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Original Article

Association of interleukin-10 polymorphisms and haplotypes with the risk of breast cancer in northern China

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Abstract: Many environmental and genetic factors are involved in the development of breast cancer. IL-10 is an immunoregulatory cytokine produced by Th2 cells, regulatory T cells, and monocytes/macrophages. We carried out a case-control study to assess the relationship of three SNPs (rs1800872, rs1800871 and rs1800896) in the promoter regions of IL-10 with the risk of breast cancer. A hospital based case-control study was implemented, including 312 patients with breast cancer and 312 control subjects. The genotyping of IL-10 rs1800872, rs1800871 and rs1800896 was implemented in a 384-well plate format on the sequenom MassARRAY platform. We observed that the homozygous AA genotype of rs1800896 was significantly associated with risk of breast cancer, when compared to the homozygous GG genotype, with an adjusted OR (and 95% CI) of 1.98 (1.12-3.49). The haplotype analysis showed linkage disequilibrium between rs1800872 and rs1800896 (D'=0.62, r^2=0.10). The C-T-G (OR=0.76, 95% CI=0.59-0.98) haplotype revealed a reduced risk of breast cancer, while the A-T-A (OR=1.78, 95% CI=1.16-2.74) indicated an elevated risk of breast cancer in the Chinese population. In conclusion, the present study indicates that IL-10 rs1800896 polymorphism and A-T-A and C-T-G haplotypes could affect the risk of breast cancer.

Keywords: IL-10, rs1800872, rs1800871, rs1800896, polymorphism, haplotype, breast cancer

Introduction

In female, breast is particularly prominent as the hallmark of pubertal development. Breast cancer begins in any part of breast, caused by abnormal cells growth and division. It is one of the oldest known forms of malignancies. Unfortunately globally, it remains a major public health issue in China as well as world. Breast cancer is the leading cause of death of women in worldwide due to spreading to other organ [1, 2]. Many environmental and genetic factors are involved in the development of breast cancer, including history of benign breast diseases, family history of cancer, lack of exercises, obesity, hormone uses and reproductive history [3-6]. However, the incidence of breast cancer varies greatly across different populations even when they are exposure to the same environmental risk factors, suggesting that hereditary factors could affect the development of breast cancer. Development of human breast cancers is a multistep process, arising from genetic alterations that drive the transformation of normal mammary epithelial cells into highly malignant derivatives.

IL-10, encoded by a gene located on chromosome 1 (1q31-1q32), is an immunoregulatory cytokine produced by Th2 cells, regulatory T cells, and monocytes/macrophages. IL-10 can inhibit the synthesis of other cytokines, such as IL-6, IL-1β and IL-1α as well as and tumor necrosis factor-α in activated macrophages [7]. Previous experimental studies have indicated that IL-10 are over expressed in breast cancer [8, 9]. Studies have revealed that high expression of IL-10 in breast tumor cells and stromal cell could be used as a predictor for the prognosis of breast cancer [10]. The single nucleotide polymorphisms influence the transcriptional activity, and induce the alterations in gene expression and consequently affect the IL-10 production [11, 12]. Currently, previous studies

Table 1. Demographic and lifestyle characteristics between patients with breast cancer and controls

Variables	Patients N=312	%	Controls N=312	%	χ^2-test or *t*-test	*P* value
Age, year		52.77±11.23		52.28±10.34	0.58	0.26
Physical activity						
Often	129	41.35	162	51.92		
Seldom	112	35.90	105	33.65		
Never	71	22.76	45	14.42	9.80	0.007
Menopausal status						
Premenopausal	210	67.31	196	62.82		
Postmenopausal	102	32.69	116	37.18	1.38	0.24
Smoking						
No	300	96.15	281	90.06		
Yes	12	3.85	31	9.94	9.02	0.003
Drinking						
No	273	87.50	240	76.92		
Yes	39	12.50	72	23.08	11.93	0.001
Body mass index (BMI), kg/m^2		22.24±3.14		22.77±3.12	-2.10	0.58
Age at first live birth, year		25.26±3.19		25.66±3.32	-1.53	0.31
Breastfeeding						
No	66	21.15	61	19.55		
Yes	246	78.85	251	80.45	0.25	0.62
Number of births						
0	18	5.77	19	6.09		
1	138	44.23	146	46.79		
≥2	156	50.00	147	47.12	0.52	0.77
Benign breast disease						
No	261	83.65	189	60.58		
Yes	51	16.35	123	39.42	41.31	<0.001

have indicated that IL-10 polymorphisms contribute to the pathogenesis of breast cancer in many populations, but the results are inconsistent [13-15]. However, no study reports the role of IL-10 polymorphisms and haplotypes in the pathogenesis of breast cancer in Northern Chinese population. Therefore, we carried out a case-control study to assess the relationship of three SNPs (rs1800872, rs1800871 and rs1800896) in the promoter regions of IL-10 with the risk of breast cancer, and interaction between IL-10 and environmental factors.

Subjects and methods

Subjects

A hospital based case-control study was implemented, including 312 patients with breast cancer and 312 control subjects. Patients with breast cancer were recruited from the thyroid and breast surgery department of the Affiliated Hospital of Inner Mongolia Medical University between May 2014 and May 2016. The diagnosis of breast cancer wasdetermined by histopathology examination. The exclusion criteria for breast cancer patients were those with a history of recurrent and metastatic breast cancer, and serious liver or renal diseases.

Simultaneously, all the control subjects were enrolled from the outpatient clinics and physical examination center of the Affiliated Hospital of Inner Mongolia Medical University. Each control was recruited in this study by matching the age (±5 years), when enrolling one breast cancer patient. All controls were confirmed without a history of tumor, endocrine disease and breast related diseases. All of the study subjects voluntary participated in our study and signed informed consent forms before enrollment. The study was approved by the Research

Table 2. Association between IL-10 rs1800872, rs1800871 and rs1800896 polymorphisms and risk of breast cancer

IL-10	Patients	%	Controls	%	χ^2	P	Patients		Controls		Crude OR (95% CI)	*P* value	Adjusted OR (95% CI)[1]	*P* value
							χ^2 for HWE	P for HWE	χ^2 for HWE	P for HWE				
rs1800872														
AA	131	41.99	141	45.19							1.0 (Ref.)	-	1.0 (Ref.)	-
AC	130	41.67	127	40.71							1.10 (0.77-1.57)	0.58	1.08 (0.75-1.56)	0.67
CC	51	16.35	44	14.10	0.92	0.63	3.64	0.06	3.05	0.08	1.25 (0.76-2.05)	0.35	1.20 (0.73-1.99)	0.47
rs1800871														
TT	124	39.74	144	46.15							1.0 (Ref.)	-	1.0 (Ref.)	-
TC	141	45.19	128	41.03							1.28 (0.90-1.82)	0.15	1.24 (0.86-1.78)	0.26
CC	47	15.06	40	12.82	2.68	0.26	0.44	0.51	1.85	0.17	1.36 (0.82-2.29)	0.21	1.24 (0.73-2.10)	0.43
rs1800896														
GG	129	41.35	131	41.99							1.0 (Ref.)	-	1.0 (Ref.)	-
AG	132	42.31	154	49.36							0.87 (0.61-1.24)	0.42	0.83 (0.58-1.19)	0.31
AA	51	16.35	27	8.65	9.09	0.01	2.96	0.09	3.82	0.06	1.92 (1.10-3.38)	0.01	1.98 (1.12-3.49)	0.02

Table 3. Interaction between rs1800896 polymorphism and environmental factors in the risk of breast cancer

Variables	rs1800896						χ^2 value	*P* value
	GG	%	AG	%	AA	%		
Age								
<50	101	38.85	108	37.76	34	43.59		
≥50	159	61.15	178	62.24	44	56.41	0.88	0.65
Physical activity								
Often	130	50.00	125	43.71	36	46.15		
Seldom	88	33.85	103	36.01	26	33.33		
Never	42	16.15	58	20.28	16	20.51	2.82	0.59
Smoking								
No	245	94.23	264	92.31	72	92.31		
Yes	15	5.77	22	7.69	6	7.69	0.87	0.65
Drinking								
No	217	83.46	234	81.82	62	79.49		
Yes	43	16.54	52	18.18	16	20.51	0.70	0.70
Benign breast disease								
No	185	71.15	210	73.43	55	70.51		
Yes	75	28.85	76	26.57	23	29.49	0.46	0.79

Ethics Committee of the Affiliated Hospital of Inner Mongolia Medical University. The implementation was carried out according to the Helsinki Declaration of 1964.

DNA extraction and genotyping

Each participant was asked to provide 3-5 ml peripheral venous blood sample after enrollment. The blood samples were stored in tube with 0.5 M ethylenediaminetetraacetic acid, and were kept in a refrigerator at 4°C until use. Genomic DNA was extracted from the whole blood using a TIANamp Blood DNA Kit (Tiangen, Beijing, China) according to the instrument, and the DNA samples were kept in -20°C until utilization. Primers of IL-10 rs1800872, rs1800871 and rs1800896 for polymerase chain reaction (PCR) amplification and single base extension assays were designed by Sequenom Assay Design 3.1 software. The genotyping of IL-10 rs1800872, rs1800871 and rs1800896 was implemented in a 384-well plate format on the sequenom MassARRAY platform (Sequenom, San Diego, USA). The PCR cocktail preparation for genotyping IL-10 rs1800872, rs1800871 and rs1800896 was prepared by Sequenom PCR Reagent Set. The PCR reaction was performed in 5 μL mixture with 2.8 μl of HPLC grade water, 0.5 μl 10× PCR buffer with 20 mM $MgCl_2$, 0.4 μl 25 mM $MgCl_2$, 0.1 μl 25 mM dNTP Mix, 1.0 μl 0.5 uM Primer Mix, 0.2 μl 5 U/μl PCR enzyme and already loaded 10 ng/uL DNA. Then the SAP and iPLEX reactions were performed. The samples were then desalted, and the reaction was dispensed to a SpectroCHIP and analyzed with Matrix-Assisted Laser Desorption/Ionization Time of Flight Mass Spectrometry (MALDI-TOF MS).

Statistical analysis

Descriptive statistics were used to summarize characteristics of the study participants by expressing the results as mean ± standard deviation (SD) or frequencies and percentage (%). Whether the genotype frequencies of IL-10 rs1800872, rs1800871 and rs1800896 were departure from Hardy-Weinberg equilibrium (HWE) was assessed using the maximum likelihood estimate and the least Pearson χ^2 test. The association of IL-10 rs1800872, rs1800871 and rs1800896 with breast cancer risk was analyzed by binary multivariate logistic regression analysis, and odds ratios (ORs) and 95% confidence intervals (CIs) were used to display their association. The linkage disequilibrium and haplotype analysis was performed using SHEsis software (http://analysis.bio-x.cn/myAnalysis.php). All data management and sta-

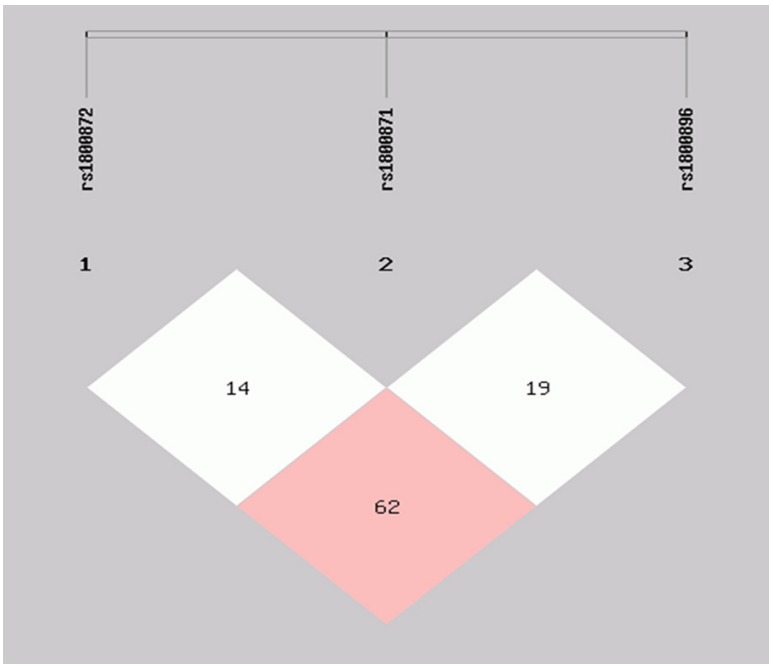

Figure 1. The D' for the linkage disequilibrium of IL-4 rs2243250-rs2227284-rs2070874.

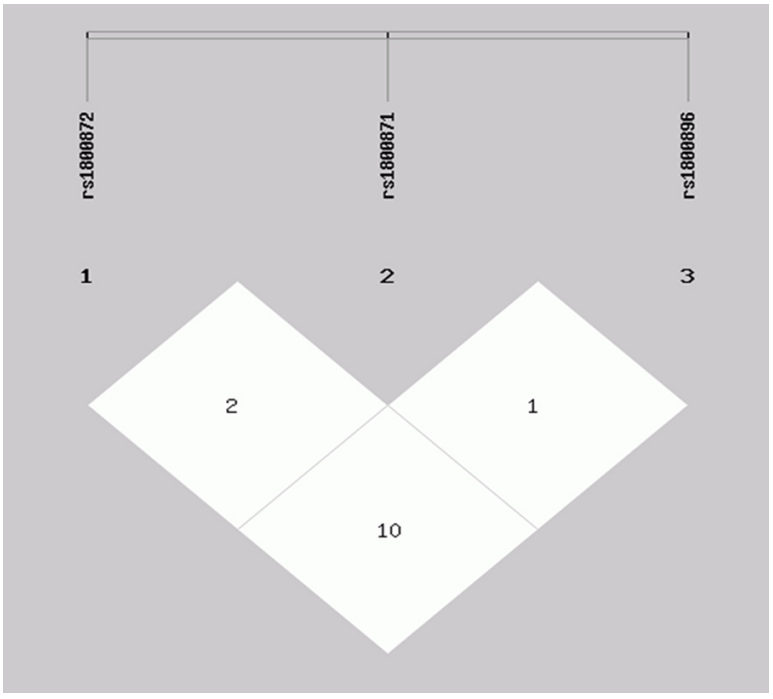

Figure 2. The r^2 for the linkage disequilibrium of IL-4 rs2243250-rs2227284-rs2070874.

tistical analyses were performed with SPSS 21.0 (SPSS, Inc., Chicago, IL, USA), and P<0.05 was considered to indicate a statistically significant difference.

Results

The mean ages of patients with breast cancer and controls were 52.77±11.23 and 52.28±10.34, respectively (**Table 1**). In comparison to controls, patients with breast cancer had a habit of smoking (χ^2=9.02, P=0.003) and drinking (χ^2=11.93, P=0.001) and a history of benign breast disease (χ^2=41.31, P<0.001) were more likely to have more physical activity (χ^2=9.80, P=0.007).

The genotype frequencies of IL-10 rs1800872, rs1800871 and rs1800896 were displayed in **Table 2**. By Chi-square test, we observed that the AA, AG and GG genotype distributions of rs1800896 were significantly differences between patients with breast cancer and controls (χ^2=9.09, P=0.01), but no significant difference was observed in the genotype frequencies of IL-10 rs1800872 and rs1800871. The maximum likelihood estimate and the least Pearson χ^2 test indicated that the genotype frequencies of the three SNPs conformed to HWE in both patients and controls. By binary multivariate logistic regression analysis, we observed that the homozygous AA genotype of rs1800896 was significantly associated with risk of breast cancer, when compared to the homozygous GG genotype, with an adjusted OR (and 95% CI) of 1.98 (1.12-3.49) (P=0.02).

No significant interaction was found between rs1800896 polymorphism and environmental factors in the risk of breast cancer (**Table 3**). The haplotype analysis showed a linkage disequilibrium between rs1800872 and rs1800896 (D'=0.62, r^2=0.10; **Figures 1**, **2**;

Table 4. Linkage disequilibrium test for IL-10 rs1800872, rs1800871 and rs1800896

	D'		r^2	
	rs1800871	rs1800896	rs1800871	rs1800896
s1800872	0.15	0.62	0.02	0.10
rs1800871	-	0.19		0.01

Table 5. Haplotype analysis of the association between IL-10 rs1800872-rs1800871-rs1800896 and breast cancer risk

Haplotype	Patients	%	Controls	%	OR (95% CI)	*P* value
A-C-A	103	33.01	79	25.32	1.37 (0.99~1.88)	0.06
A-C-G	47	15.06	37	11.86	1.28 (0.82~2.00)	0.27
C-T-G	156	50.00	190	60.90	0.76 (0.59~0.98)	0.03
A-T-G	87	27.88	104	33.33	0.81 (0.59~1.10)	0.18
C-C-A	45	14.42	60	19.23	0.72 (0.48~1.08)	0.12
C-C-G	41	13.14	32	10.26	1.28 (0.80~2.07)	0.30
C-T-A	86	27.56	87	27.88	0.99 (0.72~1.36)	0.94
A-T-A	60	19.23	35	11.22	1.78 (1.16~2.74)	0.01

Global χ^2=18.95, P=0.008.

Table 4). Eight haplotypes (frequency >0.03 in either the patients with breast cancer or controls) were selected, and the C-T-G (OR=0.76, 95% CI=0.59-0.98) haplotype revealed a reduced risk of breast cancer, while the A-T-A (OR=1.78, 95% CI=1.16-2.74) indicated an elevated risk of breast cancer in the Chinese population (**Table 5**).

Discussion

The replacement, deletion, or insertion of a single nucleotide within the genome, otherwise known as single nucleotide polymorphism, is known to be essential in regulating and modifying protein expression, and can contribute to individual disease susceptibility. Our study has been suggested that the homozygous GG genotype of rs1800896 and A-T-A and C-T-G haplotypes affect the risk of breast cancer, and linkage disequilibrium was observed between rs1800872 and rs1800896.

IL-10 has been reported to be an important factor in the pathophysiology of autoimmune and inflammation-related diseases, as the product of this gene can modify both immune function and inflammatory processes. Previous studies have indicated that the expression of IL-10 is different in individuals, and 75% protein expression is determined by genetic polymorphisms [16]. Therefore, The genetic polymorphisms could direct influence the IL-10 expression, and be associated with several kinds of diseases, such as autoimmune diseases, transplant-related diseases, infectious diseases and malignant tumors [17, 18]. However, the role of IL-10 in the pathogenesis of tumor is controversial. IL-10 could contribute to the immuneescape of tumor cells, and promote the development of tumors [19]. On the contrary, The anti-angiogenesis effect of IL-10 could inhibit the growth and metastasis of malignant tumors [20]. In an experimental study, we observed that IL-10 deficient mice are more likely to suffer from colitis and colorectal cancer [21]. Some studies indicated that the G allele of IL-10 rs1800896 could reduce the susceptibility of some solid tumors, such as cervical cancer, lung cancer and prostate cancer [22, 23], the mechanism of IL-10 could be associated with down-regulation of IL-1β, TNF-α and vascular endothelial growth factor. The high expression of IL-10 could increase the development of malignant melanoma, which might be correlated with the anti-tumor angiogenesis of IL-10 [24].

For the association between the IL-10 genetic polymorphisms and risk of breast cancer, the results are inconsistent [13, 15, 23, 25]. Atoum MF performed a study with 202 breast cancer patients and 210 age-matched healthy controls among Jordanian, and it reported that the ACC haplotype was associated with breast cancer risk [26]. However, AlSuhaibani ES et al. performed a study with 80 subjects with breast cancer and 80 controls, and they reported that the IL-10 -1082G/A polymorphism did not influence the risk of breast cancer in Egyptian [25]. Wang et al. performed a study in a Chinese population with 474 breast cancer patients and 501 female controls without cancer, and they revealed that the TT genotype of IL-10 rs1800871 was associated with risk of breast cancer [15]. Langsenlehner U et al. per-

formed a study among Austrian, and they indicated that IL-10 -592C>A promoter polymorphism may be correlated with a reduced risk of breast cancer [13]. In our study, we found the AA genotype of IL-10 rs1800896 was correlated with an increased risk of breast cancer. The AA genotype could decrease the IL-10 expression, and weaken the function of anti-tumor angiogenesis and promote the development of tumor.

Our study found the A-T-A haplotype was associated with a higher risk of breast cancer, and the main reason was that the A-T-A was correlated with weak transcriptional activity and low expression of IL-10 [16, 27]. However, Atoum MF reported that the ACC haplotype was associated with breast cancer risk among Jordanian females [26]. Further studies are greatly needed to confirm our findings.

Two limitations should be considered in our study. First, all the participants were enrolled within one hospital, which may induce selection bias into this study. Second, this was a cross-sectional study, meaning it had low power to detect causal effects. Therefore, prospective studies are needed to confirm our findings.

In summary, the present study indicates that the IL-10 rs1800896 polymorphism and the A-T-A and C-T-G haplotypes could affect the development of breast cancer. Further studies employing more number of participants are greatly needed to confirm our findings.

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Disclosure of conflict of interest

None.

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