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Association of *IL-17* genetic polymorphisms and risk of oral carcinomas and their interaction with environmental factors in a Chinese population.

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Abstract

Objective: We firstly performed a study in a population in Northern China, and investigated the association of *IL-17* gene (rs8193036 and rs2275913 in IL-17A; rs763780 and rs2397084 in IL-17F) with the risk of oral cancer and their interaction with environmental factors.

Methods: A total of 182 patients with oral cancer and 364 controls were consecutively recruited into this study. Genotyping of *IL-17* gene was performed in a 384-well plate format on the Sequenom MassARRAY Analyzer. Association between IL-17 rs8193036, rs2275913, rs763780 and rs2397084 genotype polymorphisms and risk of oral cancer was evaluated by multivariate logistic regression analysis.

Results: Statistical analysis showed significant differences in IL-17 rs2275913 GG, AG and AA genotypes (χ^2=7.70, P=0.02). We observed that female (OR=0.58, 95% CI=0.38-0.87) and individuals living in urban areas (OR=0.46, 95% CI=0.31-0.68) were related with lower risk of oral cancer, while ever tobacco smoking (OR=2.80, 95% CI=1.88-4.17) and alcohol drinking (OR=3.69, 95% CI=2.43-5.60) were associated with higher risk of this cancer. Individuals carrying the AA genotype of rs2275913 was associated with risk of oral cancer (OR=2.58, 95% CI=1.33-4.99), when compared with the GG genotype. IL-17 rs2275913 AG+AA genotype had a significant interaction with males in the risk of oral cancer (OR=1.68, 95%CI=1.06-2.65). However, we did not observe significant association between rs8193036, rs763780 and rs2397084 polymorphisms and risk of oral cancer.

Conclusion: This study suggests that the IL-17 rs2275913 plays an important role in the onset of oral cancer.

Keywords: IL-17A, IL-17F, Polymorphism, Oral cancer.

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Introduction

Oral cancer originates from the epithelial cells of the oral cavity, which is widely known as one of the most frequently developed malignant tumors among head and neck carcinomas [1]. Pathologically, over 90% of all patients suffering from oral cancer are diagnosed as Oral Squamous Cell Carcinoma (OSCC) with well or moderately differentiation [2]. In spite of advanced therapy, the 5 y survival rate of OSCC remains unsatisfactory and even lower than 50% when diagnosed during the middle or late stage of the disease [3]. The etiology of oral cancer remains unclear and is involved in various environmental and lifestyle factors, such as tobacco smoking, intake of milk and vegetables, alcohol consumption, pathogeic infections and nutrition deficiency [4]. However, not all individuals would develop oral cancer even when exposed to the similar environmental or lifestyle factors, suggesting that potential molecular factors may contribute to the pathogenesis of oral cancer. Previous molecular epidemiologic studies have been reported that many genetic factors contribute to the development of oral cancer in many population, such as TNF-α, TP53 codon 72, BRCA1, interleukin-10, CCL4 and lncRNA H19 [5-10]. Currently, many studies indicated an association of inflammation, angiogenesis and thrombosis with the pathogenesis of oral cancer [11].

Chronic inflammation is a well-known risk factor for malignant transformation, but its role in cancer initiation is not clearly understood [12,13]. The interleukin-17 (IL-17) is a novel family of cytokines, and it was originally cloned from the cDNA sequence of a hybrid rodent T cell in 1993 and named CTLA-8 [14]. Six family members were reported in IL-17A, namely IL-17A to IL-17F. It is well known that IL-17 family members contribute to inflammatory diseases, autoimmune diseases, and cancers [15]. *IL-17F* obtains great attention due to its great similarity to *IL-17A*, and the fact that both genes induce the expression of various cytokines,

chemokines and adhesion molecules, suggesting potential overlapping functions for IL-17A/F [16]. Currently studies have reported the association between over expression of IL-17 and multi-type tumors [17]. Single Nucleotide Polymorphisms (SNPs) of IL-17 can contribute to alter the function and expression of proteins, and then influence the risk of developing diseases. However, only one previous study reported the association between IL-17 rs2275913, rs763780 and rs2397084 and risk of oral cancer in a Chinese population. Therefore, we firstly performed a study in a population in Northern China, and investigated the association of *IL-17* gene (rs8193036 and rs2275913 in IL-17A; rs763780 and rs2397084 in IL-17F) with the risk of oral cancer and their interaction with environmental factors.

Material and Methods

Subjects

A total of 182 patients with oral cancer were consecutively recruited from the Urumqi Stomatological Hospital and the First Hospital of Xinjiang Medical University between May 2013-2016. All the patients were pathologically diagnosed from oral cancer within one month. Patients who had a previous history of cancer, malnutrition's and serious kidney and liver diseases were excluded from this study. During the same time period, a total of 364 healthy controls were selected from the outpatient clinics of the Urumqi Stomatological Hospital and the First Hospital of Xinjiang Medical University, and controls were free of oral cancer and other malignant tumors. Controls were matched with patients with oral cancer by age ± 5 y. The mean ages of patients with oral cancer and controls were 56.50 ± 8.40 and 55.67 ± 9.15 y, respectively.

The lifestyle characteristics of investigated subjects were collected from self-designed questionnaires, and the demographic variables were obtained from medical records. The collected information included age, sex, occupation, education level, habitat, family history of cancer, BMI, tobacco smoking, alcohol drinking, tea drinking, intake of vegetable and fruit.

Subjects were divided into never smokers and ever smokers; smokers were defined as those who smoked at least one cigarette per day for more than half a year. Individuals were categorized as never drinkers and ever drinkers; drinkers were defined as those who drank at least 50 mL white wine or a bottle of beer at least once a week for six consecutive months. Intake of vegetable and fruit were divided into few (vegetable<300 g; fruit<200 g), moderate (vegetable: 300-500 g; fruit: 200-400 g) and heavy (vegetable>500 g; fruit>400 g) intake. The body mass index was estimated by weight in kilograms divided by the square of height in meters.

A written informed consent was obtained from each subject after agreement of enrolment, and the proposal of this study was obtained by the ethics committee of the Urumqi Stomatological Hospital and the First Hospital of Xinjiang Medical University.

DNA extraction and genotyping methods

3-5 ml venous whole blood sample was obtained and stored in tubes with ethylene diaminetetraacetic acid. Tubes and plates with reagents are lightly vortexed and centrifuged prior to utilization. All the reagents are stored at -20°C when not in use. Genomic DNA was extracted with the TIANamp blood DNA kit (Tiangen Biotech, Beijing, China), and the DNA samples are preloaded and dried out in the left half of a 384-well plate format on the Sequenom MassARRAY Analyzer (Sequenom, San Diego, USA). PCR reactions in 5 μl are performed, containing 2.8 μl of HPLC grade water, 0.5 μl of 10 × PCR buffer with 20 mM $MgCl_2$, 0.4 μl of 25 mM $MgCl_2$, 0.1 μl of 25 mM dNTP Mix, 1.0 μl of 0.5 μM Primer Mix, and 0.2 μl of Sequenom PCR enzyme (5 U/μl). The cycle of the PCR reaction was performed with the following program: 95°C for 2 min, 45 cycles of 95°C for 30 sec, 56°C for 30 sec and 72°C for 60 sec, and a final extension of 72°C for 5 min. Then the SAP reaction and iPLEX extend reactions were performed. Finally, the spectroCHIP was run on a MassARRAY Typler workstation MA4 or Compact, with settings for iPLEXGold for both FlexControl and SpectroAcquire.

Statistical analysis

Comparisons of the distributions of the genotype frequencies, demographical and lifestyle variables between patients with oral cancer and controls were compared by Chi-square (χ^2) test. Whether the genotype distributions of IL-17 rs8193036, rs2275913, rs763780 and rs2397084 were in line with the Hardy-Weinberg Equilibrium (HWE) was evaluated by Chi-square test with one degree of freedom. Association between IL-17 rs8193036, rs2275913, rs763780 and rs2397084 genotype polymorphisms and risk of oral cancer was evaluated by conditional multivariate logistic regression analysis, and the results were expressed by Odds Ratio (OR) and 95% Confident Intervals (95% CI). Gene-environmental interaction was performed by univariate logistic regression analysis. The statistical significance was defined as P<0.05. SPSS Statistics for Windows, version 20.0 (IBM Corp, Armonk, NY, USA) was used to perform the statistical analysis.

Results

Comparisons of the distributions of the demographical and lifestyle variables showed a significant differences between the two study groups in terms of gender (χ^2=6.31, P=0.01), habitat (χ^2=19.45, P<0.001), family history of cancer (χ^2=4.30, P<0.001), tobacco smoking (χ^2=30.03, P<0.001) and alcohol drinking (χ^2=46.13, P<0.001) (Table 1).

Table 1. *Demographic and lifestyle variables between patients with oral cancer and controls.*

Variables	Patients N=182	%	Controls N=364	%	χ^2 value	P value
Age (y)						

<60	117	64.29	238	65.38	0.06	0.8
≥ 60	65	35.71	126	34.62		
Gender						
Male	119	65.38	197	54.12	6.31	0.01
Female	63	34.62	167	45.88		
Occupation						
Brain work	96	52.75	180	49.45	0.78	0.68
Physical work	62	34.07	138	37.91		
Other	24	13.19	46	12.64		
Education level						
Primary school or below	62	34.07	102	28.02	2.22	0.33
Secondary or high school	65	35.71	137	37.64		
Junior college or above	55	30.22	125	34.34		
Habitat						
Rural	101	55.49	130	35.71	19.45	<0.001
Urban	81	44.51	234	64.29		
Family history of cancer						
No	138	75.82	303	83.24	4.3	0.04
Yes	44	24.18	61	16.76		
BMI, kg/m^2						
<24	126	69.23	225	61.81	2.91	0.09
≥ 24	56	30.77	139	38.19		
Tobacco smoking						
Never	71	39.01	232	63.74	30.03	<0.001
Ever	111	60.99	132	36.26		
Alcohol drinking						
Never	97	53.3	295	81.04	46.13	<0.001
Ever	85	46.7	69	18.96		
Tea drinking						
Never	110	60.44	207	56.87	0.64	0.43
Ever	72	39.56	157	43.13		
Intake of vegetable						
Few	68	37.36	114	31.32	2.69	0.26
Moderate	83	45.6	171	46.98		
Heavy	31	17.03	79	21.7		
Intake of fruit						
Few	94	51.65	149	40.93	5.64	0.06
Moderate	60	32.97	147	40.38		
Heavy	28	15.38	68	18.68		

We further analyzed the genotype distributions of the IL-17 rs8193036, rs2275913, rs763780 and rs2397084 between the two study groups (Table 2). Statistical analysis showed significant differences in rs2275913 GG, AG and AA genotypes (χ^2=7.70, P=0.02), while no significant differences were found in the genotype distributions of rs8193036 (χ^2=2.09, P=0.35), rs763780 (χ^2=3.61, P=0.17) and rs2397084 (χ^2=5.25, P=0.07). All the genotype frequencies of rs8193036, rs2275913, rs763780 and rs2397084 were in line with the Hardy-Weinberg Equilibrium in both patients with oral cancer and controls (P<0.05).

Table 2. *Genotype frequencies of IL-17 genetic polymorphisms between the two study groups.*

Genes	**Patients N=182**	**%**	**Controls N=364**	**%**	**χ^2 value**	**P value**	**χ^2 for HWE in controls**	**P value**
rs8193036								
CC	101	55.49	179	49.18	2.09	0.35	3.28	0.19
CT	64	35.16	150	41.21				
TT	17	9.34	35	9.62				
rs2275913								
GG	83	45.6	197	54.12	7.7	0.02	0.1	0.76
AG	73	40.11	140	38.46				
AA	26	14.29	27	7.42				
rs763780								
TT	71	39.01	135	37.09	3.61	0.17	0.82	0.37
CT	77	42.31	180	49.45				

CC	34	18.68	49	13.46				
rs2397084								
GG	62	34.07	159	43.68				
GT	94	51.65	153	42.03	5.25	0.07	2.32	0.13
TT	26	14.29	52	14.29				

Table 3. *Association of environmental factors and IL-17 genetic polymorphisms with risk of oral cancer.*

Variables	β	S.E	OR (95% CI)	P value
Gender				
Male			1.0 (Reference)	0.008
Female	-0.55	0.21	0.58 (0.38-0.87)	
Habitat				
Rural			1.0 (Reference)	<0.001
Urban	-0.79	0.2	0.46 (0.31-0.68)	
Tobacco smoking				
Never			1.0 (Reference)	<0.001
Ever	1.03	0.2	2.80 (1.88-4.17)	
Alcohol drinking				
Never			1.0 (Reference)	<0.001
Ever	1.3	0.21	3.69 (2.43-5.60)	
rs8193036				
CC			1.0 (Reference)	
CT	-0.268	0.198	0.76 (0.52-1.13)	0.18
TT	-0.125	0.329	0.88 (0.46-1.68)	0.7
rs2275913				
GG			1.0 (Reference)	
AG	0.06	0.22	1.06 (0.70-1.62)	0.78
AA	0.95	0.34	2.58 (1.33-4.99)	0.005
rs763780				
TT			1.0 (Reference)	
CT	-0.245	0.204	0.78 (0.52-1.17)	0.23
CC	0.253	0.272	1.29 (0.76-2.20)	0.35
rs2397084				
GG			1.0 (Reference)	
GT	0.42	0.243	1.48 (0.97-2.40)	0.07
TT	0.294	0.287	1.34 (0.76-2.35)	0.31

Multivariate logistic regression analyses revealed that female (OR=0.58, 95% CI=0.38-0.87) and individuals living in urban areas (OR=0.46, 95% CI=0.31-0.68) were related with lower risk of oral cancer, while ever tobacco smoking (OR=2.80, 95% CI=1.88-4.17) and alcohol drinking (OR=3.69, 95% CI=2.43-5.60) were associated with higher risk of this cancer. Moreover, individuals carrying the AA genotype of rs2275913 was associated with risk of oral cancer (OR=2.58, 95% CI=1.33-4.99), when compared with the GG genotype (Table 3). However, we did not observe significant association between rs8193036, rs763780 and rs2397084 polymorphisms and risk of oral cancer.

Interaction analyses indicated that IL-17 rs2275913 AG+AA genotype had a significant interaction with males in the risk of oral cancer (OR=1.68, 95% CI=1.06-2.65), but no association with habitat, tobacco smoking and alcohol drinking (Table 4).

Table 4. *Interaction between IL-17 rs2275913 and environmental factors in the risk of oral cancer.*

Variables	Patients				Controls				AG+GG *vs.* AA	
	AA	%	AG+GG	%	AA	%	AG+GG	%	OR (95% CI)	P value
Gender										
Male	108	54.82	89	53.29	50	60.24	69	69.7	1.68 (1.06-2.65)	0.03
Female	89	45.18	78	46.71	33	39.76	30	30.3	1.04 (0.58-1.85)	0.9
Habitat										
Rural	70	35.53	60	35.93	43	51.81	58	58.59	1.57 (0.93-2.66)	0.09
Urban	127	64.47	107	64.07	40	48.19	41	41.41	1.22 (0.73-2.02)	0.45
Tobacco smoking										

Never	123	62.44	109	65.27	31	37.35	40	40.4	1.46 (0.85-2.49)	0.17
Ever	74	37.56	58	34.73	52	62.65	59	59.6	1.45 (0.87-2.40)	0.15
Alcohol drinking										
Never	161	81.73	134	80.24	50	60.24	47	47.47	1.13 (0.71-1.79)	0.6
Ever	36	18.27	33	19.76	33	39.76	52	52.53	1.72 (0.90-3.27)	0.1

Discussion

The inflammatory state is a necessary step to promote cancer progression and accomplish the full malignant phenotype, including tumor tissue rebuilding, angiogenesis and metastasis as well as anticancer immune response [18,19]. IL-17 is a relatively novel cytokine family, and it plays an important role in connect the innate and adaptive immunity. Previous molecular studies have indicated that *IL-17* gene is a critical proinflammatory cytokine to promote many cytokines and chemokines secreted by various cell types, such as evoking mesenchymal cells and myeloid cells to induce monocytes and neutrophils into the microenvironment of inflammation [20]. Genetic and epigenetic mutation of IL-17 would trigger cell transformation and maintains the autonomous proliferation of the transformed cells to cancer proliferation [21].

Previous studies reported that IL-17 expression can promote angiogenesis in several tumors. Serum concentration of IL-17F level was remarkably down regulated from healthy individuals to oral squamous cell carcinoma, and IL-17F can originate from the peripheral blood mononuclear cells during the development of oral cancer [22]. Another study with 67 head and neck squamous cell carcinoma and 21 healthy subjects indicated that the cell proportions and IL-17 concentrations were consistent with the tumor TNM stage of head and neck squamous cell carcinoma [23]. Lee et al. performed an *in vitro* study, and reported that IL-17 is associated with tumor-infiltrating lymphocytes from advanced stages of oral cancer [24]. Therefore, IL-17 expression and concentration is associated with risk of oral cancer.

Single nucleotide polymorphism, is known to be essential in regulating and modifying protein expression, and can contribute to individual disease susceptibility. Previous studies have reported that IL-17 polymorphisms were associated with several kinds of cancers, such as laryngeal cancer, gastric cancer, cervical cancer and lung cancer. Si et al. conducted a study with 325 patients and 325 controls, and revealed that IL-17 rs2275913 AA and GA+AA genotypes were associated with risk of laryngeal cancer compared to the GG genotype [25]. Zhao et al. revealed that rs2275913 GG genotype increased the susceptibility to gastric cancer compared to the AA genotype [26]. Wang et al. reported a study in a Chinese population of 462 gastric cancer subjects and 462 controls, and suggested that rs2275913 variation significantly increased gastric cancer risk in a Chinese population [27]. However, some studies reported inconsistent results. Yang et al. conducted a study in a Chinese population, and did not report a significant association between IL-17 rs2275913 and risk of gastric cancer, but a significant correlation between IL-17 rs3748067 and rs763780 polymorphisms and gastric cancer risk [28].

Currently, only one previous study reported the association IL-17 rs2275913, rs763780, and rs2397084 polymorphisms and risk of oral squamous cell carcinoma in a Chinese population [29]. Li et al. done a study with 121 oral squamous cell carcinoma patients and 103 healthy controls, and they found a significant association of rs2275913 and rs2397084 with oral squamous cell carcinoma risk, and was related to tumor stage and differentiation [29]. In our study, we reported that only rs2275913 was related to the risk of oral cancer, and this genetic polymorphism had interaction with gender. Discrepancies in these studies could be attributed to differences in population subtypes, sample sizes, study design and random by chance.

One limitation should be taken into consideration. Only 182 patients with oral cancer and 364 healthy controls were included into this study. The relatively small sample size would cause low statistical power to find difference between groups. Further studies with larger sample size among different population are warranted to confirm our findings.

Conclusion

In conclusion, this study suggests that the IL-17 rs2275913 plays an important role in the onset of oral cancer. However, no significant association was observed between IL-17 rs8193036, rs763780 and rs2397084 polymorphisms and disease development. The IL-17 rs2275913 could be considered a biomarker for early detection of oral cancer in this Chinese population.

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Conflicts of Interest

The authors declare no conflict of interest in preparing this article.

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