14	32	11.59	1.20 (0.72-1.98)	0.45
GA+AA	262	47.46	137	49.64	1.10 (0.81-1.48)	0.52
XRCC3 241 (Thr>Met)						
TT	362	65.58	161	58.33	1.00 (Ref)	-
TC	150	27.17	84	30.43	1.26 (0.90-1.76)	0.16
CC	40	7.25	31	11.23	1.74 (1.01-2.97)	<0.05
TC+CC	190	34.42	115	41.67	1.36 (1.01-1.85)	<0.05

Adjusted for age, sex, tobacco smoking, alcohol drinking, TSH level, family history of thyroid cancer and history of thyroid disease.

signs of any malignancy were collected for controls. The 552 controls were selected from health examination clinics in the Affiliated Hospital of Qingdao University.

Data on all TC patients and controls were obtained from face-to-face interviewers with patients and controls, medical records and pathology reports. The data collected included?. All patients and controls were informed about this study and their will to participate in this study was taken on predesigned questionnaire. The collection and use of blood samples for this study were previously approved by the Ethics Committee of the Affiliated Hospital of Qingdao University.

DNA extraction and genotype analysis

Genomic DNA was isolated from peripheral blood lymphocytes using Qiagen blood mini kit (Qiagen, Germany) by the manufacturer's protocol. The genotypes of XRCC1 at codons 194 (Arg>Trp), 280 (Arg>His) and 399 (Arg>Gln) and XRCC3 at codon 241 (Thr>Met) were analyzed by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay. The positive and reverse primer se uences of the XRCC1 at codons 194 (Arg>Trp) were 5'-GCCAGGGCCCCTCCTTCAA-3' and 5'-TACCCTCAGACCCACGAGT-3', respectively. For the XRCC1 280 (Arg>His), the positive and reverse primers were 5'-CAGTGGTGCTAACCTAATC-3' and 5'-AGTAGTCTGCTGGCTCTGG-3', respectively.For XRCC1 399 (Arg>Gln), the positive and reverse primers were 5'-CAGTGGTGCTAACCTAATC-3' and5'-AGTAGTCTGCTGGCTCTGGG-3', respectively. For XRCC3 241 (Thr>Met), the positive and reverse primers were 5'-GGTCGAGTGACAGTCCAAAC-3' and 5'-TGCAACGGCTGAGGGTCTT-3', respectively. The amplification conditions were used as follows: one initial denaturation step at 95°C for 5 min, then 30 cycles of 94°C for 0.5 min, 60°C for 0.5 min and 72°C for 1 min, at last 72°C for 10 min.

Statistical analysis

The statistical difference between cases and controls was analyzed by A Chi-squared test or student t test. The Hardy-Weinberg equilibrium (HWE) was tested by Fisher's exact test for each SNP in controls. Conditional regression models were used to calculate the strength of association between XRCC1 and XRCC3 gene polymorphisms and breast cancer risk, and the results were expressed using Odds Ratio (OR) and 95% confidence interval (CI). The link between the clinic-pathological variables with the XRCC1 and XRCC3 gene polymorphisms was assessed by Conditional regression models. Statistical significance was set at $P<0.05$. Statistical analyses were performed using SPSS 16.0 software.

Results

A total of 276 TC cases and 552 control subjects were included in this study with prior con-

Table 3. Interaction between XRCC1 194 (Arg>Trp) and XRCC3 241 (Thr>Met) gene polymorphisms and demographic characteristics in the TC risk

Characteristics	XRCC1 194 (Arg>Trp)				OR (95% CI)	*P* value	XRCC3 241 (Thr>Met)				OR (95% CI)	*P* value
	CC		CT+TT				TT		TC+CC			
	Controls	Cases	Controls	Cases			Controls	Cases	Controls	Cases		
Age	411	181	141	95			362	161	40	115		
<50	158	72	59	43	1.60 (0.96-2.66)	0.06	130	68	87	47	1.03 (0.63-1.68)	0.89
≥50	253	109	82	52	1.47 (0.95-2.27)	0.07	232	93	103	68	1.65 (1.09-2.47)	0.01
Sex												
Male	178	81	62	44	1.56 (0.95-2.55)	0.06	157	71	83	54	1.44 (0.90-2.29)	0.11
Female	233	100	79	51	1.51 (0.96-2.34)	0.06	205	90	107	61	1.30 (0.85-1.97)	0.2
BMI												
<25	248	118	95	66	1.46 (0.98-2.18)	0.05	223	105	120	79	1.40 (0.95-2.05)	0.07
≥25	163	63	46	29	1.63 (0.90-2.91)	0.08	139	56	70	36	1.28 (0.74-2.18)	0.35
Tobacco smoking												
Never	313	118	103	63	1.62 (1.09-2.41)	0.01	276	106	140	75	1.39 (0.96-2.03)	0.07
Current or ex-smoker	98	63	8	32	6.22 (2.58-16.51)	<0.05	86	55	20	40	3.12 (1.59-6.23)	<0.05
Alcohol drinking												
Never	300	98	99	47	1.45 (0.94-2.24)	0.08	267	85	132	60	1.43 (0.95-2.15)	0.07
Current or ex-drinker	111	83	12	48	5.35 (2.58-11.71)	<0.05	95	76	28	55	2.46 (1.38-4.41)	<0.05
TSH level												
>0.3 mIU/L	24	18	10	14	1.87 (0.60-5.86)	0.23	22	18	12	14	1.43 (0.47-4.32)	0.48
0.3-3.0 mIU/L	332	116	128	67	1.50 (1.02-2.19)	<0.05	297	106	163	77	1.32 (0.92-1.91)	0.12
>3.0 mIU/L	55	47	3	15	5.85 (1.50-32.99)	<0.05	43	37	15	25	1.94 (0.83-4.56)	0.09
Family history of thyroid cancer												
No	402	175	139	83	1.37 (0.98-1.92)	0.06	354	151	187	107	1.34 (0.98-1.84)	0.06
Yes	9	6	2	12	9.00 (1.18-102.58)	0.01	8	10	3	8	2.13 (0.34-16.27)	0.36
History of thyroid disease												
No	398	167	139	80	1.37 (0.97-1.93)	0.06	351	145	186	102	1.33 (0.96-1.83)	0.07
Yes	13	14	2	15	6.96 (1.18-71.44)	0.01	11	16	4	13	2.23 (0.49-11.75)	0.24

sent (**Table 1**). The mean age of TC patients and control subjects were years 55.1±9.7 and 54.4±10.3 years, respectively. Out of 276 TC cases, 125 were males and 151 were females, 147 were at I/II stage and 129 were at III/IV stage, and 156 had mass size <1 cm and 120 showed mass size ≥1 cm. No significant sex- or age-related differences were found between the groups (*P*>0.05). We found patients were more likely to have a habit of smoking and drinking, a family history of thyroid cancer and a history of thyroid disease.

The overall association between the XRCC1 194 (Arg>Trp) and XRCC3 241 (Thr>Met) polymorphisms and TC cases was found to be significant (**Table 2**). TT and CT+TT genotypes of XRCC1 194 (Arg>Trp) were significantly associated with increased risk of TC, with Ors (95% CI) of 2.12 (1.32-3.41) and 1.53 (1.10-2.12), respectively. Moreover, CC and TC+CC genotypes of XRCC3 241 (Thr>Met) revealed a significant associated with the TC risk, and the Ors (95% CI) were 1.74 (1.01-2.97) and 1.36 (1.01-1.85), respectively. However, we did not find any significant association between XRCC1 280 (Arg>His) and XRCC1 399 (Arg>Gln) polymorphisms and TC risk.

The correlation of XRCC1 194 (Arg>Trp) and XRCC3 241 (Thr>Met) polymorphisms with the demographic and clinical characteristics was carefully analyzed. We found that CT+TT genotype of XRCC1 194 (Arg>Trp) was associated with a heavy increased TC risk in those with smoking and drinking habits, TSH level >3.0 mIU/L, a family history of thyroid cancer and a history of thyroid disease, and the Ors (95% CI) were 6.22 (2.58-16.51), 5.35 (2.58-11.71), 5.85 (1.50-32.99), 9.00 (1.18-102.58) and 6.96 (1.18-71.44) (**Table 3**). Furthermore, TC+CC genotype of XRCC3 241 (Thr>Met) was associated with a moderate increased TC risk in smoking and drinking habits, and the Ors (95% CI) were 3.12 (1.59-6.23) and 2.46 (1.38-4.41), respectively. By interaction analysis, we only found that XRCC1 194 (Arg>Trp) and XRCC3 241 (Thr>Met) polymorphisms had interaction with smoking and drinking habits (Both *P* values for interaction <0.05).

Discussion

Among various DNA damage lesions caused by the by ionizing radiation, the DSBs are the principle genotoxic to pose major threats to genomic instability, integrity and carcinogenesis [18]. Increasing evidence indicate that the BER and HRR repair pathway plays an important role in repairing DSBs in mammalian cells, and XRCC1 and XRCC3 complex is critical in performing the end-joining reaction and potentially contributing to cancer tumorigenesis [19, 20]. In this case-control study, we investigated the role of XRCC1 at codons 194(Arg>Trp), 280(Arg>His) and 399 (Arg>Gln) and XRCC3 at codon 241 (Thr>Met) polymorphisms in the development of TC. Our study found that TT genotype of XRCC1 194(Arg>Trp) and CC genotype of XRCC3 241 (Thr>Met) were associated with increased risk of TC, especially in smokers and drinkers.

Since there is increasing evidence that genetic variation leads to different DNA repair capacities in the human population, and thus gene polymorphisms can play a critical role in an individual's genetic susceptibility to cancer [21]. Mutations in XRCC1 and XRCC3 genes may cause decrease or loss of DNA repair capacity and confer the variation in development of many malignant tumors.

Previous studies have reported that XRCC1 and XRCC3 gene polymorphisms may modify the risk for cancer, including lung cancer, breast cancer, glioma, gastric cancer and colorectal cancer [14, 22-25]. Zhao et al. have reported that XRCC1 Arg194Trp polymorphism has an increased gastric cancer risk in Asian population [14]. Xu et al. have suggested that the XRCC1 Arg194Trp polymorphism is a genetic risk factor for glioma, especially in Asian population [22]. Nissar et al. have shown that a significantly elevated risk of colorectal cancer in patients with XRCC3 241 (Thr>Met) polymorphism [24]. However, some studies did not find significant association between XRCC1 and XRCC3 polymorphisms and cancer risk. Dong et al. found no association between XRCC1 gene polymorphism and bladder cancer risk [26]. Zhang et al. found that XRCC3 241 (Thr>Met) polymorphism may not be a risk factor for lung cancer [27]. The divergence in results from different studies on XRCC1 and XRCC3 polymorphisms could be elucidated by differences in populations, cancer types, sample size and study design.

For the correlation between XRCC1 Arg194Trp polymorphism and thyroid cancer risk, several

studies have reported their association [28-32]. However, these studies reported inconsistent results with ours. Santos et al. did not find significant association between XRCC1 Arg194-Trp polymorphism and TC risk [31]. Sigurdson et al. found that XRCC1 Arg194Trp polymorphism was associated with a reduced risk of TC [32]. However, two recent meta-analyses demonstrated that XRCC1 Arg194Trp polymorphism conferred an increased risk for TC [33, 34].

Our study found that XRCC3 241 (Thr>Met) polymorphism was associated with TC risk, and two previous studies reported similar results with ours [35, 36]. Fayaz et al. found that XRCC3 241 (Thr>Met) polymorphism was a risk factors for development of differentiated thyroid carcinoma [35]. Bastos et al. reported that C allele of XRCC3 241 (Thr>Met) was associated to a significant higher risk of TC [36]. However, Yu et al. reported that CC genotype of XRCC3 241 (Thr>Met) was significant correlated with reduced risk of TC [37]. Therefore, further studies are greatly needed to confirm our findings.

Moreover, our study suggested that XRCC1 194 (Arg>Trp) and XRCC3 241 (Thr>Met) polymorphisms had association with smoking and drinking habits. Cigarette smoking and tobacco drinking may induce various types of DNA damage including benzopyrene diol epoxide adduct, strand breaks, cross-links, and recombination, which are repaired through different DNA repair pathways, including NER [38, 39]. Therefore, Cigarette smoking and tobacco drinking have a synergistic effect with XRCC1 194 (Arg>Trp) and XRCC3 241 (Thr>Met) polymorphisms in cancer risk.

In conclusion, the current study suggests that XRCC1 194 (Arg>Trp) and XRCC3 241 (Thr>Met) polymorphisms may be associated with TC risk in a Chinese population, especially in smokers and drinkers. However, no association was found between polymorphisms in XRCC1 280 (Arg>His) and 399 (Arg>Gln) and TC risk. Further large sample studies are needed to confirm the role of XRCC1 and XRCC3 polymorphisms in the development of TC risk.

Disclosure of conflict of interest

None.

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