Associations between polymorphisms at microRNA-binding sites in TYMS and breast cancer risk among Chinese women

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Abstract

Studies have suggested that thymidylate (TYMS) polymorphisms are associated with breast cancer. However, inconsistent results were obtained and data from Asian populations are largely lacking. In this study, the relationships between two common TYMS polymorphisms (rs2790 and rs1059394) and the breast cancer risk were evaluated. We also studied the TYMS expression between tumor and para-carcinoma tissues, and the association between TYMS levels and prognosis of breast cancer. This hospital-based study included 434 patients and 450 cancer-free individuals. Genotying was performed using Sequenom Mass-ARRAY. The microarray dataset GSE115144 was downloaded to compare the differences in TYMS expression between tumor and para-carcinoma tissues. The microarray dataset GSE20685 was used to analysis the metastasis free survival (MFS) and overall survival (OS) of patients. The rs2790 polymorphism was related to a higher risk of breast cancer (recessive model: OR=1.50, 95%CI=1.02-2.21, P=0.038) and the C allele of rs1059394 was overrepresented in patients with tumor stage III-IV (heterozygote model: OR=0.60, 95%CI=0.39-0.94, P=0.025; dominant model: OR=0.59, 95%CI=0.39-0.89, P=0.013). The tumor tissues had a higher TYMS expression levels and patients with higher TYMS expression levels had worse OS. Overall, TYMS polymorphism may increase susceptibility to breast cancer in Chinese Han women and TYMS expression levels may be a predictive factor for breast cancer patients.

1 Introduction

Benefiting from individualized and comprehensive treatment approaches, the breast cancer death rate dropped 40% from 1989 to 2017. [1] In contrast, its incidence has increased year by year. In total, 2,088,849 women worldwide were diagnosed breast cancer in 2018, including 367,900 were Chinese women, accounting for 17.6% of all cases.[2] And, the high social-development Index quintile included the highest number of breast cancer death cases.[3] Changes in life-style, such as the increased consumption of fatty foods and reduced pregnancy rates, may explain the increasing rate of breast cancer,[4] but genetic factors also contribute. Advances in genomics have improved our ability to predict the cancer risk, therapeutic responses and prognosis.

TYMS,which encodes thymidylate synthase, is associated with breast cancer development, drug resistance and prognosis.[5–7] Thymidylate synthase is a key enzyme involved in DNA synthesis and repair by catalyzing the conversion of deoxyuridine-5'-monophosphate (dUMP) to deoxythymidine-5'-monophosphate (dTMP).[8] The 21-gene recurrence score (RS) is a reliable way to predict prognosis in patients with estrogen receptor (ER) positive, human epidermal growth factor receptor 2 (Her-2) negative early-stage breast cancer and to assess the effectiveness of adjuvant chemotherapy. As one component of the 21 RS, higher TYMS expression levels are associated with a higher RS and a poorer prognosis.[5] As a proliferation marker, TYMS expression may be related to pathological complete response (pCR) rates in triple-negative breast cancer (TNBC).[7] Furthermore, TYMS is used to predict chemosensitivity[6, 9] and trastuzumab resistance[10].

Gene mutations are closely related to tumorigenesis, development, and prognosis. Single-nucleotide polymorphisms (SNPs) are the most abundant form of genetic variations. Rs2612100 in TYMS increases the breast cancer risk among European Americans and rs2853533 may increase the risk among African Americans.[11] Variation in TYMS (rs502396) is associated with reduced P16 protein expression and then related to breast carcinogenesis.[12] MicroRNAs (miRNAs) participate in various biological processes and may regulate tumor suppressor genes or oncogenes[13]. Three variants in the miRNA binding sites of TYMS (rs16430 6 bp del/ins, rs2790 A > G and rs1059394 C > T) are associated with the risk of onset and survival of gastric cancer patients.[14] Polymorphism of rs1059394 is associated with glioma risk.[15] Additionally, the rs16430 variant at an miRNA-binding site in TYMS is predicted to influence the breast cancer risk in non-Hispanic white women.[16] However, data for Chinese patients are lacking. We explored the associations of two common miRNA binding sites (rs2790 A > G and rs1059394 C > T) with breast cancer among Chinese Han patients. We further analyzed the difference of TYMS expression levels between tumor and para-carcinoma tissues, and prognostic value of TYMS expression levels in breast cancer among Chinese population.

2 Materials And Methods

2.1 Study population

In total, 434 Chinese Han women with pathologically-confirmed breast cancer who were treated at the Department of Oncology (Second Affiliated Hospital of Xi'an Jiaotong University) between 2013 and 2015 were included in this study. Patients with cancers other than breast cancer were excluded. Healthy controls were defined as individuals who were free from any cancer or any other disease, such as diabetes and cardiovascular disease. Finally, 450 healthy Chinese Han individuals who visited the medical examination center at the Second Affiliated Hospital of Xi'an Jiaotong University for a check-up during the study period met the inclusion criteria. The controls were frequency-matched to the cases according to age (± 5 years) and menopausal status.

2.2 Ethics approval and consent to participate

The study protocol was approved by the Ethics Committee of the Second Affiliated Hospital of Xi'an Jiaotong University Shaanxi Province (Xi'an, China). The study purpose and experimental procedures were conveyed to all participants and informed consent was obtained. Demographic

and personal information was collected from an epidemiological questionnaire and clinical information was collected from medical records and pathological reports.

2.3 Genotyping assay

All patients and controls contributed 5 ml of peripheral blood. The samples were collected in ethylenediaminetetraacetic acid tubes and stored at -80 °C after centrifugation. Genomic DNA was extracted from whole blood by the Universal Genomic DNA Extraction Kit (TaKaRa, Kyoto, Japan) and DNA concentrations were assessed using spectrophotometry (DU530 UV/VIS spectrophotometer; Beckman Instruments, Fullerton, CA, USA). The Multiplexed SNP Mass EXTEND assay was designed using Sequenom Mass ARRAY Assay Design (version3.0; Agena Bioscience, San Diego, CA, USA). SNP genotyping was performed using Sequenom Mass-ARRAY RS1000. Sequenom Typer 4.0 was used to analyze data. Primers for each SNP (rs2790 A > G and rs1059394 C > T) are presented in Table 1.

Table 1
Primers used for this study

SNP_ID	1st-PCRP	2nd-PCRP	UEP_SEQ
rs2790	ACGTTGGATGGGATGCCGAGGTAAAAGTTC	ACGTTGGATGAACTGATAGGTCACGGACAG	AGATTTTTGACCTAGTTCCTT
rs1059394	ACGTTGGATGCGACCTGTTGTAATTGCTCC	ACGTTGGATGGTATCGACAGGATCATACTC	taACATCCTGTGTACTTGTTTCA
PCRP: polymerase chain reaction primer; SNP:single nucleotide polymorphism; UEP-SEQ: unextension primer sequence			

2.4 Gene expression correlation analysis

The microarray dataset GSE115144 was downloaded from the GEO database. 42 Chinese samples (21 breast cancer tissues and 21 para-carcinoma tissues) were included in this dataset. The Wilcoxon test was used to compare the differences in TYMS expression between tumor and para-carcinoma tissues.

2.5 Gene expression and the prognosis of breast cancer patients

Online tools (http://bioinfo.henu.edu.cn/DatabaseList.jsp) were used to obtain metastasis-free survival (MFS) and overall survival (OS) data of Chinese patients with breast cancer based on the GSE20685 dataset. Patients were divided into groups by the median TYMS expression level.

2.6 Statistical analysis

Microsoft Excel was used for data management and SPSS (version 21.0, IBM Corporation, Armonk, NY, USA) was used for statistical analyses. Hardy Weinberg equilibrium (HWE) was examined by Fisher's exact test. Differences in allele frequencies for each SNP between patients and controls were evaluated by two-tailed Pearson's chi-squared tests and $P < 0.05$ was considered statistically significant. Five different genetic models (allele model, the co-dominant models including homozygote and heterozygote models, recessive model and dominant model) were used to evaluate the association between SNPs and breast cancer risk. SPSS was used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for each model. A stratification analysis was conducted to adjust for possible confounders.

3 Results

3.1 Characteristics of the study population

There were no differences in age, body mass index (BMI), and menopausal status between 434 cases and 450 controls ($P = 0.306$, 0.177 and 0.098, respectively). The average age of patients and healthy controls were 51.95 ± 10.35 years and 50.66 ± 9.57 years, respectively. Both general and molecular characteristics of tumors are shown in Table 2.

Table 2
The clinical characteristics of breast cancer cases and controls

Characteristics		Cases (%)	Control (%)	P value
Number		434	450	
Age (mean ± SD)		51.95 ± 10.35	50.66 ± 9.57	0.306
≦ 49		180(41.5)	202(44.9)	
>49		254(58.5)	248(55.1)	
BMI, kg/m2 (mean ± SD)		22.38 ± 2.61	22.75 ± 5.08	0.177
Menopausal status				
Premenopausal		157(36.2)	188(41.8)	0.098
Postmenopausal		277(63.8)	262(58.2)	
TNM Stage				
		114(26.3)	-	-
		192(44.2)	-	-
		89(20.5)	-	-
		39(9)	-	-
Immunohistochemistry results				
ER	–	142(32.7)	-	-
	+	292(67.3)	-	-
PR	–	189(43.5)	-	-
	+	245(56.5)	-	-
Her-2	–	250(57.6)	-	-
	+	184(42.4)	-	-

BMI: body mass index; ER: estrogen receptor; PR: progesterone receptor; Her-2: human epidermal growth factor receptor-2.

3.2 Associations between TYMS SNPs and the risk of breast cancer

As shown in Table 3, the genotype distributions of the TYMS rs2790 and rs1059394 polymorphisms in the control group did not deviate from HWE (P = 0.153 and 0.466, respectively). Compared to the AA + AG genotype of rs2790, GG genotype carriers had a higher breast cancer risk (recessive model: OR = 1.50, 95%CI = 1.02–2.21, P = 0.038). No differences were found in other genotype models of rs2790. For rs1059394, there were no statistic differences among genotypes in any models.

Table 3
Genotype frequencies of TYMS polymorphisms in cases and controls

SNP	Genetic model	Genotype	Case/Control	OR (95%CI)	P	P(HWE)
rs2790						
	Co-dominate	AA	163/173			0.153
		AG	196/222	0.94(0.70–1.25)	0.658	
		GG	71/52	1.45(0.96–2.20)	0.080	
	Dominate	AA	163/173			
		AG + GG	267/274	1.03(0.79–1.36)	0.809	
	Recessive	AA + AG	359/395			
		GG	71/52	1.50(1.02–2.21)	0.038	
	Allele	A	522/568			
		G	338/326	1.13(0.93–1.37)	0.221	
rs1059394						
	Co-dominate	TT	177/187			0.466
		TC	204/210	1.03(0.77–1.36)	0.857	
		CC	48/50	1.01(0.65–1.59)	0.950	
	Dominate	TT	177/187			
		TC + CC	252/260	1.02(0.78–1.34)	0.863	
	Recessive	TT + TC	381/397			
		CC	48/50	1.00(0.66–1.52)	0.958	
	Allele	T	558/584			
		C	300/310	1.01(0.83–1.23)	0.899	

OR: odds ratio; CI: confidence interval.

3.3 Associations between TYMS SNPs and the features of breast cancer

We conducted a subgroup analysis by the clinical and pathological characteristics of patients to find more detailed relationships. The stratification factors included age, BMI, menstrual status, TNM stage, and the expression statuses of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (Her-2), and Ki67. No associations were found between rs2790 and any clinical or pathological features (Table 4). However, the C allele of rs1059394 was more frequently expressed in patients with tumor stage III–IV than with other stages (heterozygote model: OR = 0.60, 95%CI = 0.39–0.94, P = 0.025; dominant model: OR = 0.59, 95%CI = 0.39–0.89, P = 0.013) (Table 5).

Table 4
The associations between the rs2790 Polymorphism and characteristics of breast cancer

Variables	AA	AG	GG	AG + GG
age				
>49/≦49	104/59	107/89	39/32	146/121
OR (95%CI)	1.00 (reference)	0.68(0.44–1.04)	0.69(0.39–1.22)	0.68(0.46–1.02)
P value		0.078	0.201	0.063
BMI(kg/m2)				
≥ 23/□23	58/105	72/124	35/36	107/160
OR (95%CI)	1.00 (reference)	1.05(0.68–1.62)	1.76(1.00-3.10)	1.21(0.81–1.82)
P value		0.821	0.05	0.353
Menstrual status				
Yes/No	107/56	120/76	46/25	166/101
OR (95%CI)	1.00 (reference)	0.83(0.54–1.27)	0.96(0.54–1.74)	0.86(0.57–1.29)
P value		0.387	0.899	0.468
TNM Stage				
III-IV/I-II	44/119	58/138	25/46	83/184
OR (95%CI)	1.00 (reference)	1.14(0.72–1.81)	1.47(0.80–2.66)	1.22(0.79–1.89)
P value		0.587	0.206	0.367
ER				
+/-	105/58	131/65	53/18	184/83
OR (95%CI)	1.00 (reference)	1.11(0.72–1.72)	1.63(0.88–3.09)	1.22(0.81–1.85)
P value		0.631	0.126	0.336
PR				
+/-	90/73	110/86	44/27	154/113
OR (95%CI)	1.00 (reference)	1.04(0.68–1.58)	1.32(0.75–2.36)	1.11(0.75–1.64)
P value		0.863	0.337	0.617
Her-2				
+/-	71/92	87/109	24/47	111/156
OR (95%CI)	1.00 (reference)	1.03(0.68–1.57)	0.66(0.37–1.17)	0.92(0.62–1.37)
P value		0.875	0.164	0.686

BMI: body mass index; ER: estrogen receptor; PR: progesterone receptor; Her-2: human epidermal growth factor receptor-2.

Table 5
The associations between the rs1059394 Polymorphism and characteristics of breast cancer

Variables	TT	TC	CC	TC + CC
age				
>49/≦49	98/79	121/89	32/16	153/105
OR (95%CI)	1.00 (reference)	1.18(0.78–1.77)	1.61(0.84–3.21)	1.25(0.84–1.84)
P value		0.437	0.162	0.269
BMI(kg/m2)				
≥ 23/<23	76/101	73/131	14/34	87/165
OR (95%CI)	1.00 (reference)	0.74(0.49–1.12)	0.55(0.27–1.07)	0.70(0.47–1.04)
P value		0.154	0.087	0.078
Menstrual status				
Yes/No	110/67	129/75	35/13	164/88
OR (95%CI)	1.00 (reference)	1.05(0.69–1.59)	1.64(0.83–3.42)	1.14(0.76–1.69)
P value		0.827	0.169	0.534
TNM Stage				
III-IV/I-II	64/113	52/152	11/37	63/189
OR (95%CI)	1.00 (reference)	0.60(0.39–0.94)	0.52(0.24–1.07)	0.59(0.39–0.89)
P value		0.025	0.088	0.013
ER				
+/-	125/52	137/67	27/21	164/88
OR (95%CI)	1.00 (reference)	0.85(0.55–1.31)	0.53(0.28–1.04)	0.78(0.51–1.17)
P value		0.467	0.061	0.229
PR				
+/-	100/77	119/85	23/25	142/110
OR (95%CI)	1.00 (reference)	1.08(0.72–1.62)	0.71(0.37–1.34)	0.99(0.67–1.46)
P value		0.718	0.291	0.976
Her-2				
+/-	70/107	89/115	23/25	112/140
OR (95%CI)	1.00 (reference)	1.18(0.79–1.78)	1.41(0.74–2.68)	1.22(0.83–1.81)
P value		0.421	0.298	0.313
BMI: body mass index; ER: estrogen receptor; PR: progesterone receptor; Her-2: human epidermal growth factor receptor-2.				

3.4 TYMS expression analysis

As shown in Fig. 1, the tumor tissues tends to be related to a higher level of TYMS expression than para-carcinoma tissues (P<0.001).

3.5 TYMS expression and prognosis in breast cancer

We found no association between the expression level of TYMS and the MFS of patients with breast cancer (Fig. 2A). But, patients with higher TYMS levels had a worse OS. (Fig. 2B).

4 Discussion

TYMS plays an important roles in folate metabolism and DNA repair.[14] Previous clinical studies have shown that *TYMS* polymorphisms are associated with various of cancers, such as gastric cancer,[14] lung cancer,[17] hepatocellular carcinoma,[18] and acute lymphoblastic leukemia.[19] Additionally, *TYMS* polymorphisms may predict the chemosensitivity to 5-fluorouracil, doxorubicin, cyclophosphamide, pemetrexed and so on.[20, 21, 9] *TYMS* SNPs influence cancer susceptibility and chemosensitivity via effects on *TYMS* expression[22] and its effects differ with respect to race.[23, 11] However, inconsistent results have been obtained regarding the association between the miRNA binding sites of *TYMS* SNPs and breast cancer and data from Asian populations are lacking.

Guan et al. found that rs2790 and rs1059394 have no effect in non-Hispanic white women. We found that rs2790 may increase the breast cancer risk and the C allele of rs1059394 is closely related to a more advanced clinical stage among Chinese Han people. Rs2790 is in linkage disequilibrium with a functional SNP (TSER, three or two repeats of a 28-bp sequence) in *TYMS* [14]and modulates *TYMS* expression by its effects on the binding of hsa-miR-1248 to its target gene.[19] However, little is known about the functionality of these two SNPs. More experimental studies are urgently needed to clarify the mechanism underlying the effects of *TYMS* polymorphisms.

Moreover, we used data from the GEO database to evaluate the difference of *TYMS* expression between tumor and para-carcinoma tissues among Chinese patients. And we found that tumor tissues had higher *TYMS* expression. The effect of *TYMS* expression level on the prognosis among Chinese breast cancer patients was showed that patients with higher expression levels of *TYMS* had a worse OS. D'Arcy et al. reported that African American women with breast cancer have higher expression levels of *TYMS* and a poorer prognosis than those of Caucasian women,[23] which means there are racial differences in the *TYMS* expression. China is a multi-ethnic country, so it will be valuable to compare the difference between different nationalities.

We conducted a hospital-based study and all samples were obtained from the northwest region of China; therefore, the selection bias is unavoidable. Large-scale multicenter studies are needed to verify our results. *TYMS* expression and the prognosis analyses were conducted based on GEO database; we will further detect *TYMS* expression levels among different types of breast cancer and all patients will be follow up to obtain survival statistics. Furthermore, the influence of ethnic difference on *TYMS* expression will be a major focus of future research.

In conclusion, carriers of the GG genotype of rs2790 may have a higher risk of breast cancer and the C allele of rs1059394 may signify a poorer TNM stage. In addition, the tumor tissues had higher *TYMS* than para-carcinoma tissues in breast cancer and patients with higher *TYMS* levels may be related to a worse OS.

Declarations

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Conflict of interest

The authors declare that they have no competing interests.

Authors' contributions

KL, SL, NL, ZZ and YW collected the samples. YZ, YZ, SQ W, PX and YJ D detected the SNPs. ZJ D, HF K, MW and SL also provided patients. ZJ D and HF K guided experiments. MW and JY analyzed and interpreted the data. MW was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

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Figures

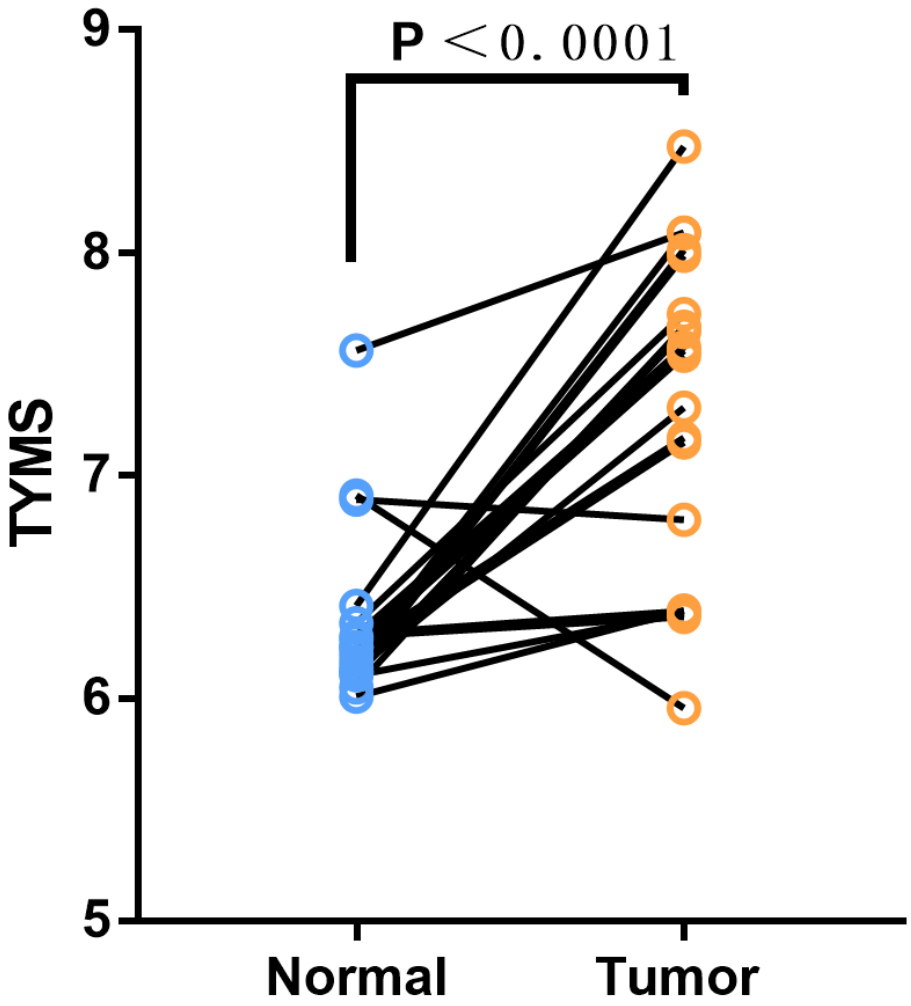

Figure 1

The TYMS expression between tumor and para-carcinoma tissues based on the microarray dataset GSE115144 from the GEO database.

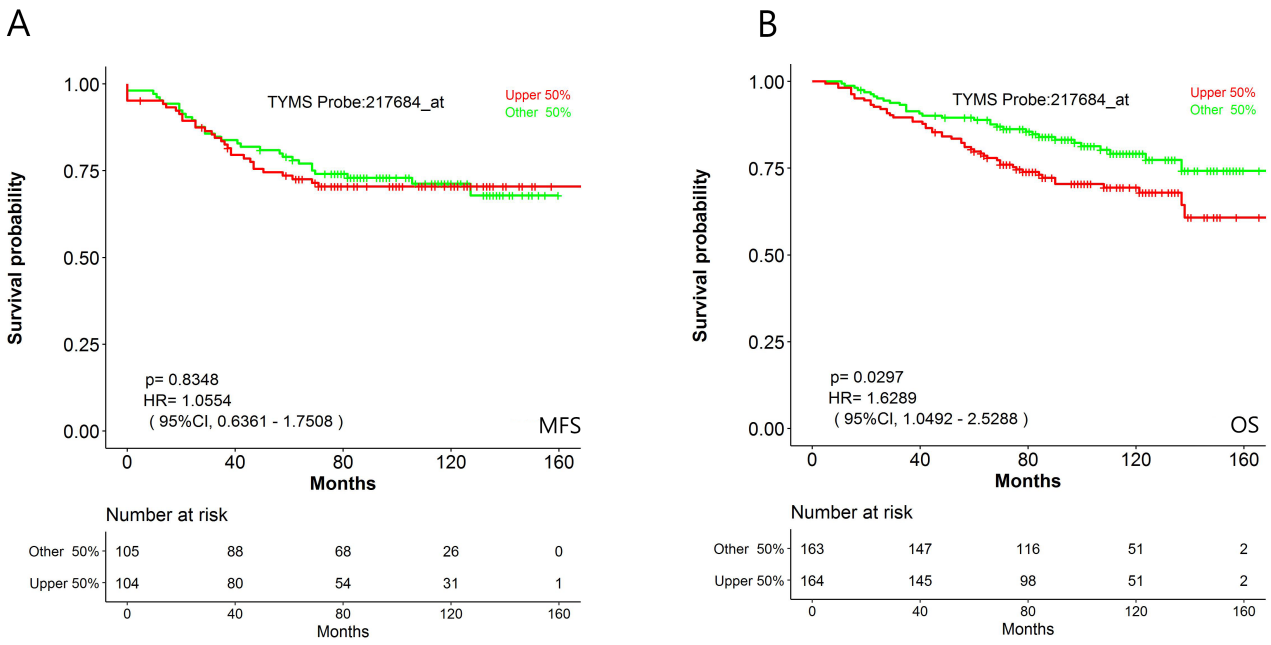

Figure 2

Association between TYMS expression level and the prognosis of breast cancer patients (http://bioinfo.henu.edu.cn/DatabaseList.jsp). A, TYMS expression and the OS of breast cancer patients in China. B, TYMS expression and the MFS of breast cancer patients in China.