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Association between *XRCC1* polymorphisms and laryngeal cancer susceptibility in a Chinese sample population

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ABSTRACT. Laryngeal cancer is the major malignant tumor affecting the upper respiratory tract. Previous studies have reported on the association between *XRCC1* genetic polymorphisms and risk of laryngeal cancer, but with conflicting results. In this study, we attempted to assess the association between *XRCC1* Arg194Trp, Arg280His and Arg399Gln polymorphisms and risk of laryngeal cancer in a Chinese population. A total of 126 laryngeal cancer patients and 254 control subjects were recruited to this study from the Second Medical College of Jinan University between December 2013 and May 2015. The *XRCC1* Arg194Trp, Arg280His, and Arg399Gln polymorphic sites were genotyped by polymerase chain reaction-restriction fragment

length polymorphism. Our results revealed a significant association between the AA genotype of *XRCC1* Arg280His [odds ratio (OR) = 2.51, 95% confidence interval (CI) = 1.29-4.87, P = 0.01] and an increased risk of laryngeal cancer susceptibility compared to the GG genotype. Moreover, the A allele showed a higher risk of laryngeal cancer susceptibility compared to the G allele (OR = 1.63, 95%CI = 1.19-2.50, P = 0.002). In conclusion, the results of our study suggest that the AA genotype and A allele of the *XRCC1* Arg280His polymorphism are associated with an increased laryngeal cancer risk in a Chinese population.

Key words: *XRCC1*; Arg194Trp; Arg280His; Arg399Gln; Polymorphism; Laryngeal cancer

INTRODUCTION

Laryngeal cancer is the major malignant tumor affecting the upper respiratory tract, with approximately 156,000 new laryngeal cancer patients and 83,000 deaths from laryngeal cancer in 2012 worldwide (IARC, 2012). The incidence of laryngeal cancer varies considerably across different populations, suggesting that many environmental and lifestyle risk factors are involved in laryngeal cancer development, such as exposure to carcinogens in the work environment, and infection with human papilloma virus and Epstein-Barr virus (Pöschl et al., 2004; La Vecchia et al., 2008). In fact, many studies have indicated that heritable factors contribute to the development of laryngeal cancer, including methylene tetrahydrofolate reductase, epidermal growth factor-like domain 7/Egfl7, necleotide excision repair pathway gene, matrix metallopreteinases 11, *P14*, B-cell translocation gene 1, special AT-rich sequence-binding protein 1 and 2, DNA repair gene and cyclin-dependent kinase (Wang et al., 2014; Sun et al., 2015; Li et al., 2015; Jiang et al., 2015; Mansour et al., 2016; Li et al., 2016; Bednarek et al., 2016).

It is reported that repair of DNA damage is under genetic control and DNA repair genes contribute to maintaining genome integrity and preventing the development of cancer (Xing et al., 2002; Hu et al., 2016). *XRCC1* is the first mammalian gene to be isolated that displays cellular sensitivity to ionizing radiation (Thompson et al., 1990). Three common polymorphisms (single nucleotide polymorphisms) in *XRCC1*, including Arg194Trp, Arg280His and Arg399Gln, have been previously elucidated by many studies (Shen et al., 2000; Stern et al., 2001). Additionally, several epidemiologic studies have shown conflicting results on the relationship between *XRCC1* genetic polymorphisms and laryngeal cancer risk, but with conflicting results (Gajecka et al., 2005; Yang et al., 2008; Krupa et al., 2011; Ayiheng and Bogela, 2013). We attempted to assess the association between *XRCC1* Arg194Trp, Arg280His and Arg399Gln polymorphisms and risk of laryngeal cancer in a Chinese population.

MATERIAL AND METHODS

Subjects

Here, a total of 126 patients with laryngeal cancer were consecutively collected from

the Second Medical College of Jinan University, China, between December 2013 and May 2015. The diagnosis of laryngeal cancer was pathologically confirmed in all patients.

During the same period, a total of 254 healthy subjects were randomly selected for this study from among individuals who received a regular health check-up at the Second Medical College of Jinan University. Individuals with a history of cancers, end-stage renal or liver disease, malnutrition were excluded from this study. The study design was approved by the Second Medical College of Jinan University. Written informed consent was obtained from all laryngeal cancer patients and control subjects.

Genotyping

Peripheral blood (5 mL) was collected from each participant. DNA was extracted from the blood samples using the QIAamp DNA Blood Mini Kit (Qiagen, Venlo, Netherlands). The Arg194Trp, Arg280His, and Arg399Gln polymorphic sites in *XRCC1* were genotyped by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP). The forward and reverse primer sequences for the Arg194Trp, Arg280His, and Arg399Gln polymorphic sites were 5'-GCCAGGGCCCCTCCTTCAA-3' and 5'-TACCCTCAGACCCACGAGT-3', 5'-GCCCCGTCCCAGGTA-3' and 5'-AGCCCCAAGACCCTTTCACT-3' (Arg195Trp), 5'-CCAGTGGTGCTAACCTAATC-3' and 5'-CACTCAGCACCACTACCACA-3', and 5'-CCCCAAGTACAGCCAGGTC-3' and 5'-TGTCCCGCTCCTCTCAGTAG-3', respectively. The conditions of PCR were set as follows: one cycle of initial denaturation at 94°C for 5 min; 35 cycles of denaturation at 94°C for 45 s, annealing at 60°C (Arg194Trp), 69.5°C (Arg280His), or 61°C (Arg399Gln) for 30 s, and extension at 72°C for 45 s; and a final one cycle of extension at 72°C for 7 min. RFLP was performed using the restriction enzymes *Pvu*II, *Rsa*I, and *Msp*I for the *XRCC1* Arg194Trp, Arg280His, and Arg399Gln polymorphisms, respectively. The restriction enzyme products was performed by 2% agarose gel electrophoresis for 45 min, and observed under gel imaging system.

Statistical analysis

A goodness-of-fit χ^2-test was performed to identify and evaluate the probable deviations of the *XRCC1* Arg194Trp, Arg280His, and Arg399Gln polymorphisms from the Hardy-Weinberg equilibrium (HWE). Relationships between the *XRCC1* Arg194Trp, Arg280His, and Arg399Gln genetic polymorphisms and laryngeal cancer susceptibility were calculated by multiple logistic regression analyses, and odds ratios (OR) and their 95% confidence intervals (CIs) were taken to express the results. $P < 0.05$ was considered to be statistically significant for all analyses. All statistical analyses were performed on the SPSS Statistics program for Windows (v.18.0; IBM, Armonk, NY, USA).

RESULTS

Our analyses revealed that laryngeal cancer patients were of a more advanced age ($t = 1.85$, $P = 0.03$), had a family history of cancer ($\chi^2 = 7.85$, $P = 0.005$), were males ($\chi^2 = 10.31$, $P = 0.001$), and were habitual tobacco smokers ($\chi^2 = 5.14$, $P = 0.02$) or alcohol consumers ($\chi^2 = 20.29$, $P < 0.001$) compared to the control subjects (Table 1). With respect to the TNM stage, 79 (62.70%) patients had tumors at stage I-II and 47 (37.30%) had tumors at stage III+IV.

Table 1. Demographic and lifestyle characteristics of study subjects.

Variables	Patients (N = 126)	%	Controls (N = 254)	%	χ^2 or *t* test	P value
Age, years	57.53 ± 9.43		55.46 ± 10.65		1.85	0.03
Gender						
Males	99	78.57	158	62.20		
Females	27	21.43	96	37.80	10.31	0.001
BMI, kg/m^2	24.64 ± 2.42		24.21 ± 2.55		1.57	0.06
Tobacco smoking						
No	47	37.30	126	49.61		
Yes	79	62.70	128	50.39	5.14	0.02
Alcohol consumption						
No	42	33.33	147	57.87		
Yes	84	66.67	107	42.13	20.29	<0.001
Family history of cancer						
No	110	87.30	242	95.28		
Yes	16	12.70	12	4.72	7.85	0.005
Tumor stage						
I+II	79	62.70				
III+IV	47	37.30				

We observed significant differences in the genotype frequencies of the *XRCC1* Arg280His (χ^2 = 9.32, P = 0.01) polymorphisms between the laryngeal cancer patients and control subjects; however, the genotype frequencies of *XRCC1* Arg194Trp (χ^2 = 0.68, P = 0.71) and Arg399Gln (χ^2 = 0.35, P = 0.84) did not differ significantly between the case and control subjects (Table 2). The goodness-of-fit chi-square test revealed that the genotypes of the *XRCC1* Arg194Trp, Arg280His, and Arg399Gln polymorphisms in the laryngeal cancer patients (P values = 0.86, 0.57, and 0.53, respectively) and the controls (P values = 0.99, 0.33, and 0.31, respectively) were according to the HWE.

Table 2. Genotype distributions of *XRCC1* Arg194Trp, Arg280His, and Arg399Gln in the laryngeal cancer and control groups.

XRCC1	Patients	%	Controls	%	χ^2 test	P value	P for HWE	
							Patients	Controls
Arg194Trp								
CC	50	39.68	110	43.31				
CT	58	46.03	115	45.28				
TT	18	14.29	30	11.81	0.68	0.71	0.86	0.99
Arg280His								
GG	38	30.16	112	44.09				
GA	60	47.62	108	42.52				
AA	29	23.02	34	13.39	9.32	0.01	0.57	0.33
Arg399Gln								
GG	44	34.92	96	37.80				
GA	58	46.03	114	44.88				
AA	24	19.05	44	17.32	0.35	0.84	0.53	0.31

HWE, Hardy-Weinberg equilibrium.

The analysis demonstrated that the AA genotype (OR = 2.51, 95%CI = 1.29-4.87, P = 0.01) of *XRCC1* Arg280His exposed an increased risk of laryngeal cancer compared to the GG genotype (Table 3). Additionally, the analysis revealed that the A allele showed an increased risk of laryngeal cancer susceptibility, compared to the G allele (OR = 1.63, 95%CI = 1.19-2.50, P = 0.002). However, no significant association was found between the *XRCC1* Arg194Trp and Arg399Gln polymorphisms and laryngeal cancer susceptibility.

Table 3. Relationship between *XRCC1* Arg194Trp, Arg280His, and Arg399Gln polymorphisms and laryngeal cancer susceptibility.

XRCC1	Patients	%	Controls	%	OR (95%CI)[1]	P value
Arg194Trp						
CC	50	39.68	110	43.31	1.0 (Reference)	-
CT	58	46.03	115	45.28	1.11 (0.68-1.81)	0.66
TT	18	14.29	30	11.81	1.32 (0.63-2.71)	0.42
Allele						
C	158	65.86	335	65.95	1.0 (Reference)	-
T	94	37.31	175	34.45	1.14 (0.82-1.58)	0.42
Arg280His						
GG	38	30.16	112	44.09	1.0 (Reference)	-
GA	59	46.83	108	42.52	1.43 (0.85-2.40)	0.15
AA	29	23.01	34	13.39	2.51 (1.29-4.87)	0.01
Allele						
G	135	53.58	332	65.35	1.0 (Reference)	-
A	117	46.43	176	34.65	1.63 (1.19-2.50)	0.002
Arg399Gln						
GG	44	34.92	96	37.80	1.0 (Reference)	-
GA	58	46.03	114	44.88	1.11 (0.67-1.84)	0.67
AA	24	19.05	44	17.32	1.19 (0.61-2.29)	0.58
Allele						
G	146	57.94	306	60.24	1.0 (Reference)	-
A	106	42.07	202	39.76	1.10 (0.80-1.51)	0.54

[1]Adjusted for age, gender, tobacco smoking, alcohol drinking, and family history of cancer. OR, odds ratio; CI, confidence interval.

DISCUSSION

In the present study, we analyze the association between the *XRCC1* Arg194Trp, Arg280His, and Arg399Gln polymorphisms and laryngeal cancer risk; the results of this study indicated the AA genotype and A allele of *XRCC1* Arg280His were correlated with a higher risk of laryngeal cancer.

So far, several studies have reported on the association between *XRCC1* polymorphisms and development of several types of cancers, including non-small cell lung cancer, gastric cancer, cervical cancer, hepatocellular carcinoma, pancreatic cancer, ovarian cancer, colorectal cancer, and thyroid cancer (Liu et al., 2012; Abdel-Fatah et al., 2013; Feng et al., 2014; Wang and Ai, 2014; Xia et al., 2014; Cătană et al., 2015; Han et al., 2015; Huang et al., 2015; Xu et al., 2015; Zhao and Chen, 2015; Ghosh et al., 2016). Liu et al. (2015) observed a significant relationship between the *XRCC1* Arg399Gln polymorphism and risk of cervical cancer in a meta-analysis comprising 2051 cervical cancer patients and 2919 control subjects. Han et al. (2015) reported, in a case-control study comprising 245 patients with non-small cell lung cancer and 257 healthy controls, that the *XRCC1* Arg399Gln polymorphism influences cancer risk in a Chinese population. Xu et al. (2015) observed a significant association between the *XRCC1* Arg280His polymorphism and risk of hepatocellular carcinoma in a meta-analysis comprising 1848 patients with hepatocellular carcinoma and 1969 controls. However, Liu et al. (2012) reported the lack of any association between the *XRCC1* Arg399Gln polymorphism and gastric cancer risk, based on a meta-analysis comprising 3278 gastric cancer patients and 6243 controls. These studies have shown that the *XRCC1* polymorphisms may play an important role in imparting susceptibility to cancer development.

However, previous studies analyzing the correlation between *XRCC1* gene

polymorphisms and laryngeal cancer susceptibility have reported conflicting results (Varzim et al., 2003; Gajecka et al., 2005; Yang et al., 2008; Krupa et al., 2011; Ayiheng and Bogela, 2013; Li et al., 2016). Yang et al. (2008) observed, in a study with 72 patients with laryngeal squamous carcinoma and 72 controls in a Chinese population, that the *XRCC1* Arg399Gln polymorphism might lead to an increased risk of laryngeal carcinoma. Ayiheng and Bogela (2013) reported, in a study with 60 patients with laryngeal squamous carcinoma and 120 healthy controls, that the *XRCC1* Arg399Gln polymorphism may be an independent biomarker for laryngeal cancer susceptibility. However, several studies have reported inconsistent results (Varzim et al., 2003; Krupa et al., 2011; Gajecka et al., 2005). Varzim et al. (2003), Gajecka et al. (2005) and Krupa et al. (2011) reported that the *XRCC1* polymorphisms may not be associated with laryngeal cancer risk in a Polish population. On the other hand, Li et al. (2016) reported, based on the results of a meta-analysis comprising 2242 laryngeal cancer patients and 3811 controls, that the *XRCC1* Arg399Gln polymorphism might contribute to laryngeal cancer susceptibility and Chen et al. (2014), in another meta-analysis with 1654 laryngeal cancer patients and 2377 cancer-free controls, suggested the lack of an association between the *XRCC1* Arg399Gln polymorphism and laryngeal cancer risk. In this study, we discovered a possible correlation between the *XRCC1* Arg280His polymorphism and the risk of developing laryngeal cancer. One limitation should be considered in this study. All patients and controls were selected from a single hospital; therefore, the sample may not be representative of the general population, thereby introducing selection bias into this study.

In conclusion, we suggest that individuals harboring the AA genotype and A allele of *XRCC1* Arg280His are associated with an increased laryngeal cancer risk in a Chinese population. But the *XRCC1* Arg194Trp and Arg399Gln genetic polymorphisms did not contribute to the development this cancer.

Conflicts of interest

The authors declare no conflict of interest.

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