

Contribution of Interleukin-10 Genotype to Triple Negative Breast Cancer Risk

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Abstract. *Background/Aim:* Triple negative breast cancer (TNBC) is characterized by increased recurrence and poor survival. Mounting evidence suggests that interleukin-10 (IL-10) plays a role in carcinogenesis, however, little is known about the contribution of IL-10 to TNBC. The study evaluated the contribution of IL-10 promoter A-1082G (rs1800896), T-819C (rs3021097), A-592C (rs1800872) genotypes to the risk of TNBC. *Materials and Methods:* IL-10 genotypes were examined among 1,232 breast cancer patients and 1,232 controls and evaluated. *Results:* The percentages of AG and GG for IL-10 A-1082G genotypes were higher in the breast cancer patient group than in the control group. The GG genotype carriers were of higher risk for breast cancer [odds ratio (OR)=2.02, 95% confidence interval (CI)=1.28-3.21, $p=0.0021$]. Interestingly, G allele carriers were of higher risk of TNBC (OR=1.25, 95%CI=1.07-1.46, $p=0.0050$). *Conclusion:* The G allele of IL-10 A-1082G genotype may serve as a predictor for TNBC risk. The finding should be validated in other populations.

Breast cancer is the most common female cancer worldwide (1, 2). Among the subtypes of breast cancer, triple negative breast cancer (TNBC) represents 15%-20% of all invasive breast cancers and is characterized by high heterogeneity with elevated chances of recurrence and poor survival rates (3, 4).

The identification of practical novel biomarkers for TNBC allows better understanding of the disease and the design of clinical targeted therapies (5, 6). Up to now, limited epidemiological studies have reported that several polymorphisms in specific genes, such as adipocyte fatty acid binding protein 4 (AFABP4) (7), breast cancer type 1 susceptibility protein (BRCA1) (8), excision repair cross complementing-group 1 (ERCC1) (9), ERCC2 (10), glucuronic acid epimerase (GLCE) (11), human 8-oxoguanine glycosylase 1 (hOGG1) (12), poly(ADP-ribose) polymerase 1 (PARP1) (13), pre-mir-34a (14), tumor necrosis factor- α (TNF α) (15), transmembrane serine protease 6 (TMPRSS6) (16), and X-ray repair cross-complementing group 3 (XRCC3) (17), associate with TNBC across various regions and populations. However, the genomic information is far from satisfying and need further investigations.

Interleukin-10 (IL-10) is an important immuno-regulatory cytokine playing critical role in activating and/or suppressing immuno-responses. IL-10 gene is located on chromosome 1q32.1. The single nucleotide polymorphisms found in the IL-10 promoter region, are thought to affect the expression of IL-10 protein and may contribute to cancer risk and prognosis prediction. For instance, the GG genotype at IL-10 A-1082G (rs1800896) has been shown to

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Table I. Demographics and life-style of the investigated breast cancer patients and the control healthy women.

Characteristic	Controls (n=1,232)			Patients (n=1,232)			p-Value
	n	%	Mean (SD)	n	%	Mean (SD)	
Age (years)							
<40	359	29.1%		362	29.4%		0.89 ^a
40-55	558	45.3%		547	44.4%		
>55	315	25.6%		323	26.2%		
Age at menarche (years)			12.4 (0.7)			12.1 (0.6)	0.79 ^b
Age at first birth of child (years)			29.4 (1.2)			29.8 (1.4)	0.63 ^b
Age at menopause (years)			48.8 (1.8)			49.3 (2.0)	0.59 ^b
Site							
Unilateral				1198	97.2%		
Bilateral				34	2.8%		
Family History							
First degree (Mother, sister, and daughter)				55	4.5%		
Second degree				6	0.5%		
No history				1171	95%		
Habit							
Cigarette smokers	86	7.0%		170	13.8%		<0.0001 ^a
Alcohol drinkers	91	7.4%		162	13.1%		<0.0001 ^a

Statistical results based on ^aChi-squared or ^bunpaired Student's *t*-test.

contribute to up-regulation of IL-10 (18-20). However, another study focused on IL-10 expression in serum from patients with renal cell carcinoma showed no significant difference in the expression levels of IL-10 among the patients with GG, AA or AG genotypes at *IL-10* A-1082G (21). This may indicate that multiple polymorphic sites may determine the expression levels of IL-10. In support, Yao and his colleagues found that the genotypes of *IL-10* at T-819C (rs3021097) and A-592C (rs1800872) sites also have impact on the expression of *IL-10* mRNA (22). Thus, to reveal the role of *IL-10* genotypes at the promoter site in determining the risk for TNBC, we simultaneously investigated the genotypes at the promoter region of *IL-10*, A-1082G (rs1800896), T-819C (rs3021097) and A-592C (rs1800872) in a representative Taiwanese breast cancer population.

Materials and Methods

The breast cancer population. Up to 1,232 female patients diagnosed with breast cancer were recruited from China Medical University Hospital, a hospital located in the center of Taichung city. An equal number of healthy controls were recruited from the Health Examination Cohort of the same hospital. The detail procedure has been published previously (9). All the participants had offered peripheral blood samples for the genotyping. The contents of the questionnaire included questions focused on personal medical history and personal habits and diets such as alcohol consumption and cigarette smoking, and are listed in Table I. Our study was approved by the Institutional Review Board (DMR-99-IRB-108).

***IL-10* genotyping.** The genomic DNA was extracted from the leucocytes of peripheral blood of each subject within 24 h (23, 24). The polymerase chain reaction (PCR) programs for *IL-10* were set as: one cycle at 95°C for 5 min; 35 cycles at 95°C for 30 s, 55°C for 30 s and 72°C for 30 s; and a final extension at 72°C for 10 min. The designed PCR primer sequences and specific restriction endonuclease for each DNA product of *IL-10* polymorphisms are listed in Table II.

Statistical analyses. Student's *t*-test was used for the comparison of ages between the breast cancer patient and control groups. Pearson's Chi-square test was used for the comparison of the distribution of the *IL-10* genotypes. The association between *IL-10* genotypes and breast cancer risk was estimated by odds ratios (ORs) and 95% confidence intervals (CIs). Any difference was recognized as significant when the *p*-value was less than 0.05.

Results

Comparison of demographics and lifestyles between the breast cancer and control groups. Selected characteristics of patients are shown in Table I. The results showed that characteristics including age, age at menarche, and the age each individual gave birth for the first time were all well-matched among the breast cancer patients and healthy controls (*p*>0.05). Also, the lifestyle factors including cigarette smoking and alcohol consumption were also well recorded and is shown that cigarette smoking and alcohol consumption were significantly different between the breast cancer patient and control groups (*p*<0.05) (Table I). The results indicated that cigarette smoking and alcohol drinking may be risk factors for breast cancer in Taiwan.

Table II. The primer sequences, polymerase chain reaction and restriction fragment length polymorphism conditions for identifying the interleukin-10 (*IL-10*) A-1082G, T-819C and A-592C genotypes among the investigated individuals.

Polymorphism (rs number)	Primer sequences	Restriction enzyme	SNP sequence	DNA fragment size (bp)
A-1082G (rs1800896)	F: 5'-CTCGCTGCAACCCAACTGGC-3' R: 5'-TCTTACCTATCCCTACTTCC-3'	<i>Mnl</i> I	A G	139 106+33
T-819C (rs3021097)	F: 5'-TCATTCTATGTGCTGGAGAT-3' R: 5'-TGGGGGAAGTGGGTAAGAGT-3'	<i>Mae</i> III	T C	209 125+84
A-592C (rs1800872)	F: 5'-GGTGAGCACTACCTGACTAG-3' R: 5'-CCTAGGTCACAGTGACGTGG-3'	<i>Rsa</i> I	C A	412 236+176

F: Forward primer; R: reverse primer.

Table III. Distributions of interleukin-10 (*IL-10*) genotypic frequencies among the breast cancer patients and healthy controls.

	Cases (%)	Controls (%)	OR (95%CI)	Adjusted OR (95%CI)	p-Value ^a
A-1082G					
AA	874 (70.9)	918 (74.5)	1.00 (reference)	1.00 (reference)	
AG	302 (24.5)	285 (23.1)	1.13 (0.92-1.34)	1.24 (1.12-1.56)	0.2604
GG	56 (4.6)	29 (2.4)	2.02 (1.28-3.21)	1.98 (1.41-2.89)	0.0021*
AG+GG	358 (29.1)	314 (25.5)	1.20 (1.00-1.43)	1.47 (1.26-1.68)	0.0466*
<i>P</i> _{trend}					0.0063*
T-819C					
TT	695 (56.4)	683 (55.4)	1.00 (reference)	1.00 (reference)	
TC	433 (35.2)	454 (36.9)	0.94 (0.79-1.11)	0.92 (0.68-1.08)	0.4519
CC	104 (8.4)	95 (7.7)	1.08 (0.80-1.45)	0.98 (0.72-1.24)	0.6301
TC+CC	547 (43.6)	549 (44.6)	0.98 (0.84-1.15)	0.96 (0.75-1.09)	0.7947
<i>P</i> _{trend}					0.6039
A-592C					
AA	772 (62.7)	789 (64.0)	1.00 (reference)	1.00 (reference)	
AC	405 (32.9)	393 (31.9)	1.05 (0.89-1.25)	1.09 (0.85-1.37)	0.5513
CC	55 (4.4)	50 (4.1)	1.12 (0.76-1.67)	1.07 (0.54-2.53)	0.5617
AC+CC	460 (37.3)	443 (36.0)	1.06 (0.90-1.25)	1.03 (0.87-1.32)	0.4772
<i>P</i> _{trend}					0.7395

OR: Odds ratio; CI: confidence interval. ^aBased on Chi-square test with Yate's correction; **p*<0.05. Bold values represent statistical significance.

Association of *IL-10* genotypes and breast cancer risk among Taiwanese. In the current study, three promotor *IL-10* polymorphisms, A-1082G (rs1800896), T-819C (rs3021097) and A-592C (rs1800872), were examined among breast cancer patients and controls. Table III shows the distribution of *IL-10* genotypes of each polymorphism between breast cancer patient and non-cancer control groups. First, all *IL-10* genotypes in the control group fit the Hardy-Weinberg equilibrium (*p*>0.05). Second, the genotypes of *IL-10* A-1082G were differently distributed among breast cancer patient and control groups (*P*_{trend}=0.0063, Table III). At the same time, the distributions

of *IL-10* T-819C (rs3021097) and A-592C (rs1800872) genotypes were found to be of the same frequency among 1,232 breast cancer patients and 1,232 controls (*P*_{trend}=0.6039 and 0.7395, respectively) (Table III). In detail, the homozygous GG variant and the heterozygous AG variant *IL-10* A-1082G were associated with increased risk of breast cancer (adjusted OR=1.98 and 1.24, 95%CI=1.41–2.89 and 1.12–1.56, *p*=0.0021 and 0.2604, respectively) (Table III). In addition, the dominant model of *IL-10* A-1082G showed a positive association between *IL-10* A-1082G genotypes and breast cancer risk (adjusted OR=1.47, 95%CI=1.26–1.68, *p*=0.0466) (Table III).

Table IV. Allelic frequencies for interleukin-10 (IL-10) polymorphisms in the breast cancer patients and control groups.

Polymorphic site allele	Breast cancer (%) N=2464	Controls (%) N=2464	OR (95%CI)	p-Value ^a
A-1082G				
Allele A	2050 (83.2)	2121 (86.1)	1.00 (reference)	0.0050*
Allele G	414 (16.8)	343 (13.9)	1.25 (1.07-1.46)	
T-819C				
Allele T	1823 (74.0)	1820 (73.9)	1.00 (reference)	0.9225
Allele C	641 (26.0)	644 (26.1)	0.99 (0.88-1.13)	
A-592C				
Allele A	1949 (79.1)	1971 (80.0)	1.00 (reference)	0.4372
Allele C	515 (20.9)	493 (20.0)	1.06 (0.92-1.21)	

OR: Odds ratio; CI: confidence interval. ^ap-Value based on Chi-square test with Yate's correction; **p*<0.05. Bold values represent statistical significance.

Table V. Association of interleukin-10 (IL-10) A-1082G genotypes with breast cancer risk stratified by clinicopathological characteristics compared with non-cancer healthy controls.

Character	Genotype, number (%) ^a			OR (95%CI) ^b	p-Value ^c
	AA	AG	GG		
Control	918 (74.5)	285 (23.1)	29 (2.4)	1.00 (Reference)	
Triple-negative status					
No	408 (73.8)	130 (23.5)	15 (2.7)	1.04 (0.83-1.31)	0.8826
Yes	66 (63.5)	30 (28.8)	8 (7.7)	1.68 (1.11-2.56)*	0.0017*
Ki67 status					
Negative	203 (73.3)	66 (23.8)	8 (2.9)	1.07 (0.79-1.43)	0.8370
Positive	240 (71.0)	81 (24.0)	17 (5.0)	1.19 (0.91-1.56)	0.0302*

^aTriple-negative and Ki67 status databases were available for only 657 and 615 patients, respectively. All data are given as number of patients (%).
^bOR: Odds ratio; CI: confidence interval, variant AG + GG versus AA; ^cBased on Chi-squared test without Yate's correction;

*Statistically significant.

Association of IL-10 allelic subtypes and breast cancer risk among Taiwanese. The allelic frequencies of IL-10 genotypes among the investigated 1,232 breast cancer patients and 1,232 non-cancer healthy controls were also examined (Table IV). Supporting the results shown in Table III, the distribution of IL-10 A-1082G allelic frequencies was significantly associated with elevated breast cancer risk (OR=1.25, 95%CI=1.07-1.46, *p*=0.0050), while IL-10 T-819C and A-592C allelic frequencies were not found to be related to breast cancer risk (*p*=0.9225 and 0.4372, respectively) (Table IV).

Association of IL-10 A-1082G genotypes with breast cancer risk stratified by clinicopathological characteristics. Regarding clinicopathological index evaluation, 657 patients were available for triple-negative status and 615 patients were available for Ki67 status analysis. Interestingly, IL-10 A-1082G genotypes were statistically differentially distributed

among the breast cancer patients who had triple-negative status (OR=1.68, 95%CI=1.11-2.56, *p*=0.0017). However, a borderline differential distribution of IL-10 A-1082G genotypes was observed for positive Ki67 status (OR=1.19, 95%CI=0.91-1.56, *p*=0.0302).

In summary, these findings indicate that IL-10 A-1082G was associated with increased breast cancer risk in Taiwan, especially TNBC. Therefore, IL-10 A-1082G genotypes may serve as a novel marker for the early detection of TNBC.

Discussion

TNBC is extremely invasive and aggressive, with greater risk of relapse and death. Since it is difficult to manage this disease, the search for practical TNBC biomarkers for early prediction is in urgent need. To fulfill this purpose, we have been looking for novel biomarkers for TNBC in a large Taiwanese population for years. First, the *Cyclin D1*

(*CCND1*) A870G (rs9344) GG genotype seemed to be at significantly higher frequency in Taiwanese TNBC patients (25). Second, the *XRCC3* rs861539 TT was found to serve as a potential predictive marker for TNBC in Taiwanese women (17). Third, the CC genotype of tissue inhibitor of metalloproteinase-1 (*TIMP-1*) rs4898 was also found to increase the risk for TNBC in Taiwan (26).

In this study, the association of *IL-10* polymorphic genotypes and TNBC risk was examined. It was found that people carrying the AG or GG genotypes were of significantly higher risk of breast cancer compared with those carrying wild-type AA genotype on *IL-10* T-1082G (Table III). However, no association of *IL-10* T-819C and A-592C with breast cancer risk was found (Table III). We further investigated the association of *IL-10* T-1082G with TNBC cancer risk. Our results indicated that AG and GG also contributed to the higher risk of TNBC (Table V).

There are numerous epidemiological studies investigating the association between *IL-10* promoter genotypes, which may alter the function of this cytokine, with the development of human disorders. For example, the genotypes at *IL-10* A-1082G have been reported to be associated with renal cell carcinoma (18, 21), lymphoma (27), gastric cancer (28-30), oral cancer (31), nasopharyngeal carcinoma (32), papillary thyroid cancer (33) and lymphoid leukemia (34). The *IL-10* T-819C genotypes have been associated with lung cancer (35, 36), gastric cancer (37) and adult leukemia (22, 38). Concerning *IL-10* A-592C, its genotypes have been associated with lung cancer (35), gastric cancer (39, 40), esophageal cancer (41) and adult leukemia (38). This diversity may be explained by the different background between Caucasians and Asians and needs to be validated in more populations.

Among the breast cancer patients we investigated, 104 were identified to be TNBC patients, and 338 were Ki-67 positive patients. The results showed that the percentage of *IL-10* A-1082G GG genotype was increased from 2.4% to 7.7% among the patients with TNBC (Table V). Since the upregulated Ki-67 is a potential indicator for TNBC, it seems that the expression of Ki-67 displays a borderline interaction with the *IL-10* A-1082G genotype in elevating the susceptibility of TNBC (Table V). In the near future, we will validate the genotype-phenotype correlation among the breast cancer patients by comparing the expression levels of *IL-10* in tumor sites and non-tumor sites, and the genotypes of *IL-10*. Also, validation of our findings should be carried out by multi-institute, multi-center, and even in different populations. All these studies should increase understanding of the role of *IL-10* in carcinogenesis, especially TNBC.

In conclusion, the present case-control study provided evidence showing that the A-1082G genotypes at the promoter of *IL-10* are associated with the risk of breast cancer, especially TNBC among Taiwanese. The G allele of

IL-10 A-1082G may potentially serve as a powerful marker for the prediction of breast cancer, especially for TNBC. Further functional studies are warranted to reveal the role of *IL-10* in TNBC cancer progression. However, the findings have to be validated in other populations.

Conflicts of Interest

The Authors declare no conflicts of interest in regard to the current study.

Authors' Contributions

Research design: Chen KY, Chien WC and Liao JM; patient and questionnaire summaries: Su CH and Wang HC; experimental work: Chang WS and Tsai CW; statistical analysis: Chien WC, Liao JM and Chang WS; article writing: Tsai CW and Bau DT; review and revision: Bau DT.

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