



Association between *IL-10* genetic variations and cervical cancer susceptibility in a Chinese population

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Genet. Mol. Res. 15 (3): gmr.15038116
Received November 25, 2015
Accepted January 15, 2016
Published August 5, 2016
DOI <http://dx.doi.org/10.4238/gmr.15038116>

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ABSTRACT. We conducted an investigation into the role of the *IL-10* polymorphisms -592A/C (rs1800872), -819C/T (rs1800871), and -1082A/G (rs1800896) in cervical cancer risk in a Chinese population. A case-control study was carried out, including 165 newly diagnosed cervical cancer patients and 165 control subjects. The polymerase chain reaction-restriction fragment length polymorphism method was used to genotype the three *IL-10* variant loci. Using conditional logistic regression analysis, we observed that homozygous *IL-10* -819C/T TT carriers were at significantly increased risk of cervical cancer compared to homozygous CC individuals, with an adjusted odds ratio (OR) of 2.23 and a 95% confidence interval (CI) of 1.16-4.30. Moreover, the CT+TT genotype was significantly associated with cervical cancer in comparison to the wild-type variant (OR = 1.69, 95%CI = 1.04-2.76; P = 0.03). In conclusion, our study suggests that the *IL-10* -819C/T

genetic variation may contribute to cervical cancer risk in the Chinese population examined.

Key words: Interleukin-10; Polymorphism; Cervical cancer

INTRODUCTION

Cervical cancer is the third most common malignancy among women, with an estimated global incidence of over 500,000 new cases per year (Siegel et al., 2012). The etiology of this disease has been widely studied, and previous research has demonstrated that infection with human papillomavirus (HPV) contributes to its development (Woodman et al., 2001; Duenas-Gonzalez et al., 2014). Moreover, risk factors are reported to include having multiple sexual partners, sexual intercourse under 16 years of age, multiple pregnancies, and multiparity (Memiah et al., 2015; Rigaud, 2015). Moreover, previous studies have reported that many genes play an important role in cervical cancer risk, including *CXCL12*, *TNF- α* , *miR-146a*, *miR-143*, *miR-145*, *MMP-9*, and *CD192* (Chen et al., 2015; Xie et al., 2015; Yin et al., 2015; Zhang et al., 2015).

Interleukin-10 (IL-10) can inhibit the synthesis of other cytokines such as IL-6, IL-1 β , IL-1 α , and tumor necrosis factor- α in activated macrophages, and interferon- γ in T cells (D'Andrea et al., 1993). Previous studies have revealed that HPV infection is associated with elevated expression of *IL-10* in cervical tissue (Torres-Poveda et al., 2012). It has been reported that variation in the *IL-10* gene can influence expression of the corresponding protein, and thus may affect its role in cervical carcinogenesis (Turner et al., 1997; Roh et al., 2002). In our study, we assessed the influence of the *IL-10* polymorphisms -592A/C (rs1800872), -819C/T (rs1800871), and -1082A/G (rs1800896) on cervical cancer risk in a Chinese population.

MATERIAL AND METHODS

Patients

A case-control study was carried out, including 165 newly diagnosed cervical cancer patients and 165 control subjects. All participants were recruited from the Affiliated Hospital of Yanan University between January 2013 and December 2014. Cervical cancer patients were diagnosed by biopsy or resected tissue examined by two pathologists.

Control subjects, all of whom were selected from individuals attending the hospital for a regular gynecological examination, were matched to patients by age (± 5 years). Those with a history of tumors, or serious infectious or gynecological diseases were excluded from our study. The present study was approved by the Ethics Committee of the Affiliated Hospital of Yanan University, and was performed based on the Declaration of Helsinki. Informed consent was obtained from each study subject.

Each patient and control subject was interviewed regarding demographic and lifestyle characteristics using a self-designed questionnaire including the following information: age, age at first sexual intercourse, age at menarche, body mass index (BMI), lifetime number of sexual partners, HPV-16 or -18 infection status, and family history of cancer.

Genotyping method

A venous blood sample (5 mL) was obtained for DNA extraction from each subject after enrollment into this study. Genomic DNA was extracted from collected peripheral blood with a TIANamp Blood DNA Kit (TIANGEN, Beijing, China) following the manufacturer protocol. A polymerase chain reaction (PCR)-restriction fragment length polymorphism assay was conducted to detect *IL-10* -592A/C (rs1800872), -819C/T (rs1800871), and -1082A/G (rs1800896) genotypes. The primers and restriction enzymes used are shown in Table 1. The PCR cycling conditions were as follows: 95°C for 10 min, then 35 cycles of 95°C for 30 s, 62°C for 30 s, and 72°C for 30 s, followed by 72°C for 10 min.

Table 1. Primers and restriction enzymes used to genotype *IL-10* -592A/C, -819C/T, and -1082A/G polymorphisms.

<i>IL-10</i>	SNP	Primers	Restriction enzyme
-592A/C	rs1800872	5'-AATGAGCACTAGGTGACTAGC-3' 5'-CCTACCTCTCTGAGACGTAA-3'	<i>RsaI</i>
-819C/T	rs1800871	5'-GCTTCTCCTATGCTAGTCAGGTA-3' 5'-TGGTCTCAAGTGGGTAAGAGT-3'	<i>MseI</i>
-1082A/G	rs1800896	5'-AGAAAGTCCTGATGTCACCTGC-3' 5'-AAGTCAGGATCCATGGAG-3'	<i>MnII</i>

SNP = single nucleotide polymorphism.

Statistical analysis

Comparisons of baseline information between the two groups was carried out using the chi-square test and the Student *t*-test. Associations between genetic polymorphisms and cervical cancer risk were analyzed using conditional regression analysis, and odds ratios (ORs) and corresponding 95% confidence intervals (CIs) were obtained. The Stata version 9.0 statistical software (StataCorp., College Station, TX, USA) was employed to analyze results, and P values less than 0.05 were considered to represent a statistically significant difference.

RESULTS

The demographic and lifestyle characteristics of the study subjects are reported in Table 2. The mean ages of patients and controls were 42.55 ± 9.46 and 40.94 ± 10.42 years, respectively. In comparison to healthy controls, cervical cancer patients were younger at the time of first sexual intercourse (*t* = 6.40, *P* < 0.001) and were more likely to be infected with HPV-16 or -18 (chi-square = 91.80, *P* < 0.001). However, no significant difference was found for BMI (*t* = 0.41, *P* = 0.34), age at menarche (*t* = 0.80, *P* = 0.21), lifetime number of sexual partners (*t* = 1.92, *P* = 0.38), or family history of cancer (*t* = 1.12, *P* = 0.29).

We then analyzed the distributions of *IL-10* -592A/C, -819C/T, and -1082A/G genotypes among cervical cancer patients and control subjects (Table 3). The chi-square test revealed no significant difference in AA, AC, and CC -592A/C genotype frequencies between these two groups (chi-square = 1.11, *P* = 0.58). Using conditional logistic regression analysis, we observed that homozygous *IL-10* -819C/T TT carriers demonstrated a significantly increased risk of cervical cancer when compared to homozygous CC individuals, with an adjusted OR (and 95%CI) of 2.23 (1.16-4.30). Moreover, the CT+TT genotype was significantly associated with cervical cancer in comparison to the wild-type variant (OR = 1.69, 95%CI = 1.04-2.76; *P* = 0.03).

Table 2. Demographic and lifestyle characteristics of study subjects.

Variable	Patients	%	Controls	%	Chi-square test or <i>t</i> -test	P value
Age (mean, years)	42.55 ± 9.46		40.94 ± 10.42		1.47	0.07
Age at first sexual intercourse (years)	16.42 ± 6.84		20.55 ± 4.69		6.40	<0.001
BMI (kg/m ²)	24.20 ± 3.51		24.05 ± 3.20		0.41	0.34
Age at menarche (years)	12.67 ± 1.76		12.82 ± 1.64		0.80	0.21
Lifetime number of sexual partners						
≤3	132	80.00	141	85.45		
4-9	29	17.58	22	13.33		
>9	4	2.42	2	1.21	1.92	0.38
HPV-16 or -18 infection						
Negative	41	24.85	128	77.58		
Positive	124	75.15	37	22.42	91.80	<0.001
Family history of cancer						
No	144	87.27	150	90.91		
Yes	21	12.73	15	9.09	1.12	0.29

BMI = body mass index; HPV = human papillomavirus.

Table 3. Association between *IL-10* genetic variations and development of cervical cancer.

Genotype	Patients	%	Controls	%	Chi-square	P	P for HWE	OR (95%CI) ¹	P
-592A/C									
AA	63	38.18	70	42.42				1.0 (Ref.)	-
AC	82	49.70	80	48.48				1.14 (0.70-1.85)	0.58
CC	20	12.12	15	9.09	1.11	0.58	0.24	1.48 (0.66-3.39)	0.30
AC+CC	102	61.82	95	57.58				1.19 (0.75-1.90)	0.43
-819C/T									
CC	45	27.27	64	38.79				1.0 (Ref.)	-
CT	76	46.06	73	44.24				1.48 (0.87-2.52)	0.12
TT	44	26.67	28	16.97	6.93	0.03	0.36	2.23 (1.16-4.30)	0.01
CT+TT	120	72.73	101	61.21				1.69 (1.04-2.76)	0.03
-1082A/G									
AA	74	44.85	80	48.48				1.0 (Ref.)	-
AG	75	45.45	72	43.64				1.13 (0.70-1.82)	0.61
GG	16	9.70	13	7.88	0.61	0.74	0.56	1.33 (0.56-3.23)	0.48
AG+GG	91	55.15	85	51.52				1.16 (0.73-1.83)	0.51

¹Adjusted for age, age at first sexual intercourse, and HPV-16 or -18 infection. HWE = Hardy-Weinberg equilibrium, OR = odds ratio, CI = confidence interval.

DISCUSSION

In our study, we assessed the role of *IL-10* -592A/C, -819C/T, and -1082A/G polymorphisms in cervical cancer risk, finding that the -819C/T genetic variation contributes to development of this disease in a Chinese population.

Previous studies have examined associations between the *IL-10* -592A/C, -819C/T, and -1082A/G polymorphisms and several conditions related to inflammation, including deep venous thrombosis, chronic hepatitis B virus infection, sepsis, *Helicobacter pylori* infection, valvular calcification, and peptic ulcer diseases (Tang et al., 2014; Tunçbilek, 2014; An et al., 2015; Miftahussurur and Yamaoka, 2015; Pan et al., 2015; Ramis et al., 2015). For instance, Tang et al. (2014) carried out an investigation of 660 deep venous thrombosis patients and 660 control subjects, from which they found that the *IL-10* -1082A/G polymorphism is associated with risk of this disease among Chinese individuals. Tunçbilek (2014) revealed that sequence variations in this same gene are involved in different clinical presentations of HBV infection, while Pan et al. (2015) conducted a meta-analysis indicating that *IL-10* -592A/C and -1082A/

G polymorphisms can affect susceptibility to sepsis. Ramis et al. (2015) failed to identify a significant association between *IL-10* gene variants and *H. pylori* infection; however, An et al. (2015) reported that *IL-10* -592A/C and -819C/T polymorphisms can influence valvular calcification risk in Han and Kazak populations. Finally, Miftahussurur and Yamaoka (2015) found no significant association between *IL-10* genetic variations and peptic ulcer disease.

To date, several studies have assessed the association between *IL-10* gene polymorphisms and development of cervical cancer, but with inconclusive results (Roh et al., 2002; Singh et al., 2009; Matsumoto et al., 2010; Wang et al., 2011; Barbisan et al., 2012; Chagas et al., 2013; Zidi et al., 2015). Matsumoto et al. (2010) and Chagas et al. (2013) reported that the *IL-10* -1082 variant locus may contribute to cervical cancer development in Japanese and Brazilian populations. In contrast, four other case-control studies failed to establish an association between *IL-10* polymorphisms and susceptibility to this disease (Roh et al., 2002; Singh et al., 2009; Wang et al., 2011; Barbisan et al., 2012). However, Zidi et al. (2015) conducted a study of Tunisian patients, concluding that variations in this gene may contribute to cervical oncogenesis, while in our investigation, we observed that the -819C/T polymorphism in *IL-10* may affect cervical cancer risk. The discrepancy between these results may be due to the differences caused by ethnicity, or sample-size effects. Further studies are greatly needed to confirm our findings.

In conclusion, our study suggests that the *IL-10* -819C/T genetic variation may contribute to cervical cancer risk in the Chinese population under investigation, but no such association was observed in relation to the -592A/C and -1082A/G polymorphisms.

Conflicts of interest

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

We thank the great help of staffs from the Affiliated Hospital of Yanan University and Affiliated Hospital of Yanan University by performing the interview of the included subjects.

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