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Original Article

Genetic variant of PSCA rs2294008 increases susceptibility and predicts poor prognosis of colorectal cancer

Fei Qian[1,2], Hongyu Cai[1,2], Lirong Zhu[1,2], Zhong Chen[1,2]

[1]*Department of General Surgery, The First Affiliated Hospital of Soochow University, Soochow 215006, China;* [2]*Department of General Surgery, Affiliated Hospital of Nantong University, Nantong 226001, China*

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Abstract: The single nucleotide polymorphism (SNP) rs2294008 in prostate stem cell antigen (PSCA) has been widely reported in several types of cancer, including prostate cancer and gastric cancer. In this study, we hypothesized that PSCA rs2294008 was also associated with the risk and survival of colorectal cancer (CRC) in Chinese patients. We conducted genotyping by TaqMan method in 165 CRC patients and 389 healthy controls (HC). Our results showed that the frequency of TT allele was significantly high in cases compared with that in HC. This SNP was significantly associated with CRC risk in recessive model (TT vs. TC+CC, OR=2.293, 95% CI=1.149-4.574, p=0.019), while no significant association was found in dominant model (CC vs. TT+TC, OR=1.259, 95% CI=0.870-1.821, p=0.221). Stratified analysis by age, gender, smoking and alcohol history also showed similar results. Moreover, we found that rs2294008 TC/TT genotypes was correlated with shorter survival of CRC patients. However, using univariate and multivariate Cox regression analysis, we suggested that PSCA rs2294008 could indicate poor prognosis although it wasn't an independent prognostic factor. In summary, these results implied that PSCA rs2294008 could be involved in the risk and prognosis of colorectal cancer patients.

Keywords: PSCA, rs2294008, colorectal cancer, prognosis

Introduction

Colorectal cancer (CRC) is one of the most common types of cancer, with an estimated 376300 new cases in 2015, and the fifth most frequent cause of cancer-related death in China [1]. Due to the progression in the therapeutic strategy, majority of patients have been administrated the neoadjuvant chemotherapy and surgery, which are demonstrated to improve the long-term survival rate [2]. Despite this, the 5-year survival of CRC is still less than 50% in the developing countries and the underlying mechanism of CRC initiation and development remains elusive. Recently, the studies on the association between genomic alternation and cancer demonstrated that genetic variants could be the biomarkers and had biological functions in cancers [3-5]. Therefore, identifying the roles of genetic variants could help to improve the early diagnosis and treatments of colorectal cancer.

Prostate stem cell antigen (PSCA) is a member of glycosylphosphatidylinositol-anchored cell membrane glycoproteins. The *psca* gene is located on chromosome 8q24.3, encoding a 114-amino-acid protein. PSCA is highly expressed in prostate and up-regulated in a large proportion of cancers, such as prostate cancer, bladder cancer, pancreatic cancer and ovarian cancer [6, 7]. However, PSCA was also reported to be down-regulated in esophagus cancer, indicating that the role of PSCA was varying according to the type of cancers [8].

The single nucleotide polymorphism (SNP) rs2294008 in PSCA Exon 1 causes a change from C to T, leading to the reduced transcriptional activity of PSCA upstream fragments [9]. Notably, PSCA rs2294008 was identified as a significant risk factor of gastric cancer in Chinese and Japanese population [10, 11]. Similar results were found in the study of bladder cancer [12]. Interestingly, Kupcinskas reported that

Table 1. Distribution of selected characteristics of patients with colorectal cancer and controls

Variable	Patients (%) (n=165)	Controls (%) (n=389)	*p* value
Mean age ± SD, year	62.82±11.00	64.51±7.69	
Age (years)			0.772
≤60	64 (38.8)	156 (40.1)	
> 60	101 (61.2)	233 (59.9)	
Gender			0.408
Male	100 (60.6)	221 (56.8)	
Female	65 (39.4)	168 (43.2)	
Smoking history			0.089
No	89 (53.9)	240 (61.7)	
Yes	76 (46.1)	149 (38.3)	
Alcohol history			0.021*
No	71 (43.0)	209 (53.7)	
Yes	94 (57.0)	180 (46.3)	
pT status			
pT1-2	77 (46.7)	-	
pT3-4	88 (53.3)	-	
pN status			
N0	82 (49.7)	-	
N1-N2	83 (50.3)	-	

*$p<0.05$.

in 574 European subjects, the distribution of PSCA rs2294008 was similar between controls and CRC patients, implying that this variant was not associated with CRC risk [13]. However, its effect on colorectal cancer is still inconclusive. The role of PSCA rs2294008 in Chinese population remains to be further investigated.

Accordingly, the present study explored the association between PSCA rs2294008 polymorphism and the risk and prognosis of CRC patients. A genotyping analysis of PSCA rs2294008 C/T was conducted, and its association with susceptibility was assessed in case-control study with 165 CRC patients and 389 healthy controls. Furthermore, we investigated the potential of PSCA rs2294008 as a prognostic marker for CRC.

Materials and methods

Study population

Our study was approved by the Ethics Committee board of Affiliated Hospital of Nantong University. A total of 165 colorectal cancer cases were enrolled between July 2008 and December 2011. The patients were diagnosed without pervious chemotherapy or radiotherapy before surgery and had surgical resection at the hospital. In addition, 389 age and gender-matched health control cases were recruited in this study. 5 ml of peripheral blood samples from both cancer patients and healthy controls were collected for DNA extraction. The blood samples were aliquoted and stored at -80°C until analysis. All participants agreed to the study and gave written informed consent.

The histology and TNM stages were classified according to the 7th edition of the American Joint Committee on Cancer staging (AJCC). The follow-up of each CRC patient was performed at 3-month intervals in the first year and thereafter at 6-month intervals. The latest follow-up data in the present study were obtained in December 2015.

Genotyping

Genomic DNA was extracted from ethlyenediamine-tetracetic acid preserved blood using QIAamp DNA blood Mini extraction kit (Qiagen) according to the manufacturer's protocol. The rs2294008 SNP was genotyped by the TaqMan SNP assay with 384-well ABI 7900HT real-time PCR System (Applied Biosystem) as described previously [14]. The probe we used was as followed: "CTCCACCACAGCCCACCAGTGACCA[C/T]GAAGGCTGTGCTGCTTGCCCTGTTG", which was obtained from ThermoFisher Scientific. The reaction volume was 10 μl, and the PCR was performed by 95°C for 5 minutes, and 45 cycle of 92°C for 15 seconds and 60°C for 1 minute. About 10% of the samples were randomly used as repeated genotyping, and the results were 100% concordant.

Statistical analysis

Hardy-Weinberg equilibrium in controls was measured by asymptotic X^2 test. The X^2 test was also employed to evaluate the difference in the association between the demographic characteristics. The association between distribution of PSCA SNP and colorectal cancer risk was assessed by binary logistic regression analysis and Odds ratios (OR) and 95% confidence intervals (CI) were also measured. Moreover, the association between the PSCA SNP and colorectal cancer risk was also strati-

Table 2. Logistic regression analysis of associations between genotype frequency of PSCA rs2294008 and colorectal cancer risk

Genotype	n (%)		OR (95% CI)[1]	*p* value
	Cases (n=165)	Controls (n=389)		
PSCA rs2294008				
CC	84 (50.9)	224 (57.6)	1	
TC	64 (38.8)	146 (37.5)	1.115 (0.754-1.647)	0.586
TT	17 (10.3)	19 (4.9)	2.396 (1.179-4.871)	0.016*
Dominant model (CC vs. TT+TC)			1.259 (0.870-1.821)	0.221
Recessive model (CC+TC vs. TT)			2.293 (1.149-4.574)	0.019*

[1]ORs and *p* value were obtained after the adjustment of age, gender, smoking and drinking statues; *p<0.05.

fied by age, gender, smoking and drinking history. The overall survival rate according to the clinical information was depicted by Kaplan-Meier method and assessed by the log-rank test. Univariate and multivariate Cox regression analysis were performed to assess the predictive factors that had significant influence colorectal cancer prognosis. All statistical analyses were achieved by SPSS 21.0 (IBM). A *p* value less than 0.05 was considered statistically significant.

Results

Characteristics of patients

Table 1 described the demographic characteristics and clinical information of case-control study. Briefly, 165 colorectal cancer patients were averagely aged at 62.82±11.00 years, and 61.2% of them was male. Age, gender, T stages and lymph node invasion status were indicated. 389 age and sex matched healthy controls were aged at 64.51±7.69 years, and 63.8% of them was male. Age, gender, smoking and drinking history were indicated. Among controls, genotype distribution for PSCA was in Hardy-Weinberg equilibrium (x^2=0.600, *p*=0.439).

Genotyping distribution of PSCA rs2294008 and risk of colorectal cancer

The allele frequencies of the PSCA rs2294008 C > T between cases and controls were listed in **Table 2**. The detail data were shown in Supplementary Data. Furthermore, the association between rs2294008 and the CRC risk was shown. We found that the frequency of TT allele was significantly higher than that of CC allele in the CRC patients. The dominant model indicated that overall T carriers (TT/TC) showed no association with increased CRC susceptibility compared to CC carriers (OR=1.259, 95% CI=0.870-1.821, *p*=0.221). However, the recessive model (TT vs. TC/CC) showed that there was a significant association between PSCA rs2294008 and CRC risk (OR=2.293, 95% CI=1.149-4.574, *p*=0.019). The associations between rs2294008 and risk of colorectal cancer were further examined by stratification analyses of age, gender, smoking and alcohol history. As shown in **Table 3**, it was consistent that TC/TT allele increased the risk of CRC.

Association of PSCA rs2294008 with overall survival

Among the 165 patients with colorectal cancer, the estimated 5-year survival rate was 52.5% (95% CI=43.5% to 61.5%). Interestingly, the Kaplan-Meier analysis indicated that the TT and CT genotype of rs2294008 was associated with poor survival compared with that of the CC genotype (**Figure 1**). The univariate Cox regression analysis showed that carrier TT and CT could indicate poor prognosis, as well as clinical T status and N status. However, the multivariate regression result suggested that N status could be an independent prognostic factor of CRC patients rather than PSCA rs2294008 (**Table 4**).

Discussion

Genetic variants have shown critical roles in cancer development and clinical diagnosis. Recently, PSCA has been demonstrated to be involved in a variety types of cancers, including prostate cancer and gastric cancer [9, 15]. Several studies reported that the common PSCA SNP rs2294008 served as a significant risk allele for gastric cancer and could be a

Table 3. Stratified analysis of the association between PSCA rs2294008 and colorectal cancer risk

Variables	Rs2294008 (Cases/Controls)				OR (95% CI)[1]	*p* value
	CC		TT/TC			
	N	%	N	%		
Age						
≤60	32/90	50.0/57.7	32/66	50.0/42.3	1.238 (0.682-2.250)	0.483
> 60	52/134	51.2/57.5	49/99	48.8/42.5	1.242 (0.774-1.991)	0.369
Gender						
Male	52/124	52.0/56.1	48/97	48.0/43.9	1.167 (0.725-1.878)	0.526
Female	32/100	49.2/59.5	33/68	50.8/40.5	1.334 (0.742-2.435)	0.329
Smoking history						
No	49/140	55.1/58.3	40/100	44.9/41.7	1.112 (0.679-1.822)	0.673
Yes	35/84	46.1/56.4	41/65	53.9/43.6	1.448 (0.825-2.542)	0.198
Drinking history						
No	41/125	57.7/59.8	30/84	42.3/40.2	1.076 (0.622-1.862)	0.793
Yes	43/99	45.7/55.0	51/81	54.3/45.0	1.421 (0.859-2.352)	0.172

[1]ORs and *p* value were obtained after the adjustment of age, gender, smoking and drinking statues.

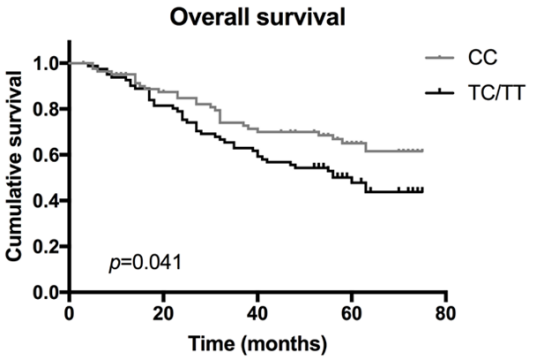

Figure 1. Overall survival of PSCA rs2294008 in colorectal cancer patients.

potential marker for predicting the gastric cancer patients' prognosis [11, 16, 17]. Moreover, it was found that rs2294008 had no association with colorectal cancer susceptibility in European population, as well as MUC1 rs4072037 and PLCE1 rs2274223 SNPs [13]. However, in Chinese population, it has been demonstrated that rs2274223 is significantly correlated with high risk of colorectal cancer [18, 19], while rs4072037 shows a weak association with CRC [20]. Therefore, we perceived that the role of PSCA rs2294008 in colorectal cancer remains to be further investigated.

In the present study including 165 cases of colorectal cancer patients with over 5-years follow-up, and 389 healthy controls, we explored PSCA rs2294008 with the risk and survival of colorectal cancer and found that there was a significant association between PSCA rs2294008 and colorectal cancer risk. This observation was not consistent with previous study [13]. Kupcinskas reported that PSCA SNPs were unlikely to have a role in CRC development in Caucasians. So, we hypothesized that these results in our study could be partially explained by the different ethnical background of patients' cohorts. Further study would be performed to investigate the potential of the combination of multiple biomarkers including rs2294008, rs2976392 and other SNPs in evaluating CRC susceptibility.

Interestingly, we also found that patients harbored this SNP had a relative shorter survival rate. Cox regression model analyses indicated that PSCA TT genotype could be a potential prognostic factor of CRC patients, which hasn't been reported before. However, the multivariate analysis showed that PSCA rs2294008 wasn't an independent prognostic factor in our study.

We acknowledged several strengths and limitations of the present study. This investigation was the first to analyze the relevance of PSCA SNP rs2294008 on the prognosis of CRC patients. We made a follow-up and had above 5-year survival data of 165 cases of patients. The frequency of the variant allele T in our control group (23.7%) wasn't comparable to those in the control group of gastric cancer study [21]. To our knowledge, these finding also

Table 4. Univariate and multivariate analysis for overall survival (Cox regression analysis)

Parameters	Univariate analysis			Multivariate analysis[a]		
	OR	95% CI	*p*	OR	95% CI	*p*
Age	0.976	0.600-1.589	0.923	-	-	-
Gender	1.442	0.869-2.392	0.157	-	-	-
Smoking history	1.410	0.877-2.265	0.156	-	-	-
Alcohol history	1.345	0.823-2.198	0.237	-	-	-
pT status	1.738	1.058-2.855	0.029*	1.254	0.714-2.201	0.431
pN status	2.033	1.266-3.265	0.003*	1.754	1.011-3.042	0.046*
Rs2294008 (CC vs. TC/TT)	1.642	1.012-2.664	0.045*	1.484	0.911-2.418	0.113

[a]Final multivariate analysis includes only those covariates that were significantly associated with survival ($p<0.05$). *$p<0.05$.

proved the heterogeneity of cancer types. The limitations also should be considered. Firstly, the case number would be further extended so that we could have more prevalent conclusion. A relative small population might have impact on the statistical analysis. Secondly, although we have examined the common parameters in cases such as age, gender, smoking and drinking history, other important risk factors, for instance, diet, primary site, adjuvant chemotherapy were missing in the study [22-24]. These data might be further explored and could contribute to the study of etiology of colorectal cancer.

In summary, we suggested that PSCA SNP rs2294008 was associated with increased susceptibility and poor prognosis of colorectal cancer in this Chinese cohort. A better understanding of this variant would help to elucidate the pathology of colorectal cancer.

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Disclosure of conflict of interest

None.

Address correspondence to: Dr. Zhong Chen, Department of General Surgery, Affiliated Hospital of Nantong University, #20, Xisi Road, Nantong 226001, China. Tel: 86-051385052504; E-mail: 79731570@qq.com

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