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Association of *IL-8* genetic polymorphisms and breast cancer risk in a Chinese population.

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Abstract

Breast cancer is the most common cancer among women worldwide. The development of breast cancer is a multistep process. *IL-8* belongs to the superfamily of CXC chemokines, and it could promote the growth of tumors by elevating angiogenesis. We aimed to investigate the association risk of *IL-8* -251T/A (rs4073), +781C/T (rs2227306) and +396T/G (rs2227307) polymorphisms with breast cancer in a Chinese population. A total of 411 breast cancer patients and 411 control subjects were recruited in this study. Genotyping of *IL-8*-251T/A (rs4073), +781C/T (rs2227306) and +396T/G (rs2227307) was carried out in a 384-well plate format on the sequenom MassARRAY platform. Information on demographic, lifestyle and clinical characteristics were collected from medical records and questionnaire interviews. After adjusting for the environmental factors, we observed that the AA genotype of *IL-8* -251T/A (rs4073) was associated with an increased risk of breast cancer in comparison to the TT genotype (OR=2.36, 95% CI=1.29-4.32). No association was observed between *IL-8* +781C/T (rs2227306) and +396T/G (rs2227307) and risk of breast cancer. This study suggests that the *IL-8* polymorphisms contribute to the risk of breast cancer in a Chinese population.

Keywords: *IL-8*, Polymorphism, Breast cancer.

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Introduction

Breast cancer is the most common cancer among women worldwide and is the second remains a major public health issue in China as well as world. Many research studies were dedicated in tumorigenesis, pathology, therapy, prognosis of breast cancer. The development of breast cancer is a multistep process, and several environmental and genetic factors contribute to its development [1,2]. Previous studies have reported that several environmental factors and medical history, such as family history of cancer, lack of exercises, obesity, alcohol drinking, early menarche, late menopause, age at the birth of first child, number of months of breastfeeding and hormone uses and reproductive history, are involved in the breast cancer etiology [3-6]. However, the incidence of breast cancer varies tremendously across different populations if they exposed to the same lifestyle and dietary factors, which suggests that the hereditary factors are involved in the pathogenesis of breast cancer. Low-grade chronic systemic inflammation has emerged as an important factor in the pathogenesis of chronic diseases, such as diabetes, spontaneous abortion and of certain types of cancer [7-9]. Several experimental and observational study have indicated that inflammation related genes are involved in the development of breast cancer, such as Interleukin (IL)-IL1A [10], IL-6 [11], IL-10 [12], tumor necrosis factor alpha gene-α gene [13] and plasma C-reactive protein [14].

IL-8 (*CXCL8*) gene is located on chromosome 4q 13-3 in humans, and is consisted of four exons, three introns and a proximal promoter region [15]. *IL-8* belongs to the superfamily of CXC chemokines, which attracts neutrophils and macrophages and displays extensive proinflammatory effects [16,17]. Previous *intro* and *vitro* studies reported that the *IL-8* could promote the growth of tumors by elevating angiogenesis, and *IL-8* concentrations was related to the development, progression, metastasis of malignant tumors, including breast cancer [18-21]. Therefore, the *IL-8* gene might be involved in the pathogenesis and progression of tumors. Three common polymorphisms are observed in the promoter region of the *IL-8* gene, including -251T/A (rs4073), +781C/T (rs2227306) and +396T/G (rs2227307). Previous studies have showed that the three SNPs are associated with several tumors [22-27]. Moreover, relationship among *IL-8*-251T/A (rs4073) and +781C/T (rs2227306) and some autoimmune diseases have been observed in previous studies [28-30]. However, few

studies investigated the association of *IL-8*+781C/T (rs2227306) and +396T/G (rs2227307) with the development of breast cancer. The aim of this study is to investigate the association risk of *IL-8*-251T/A (rs4073), +781C/T (rs2227306) and +396T/G (rs2227307) polymorphisms with breast cancer in a Chinese population.

Subjects and Methods

This case-control population is composed of 822 Chinese unrelated adult who were colligated from Department of Thyroid and Breast Surgery, the Affiliated Hospital of Inner Mongolia Medical Collage and Inner Mongolia People's Hospital between December 2013 and January 2016. A total of 411 breast cancer patients were recruited, and they were selected for their breast cancer diagnosis. The patients were newly diagnosed within one week by histopathologic examination, and did not receive any anti-cancer treatment. The patients had a mean age of 57.47 ± 9.69 y.

Simultaneously, one healthy control subject was recruited into our study after enrolling one patient, and a total of 411 healthy controls were collected and were frequency matched to cases by age (within 5 y). All the healthy controls were recruited from physical examination center and outpatient clinics of the Affiliated Hospital of Inner Mongolia Medical Collage and Inner Mongolia People's Hospital.

The mean age of control group was 58.10 ± 8.55 y. Information on demographic, lifestyle and clinical characteristics were collected from medical records and questionnaire interviews for both breast cancer patients and healthy controls. The information included age, Body Mass Index (BMI), physical activity, menopausal status, age of menarche, age at first live birth, nulliparous, breastfeeding, months of breastfeeding, smoking habit, drinking habit, history of hormone uses and family history of cancer in the first-degree relatives.

Body Mass Index (BMI) was calculated as body weight (kg) divided by the square of the body height (m^2). Frequent physical activity was defined as walking or riding a bicycle for more than 30 min per day, doing physical exercise for more than 2 h per week, or carrying heavy objects at work daily. Occasional physical activity was considered as walking or riding a bicycle for less than 30 min daily, doing physical exercise less than 2 h per week, or carrying heavy objects at work 1-2 times per week. Smokers were defined as those smoking more than one cigarette per day for at least half a year.

All data and blood sample collected for this study was approved by the Research Ethics Committee of the Affiliated Hospital of Inner Mongolia Medical Collage and Inner Mongolia People's Hospital. All study subjects agreed to participate into our study with informed consents.

Genotyping of IL-8 gene polymorphisms

Five ml peripheral blood was obtained from each patient and control subject for DNA extraction, and the samples were kept in tubes with 0.5 M EDTA at -20°C until use. DNA extraction was extracted by TIANGEN blood DNA kit according to the standard procedures (Tiangen, Beijing, China). Genotyping was carried out in a 384-well plate format on the sequenom MassARRAY platform (Sequenom, San Diego, USA). Primers of the three SNPs for Polymerase Chain Reaction (PCR) were designed by Sequenom Assay Design 3.1 software. The PCR reactions were performed in 5 µl, including 1.8 µl $dddH_2O$, 0.5 µl 10X buffer, 0.4 µl Mg^{2+}, 0.1 µl dNTP, 0.2 µl Hotstar, 1 µl forward primer/reverse primer and 1µl DNA sample (10 ng/µl). The genomic DNA of *IL-8*-251T/A (rs4073), +396T/G (rs2227307) and +781C/T (rs2227306) was amplified using the following PCR conditions: 95 for 2 min; 45 cycles of 95°C for 30 s, 56°C for 30 s, and 72°C for 60 s; a final extension at 72°C for 5 min. Then the SAP and iPLEX reactions were performed. The PCR products are then desalted, and dispensed to a SpectroCHIP and analysed with MALDI-TOF MS.

Statistical analysis

Categorical and continued variables are analysed by Chi-square (χ^2) test or student t-test. Whether the genotype frequencies of *IL-8*-251T/A (rs4073), +781C/T (rs2227306) and +396T/G (rs2227307) were according to the Hardy-Weinberg Equilibrium (HWE) was estimated by Chi-square with one degree of freedom. The association of the three SNPs with the risk of breast cancer was analysed by binary multivariate logistic regression, with the results of Odds Ratio (OR) and 95% Confident Intervals (95% CI). All analyses were conducted by using IBM SPSS Statistics for Windows, Version 21.0. (IBM Corp, Armonk, NY). All statistical analyses were two-sided and P value significance was set at less than 0.05.

Results

Using Chi-square test or student t test, there were significant differences between the patients with breast cancer and controls in terms of BMI (t=6.07, P<0.001), age of menarche (t=-5.49, P<0.001), physical activity (χ^2=29.19, P<0.001), age at first live birth (t=4.25, P<0.001), months of breastfeeding (t=-5.47, P<0.001), history of hormone uses (χ^2=8.93, P=0.003) and time of hormone uses (t=21.72, P<0.001) (Table 1).

A significant difference was observed in the genotype distributions of *IL-8* rs4073 between the two study groups (χ^2=15.50, P<0.001), but no significant differences were found in the +396T/G (rs2227307) and +781C/T (rs2227306). The genotype frequencies of *IL-8*-251T/A (rs4073), +396T/G (rs2227307) and +781C/T (rs2227306) were according to the HWE in both patients with breast cancer and controls (Table 2).

The binary logistic regression analysis indicated that a history of hormone uses (OR=3.14, 95% CI=1.86-5.31), higher BMI (OR=1.15, 95% CI=1.07-1.22), older age at first live birth (OR=1.07, 95% CI=1.01-1.14) and longer time of hormone uses (OR=1.91, 95% CI=1.73-2.10) were the risk factors for the pathogenesis of breast cancer. However, individuals with

more frequent physical activity (OR=0.28, 95% CI=0.18-0.45), later age of menarche (OR=0.85, 95% CI=0.78-0.92) and more months of breastfeeding (OR=0.87, 95% CI=0.81-0.93) had less risk of developing breast cancer.

After adjusting for the environmental factors, we observed that the AA genotype of *IL-8* -251T/A (rs4073) was associated with an increased risk of breast cancer in comparison to the TT genotype (OR=2.36, 95% CI=1.29-4.32) (Table 3). However, the other two SNPs (+781C/T (rs2227306) and +396T/G (rs2227307)) were not associated with the development of breast cancer.

Table 1. Environmental and clinical characteristics of patients with breast cancer and controls.

Variables	Patients	%	Controls	%	χ^2 or t values	P values
	N=411		N=411			
Age, years	57.47 ± 9.69		58.10 ± 8.55		-0.99	0.32
BMI, kg/m^2	23.42 ± 3.07		22.10 ± 3.14		6.07	<0.001
Age of menarche, years	12.48 ± 2.24		13.41 ± 2.60		-5.49	<0.001
Physical activity						
Never	242	58.88	181	44.04		
Occasional	88	21.41	81	19.71		
Frequent	81	19.71	149	36.25	29.19	<0.001
Menopausal status						
Premenopausal	165	40.15	192	46.72		
Postmenopausal	246	59.85	219	53.28	3.61	0.06
Age at first live birth, years	25.73 ± 3.24		24.77 ± 3.24		4.25	<0.001
Nulliparous						
No	390	94.89	396	96.35		
Yes	21	5.11	15	3.65	1.05	0.31
Breastfeeding						
Never	73	17.76	58	14.11		
Ever	338	82.24	353	85.89	2.04	0.15
Months of breastfeeding, months	5.27 ± 2.71		6.34 ± 2.87		-5.47	<0.001
Alcohol drinking						
Never	331	80.54	334	81.27		
Ever	80	19.46	77	18.73	0.07	0.79
Tobacco smoking						
Never	386	93.92	385	93.67		
Ever	25	6.08	26	6.33	0.02	0.89
History of hormone uses						
Never	320	77.86	353	85.89		
Ever	91	22.14	58	14.11	8.93	0.003
Time of hormone uses, months	8.33 ± 3.30		4.38 ± 1.63		21.72	<0.001
Family history of cancer in the first-degree relatives						
No	365	88.81	381	92.7		

Yes	46	11.19	30	7.3	3.71	0.06

Table 2. *Genotype frequencies of IL-8-251T/A (rs4073), +781C/T (rs2227306) and +396T/G (rs2227307) between the two study groups.*

IL-8	CAD patients	Controls	χ^2 value	P value	Patients	P value	Controls	**P value**
					χ^2 for HWE		χ^2 for HWE	
rs4073								
TT	159	207						
AT	179	162						
AA	73	42	15.5	<0.001	3.26	0.07	1.49	0.22
rs2227306								
CC	196	200						
CT	166	177						
TT	49	34	6.38	0.04	2.23	0.14	0.35	0.55
rs2227307								
TT	357	366						
TG	50	43						
GG	4	2	1.31	0.52	2.16	0.14	0.36	0.55

Table 3. *Association of environmental factors and IL-8-251T/A (rs4073), +781C/T (rs2227306) and +396T/G (rs2227307) with the risk of breast cancer.*

Variable	**B**	**S. E**	**Wald**	**P value**	**OR (95% CI)**
Physical activity					
Never			27.3	<0.001	1.0 (Ref.)
Occasional	-0.43	0.26	2.76	0.1	0.65 (0.39-1.08)
Frequent	-1.27	0.24	27.3	<0.001	0.28 (0.18-0.45)
History of hormone uses					
Never					1.0 (Ref.)
Ever	1.14	0.27	18.18	<0.001	3.14 (1.86-5.31)
BMI, kg/m^2	0.14	0.03	16.4	<0.001	1.15 (1.07-1.22)
Age of menarche	-0.17	0.04	16.4	<0.001	0.85 (0.78-0.92)
Months of breastfeeding	-0.14	0.04	15.46	<0.001	0.87 (0.81-0.93)
Age at first live birth, years	0.07	0.03	4.83	0.03	1.07 (1.01-1.14)
Time of hormone uses, months	0.65	0.05	170.06	<0.001	1.91 (1.73-2.10)
-251T/A (rs4073)					
TT			7.79	0.02	1.0 (Ref.)
AT	0.23	0.22	1.14	0.29	1.26 (0.82-1.94)
AA	0.86	0.31	7.78	0.01	2.36 (1.29-4.32)
AT+TT	0.38	0.2	3.46	0.06	1.46 (0.98-2.16)
+781C/T (rs2227306)					
CC			1.63	0.44	1.0 (Ref.)
CT	-0.06	0.21	0.07	0.79	0.95 (0.63-1.43)
TT	0.39	0.35	1.27	0.26	1.48 (0.75-2.93)
CT+TT	0.02	0.2	0.01	0.92	1.02 (0.69-1.50)
+396T/G (rs2227307)					
TT			0.45	0.8	1.0 (Ref.)
TG	0.21	0.31	0.45	0.5	1.23 (0.67-2.25)
GG	<0.001	1.12	<0.001	1	1.00 (0.11-8.88)
TG+GG	0.22	0.3	0.53	0.47	1.24 (0.69-2.23)

Discussion

Inflammation related cytokines involved in altering epithelial tissues in many types of cancer [31-34]. The inflammatory status of the human body can affect the acceleration of tumor progression, the reconstruction of tumor tissue, the promotion

of angiogenesis, and the inhibition of the natural antitumor immune response [35]. In this large population-based case-control study, we observed a statistically significant positive association between *IL-8*-251T/A (rs4073) polymorphism and risk of breast cancer in a Chinese population.

IL-8 is one kind of chemokine, which is produced by leukocytes and several tissues upon inflammatory conditions and neutrophils are regarded to be the main specific targets for *IL-8* action [36]. Various normal cells and tumor cells express *IL-8*. It is reported that this gene plays a critical role in the molecular mechanism of tumor occurrence, invasion and angiogenesis, since it contributes to the modulation of tumor response or enhanced angiogenesis [37-39]. Increasing evidences have showed that abnormal expression of *IL-8* could contribute to many kinds of solid tumors, such as breast cancer, lung cancer, hepatocellular carcinoma and gastric cancer [33,40-42]. *IL-8* genetic variations could change the expression levels and function of *IL-8* and then affect the immune responses [43]. Therefore, the genetic variations of *IL-8* could influence the tumorigenesis process and prognosis.

IL-8 -251T/A (rs4073) polymorphism is located at the promoter region of *IL-8*, and the A allele of this SNP is related to an increased expression level of *IL-8*. Previous studies have investigated the association between *IL-8* rs4073 polymorphism and several kinds of cancers [22-27]. Felipe et al. performed a study on 104 gastric cancer patients and 196 healthy controls, and they reported that AA genotype of *IL-8* rs4073 showed a protective effect for the risk of gastric cancer [22]. A meta-analysis with 1324 oral cancer patients and 1879 healthy controls indicated that the AA and AT genotypes of *IL-8* rs4073 polymorphism were correlated with the risk of oral cancer [24]. Wang et al. indicated that the A allele of *IL-8* rs4073 and rs2227306 conferred a high risk of the development of lung cancer among Asians [26]. However, some studies reported inconsistent results. Chen et al. performed a case-control study on 439 prostate cancer patients and 524 controls, and they did not find a significant association between *IL-8* rs4073 and prostate cancer risk [27]. Burada et al. performed a study with 105 gastric cancer patients and 242 controls, and no association was observed between *IL-8* rs4073 and gastric cancer risk [23].

For the association of *IL-8* polymorphisms with the risk of breast cancer, only several studies reported inconsistent results between them. Snoussi et al. carried out a study in a Tunisian population, and they suggested that the *IL-8* rs4073 A allele conferred an increased risk of developing breast cancer [44]. Kamali-Sarvestani et al. revealed that the *IL-8* rs4073 AA genotype had higher frequency in breast cancer patients than those in controls in a population of Iran [34]. Wang et al. reported that *IL-8* rs4073 TT genotype displayed a reduced risk of breast cancer in a Chinese population [45]. In our study, we found the AA genotype of *IL-8* -251T/A (rs4073) also conferred an increased risk of breast cancer, which is in line with previous findings. However, Smith et al. performed a study with 144 breast cancer patients and 263 controls among the British population, and they did not find the association between *IL-8* rs4073 and the susceptibility to breast cancer [46]. The inconsistencies in the results of these studies could be attributed to the discrepancies in sample selection, ethnic groups and by chance.

Two limitations should be considered in this study. First, selection bias might be occurred during the process of selection of hospital-based control subjects. Second, the limited sample size may have reduced the statistical power of differentiating between patients with breast cancer and controls.

In summary, we suggest that the AA genotype of *IL-8* -251T/A (rs4073) confers an increased risk of breast cancer. Therefore, further studies are warranted to investigate the potential biological mechanism of *IL-8* in the risk of breast cancer.

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