Original Article

Genetic Polymorphism of *PSCA* and Risk of Advanced Precancerous Gastric Lesions in a Chinese Population

Hong-mei Mu[1], Chen Wu[2], Lian Zhang[1*], Kai-feng Pan[1], Jun-ling Ma[1], Yang Zhang[1] Wen-qing Li[1], Hua-kang Tu[1], Hong-mei Zeng[1], Wei-dong Liu[3], Tong Zhou[1] Dong-xin Lin[2], Wei-cheng You[1]

[1]Key Laboratory of Carcinogenesis and Translational Research (Ministry of Education), Department of Epidemiology, Peking University School of Oncology, Beijing Cancer Hospital & Institute, Beijing 100142, China; [2]Department of Etiology and Carcinogenesis, Cancer Institute and Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing 100021, China; [3]Linqu Public Health Bureau, Linqu, Shandong, China

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ABSTRACT

Objective: To evaluate the relationship between the genetic polymorphism of prostate stem cell antigen (*PSCA*) and the risk of advanced precancerous gastric lesions including intestinal metaplasia(IM) and dysplasia(Dys), a population-based study was conducted in Linqu County, a high-risk area of gastric cancer (GC) in China.

Methods: The prevalence of gastric lesions including superficial gastritis(SG), chronic atrophic gastritis(CAG), IM and Dys was determined by histopathologic examination. The genotypes were determined by polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) technique. The effects of *PSCA* genetic variant on the risks of IM and Dys were calculated by unconditional logistic regression.

Results: Multivariate analysis revealed subjects carrying *PSCA* rs2294008 CT/TT genotype were associated with an increased risk of IM (OR=1.38, 95% CI=1.11-1.71) and Dys (OR=1.75, 95% CI=1.36-2.26), especially for subjects with *H.pylori* infection (IM: OR=1.34, 95% CI=1.05-1.71; Dys: OR=1.82, 95% CI=1.37-2.42). Furthermore, *H. pylori* infection and *PSCA* rs2294008 CT/TT genotype were observed to jointly elevate the risk of IM (OR=3.32, 95% CI=2.33-4.71) and Dys (OR=4.58, 95% CI=2.99-7.04).

Conclusion: This study suggested that PSCA rs2294008 might have an impact on the risk of IM or Dys among the high risk population of GC.

Key words: Polymorphism; Prostate stem cell antigen; Advanced precancerous gastric lesions; *Helicobacter pylori*

INTRODUCTION

Gastric cancer (GC) is one of the most common cancers in the world[1]. Linqu County, Shandong Province, China, has one of the highest mortality rates of GC in the world (70/10^5 for males)[2]. In this region, chronic atrophic gastritis (CAG) was nearly universal, while intestinal metaplasia (IM) and dysplasia (Dys) affected 33% and 20% of the adult residents, respectively[2]. Studies have shown that the process of intestinal gastric carcinogenesis involves a continuous stepwise evolution from glandular atrophy to IM, followed by Dys, and finally, to carcinoma[3,4]. Previous studies in Linqu identified several environmental risk factors associated with IM, Dys or GC, including *Helicobacter pylori* (*H. pylori*)

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*Corresponding author.
E-mail: zhanglmail@yahoo.com.cn

infection, smoking, consumption of sour pancakes or salty foods[5-7]. In addition, the genetic factors play a crucial role in GC and precancerous gastric lesions pathogenesis as well[8,9].

The prostate stem cell antigen (*PSCA*) protein is a cell surface antigen originally identified in the Los Angeles prostate cancer-4 (LAPC-4) xenograft mouse[10]. *PSCA* is located on chromosome 8q24.2, encoding a 123-amino-acid glycoprotein[10]. In humans, *PSCA* expression is largely restricted to the prostate, bladder, stomach and oesophagus[10,11]. In the stomach, *PSCA* is predominantly expressed in the isthmus, the middle portion of the gastric epithelium where contains stem cells and precursors of three cell lineages (pit-cell lineage, parietal-cell lineage, and zymogenic-cell lineage)[12]. Also, *PSCA* expression associated with proliferation activities[12]. Studies showed that *PSCA* expression was suppressed in gastric cancer cells[11-13].

PSCA rs2294008 is located in the first exon. This genetic polymorphism changes the amino acid, which may decrease transcriptional activity of *PSCA* and lead to a change in the function of *PSCA* protein[12].

In the present study, we investigated genetic polymorphism of *PSCA* with the risk of IM and Dys in a Chinese population, and its joint effect with environmental factors in the risks of advanced precancerous gastric lesions.

MATERIALS AND METHODS

Study Population

A large population-based cross-sectional study of precancerous gastric lesions in Linqu in 1989 was described previously[3,14]. Briefly, a total of 3,433 subjects participated in an endoscopic examination; representing 83% of the eligible residents aged 34 to 65 in 14 villages selected at random in Linqu County. Blood samples were collected from all subjects. During the examination, each subject was interviewed with a structured questionnaire to obtain the information on cigarette and alcohol consumptions, diet, socioeconomic status, and other variables[15].

The study was approved by the Institutional Review Board of the National Cancer Institute and the Beijing Institute for Cancer Research, and all subjects provided written informed consent.

For the current study, a total of 2350 subjects were randomly selected. A total of 1169 subjects with SG and CAG in the control were assayed compared with subjects who had IM (n = 739) or Dys (n = 442).

Gastric Histopathology

Details of the pathologic procedures and classification criteria of SG, CAG, IM, Dys, and quality control procedures were provided elsewhere[3,14]. Briefly, three experienced gastroenterologists carried out the endoscopic examinations using fiber-optic gastroscopes (Olympus, Tokyo, Japan). Seven biopsies were obtained from standard locations of the stomach, two in the body, one in the angulus, and four in the antrum. Then, three senior pathologists from Beijing Institute for Cancer Research made histopathologic diagnoses. The presence or absence of SG, CAG, IM or Dys was recorded for each biopsy, and each subject was assigned a global diagnosis based on the most severe lesion among the seven biopsies.

H. pylori Antibody Assays

Details of serologic assay were previously described[6]. In brief, *H. pylori* strains cultured from gastric biopsies of two patients in Linqu were used to provide a local antigen preparation for serology. Serum *H. pylori* IgG and IgA antibody concentrations were measured by ELISA at baseline at Beijing Institute for Cancer Research. An individual was considered the positive of *H. pylori* infection if the mean ELISA absorbance reading for either the IgG or IgA was above 1.0, a cutoff value based on negative control. Quality-control samples were assayed at Vanderbilt University.

DNA Preparation

The blood clot was washed extensively with TE buffer (50 mmol/L Tris-HCl, pH 8.5 and 1 mmol/L EDTA). After centrifugation, the pellet was incubated with rotation in the lysis buffer (TE buffer containing 0.2% SDS and 200 μg/ml proteinase K) for 12 h at 55°C. The lysate was then extracted with phenol-chloroform and precipitated with isopropyl alcohol. The precipitate was washed with 70% ethanol and dissolved in TE buffer. The purity and concentration of DNA were determined by spectrophotometry at A_{260nm} and A_{280nm}.

PCR Amplification and Determination of Genotypes

PSCA rs2294008 genotypes were determined by polymerase chain reaction –restriction fragment length polymorphism (PCR-RFLP) technique, using the PCR primer pairs: F5'-GAAACCCGCTGGT GTTGACTGT-3'/R5'-GGGCAAGCAGCACAGCCC-3'. PCR products were digested with Nco I (New England BioLabs, Inc., Beverly, MA), and digested

products were separated on 3.5% agarose gel containing ethidium bromide and visualized under UV light. Genotypes revealed by PCR-RFLP were further confirmed by DNA sequencing of the PCR products, and genotyping was conducted without information of subjects' histopathologic diagnoses. The reaction was started at 95°C for 2 min followed by 35 PCR cycles. The temperatures for denaturing, annealing, and elongation in each cycle were 94°C (30s), 66°C (30s) and 72°C (30s), respectively. At the end, the reaction was extended for 10 min at 72°C. PCR was accomplished with a 25-μl reaction mixture containing 100ng of genomic DNA, 0.1mmol/L of each primer, 0.2 mmol/L of dNTP , 1.0 U Taq DNA polymerase in 2×GC buffer Ⅰ (5mol/L Mg^{2+}Plus).

Quality Control Procedures

Rigorous quality control procedures were applied throughout the genotyping process. The coding and analysis of DNA samples were double-blinded. Two investigators checked sample codes and data entry into the electronic database. To avoid PCR contamination, reagents for PCR reaction were carefully aliquoted and each aliquot was used no more than three times. For each assay, a negative control (with no DNA template) was added to monitor PCR contamination. Pilot experiments were conducted to optimize the restriction digestion conditions. After genotyping of all samples, approximately 10% to 15% of the samples in each genotype group were randomly selected for repeated assays to validate the results. The average concordance rate was 99.9% (range 97-100%).

Statistical Methods

The Hardy-Weinberg equilibrium equation was used to determine whether the proportion of each genotype obtained was in agreement with the expected values as calculated from allele frequencies. The difference in age between the SG/CAG and IM or Dys was evaluated with the Mann-Whitney U test. The χ^2 test was used to examine the differences between gender, *H. pylori* infection, smoking and drinking. Odds ratios (ORs) and 95% confidence intervals (CIs) for the association of polymorphism with IM or Dys were computed by unconditional logistic regression, adjusting for age, gender, *H. pylori* infection, smoking and drinking. All statistical tests were two-sided and the level of significance was set at 0.05. Rothman's synergy index (S) was calculated to determine the joint effect of *PSCA* genotypes and *H. pylori* infection on the risk of IM or Dys[16,17]. The index (S) was calculated as follows[18]:

$$S^{*} = \frac{OReg - 1}{ORg + ORe - 2}$$

*S＞1.0, positive interaction; S=1.0, no interaction; S ＜1.0 negative interaction

The OR for subjects exposed to both environmental and genetic factors in comparison to those not exposed to the two factors was defined as OReg. The ORs for subjects exposed to genetic factors only or environmental factors only were defined as ORg and ORe, respectively. These analyses were carried out with Statistical Analysis System Software (version8.0; SAS Institute, Cary, NC).

RESULTS

The proportion of gastric lesions in the study population (SG/CAG: 49.7%; IM: 31.5%; Dys: 18.8%) was similar to that in the population of this region[2]. The baseline characteristics of subjects are shown in Table 1. The information on smoking status, drinking status and *H. pylori* seropositivity was available for 2178, 2177 and 2066 subjects, respectively. The distributions of cigarette smoking and alcohol drinking between SG/CAG and IM or Dys were similar. The distributions of gender between SG/CAG and IM were similar. However, the distributions of age between SG/CAG and IM was different (P<0.001). The distributions of age and gender in Dys were different (P<0.001) from that in the SG/CAG. The percentages of *H. pylori* infection were higher in IM or Dys than in SG/CAG (P<0.001, Table 1).

The frequencies of *PSCA* rs2294008 TT, CT, and CC genotypes were 7.6%, 32.9%, and 59.5% respectively among the 1169 subjects with SG/CAG. The allele frequencies for the T and C were 24.1% and 75.9% in SG/CAG, respectively. The genotype distributions of the polymorphism of all subjects fitted the Hardy-Weinberg equilibrium. The frequencies of *PSCA* rs2294008 TT, CT, and CC genotypes were 7.7%, 41.7%, and 50.6% among 739 subjects with IM and 7.2%, 46.2%, and 46.6% among 442 subjects with Dys respectively (Table 2). Elevated risks of IM and Dys were found for CT carriers. The ORs were 1.47 (95% CI: 1.17-1.85) and 1.92 (95% CI: 1.47-2.50), respectively. Dominant genetic model revealed that subjects with CT/TT genotype were associated with increased risks of IM (OR: 1.38, 95% CI: 1.11-1.71) and DYS (OR: 1.75, 95% CI: 1.36-2.26) (Table 2).

The risks of IM and Dys associated with *PSCA* rs2294008 were further examined with stratification

by *H. pylori* infection (Table 3). The association of *PSCA* rs2294008 CT/TT genotype with risk of IM was more pronounced for subjects with *H. pylori* infection (OR 1.34, 95% CI 1.05-1.71). Similar results were observed for Dys. Subjects with *PSCA* rs2294008 CT/TT genotype and *H. pylori* infection have an elevated risk of Dys (OR 1.82, 95% CI 1.37-2.42). (Table 3).

Table 1. *The baseline characteristics of subjects with gastric precancerous lesions*

	SG/CAG	IM		Dys	
	n=1169	n=739	*P*	n=442	*P*
Age(year)($\bar{x}\pm s$)	43.5±7.4	46.4±8.5	<0.001	47.6±8.7	<0.001
Sex(%)			0.55		<0.001
Male	542(46.4)	353(47.8)		269(60.9)	
Female	627(53.6)	386(52.2)		173(39.1)	
H.pylori infection(%)			<0.001		<0.001
Yes	676(67.6)	548(83.2)		339(83.3)	
No	324(32.4)	111(16.8)		68(16.7)	
Smoking(%)			0.74		0.93
Yes	499(45.6)	313(46.4)		186(45.4	
No	595(54.4)	361(53.6)		224(54.6)	
Drinking(%)			0.26		0.59
Yes	487(44.6)	282(41.8)		189(46.1)	
No	606(55.4)	392(58.2)		221(53.9)	

SG: Superficial gastritis; CAG: Chronic atrophic gastritis; IM: Intestinal metaplasia; Dys: Dysplasia

Table 2. *The frequencies of PSCA rs2294008 in SG/CAG, IM and Dys*

Genotype	SG/CAG	IM			Dys		
	n (%)	n (%)	OR (95%CI)[a]	*P*	n (%)	OR (95%CI)[a]	*P*
CC	696(59.5)	374(50.6)	1		206(46.6)	1	
CT	384(32.9)	308(41.7)	1.47(1.17-1.85)	<0.001	204(46.2	1.92(1.47-2.50)	<0.001
TT	89(7.6)	57(7.7)	1.02(0.68-1.53)	0.93	32(7.2)	1.13(0.70-1.83)	0.62
CT/TT	473(40.5)	365(49.4)	1.38(1.11-1.71)	0.003	236(53.4)	1.75(1.36-2.26)	<0.001

[a]Adjusted for age, gender, drinking, smoking, and *H.pylori* infection.
SG: Superficial gastritis; CAG: Chronic atrophic gastritis; IM: Intestinal metaplasia; Dys: Dysplasia;
OR: Odds ratio; 95%CI: 95% confidence interval

Table 3. *Risks of IM and Dys Associated PSCA-ThrlMet by H.pylori Infection*

Genotype	SG/CAG	IM			Dys		
	n (%)	N (%)	OR (95%CI)[a]	*P*	n (%)	OR (95%CI)[a]	*P*
H.pylori infection positive							
CC	406(60.1)	279(50.9)	1		153(45.1)	1	
CT/TT	270(39.9)	269(40.1)	1.34(1.05-1.71)	0.02	186(54.9)	1.82(1.37-2.42)	<0.001
H.pylori infectiion negative							
CC	205(63.3)	61(54.9)	1		36(52.9)	1	
CT/TT	119(36.7)	50(45.1)	1.54(0.97-2.44)	0.07	32(47.1)	1.48(0.83-2.67)	0.19

[a]Adjusted for age, gender, drinking and smoking.
SG: Superficial gastritis; CAG: Chronic atrophic gastritis; IM: Intestinal metaplasia; Dys: Dysplasia;
OR: Odds ratio; 95%CI: 95% confidence interval

Furthermore, we examined the joint effects of *PSCA* rs2294008 and *H. pylori* infection. Compared with carriers of CC genotype without *H. pylori* infection, the subjects of TT or CT genotype without

H. pylori infection did not increase the risks of IM and Dys. However, among the subjects who carried the TT/CT genotype and were infected with *H. pylori* infection, there was a more than 2-fold elevated risk for IM (OR 3.32, 95% CI, 2.33-4.71) and a more than 3-fold increased risk for Dys (OR 4.58, 95% CI, 2.99-7.04) in this study (Table 4). The Rothman's synergy indices of the interaction between *PSCA* rs2294008 CT/TT genotype and *H. pylori* infection were 1.21 in subjects with IM and 1.85 in subjects with Dys, respectively.

Table 4. *The joint effect of H.pylori infection and PSCA genotypes*

H.pylori infection	Genotype	SG/CAG	IM			Dys		
		n=1169	n(%)	OR(95%CI)[a]	*P*	n(%)	OR(95%CI)[a]	*P*
Negative	CC	204(20.4)	61(93)	1		38.96()	1	
Positive	CC	407(40.7)	279(42.3)	2.42(1.72-3.40)	<0.001	153(37.5)	2.47(1.61-3.79)	<0.001
Negative	CT/TT	120(12.0)	50(7.6)	1.49(0.95-2.35)	0.08	32(7.9)	1.47(0.84-2.56)	0.18
Positive	CT/TT	269(26.9)	269(40.8)	3.32(2.33-4.71)	0.001	186(45.7)	4.58(2.99-7.04)	<0.001

[a]Adjusted for age, gender, drinking and smoking.
SG: Superficial gastritis; CAG: Chronic atrophic gastritis; IM: Intestinal metaplasia; Dys: Dysplasia;
OR: Odds ratio; 95%CI: 95% confidence interval

DISCUSSION

Previous study showed that *PSCA* rs2294008 was associated with risk of GC[19]. In our present study, a relatively large sample was selected from a Chinese population with a high mortality of GC to evaluate the associations between genetic polymorphism of *PSCA* and risk of advanced precancerous gastric lesions. Our study indicated elevated risk of IM or Dys correlated with *PSCA* rs2294008 CT/TT genotype, especially for subjects with *H. pylori* infection. To our best knowledge, this is the first study that explores the impact of *PSCA* rs2294008 on the risk of advanced precancerous gastric lesions.

Sakamoto et al[19] reported that subjects carrying at least one *PSCA* rs2294008 T allele were associated with an increased risk of GC(diffuse GC: OR=1.67, 95%CI=1.47-1.90; intestinal GC: OR=1.29, 95%CI=1.11-1.49, *P*<0.001). In the present study, we found that subjects who carried *PSCA* rs2294008 CT/TT genotype had an increased risk for advanced precancerous gastric lesions (IM and Dys). Present study provides a population-base evidence of the relationship between *PSCA* rs2294008 polymorphism and gastric cancer.

The *PSCA* gene was originally identified in the prostate cancer cells in 1998[20]. Studies reported *PSCA* was highly expressed in a large proportion of human prostate tumors, which had an importance association with the occurrence of prostate cancer[20-22]. But the subsequent series of studies indicated that *PSCA* was suppressed in the cancers of the bladder, esophagus, skin and stomach[19,23,24]. Sakamoto et al[19] found that among gastric cancer tissues, quantitative RT-PCR and immunohisto-chemical analyses showed frequent suppression of *PSCA* expression in both the intestinal and diffuse types. In vitro, the growth of GC cells with stable *PSCA* expression was slower than the GC cells without *PSCA* expression[19], which suggested that *PSCA* may have a tumor suppressor-like character in gastric cancers.

The regulation mechanism of *PSCA* expression is largely unknown. Sakamoto et al[19] sequenced *PSCA* and its 5' upstream region and identified 17 SNPs, including a missense SNP located at the presumed translation-initiating codon, rs2294008. Substitution of C with T at *PSCA* rs2294008 can alter the threonine to methionine. This genetic variation changes the length of the N-terminal signal peptide, which may alter the protein folding, intracellular processing, and subcellular localization. Meanwhile, research showed that rs2294008 T-allele can decrease transcriptional activity of the upstream region of *PSCA*[19].

Similar with the evidences of previous functional study[19] or association studies[19,23], our study provided evidence that *PSCA* rs2294008 polymorphism may have an important role in the development of IM and Dys. Previous studies in Linqu indicated that *H. pylori* infection, cigarette smoking, and low levels of dietary vitamin C were the important environmental factors for GC[7,14]. In the present study, stratified analysis found that the presence of both *PSCA* rs2294008 CT/TT genotype and *H. pylori* infection significantly elevated the risks of IM and Dys.

H. pylori is a bacterium that colonizes in the human gastric epithelial cells. The infection was

demonstrated as an important etiological factor of GC and precancerous gastric lesions[6,7,25]. We have conducted a randomized intervention trial in Linqu Country and found that eradication of *H.pylori* caused a significant decrease in the combined prevalence of severe CAG, IM and Dys[26]. However, the outcome of subjects with *H. pylori* infection is highly variable, and only a small fraction of infected individuals (probably<3%) developed GC[27], which may be influenced by both microbial and host factors[28]. Accumulating evidences have shown that *H. pylori* can modulate cell proliferation, which plays an important role in the development of GC and precancerous gastric lesions[29]. Several studies have suggested that *PSCA* involved in the cell growth regulation[19,30-33]. *PSCA* rs2294008 CT/TT genotype and *H. pylori* infection may co-contribute to the development of IM and Dys by modulating cell proliferation. Further studies are needed to test this hypothesis.

In conclusion, this study suggested that *PSCA* rs2294008 CT/TT genotype increased the genetic susceptibility of IM and Dys, especially for subjects with *H. pylori* infection, suggesting that this polymorphism may play a role in the occurrence of advanced precancerous gastric lesions.

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