A Genetic Variant of BTLA Gene is Related with Increased Risk and Clinical Manifestations of Breast Cancer in Chinese Women

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Abstract

Background: B and T lymphocyte attenuator (BTLA), an immunoinhibitory receptor, is shown to suppress the lymphocyte activation. Several studies addressed the relationship between BTLA rs1982809 polymorphism and cancer's risk.

Methods: To identify the effects of this polymorphism on the risk of breast cancer (BC), this study was designed in Chinese women from China, Jiangsu Province. This study involved 324 BC patients and 412 controls.

Results: We observed that BTLA rs1982809 polymorphism elevated the risk of BC. Similar finding was also shown in the subgroup of premenopausal women and those aged < 55 years old. In addition, this polymorphism correlated with the estrogen receptor (ER) status, C-erbB-2 status, Ki-67 status, tumor node metastasis (TNM) stage and tumor size of BC patients.

Conclusions: Collectively, BTLA rs1982809 polymorphism shows a significant association with elevated risk and clinical features of BC in Chinese women. Further studies involving other races are urgently needed to replicate these findings.

Introduction

Breast cancer (BC) is the second frequent cancer, and it is also the most common malignancy in women worldwide [1]. Nearly 2.1 million new diagnosed BC patients and approximately 627,000 BC-related deaths occurred in 2018 [2]. BC is a heterogeneous disorder clinically, which has diverse pathology subtypes and molecular subtypes with varied aetiologies, risk factors, and responses to prognoses and treatments [3, 4]. Due to the implementation of mammographic screening and improvement of treatment methods for BC, the diagnosis and prognosis of BC improved increasingly. Endogenous hormone levels, exogenous hormone intake, high alcohol consumption, smoking, less physical activity, some breast diseases, and genetic susceptibility are all risk factors for BC [5–7]. Up to date, several GWAS studies have demonstrated important loci associated with BC susceptibility [8–12].

B and T lymphocyte attenuator (BTLA) is a suppressor molecule, which belongs to the immunoglobulin superfamily. BTLA is mainly expressed in B lymphocytes, T lymphocytes, macrophages and dendritic cells. BTLA is an immunoinhibitory receptor which could suppress lymphocyte activation by delivering inhibitory signals, with similarities to programmed cell death-1 (PD-1) or cytotoxic T lymphocyte antigen-4 (CTLA-4) [13, 14]. BTLA could negatively regulate immune responses, and BTLA-deficient T cells led to the elevated proliferation of T cells [15]. Herpes virus entry mediator (HVEM), the ligand of BTLA, could interact with BTLA, thereby resulting in the inhibition of T-cell activation and cytokine production [13, 16, 17]. Liu et al. indicated that BTLA/HVEM pathway was associated with peripheral T cell suppression in hepatocellular carcinoma patients, which may serve as a promising target for hepatocellular carcinoma immunotherapy [18]. Sekar et al. observed the effects of BTLA on type I Natural Killer T cells in limiting anti-tumor immunity [19]. Considering the important role of BTLA in cancer immunology, we assumed that genetic variations in BTLA gene may be associated with cancer susceptibility.

The BTLA gene is located on the chromosome 3q13.2. Previous studies have investigated whether BTLA rs1982809 polymorphism was linked with the risk of cancer, including renal cell carcinoma [20], chronic lymphocytic leukemia [21], esophagogastric junction adenocarcinoma [22], esophageal squamous cell carcinoma [23] and lung cancer [24]. However, no studies explored the association of this polymorphism and BC risk. Thus, we aimed to determine whether BTLA rs1982809 polymorphism conferred susceptibility to BC in Chinese women.

Material And Methods

Subjects

This research enrolled a total of 324 BC patients and 412 age-matched controls from Huaian No.1 People's Hospital. BC was diagnosed according to imaging and pathological manifestations. Clinical information of all individuals was recorded from electronic medical records and questionnaires. In addition, 412 healthy volunteers, receiving health examination in the same hospital, were selected as controls. Controls with other cancers or family history of cancer were not recruited in this study. The Institutional Review Board of our hospital approved this study. Informed consents were obtained from all individuals. This research was also in compliance with the standards of Declaration of Helsinki.

Genotyping

Venous samples were got from all subjects. Peripheral venous blood samples from all subjects were used to extract DNA. BTLA rs1982809 polymorphism was genotyped using the PCR method. The primers for this polymorphism were 5'- GCTCTCGAGTCCCGTCCCAGTAGTTGAAGGGTCCTGCTA-3'(F) and 5'-TGCCAGCTGCTTCGAGCGAAGCCATTGCTGC-3'(R). We genotyped 10% chosen samples again to evaluate the genotyping error; and the concordance rate was 100%.

Statistical analysis

χ^2 test and t test were utilized to analyze the categorical variables and continuous variables, respectively. A goodness-of-fit χ^2 test was intended to estimate the deviation from HWE in controls. The odds ratios (ORs), as well as 95% confidence intervals (95% CIs), were determined with logistic regression analysis with adjustment of age and Body Mass Index (BMI), and menopausal status or not. *P* value < 0.05 was regarded as significant. Statistical analysis was performed by SPSS 22.0.

Results

Characteristics of all enrolled individuals

The characteristic information and clinical features of all subjects are listed in Table 1. This study recruited 324 cases and 412 controls aged 50.48 ± 10.16 and 49.62 ± 9.54 years old, respectively. No obvious

differences were obtained among age, BMI and menopausal status ($P>0.05$). Other clinical features of BC are also summarized in Table 1.

Table 1
Distribution of selected demographic variables among breast cancer patients and controls.

Characteristics	Case (N = 324)	Control (N = 412)	<i>P</i>
Age	50.48 ± 10.16	49.62 ± 9.54	0.244
BMI	24.75 ± 3.16	24.99 ± 2.94	0.287
Menopausal status			0.276
Premenopausal	179(55.2%)	211(51.2%)	
Postmenopausal	145(44.8%)	201(48.8%)	
Site of tumor			
Left	170(52.5%)		
Right	154(47.5%)		
ER			
Positive	220(16.8%)		
Negative	104(83.2%)		
PR			
Positive	192(59.3%)		
Negative	132(40.7%)		
C-erbB-2			
Positive	57(17.6%)		
Negative	267(82.4%)		
Ki67			
> 30%	83(25.6%)		
≤ 30%	241(74.4%)		
Histologic type			
IDC	298(92.0%)		
ILC	12(3.7%)		
Others	14(4.3%)		
Histologic grade			
G1	38 (11.7%)		

BMI, Body Mass Index; ER, Estrogen receptor; PR, Progesterone receptor; IDC, Invasive ductal carcinoma; ILC, Invasive lobular carcinoma.

Characteristics	Case (N = 324)	Control (N = 412)	<i>P</i>
G2	212(65.4%)		
G3	74(22.8%)		
TNM			
I	84(25.9%)		
II	167(51.5%)		
III	73(22.5%)		
Tumor size			
> 2 cm	177(54.6%)		
≤ 2 cm	147(45.4%)		
BMI, Body Mass Index; ER, Estrogen receptor; PR, Progesterone receptor; IDC, Invasive ductal carcinoma; ILC, Invasive lobular carcinoma.			

Relationship Between Btla Rs1982809 Polymorphism And Bc Risk

BTLA rs1982809 polymorphism was in line with the HWE test in controls ($P_{HWE} = 0.657$). The genotype and allele distributions of this polymorphism are presented in Table 2. Overall, BTLA rs1982809 polymorphism presented significant association with increased susceptibility to BC after adjustment of BMI, age, and menopausal status (AA versus GG, adjusted OR, 1.95; 95%CI, 1.05–3.61; $P = 0.026$). Next, we found that A allele carriers showed elevated risk for BC (A versus G, OR, 1.35; 95% CI, 1.06–1.71; $P = 0.014$).

Table 2
Logistic regression analysis of associations between BTLA rs1982809 polymorphism and risk of breast cancer.

Models	Genotype	Case (n, %)	Control (n, %)	OR (95% CI)	<i>P</i> value	*OR (95% CI)	* <i>P</i> value
Co-dominant	GG	171(52.8%)	249(60.4%)	1.00	-	1.00	-
Heterozygote	GA	126(38.9%)	143(34.7%)	1.28(0.94–1.75)	0.113	1.25(0.91–1.73)	0.111
Homozygote	AA	27(8.3%)	20(4.9%)	1.97(1.07–3.62)	0.028	1.95(1.05–3.61)	0.026
Dominant	GG	171(52.8%)	249(60.4%)	1.00	-	1.00	-
	AA + GA	153(47.2%)	163(29.6%)	1.37 (1.02–1.83)	0.037	1.35(1.01–1.81)	0.034
Recessive	GA + GG	297(91.7%)	392(95.1%)	1.00	-	1.00	-
	AA	27(8.3%)	20(4.9%)	1.78(0.98–3.24)	0.055	1.75(0.95–3.21)	0.054
Allele	G	468(72.2%)	641(77.8%)	1.00	-	-	-
	A	180(27.8%)	183(22.2%)	1.35(1.06–1.71)	0.014	-	-
*Adjust age, BMI, and menopausal status. Bold values are statistically significant ($P < 0.05$).							

In addition, we interpreted the effects of the BTLA rs1982809 polymorphism on the risk of BC in the subgroups by BMI, age, and menopausal status (Table 3). Data detected that the rs1982809 polymorphism was more likely to intensify the risk of BC among premenopausal women and those aged < 55 years old.

Table 3
Stratified analyses between BTLA rs1982809 polymorphism and the risk of breast cancer.

Variable	(case/control)			GA vs. GG	AA vs. GG	AA vs. GG + GA	AA + GA vs. GG
	GG	GA	AA				
BMI							
< 25	98/119	73/74	14/9	1.20(0.79–1.82); 0.399	1.89(0.78–4.55); 0.151	1.76(0.74–4.16); 0.196	1.30(0.87–1.95); 0.197
≥ 25	73/130	53/69	13/11	1.37(0.87–2.16); 0.180	2.10(0.90–4.94); 0.082	1.87(0.81–4.30); 0.137	1.47(0.95–2.27); 0.082
Age (years)							
< 55	116/174	92/91	21/17	1.52(1.04–2.02); 0.028	1.85(0.94–3.66); 0.073	1.57(0.81–3.06); 0.178	1.57(1.10–2.23); 0.012
≥ 55	55/75	34/52	6/3	0.89(0.51–1.55); 0.685	2.73(0.65–11.38); 0.282	2.85(0.70–11.72); 0.130	0.99(0.58–1.69); 0.976
Menopausal status							
Premenopausal	89/130	70/68	20/13	1.50(0.98–2.31); 0.062	2.25(1.06–4.75); 0.031	1.92(0.92–3.97); 0.076	1.62(1.08–2.43); 0.018
Postmenopausal	82/119	56/75	7/7	1.08(0.69–1.69); 0.724	1.45(0.49–4.29); 0.499	1.41(0.48–4.10); 0.531	1.12(0.72–1.72); 0.622
BMI, Body Mass Index; Bold values are statistically significant ($P < 0.05$).							

Association with BTLA rs1982809 polymorphism and clinicopathological features of BC

Last, we depicted the link between this SNP and the clinical feature of BC (Table 4). Data revealed that BTLA rs1982809 polymorphism was connected to the ER status, Ki-67 status, TNM stage and tumor size of BC patients. No significance association was shown in other clinical features of BC, including histological grade, and tumor site and so on.

Table 4

The associations between BTLA rs1982809 polymorphism and clinical characteristics of breast cancer.

Characteristics	Genotype distributions			
	GG	GA	AA	GA + AA
Histologic grade				
G2/G1	112/19	85/15	15/4	100/19
OR (95%CI); <i>P</i> -value	1.0 (reference)	0.96(0.46-2.00); 0.916	0.64(0.19–2.12); 0.689	0.89(0.45–1.78); 0.748
Histological grade				
G3/G1	40/19	26/15	8/4	34/19
OR (95%CI); <i>P</i> -value	1.0 (reference)	0.82(0.36–1.90); 0.649	0.95(0.25–3.55); 1.000	0.85(0.39–1.86); 0.684
Site of tumor				
Left/Right	91/80	65/61	14/13	79/74
OR (95%CI); <i>P</i> -value	1.0 (reference)	0.94(0.59–1.49); 0.781	0.95(0.42–2.13); 0.895	0.94(0.61–1.45); 0.776
ER				
Positive/Negative	107/64	95/31	18/9	113/40
OR (95%CI); <i>P</i> -value	1.0 (reference)	1.83(1.10–3.05) 0.019	1.20(0.51–2.82); 0.682	1.69(1.05–2.72); 0.030
PR				
Positive/Negative	98/73	79/47	15/12	94/59
OR (95%CI); <i>P</i> -value	1.0 (reference)	0.77(0.46–1.31); 0.335	0.94(0.51–1.76); 0.856	1.19(0.76–1.85); 0.450
C-erbB-2				
Positive/Negative	22/149	30/96	5/22	35/118
OR (95%CI); <i>P</i> -value	1.0 (reference)	2.12(1.15–3.88); 0.014	1.54(0.53–4.48); 0.426	2.01(1.12–3.61); 0.018
Ki67				
> 30%/≤30%	39/132	32/94	12/15	44/109
OR (95%CI); <i>P</i> -value	1.0 (reference)	1.15(0.67–1.97); 0.605	2.71(1.17–6.27); 0.017	1.37(0.83–2.25); 0.221

ER, Estrogen receptor; PR, Progesterone receptor; IDC, Invasive ductal carcinoma; Bold values are statistically significant ($P < 0.05$).

Characteristics	Genotype distributions			
TNM				
☐/☐+☐	33/138	28/98	12/15	40/113
OR (95%CI); P-value	1.0 (reference)	1.20(0.68–2.11); 0.538	3.35(1.43–7.82); 0.004	1.48(0.88–2.50); 0.141
Tumor size				
> 2 cm/≤2 cm	83/88	81/45	13/14	94/59
OR (95%CI); P-value	1.0 (reference)	1.91(1.19–3.06); 0.007	0.99(0.44–2.22); 0.970	1.69(1.09–2.63); 0.020
Histologic type				
IDC/Not	159/12	114/12	25/2	139/14
OR (95%CI); P-value	1.0 (reference)	0.72(0.31–1.65); 0.433	0.94(0.20–4.47); 1.000	0.75(0.34–1.67); 0.481
ER, Estrogen receptor; PR, Progesterone receptor; IDC, Invasive ductal carcinoma; Bold values are statistically significant (<i>P</i> <0.05).				

Discussion

In this presented study, we observed that BTLA rs1982809 polymorphism intensified the risk of BC in Chinese women. Further subgroup analyses obtained that this increased risk effect was more evident in premenopausal women and those aged < 55 years old. Additionally, we found that rs1982809 polymorphism was linked to ER status, C-erbB-2 status, Ki-67 status, TNM stage and tumor size of BC patients.

Previous studies showed that the HVEM–BTLA pathway was involved in the progression of inflammation, autoimmunity, and immune tolerance [25, 18, 26, 27]. BTLA was shown to participate in tumor immunity and genesis [28–32]. Polymorphisms of BTLA gene might exert effects on the predisposition to immune-related disorders, including cancer.

Recently, several studies paid attention to the link between BTLA rs1982809 polymorphism and cancer risk. Partyka et al. showed that this SNP strengthened the risk of renal cell carcinoma in a Polish population [20]. A similar finding was shown in another study by their research team, and they found that BTLA rs1982809 polymorphism elevated the risk of chronic lymphocytic leukemia [21]. A Caucasian study from Tunisia also replicated this positive result; they observed that rs1982809 polymorphism was shown to elevate the risk of lung cancer in Tunisian patients [24]. As for Asian populations, no positive relationship was observed between this SNP and esophageal squamous cell carcinoma [23] or esophagogastric junction adenocarcinoma risk in Chinese Han population [22]. From the findings of abovementioned studies, we assumed that BTLA rs1982809 polymorphism might be specific for Caucasians, but not for Asians. However, we observed that BTLA rs1982809 polymorphism elevated the risk of BC in Chinese women in this study. Fu et al. revealed that BTLA gene polymorphisms were connected to the intensified risk of BC in Chinese women [24]. Nevertheless,

they did not investigate rs1982809 polymorphism [24]. Honestly, this was the first Chinese study to observe this finding. Further studies in other Chinese populations should be conducted to verify the findings of this study.

In addition, we performed subgroup analyses, and revealed that BTLA rs1982809 polymorphism enhanced the risk of BC in premenopausal women and those aged < 55 years old. Thus, we should pay more attention to those populations who had mutation of this SNP, because these individuals were more prone to the occurrence of BC. Last, we observed that BTLA rs1982809 polymorphism was associated with the ER status, Ki-67 status, C-erbB-2 status, TNM stage and tumor size of BC patients, suggesting that this SNP was significantly associated with the clinical manifestations of BC. It is worth noting that other SNPs of BTLA gene were also shown to be related with some clinical features of BC in Chinese women from Heilongjiang Province [33].

This study had several limitations. One, the sample size was not large enough. Two, the findings of this study might not be not applicable to other races, because all enrolled individuals were Chinese. Three, we only investigated one SNP of BTLA gene. Four, whether BTLA rs1982809 polymorphism was associated with the gene and protein levels is unknown. Five, whether this SNP affected the prognosis of BC needs further investigation. Six, the biological functions of rs1982809 polymorphism remained to be explored. Last, the interaction between this polymorphism and environmental factors should be considered.

Collectively, this case-control study observes that BTLA rs1982809 polymorphism is remarkably associated with higher risk and clinical manifestations of BC in Chinese females. Further retrospective studies are needed to validate these findings.

Abbreviations

BTLA: B and T lymphocyte attenuator; BC: breast cancer; TNM: tumor node metastasis; PD-1: programmed cell death-1; CTLA-4: cytotoxic T lymphocyte antigen-4; HVEM: Herpes virus entry mediator; ORs: odds ratios; 95% CIs: 95% confidence intervals.

Declarations

Ethics approval and consent to participate

The Institutional Review Board of The Affiliated Huaian No.1 People's Hospital of Nanjing Medical University approved this study. Informed consents were obtained from all individuals.

Consent for publication

Not applicable.

Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Conflict of interest

None

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No funds.

Author contribution

Conceptualization: Zhi Li, Jianhua Shi and Ruipeng Zhao; Methodology: Zhi Li, Jianhua Shi and Chang Li.; Software and data analysis: Kang Xu and Wei Song; Validation: Linlin Zhen; Writing - original draft preparation: Zhi Li, Jianhua Shi and Ruipeng Zhao; Writing-review and editing: Zhi Li, Jianhua Shi and Ruipeng Zhao.

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None

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