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Original Article

Association of IL-8 -251T/A, +781C/T and +396T/G genetic polymorphisms and haplotypes with breast cancer risk in a Northern Chinese population

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Abstract: Breast cancer is one of the most common cancers among women worldwide. IL-8 belongs to the superfamily of CXC chemokines, and promotes the growth of tumors by elevating angiogenesis. We aimed to investigate the association of IL-8 -251T/A (rs4073), +781C/T (rs2227306) and +396T/G (rs2227307) polymorphisms and haplotypes with breast cancer risk in a Northern Chinese population. A total of 411 breast cancer patients and 411 control subjects were recruited. 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. Demographic, lifestyle and clinical characteristics were collected from medical records and questionnaire interviews. We observed that the AA genotype of IL-8 -251T/A (rs4073) was associated with an increased risk of breast cancer compared 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. The T(251)C(781)T(396) (OR=0.67, 95% CI=0.55-0.83) haplotype was associated with a reduced risk of breast cancer, while the A(251)C(781)T(396) (OR=1.43, 95% CI=1.05-1.94) and A(251)T(781)T(396) (OR=1.50, 95% CI=1.03-2.20) haplotypes were correlated with an elevated risk. This study suggests that the IL-8 -251T/A (rs4073) polymorphism and haplotypes contribute to the risk of breast cancer.

Keywords: IL-8, polymorphism, haplotype, breast cancer

Introduction

Breast cancer is one of the most common cancers among women worldwide and remains a major public health issue in China as well as world. Many research studies have been dedicated to tumorigenesis, pathology, therapy, prognosis of breast cancer. The etiology of breast cancer is complex and unclear, and several environmental and genetic factors are involved in its development [1, 2], 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, hormone uses and reproductive history [3-6]. However, the incidence of breast cancer varies tremendously across different populations even if they are exposed to the similar 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 certain types of cancers [7-9]. Previous experimental and observational studies indicated that inflammation related genes contribute to 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 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 an extensive proinflammatory effects [16, 17]. Previous *in vivo* and *in vitro* studies reported that the IL-8 could promote the growth of tumors by elevating angio-

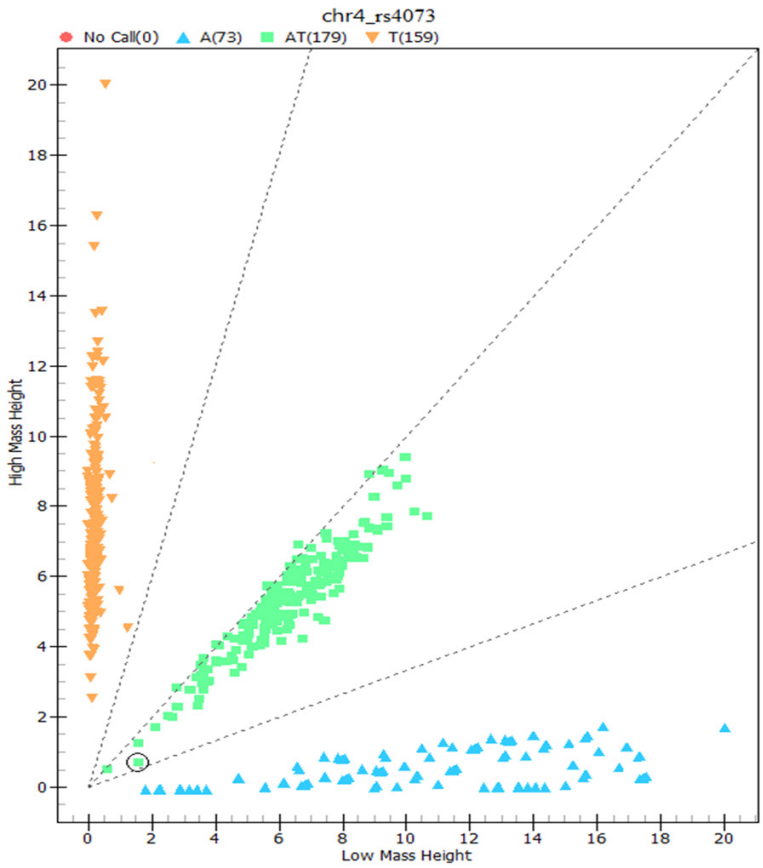

Figure 1. Scatter plot of -251T/A (rs4073) gene polymorphism.

genesis, and IL-8 concentrations were associated with the development, progression, metastasis of malignant tumors, including breast cancer [18-21]. Three common polymorphisms are observed in the promoter regions of IL-8, including -251T/A (rs4073), +781C/T (rs2227306) and +396T/G (rs2227307). The three SNPs of IL-18 are reported to be related to the development of several tumors [22-27]. Moreover, association of IL-8 -251T/A (rs4073) and +781C/T (rs2227306) haplotypes with some autoimmune diseases have been observed in some studies [28-30]. However, no study reported the relationship between IL-8 haplotypes and breast cancer risk, and few studies investigated the association of IL-8 +781C/T (rs2227306) and +396T/G (rs2227307) with breast cancer risk. The aim of this study is to evaluate the association of IL-8 -251T/A (rs4073), +781C/T (rs2227306) and +396T/G (rs2227307) polymorphisms and haplotypes with breast cancer risk in a Northern Chinese population.

Subjects and methods

Subjects

This case-control population is composed of 822 Chinese unrelated adults who were collected from Department of Thyroid and Breast Surgery, the Affiliated Hospital of Inner Mongolia Medical Collage between December 2013 and January 2016. A total of 411 patients with newly diagnosed breast cancer were recruited, and they were aged 57.47±9.69. The breast cancer patients did not receive any anti-cancer treatment.

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

The mean age of control group was 58.10±8.55. Demographic, lifestyle and clinical characteristics were collected from medical records and questionnaire interviews for both breast cancer patients and healthy controls. Collected 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 minutes per day, doing physical exercise for more than 2 hours per week, or carrying heavy objects at work daily. Occasional physical activity was considered as walking or

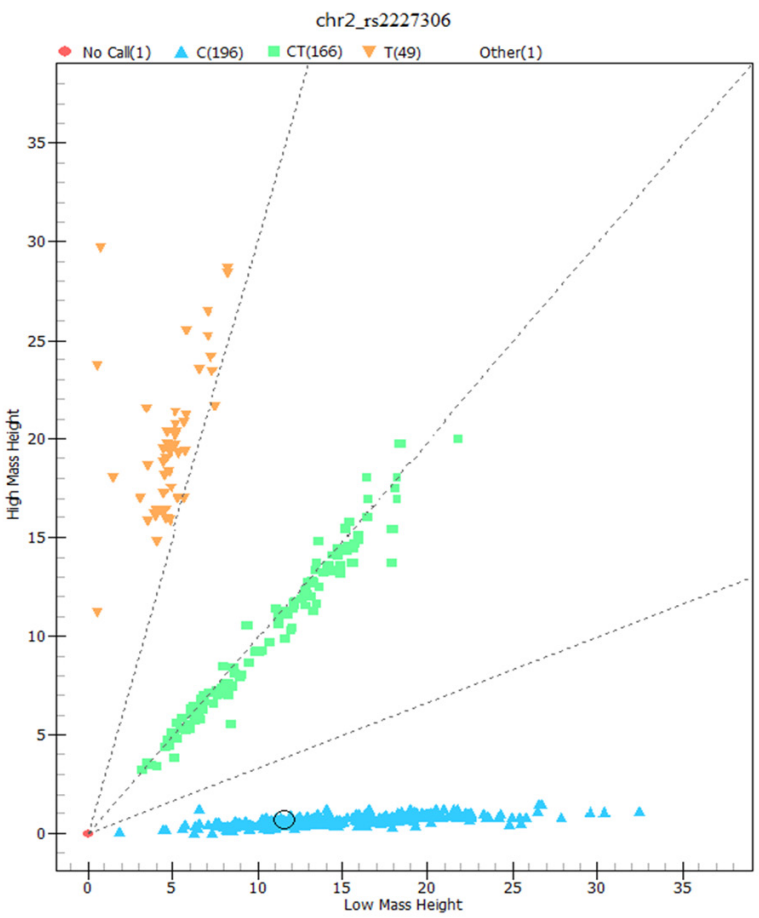

Figure 2. Scatter plot of +781C/T (rs2227306) gene polymorphism.

riding a bicycle for less than 30 minutes daily, doing physical exercise less than 2 hours 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 samples were approved by the Research Ethics Committee of the Affiliated Hospital of Inner Mongolia Medical Collage. All study subjects agreed to participate into our study after a full explanation of the purpose, and signed an informed consents.

Genotyping of IL-8 gene polymorphisms

Five ml peripheral blood was obtained from each 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 of IL-8 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 ddH_2O, 0.5 μL 10× buffer, 0.4 μL Mg^{2+}, 0.1 μL dNTP, 0.2 μL Hotstar, 1 μL forward primer/reverse primer and 1 μL 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°C 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 were then desalted, and dispensed to a SpectroCHIP and analyzed with MALDI-TOF MS (**Figures 1-3**).

Statistical analysis

Categorical and continued variables were analyzed 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 in line with the Hardy-Weinberg equilibrium (HWE) was estimated by Chi-square with one degree of freedom. The relationship between the three SNPs and breast cancer risk was analyzed by binary multivariate logistic regression, with the results of odds ratio (OR) and 95% confident intervals (95% CI). The linkage disequilibrium and haplotype analyses of three SNPs were estimated by SHEsis software (http://analysis.bio-x.cn/myAnalysis.php). All statistical analyses were carried out using IBM SPSS Statistics for Windows, Version 21.0. (IBM Corp, Armonk, NY). All *P* values were two-sided.

Results

Using Chi-square test or student *t* test, there were significant differences between patients

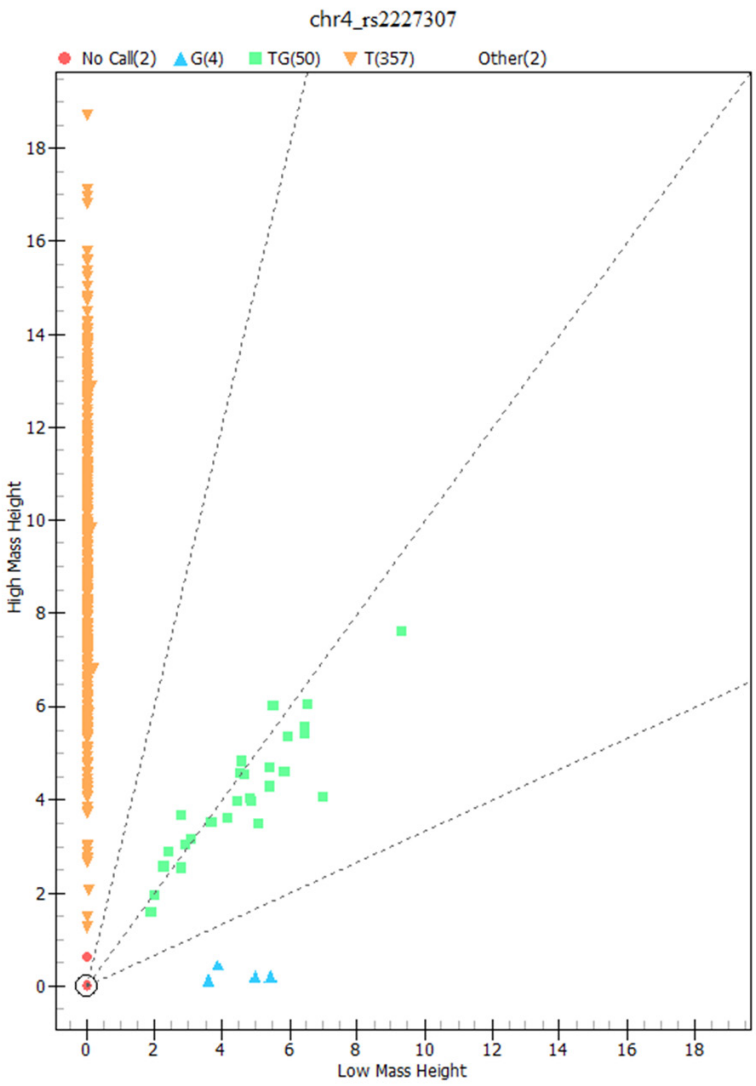

Figure 3. Scatter plot of +396T/G (rs2227307) gene polymorphism.

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**).

The genotype distributions of IL-8 rs4073 were significant difference between the two study groups (χ^2=15.50, P<0.001). The genotype frequencies of IL-8 -251T/A (rs4073), +396T/G (rs2227307) and +781C/T (rs2227306) were in line with the HWE in both breast cancer patients and controls (**Table 2**).

The binary logistic regression analysis showed 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 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 breast cancer.

After adjusting for the environmental factors, the AA genotype of IL-8 -251T/A (rs4073) was associated with an increased risk of breast cancer compared 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 risk of breast cancer.

A significant linkage disequilibrium was observed between rs4073 and rs2227306 through Linkage disequilibrium test (D'=0.723, r^2=0.02; **Figure 4**). Totally four common haplotypes (frequency <0.03 in both control and case) were observed, and the T(251)C(781)T(396) (OR=0.67, 95% CI=0.55-0.83) haplotype was associated with a reduced risk of breast cancer, while the A(251)C(781)T(396) (OR=1.43, 95% CI=1.05-1.94) and A(251)T(781)T(396) (OR=1.50, 95% CI=1.03-2.20) haplotypes were positively associated with the risk of breast cancer (**Table 4**).

Discussion

Inflammation related cytokines are 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, reconstruction of tumor tissue, promotion of angiogenesis, and inhibition of the natural antitumor immune response

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

Variables	Patients N=411	%	Controls N=411	%	χ^2 or t values	*P* values
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	92.70		
Yes	46	11.19	30	7.30	3.71	0.06

[35]. In this large population-based case-control study, we observed a significant positive association between IL-8 -251T/A (rs4073) polymorphism and risk of breast cancer in a Chinese population, and the T(251)C(781)T(396), A(251)C(781)T(396) and A(251)T(781)T(396) haplotypes were associated with risk of this cancer.

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. IL-8 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 contributes to several kinds of solid tumors, such as breast cancer, lung cancer, hepatocellar carcinoma and gastric cancer [33, 40-42]. IL-8 genetic variations can alter 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 rs4073 is related to an elevated expression

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		Controls	
							χ^2 for HWE	*P* value	χ^2 for HWE	*P* value
rs4073										
TT	159		207							
AT	179		162							
AA	73		42		15.50	<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			27.30	<0.001	1.0 (Ref.)
Occasional	-0.43	0.26	2.76	0.10	0.65 (0.39-1.08)
Frequent	-1.27	0.24	27.30	<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	16.40	<0.001	1.15 (1.07-1.22)
Age of menarche	-0.17	0.04	16.40	<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	0.20	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	0.20	0.01	0.92	1.02 (0.69-1.50)
+396T/G (rs2227307)					
TT			0.45	0.80	1.0 (Ref.)
TG	0.21	0.31	0.45	0.50	1.23 (0.67-2.25)
GG	<0.001	1.12	<0.001	1.00	1.00 (0.11-8.88)
TG+GG	0.22	0.30	0.53	0.47	1.24 (0.69-2.23)

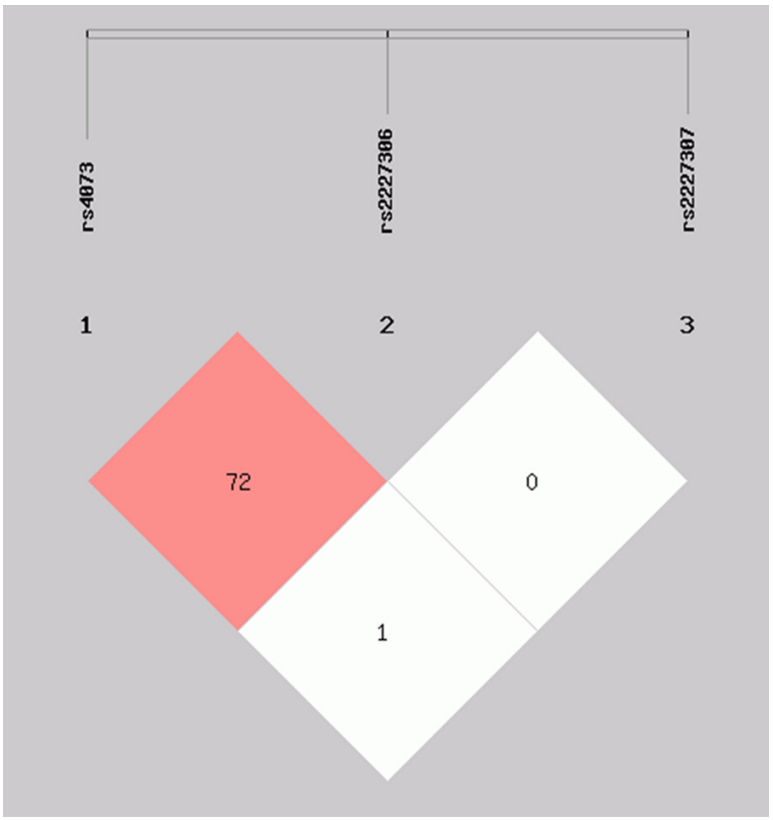

Figure 4. Linkage disequilibrium test for IL-8 -251T/A (rs4073), +781C/T (rs2227306) and +396T/G (rs2227307).

level of IL-8. Previous studies have evaluated 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 reported that the AA genotype of IL-8 rs4073 showed a protective effect for 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 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 lung cancer among Asians [26]. However, some studies reported inconsistent results. Chen *et al*. carried out a study on 439 prostate cancer patients and they did not find a significant relationship between IL-8 rs4073 and prostate cancer risk [27]. Burada *et al*. reported no association between IL-8 rs4073 and gastric cancer risk [23].

Only several studies reported the association between IL-8 polymorphisms and the risk of breast cancer. 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 breast cancer [44]. Kamali-Sarvestani *et al*. revealed that the frequencies of IL-8 rs4073 AA genotype in breast cancer patients were higher 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 that the AA genotype of IL-8 -251T/A (rs4073) conferred an increased risk of breast cancer, which was in line with previous findings [34]. However, Smith *et al*. performed a study with 144 breast cancer patients and 263 controls, and reported no association between IL-8 rs4073 and the risk of breast cancer [46]. The inconsistency of these findings can be attributed to the discrepancies in sample selection, ethnic groups and by chance.

Our study firstly reported a linkage disequilibrium between rs4073 and rs2227306, and the A(251)C(781)T(396) and A(251)T(781)T(396) haplotypes conferred a higher risk of breast cancer, while the T(251)C(781)T(396) haplotype showed a reduced risk. Several previous studies have reported that the IL-8 A(251)C(781) and A(251)T(781) haplotypes contributed to the risk of gastric cancer, hepatocellular and preeclampsia [47-49], but no study reported the relationship between IL-8 haplotypes and the risk of breast cancer. Therefore, further studies should be taken to confirm our results.

Two limitations should be highlighted. First, selection bias might be occurred during the process of sample selection, since we recruited subjects from one hospital in China. Second, the limited sample size may reduce 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, and we firstly report a significant association of T(251)C(781)T(396), A(251)C(781)T(396) and A(251)T(781)T(396)

Table 4. Haplotype analysis of rs4073-rs2227306-rs2227307

	Cases	%	Controls	%	χ^2 value	*P* value	OR (95% CI)
T(251)C(781)T(396)	310	37.71	390	47.45	14.7	<0.001	0.67 (0.55-0.83)
T(251)T(781)T(396)	153	18.61	157	19.10	0.007	0.93	0.74 (0.77-1.27)
A(251)C(781)T(396)	210	25.55	163	19.83	8.72	0.003	1.43 (1.05-1.94)
A(251)T(781)T(396)	91	11.07	66	8.03	5.04	0.02	1.50 (1.03-2.20)

Total control = 822, total case = 822, global χ^2=19.16, P<0.001.

haplotypes with the risk of breast cancer. Further studies are warranted to investigate the potential biological mechanism of IL-8 in the risk of breast cancer.

Disclosure of conflict of interest

None.

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