A functional polymorphism of *TGFBR2* is associated with risk of breast cancer with ER^+, PR^+, ER^+PR^+ and $HER2^-$ expression in women

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Abstract. Little is known about the correlation between *TGFBR2* G-875A and breast cancer risk. Moreover, the associations of the expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER2) in breast cancer tissues with the *TGFB1* C-509T, T+29C and *TGFBR2* G-875A polymorphisms remain to be determined. In this study, we genotyped for *TGFB1* C-509T, T+29C and *TGFBR2* G-875A in fresh surgically resected tissues (n=82) and archived paraffin-embedded specimens (n=88) from 170 patients with breast cancer, as well as peripheral blood samples from 178 cancer-free female individuals. Evaluation of ER, PR and HER2 expression was performed using immunohistochemical staining. Logistic regression analysis was carried out to determine the risk of breast cancer by calculating the odds ratios (ORs) and their 95% confidence intervals (CIs). As a result, no difference was observed in the *TGFB1* C-509T, T+29C genotype and allele frequencies between patients and controls. However, the frequency of the *TGFBR2* -875A allele was marginally higher in cancer-free female individuals than that of women with breast cancer (24.2 vs. 17.9%, P=0.05). Notably, when stratification was performed by ER, PR and HER2 expression, the *TGFBR2* -875A allele was found to correlate significantly to a decreased risk of breast cancer with ER^+ (OR=0.57, 95% CI 0.35-0.92), PR^+ (OR=0.54, 95% CI 0.34-0.88), ER^+PR^+ (OR=0.55, 95% CI 0.33-0.92) and $HER2^-$ (OR=0.55, 95% CI 0.34-0.88) under a dominant genetic model. In conclusion, this is the first study to suggest that the *TGFBR2* -875A allele modifies predisposition to breast cancer with an expression of ER^+, PR^+, ER^+PR^+ and $HER2^-$.

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Introduction

Breast cancer is the leading cause of death from cancer in America, and its incidence is currently increasing in China. By 2021, it is anticipated to have increased substantially from the current rate, estimated at 10-60 cases per 100,000 women, to more than 100 new cases per 100,000 women aged 55-69 years (1,2). Breast cancer has been suggested to be caused by interactions between genetic and environmental factors. Of these factors, genetic factors, such as family history and gene-related variants, may play an important role in the development and progression of breast cancer.

Signaling from transforming growth factor-β (TGF-β) was conducted through serine-threonine kinases of transmembrane receptors, including TGFBR1 and TGFBR2. TGF-β1 is the most abundant form of TGF-β and regulates cellular processes by binding to TGFBR2, which then activates TGFBR1 through phosphorylation (3). Inactivation of the TGF-β signaling pathway may lead to acquisition of resistance to the anti-mitogenic effects of TGF-β and contribute to tumor development and progression (4,5). Therefore, defective expression or inactivation of TGF-β1 and its receptors, such as TGFBR2, may play a significant role in carcinogenesis. Compelling evidence shows that TGF-β signaling may play a crucial role in mammary development (6,7) and a complex role in breast cancer tumorigenesis via both tumor-suppressor and oncogenic activities (8).

Although a number of polymorphisms in *TGFB1* and its receptor *TGFBR2* were originally reported in the western population (9,10), no frequency of the polymorphisms G-800A, codon25 and codon263 of *TGFB1* was detected in the Chinese population (11). Two polymorphisms (C-509T and T+29C) in *TGFB1* have been associated with increased levels of TGF-β1 in serum from breast cancer patients (12). The

TGFBR2 -875A allele was reported to enhance transcriptional activity in normal epithelial cells (10). Based on previous findings, we hypothesize that polymorphisms affecting the activity of genes involved in the TGF-β signaling pathway play a role in the development of breast cancer. However, little is known about the relationship between *TGFBR2* G-875A and breast cancer risk in the Chinese population. Furthermore, the correlation of the expression of estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor-2 (HER2) in breast cancer tissue with *TGFB1* C-509T, T+29C and *TGFBR2* G-875A polymorphisms remains to be determined. In this study, three functional polymorphisms, *TGFB1* C-509T, T+29C and *TGFBR2* G-875A, were selected to evaluate whether they modify predisposition to breast cancer.

Materials and methods

Study participants. A total of 170 breast cancer patients and 178 cancer-free female controls were enrolled in this study. Fresh surgically resected tissues (n=82) and archived paraffin-embedded specimens (n=88) from patients diagnosed with breast cancer between 2006 and 2010 were selected from the Second Affiliated Hospital of Soochow University, China. In addition, blood samples from 178 cancer-free donors, frequency-matched to the patients by age (Table I), were collected for use as controls at the same hospital. With respect to immunohistochemistry, expression data on ER were available for 138, PR for 138 and HER2 for 103 patients among all of the breast cancer cases. Immunohistochemistry staining permitted the detection and localization of ER, PR and HER2 within sections of paraffin-embedded tissues. Positive expression is considered as >20% of tumor cell nuclei staining, borderline is 5-19% and negative is <5%. Both borderline and overtly positive results were considered as positive (13,14). HER2 expression was considered as positive (score 3+) and negative (score 0-1+). Samples with a score of 2+ were excluded from the analysis (15). This study was approved by the Academic Advisory Board of Soochow University.

DNA isolation and genotyping. Genomic DNA from fresh tissues and peripheral blood samples was extracted using the proteinase K digestion standard method. Isolation of DNA from paraffin-embedded tissues was performed using a microwave-based DNA extraction method, as previously described (16,17). Single nucleotide polymorphism (SNP) analysis was performed using a polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) assay. In total, two SNPs in *TGFB1* and one SNP in *TGFBR2* were genotyped. C-509T and G-875A were located in the promoter region of *TGFB1* and *TGFBR2*, respectively. Additionally, T+29C was located in exon 1 of *TGFB1*. The primer sequences, annealing temperatures, sizes of PCR products and restriction enzymes are shown in Table II. The PCR reaction was carried out in a total volume of 25 μl, containing 50-100 ng of genomic DNA, 1 unit of Ex Taq DNA polymerase (Takara, Japan), 0.2 μmol/l of each primer, 1X Ex Taq Buffer (Mg^{2+} Plus) and 0.25 mmol/l of each deoxynucleotide triphosphate. Briefly, PCR amplification was performed according to the following conditions: initial denaturation at 95˚C for 5 min followed by 35 cycles of 94˚C for 45 sec, 63 or 59˚C for 45 sec and 72˚C for 45 sec. PCR was completed by a final extension cycle at 72˚C for 10 min.

Table I. Characteristics of breast cancer cases and controls.

	Cases	Controls	P-value[a]
Age (mean ± SD)	53.75±11.22	52.67±10.28	0.35
Tumor stage			
0	3		
I	26		
II	34		
III	60		
IV	0		
Missing	47		
Cancer type			
Intraductal carcinoma	5		
Infiltrative ductal carcinoma	158		
Infiltrative lobular carcinoma	1		
Mucinous adenocarcinoma	4		
Adenocarcinoma infiltrating	2		
Histologic grade			
Well-differentiated	5		
Moderately differentiated	115		
Poorly differentiated	12		
Missing	26		
Tumor size			
≤2 cm	38		
2.1-5 cm	81		
>5 cm	4		
Missing	47		
Lymph node status			
Positive	61		
Negative	63		
Not examined	46		
Tumor subtypes[b]			
ER^+	88		
ER^-	50		
PR^+	88		
PR^-	50		
ER^+ and PR^+	74		
ER^+ or PR^+	28		
ER^- and PR^-	36		
$HER2^+$	9		
$HER2^-$	94		

[a]Independent t-test applied to age. [b]+, positive expression; -, negative expression.

Table II. Primers and restriction enzymes used in PCR-RFLP assays for genotyping.

Gene	Polymorphism	Primer sequence 5'→3'	T (°C)	Size (bp)	Restriction enzyme
TGFB1	C-509T	F: TTG AGT GAC AGG AGG CTG CTT A R: GCT GGG AAA CAA GGT AGG AGA A	63	178	Eco81I
	T+29C	F: CCA CCA CAC CAG CCC TGT T R: TCC GCT TCA CCA GCT CCA T	63	186	MspA1I
TGFBR2	G-875A	F: GGA ATG TCT TGG GCA AAT CT R: ACC TGA ATG CTT GTG CTT TTA TT	59	152	TaaI

F, forward primer sequence; R, reverse primer sequence.

Table III. Genotype and allele distributions for the polymorphisms of *TGFB1* and *TGFBR2* in breast cancer patients and controls.

Gene	Genotype	Case		Control		OR (95% CI)	P-value
		n	%	n	%		
TGFB1	C-509T						
	CC	28	16.5	41	23.0	1	
	CT	93	54.7	84	47.2	1.35 (0.73-2.50)	0.35
	TT	49	28.8	53	29.8	1.59 (0.91-2.81)	0.11
	CT/TT	142	83.5	137	77.0	1.50 (0.88-2.56)	0.14
	C	149	43.8	166	46.6	1	
	T	191	56.2	190	53.4	1.12 (0.83-1.51)	0.46
	T+29C						
	TT	38	22.4	49	27.5	1	
	TC	76	44.7	79	44.4	1.24 (0.73-2.10)	0.43
	CC	56	32.9	50	28.1	1.45 (0.82-2.57)	0.20
	TC/CC	132	77.6	129	72.5	1.32 (0.81-2.15)	0.27
	T	152	44.7	177	49.7	1	
	C	188	55.3	179	50.3	1.22 (0.91-1.65)	0.19
TGFBR2	G-875A						
	GG	114	67.1	104	58.4	1	
	GA	51	30.0	62	34.8	0.74 (0.47-1.17)	0.20
	AA	5	2.9	12	6.7	0.38 (0.13-1.12)	0.08
	GA/AA	56	32.9	74	41.5	0.68 (0.44-1.06)	0.09
	G	279	82.1	270	75.8	1	
	A	61	17.9	86	24.2	0.69 (0.48-0.99)	0.05

Odds ratios; 95% confidence intervals (CIs) and P-values were assessed by the logistic regression analysis, which was adjusted for age.

Statistical analysis. The independent samples t-test was used to compare the difference in age between breast cancer patients and the controls. Differences in the distributions of genotypes and alleles of *TGFB1* and *TGFBR2* variants between patients and controls were evaluated using the χ^2 test. The odds ratios (ORs), their 95% confidence intervals (CIs) and the P-value were assessed by logistic regression analyses, which were adjusted for age. Hardy-Weinberg equilibrium (HWE) was tested by a goodness-of-fit χ^2 test. Statistical analysis was performed using SPSS 16.0.

Results

Association of polymorphisms in TGFB1 and TGFBR2 with risk of breast cancer. As summarized in Table III, the genotype and allele frequencies were obtained for *TGFB1* C-509T, T+29C and *TGFBR2* G-875A in breast cancer cases and controls. The genotype distributions for the three polymorphisms did not deviate from HWE in the patients (P=0.17, 0.22 and 1.00, respectively) or controls (P=0.55, 0.14 and 0.54, respectively). No statistical difference was found between the

patients and controls for *TGFB1* C-509T, T+29C genotype and allele frequencies. Additionally, no overall association was found between *TGFBR2* G-875A genotype and breast cancer risk. However, the frequency of the *TGFBR2* -875A allele was marginally higher in cancer-free individuals than that in breast cancer patients (24.2 vs. 17.9%, P=0.05), indicating that *TGFBR2* -875A may predispose to breast cancer (adjusted OR=0.69, 95% CI 0.48-0.99).

Relationship of TGFBR2 -875A allele to breast cancer with the expression of ER, PR and HER2. Based on the effects of hormones on breast carcinogenesis, the specimens were divided into various subgroups, including ER^-, ER^+, PR^-, PR^+, ER^+PR^+, ER^+PR^-/ER^-PR^+ and ER^-PR^- (Fig. 1A-D). The samples were additionally classified into subgroups of $HER2^-$ and $HER2^+$ (Fig. 1E and F). Information on ER, PR and HER2 expression was available for 138, 138 and 103 patients with breast cancer, respectively. In detail, 88 ER^+, 50 ER^-, 88 PR^+, 50 PR^-, 74 ER^+PR^+, 28 ER^+PR^-/ER^-PR^+, 36 ER^-PR^-, 94 $HER2^-$ and 9 $HER2^+$ breast cancer cases were included (Table I). When performing stratification by ER, PR and HER2 expression, we found no difference in the frequencies of *TGFB1* C-509T, T+29C and *TGFBR2* G-875A between ER^+ and ER^-, PR^+ and PR^-, and $HER2^+$ and $HER2^-$ breast cancer cases (data available upon request). However, when comparing the ER^+, ER^-, PR^+, PR^-, ER^+PR^+, ER^+PR^-/ER^-PR^+, ER^-PR^-, $HER2^-$, $HER2^+$ breast cancer cases to the controls, our results showed that *TGFBR2* G-875A was associated with a decreased risk of breast cancer with ER^+ (OR=0.57, 95% CI 0.35-0.92), PR^+ (OR=0.54, 95% CI 0.34-0.88), ER^+PR^+ (OR=0.55, 95% CI 0.33-0.92) and $HER2^-$ (OR=0.55, 95% CI 0.34-0.88) under the dominant genetic model (Table IV).

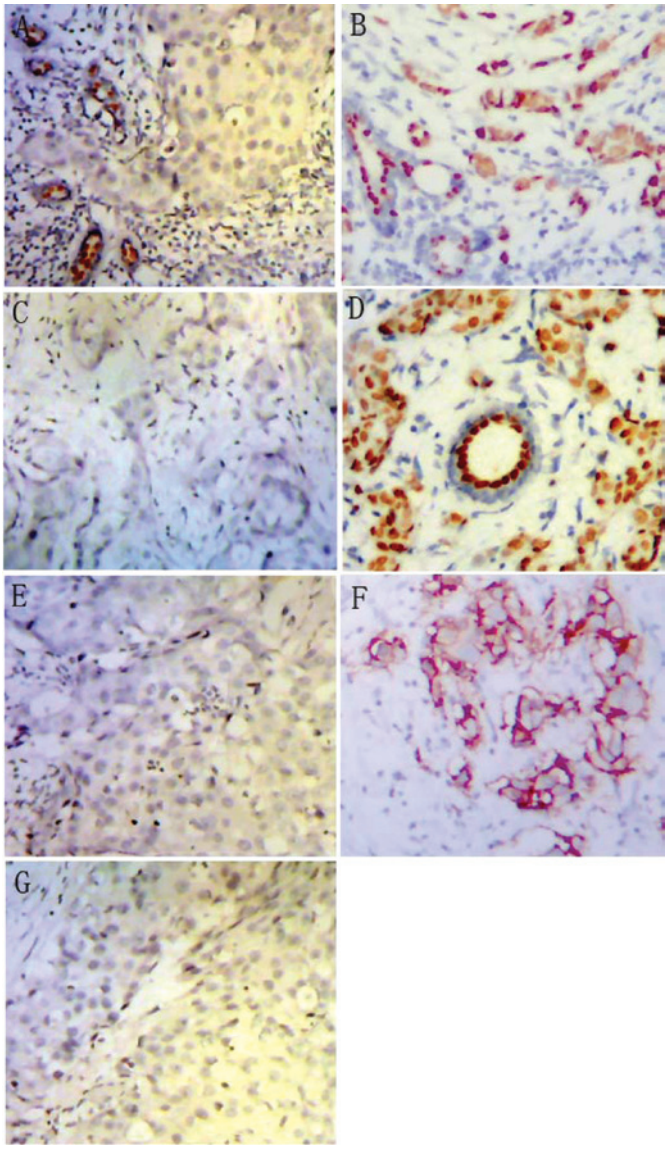

Figure 1. Schematic representation of the expression of ER, PR and HER2 in breast cancer specimens by immunohistochemical staining (magnification, x100). Breast cancer with (A) ER^-, (B) ER^+, (C) PR^-, (D) PR^+, (E) $HER2^-$ and (F) $HER2^+$, (G) negative control.

Discussion

In this study, no difference was found in the genotype and allele frequencies of *TGFB1* C-509T and T+29C between breast cancer patients and cancer-free female controls. This finding is consistent with a meta-analysis involving 10,633 cases and 13,648 controls for the C-509T polymorphism and 20,022 cases and 24,423 controls for T+29C (18). A previous study concerning T+29C showed decreased risk for Japanese pre-menopausal women with *CC* genotype, but not for post-menopausal women (19). Kaklamani *et al* found that breast cancer patients carrying the *TGFB1**CC allele of the polymorphism T+29C were more likely to have ER^- and PR^- tumors (14). Cox *et al* found that an 18% decreased risk of ER^+/PR^+ breast cancer occurred among women heterozygous at C-509T and a 38% decrease occurred among women homozygous for the T allele as compared to those with *CC* genotype (20). In this study, breast cancer cases were stratified with ER, PR and HER2 expression. No significant association was found between the two polymorphisms (C-509T and T+29C) and breast cancer risk in the Chinese population.

Additionally, previous studies indicated that the *TGFBR2* G-875A variant was not associated with breast cancer risk in the European population (21). However, results of the present study have shown that the -875A allele was marginally associated with a decreased risk of breast cancer. These findings are consistent with previous ones indicating that the *TGFBR2* G-875A polymorphism significantly correlates with a decreased risk of gastric and esophageal squamous cell carcinomas in the Chinese population (22,23). In particular, we found that the *TGFBR2* G-875A polymorphism may modify the risk of breast cancer with ER^+, PR^+, ER^+PR^+ and $HER2^-$.

Activation of the TGF-β-mediated signal transduction is subject to hormonal regulation (24). TGF-β signal transduction may play a crucial role in the activation of various complex TGF-β receptors, including TGFBR1 and TGFBR2 (25). The expression of *TGFBR2* is hormonally regulated and anti-estrogen may induce activation of the *TGFBR2* promoter (26). For instance, breast cancer cell lines expressing ER^+ are refractory to TGF-β effects, whereas ER^- cells are sensitive (27). Loss or undetectable expression of TGFBR2 has been reported to contribute to TGF-β resistance in ER^+ breast cancer cells (28). Paiva *et al* have suggested that the absence of TGFBR2 was associated with poorer prognosis in $HER2^-$ breast tumors (15).

Table IV. Association of TGFBR2 G-875A genotypes and alleles with ER, PR and HER2 expression.

Genotype	Cases (%)/Controls (%)	OR (95% CI)	P-value
ER^+ breast cancer cases vs. controls			
GG	62 (70.5)/104 (58.4)	1	
GA	25 (28.4)/62 (34.8)	0.66 (0.37-1.16)	0.15
AA	1 (1.1)/12 (6.7)	0.14 (0.02-1.12)	0.06
GA+AA	26 (29.5)/74 (41.6)	0.58 (0.33-1.00)	0.05
G	149 (84.7)/270 (75.8)	1	
A	27 (15.3)/86 (24.2)	0.57 (0.35-0.92)	0.02
PR^+ breast cancer cases vs. controls			
GG	64 (72.7)/104 (58.4)	1	
GA	22 (25)/62 (34.8)	0.57 (0.32-1.01)	0.06
AA	2 (2.3)/12 (6.7)	0.27 (0.06-1.26)	0.10
GA+AA	24 (27.3)/74 (41.5)	0.52 (0.30-0.91)	0.02
G	150 (85.2)/270 (75.8)	1	
A	26 (14.8)/86 (24.2)	0.54 (0.34-0.88)	0.01
ER^+ and PR^+ breast cancer cases vs. controls			
GG	53 (71.6)/104 (58.4)	1	
GA	20 (27)/62 (34.8)	0.62 (0.34-1.14)	0.13
AA	1 (1.4)/12 (6.7)	0.17 (0.02-1.31)	0.09
GA+AA	21 (28.4)/74 (41.5)	0.55 (0.31-0.99)	0.05
G	126 (85.1)/270 (75.8)	1	
A	22 (14.9)/86 (24.2)	0.55 (0.33-0.92)	0.02
$HER2^-$ breast cancer cases vs. controls			
GG	67 (71.3)/104 (58.4)	1	
GA	26 (27.7)/62 (34.8)	0.62 (0.36-1.09)	0.09
AA	1 (1.1)/12 (6.7)	0.13 (0.02-1.01)	0.05
GA+AA	27 (28.8)/74 (41.5)	0.54 (0.32-0.93)	0.03
G	160 (85.1)/270 (75.8)	1	
A	28 (14.9)/86 (24.2)	0.55 (0.34-0.88)	0.01

Odds ratios (ORs), 95% confidence intervals (CIs) and P-values were assessed by the logistic regression analysis, which was adjusted for age.

TGFBR2 -875A allele was proven to enhance the transcriptional activity of *TGFBR2* in normal epithelial cells (10). In this study, breast cancer subgroups, comprising ER^+, PR^+, ER^+PR^+ and $HER2^-$, had a higher frequency of *TGFBR2* -875G than the controls, indicating that the *TGFBR2* -875A allele correlated significantly to a decreased risk of breast cancer with ER^+, PR^+, ER^+PR^+ and $HER2^-$.

In conclusion, the present study suggests that the functional polymorphism G-875A in *TGFBR2,* but neither of the common genetic variants (C-509T and T-29C) in *TGFB1,* modify the predisposition to breast cancer in Chinese females. Notably, the *TGFBR2* -875A allele is significantly associated with a decreased risk of breast cancer with ER^+, PR^+ and $HER2^-$ expression.

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