

## RESEARCH COMMUNICATION

# Association of the PSCA rs2294008 C>T Polymorphism with Gastric Cancer Risk: Evidence from a Meta-Analysis

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### Abstract

**Background:** Multiple studies have reported associations between the PSCA rs2294008 C > T polymorphism and GC, but susceptibility has proven inconsistent. Therefore, we estimate the relationship between the rs2294008 C > T polymorphism and GC by meta-analysis. **Methods:** PubMed, Embase and Web of Science databases were searched and nine independent case-control studies were included in this meta-analysis. Crude ORs with 95% CIs were extracted according to the Mantel-Haenszel method and pooled to assess the strength of the association. **Results:** We observed that the PSCA rs2294008 C > T polymorphism was significantly correlated with GC risk when all studies were pooled into the meta-analysis. Further subgroup analysis showed the polymorphism to be linked with diffuse and noncardia GC in the allele contrast model, homozygote codominant model, dominant model, and recessive model. However, no connection was apparent for intestinal and cardia GC. In the stratified analysis by ethnicity, significant associations were observed in Asians for the recessive model. Interestingly, the relationship was particularly significant in the Chinese population. **Conclusions:** Our findings suggest that the PSCA rs2294008 C > T polymorphism is a risk factor for GC, especially in diffuse and noncardia GC and in Chinese.

**Keywords:** Prostate stem-cell antigen - gastric cancer - genetic polymorphisms - risk

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### Introduction

GC is the fourth most common malignancy and the second leading cause of cancer associated death worldwide (Ferlay et al., 2010), so it is the major public health problem faced all around the world. The incidence of gastric cancer is regulated by multi-factors, including oncogene tumor suppressor gene in abnormal activation/inactivation, immune changes, and etc. With the depth of new technologies, many efforts have been invested in identifying sources of genetic susceptibility to cancer in the last few decades (Dong et al., 2008; Lao-Sirieix et al., 2010).

PSCA gene encodes a 123-amino acid glycoprotein, which is a cell surface antigen. Its name was inaccurate, because it is not exclusively expressed in prostate cancer; and highly expressed by a large proportion of human tumors, including metastatic and hormone-related cancers (Reiter et al., 1998; Bahrenberg et al., 2000). Recently, scientists found that PSCA gene is either abnormally expressed or shown different genetic variant in several cancers. GWAS have identified a strong association between PSCA gene rs2294008 C > T polymorphism and risk of GC, especially in Asians (Sakamoto et al., 2008; Shi et al., 2011). Moreover, its genetic variant may correlate with other risk factors or clinicopathologic features, such as sex, age, smoking status, tumor size or stage, location

and histological type of GC. More recently, several studies have assessed the relationship between the polymorphism of PSCA C > T and the susceptibility to GC. Nevertheless, controversial results exist regarding the association of PSCA with the risk of GC (Sakamoto et al., 2008; Matsuo et al., 2009; Wu et al., 2009; Lu et al., 2010; Ou et al., 2010; Lochhead et al., 2011; Song et al., 2011; Zeng et al., 2011; Sala et al., 2012). Therefore, we conducted this meta-analysis to confirm these associations.

### Materials and Methods

#### Identification and eligibility of relevant studies

Search terms "PSCA", "gastric cancer", "genotype", "polymorphism" and "variant" were employed to explore publications in PubMed, ISI Web of Knowledge and Embase databases for relevant reports (last search update February 2012). Only studies published in the English language were included. We did not define any minimum number of patients to be included for meta-analysis. When multiple studies of the same patient population were identified, we included the published report with the largest sample size.

#### Inclusion and exclusion criteria

The following inclusion criteria were used to select literatures for this analysis: (a) evaluation of the PSCA

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**Table 1. Characteristics of GC Studies Included in the Meta-analysis**

First author/Published year	Study population of cases	method	Cases	Controls	HWE of controls
Lochhead 2011	Polish	SNP Genotyping assays	292	382	0.01
Lochhead 2011	US	SNP Genotyping assays	308	208	0.41
Sala 2011	European countries	SNP Genotyping assays	409	1515	0.09
Song 2011	Korean	HRM assays	3245	1700	0.13
Zeng 2011	Chinese	PCR-RFLP assays	460	549	0.49
Ou 2010	Tibetan	PCR/LDR assays	196	246	0.92
Lu 2010	Chinese	SNP Genotyping assays	1023	1069	0.17
Matsuo 2009	Japanese	TaqMan assays	578	578	0.71
Wu 2009	Chinese	PCR-RFLP assays	1710	995	0.59
Sakamoto 2008	Japanese	SNP Genotyping assays	1524	1396	0.57
Sakamoto 2008	Korean	SNP Genotyping assays	971	390	0.07

**Table 2. Genotypes of PSCA rs2294008 C>T Polymorphism Included in the Meta-analysis**

First author	Cases					Controls				
	CC	CT	TT	C	T	CC	CT	TT	C	T
Lochhead (Polish)	47	143	102	237	347	101	166	115	368	396
Lochhead (US)	85	129	94	299	317	49	110	49	208	208
Sala	93	198	118	384	434	491	714	310	1696	1334
Song	576	1620	1049	2772	3718	414	818	468	1646	1754
Zeng	202	216	42	620	300	289	223	37	801	297
Ou	85	93	18	263	129	132	96	18	360	132
Lu	547	404	72	1498	548	605	387	77	1597	541
Matsuo	271	269	38	811	345	219	277	82	715	441
Wu	759	819	132	2337	1083	506	412	77	1424	566
Sakamoto (Japan)	96	900	728	1092	2356	210	650	536	1070	1722
Sakamoto (Korean)	133	461	277	727	1015	122	176	92	420	360

First author	Intestinal cases					Diffuse cases				
	CC	CT	TT	C	T	CC	CT	TT	C	T
Lochhead (Polish)	35	93	64	163	221	5	24	21	34	66
Lochhead (US)	15	25	18	55	61	18	32	30	68	92
Sala	30	74	44	134	162	31	62	48	124	158
Zeng	142	170	29	454	228	56	46	12	158	70
Lu	385	285	46	1055	377	91	75	14	257	103
Matsuo	162	127	15	451	157	109	142	23	360	188
Sakamoto (Japan)	58	274	267	390	808	38	426	461	502	1348
Sakamoto (Korean)	84	215	118	383	451	49	246	159	344	564

rs2294008 C > T polymorphism and GC, (b) only the case-control studies were considered, (c) sufficient published data for estimating an OR with 95% CI. Major exclusion criteria were: (1) no control population, (2) no available genotype frequency, and (3) duplicated studies.

#### Data extraction

For each study, the following data were collected: first author's surname, year of publication, country of origin, ethnicity, criteria of enrolled patients, genotyping method, total numbers of cases and controls as well as numbers of cases and controls with CC, CT and TT genotypes. The strength of the association between PSCA rs2294008 C > T polymorphism and GC risk was estimated using OR, with the corresponding 95% CI. Disagreement was resolved by discussion until a consensus was reached between the two authors. We did not define any minimum number of patients for inclusion in our meta-analysis.

#### Statistical methods

The risk of GC associated with PSCA rs2294008 C > T was estimated for each study by OR with 95% CI. For all studies, we estimated the association under five

different types of ORs, namely the allele contrast model (C vs T), the homozygote codominant model (CC vs TT), the heterozygote codominant model (CT vs TT), the dominant model (CC+CT vs TT) and the recessive model (CC vs CT+TT). HWE was tested by the Chi-square test. The Q-statistic was used to investigate the degree of heterogeneity between the trials, and a P-value 0.10 for the Q-test indicated a lack of heterogeneity among studies. We used the fixed-effects model and the random-effects model based on the Mantel-Haenszel method (Jose et al., 2008) and the DerSimonian and Laird method (Kjellsson et al., 2008), respectively, to combine values from each of the studies. A sensitivity analysis was also performed by omitting each study in turn to identify potential outliers. All of the statistical analyses were performed with Review Manage version 4.3 and STATA version 12.0 using two-sided P-values.

## Results

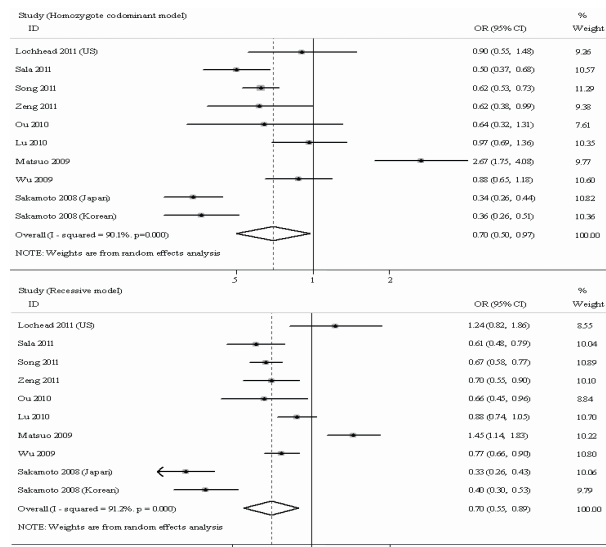
#### Study characteristics

We obtained 14 studies about the association between PSCA rs2294008 polymorphism. Following the above

**Table 3. Results of Meta-analysis for PSCA rs2294008 Polymorphisms and GC Risk**

Study groups	Variables <sup>a</sup>	Allele contrast model		Homozygote codominant		Heterozygote codominant		Dominant model		Recessive model	
		OR (95% CI)	Ph	OR (95% CI)	Ph	OR (95% CI)	Ph	OR (95% CI)	Ph	OR (95% CI)	Ph
Total	9	0.87 (0.74-1.01)	0	0.70 (0.50-0.97) <sup>a</sup>	0	0.97 (0.83-1.13)	0.02	0.87 (0.73-1.03)	0	0.70 (0.55-0.89) <sup>a</sup>	0
Two major gastric cancer types											
Intestinal	5	0.91 (0.73-1.14)	0	0.82 (0.51-1.32)	0	0.96 (0.76-1.21)	0.001	0.94 (0.56-1.60)	0	0.80 (0.57-1.11)	0
Diffuse	5	0.73 (0.59-0.91) <sup>a</sup>	0	0.50 (0.29-0.89) <sup>a</sup>	0	0.81 (0.62-1.06)	0.012	0.68 (0.53-0.88) <sup>a</sup>	0.008	0.65 (0.44-0.95) <sup>a</sup>	0
Location											
Cardia	4	0.96 (0.81-1.14)	0.136	1.01 (0.78-1.31)	0.267	1.05 (0.82-1.35)	0.576	1.02 (0.80-1.30)	0.795	0.96 (0.70-1.36)	0.016
Noncardia	4	0.76 (0.69-0.84) <sup>a</sup>	0.34	0.62 (0.50-0.77) <sup>a</sup>	0.217	0.76 (0.55-1.06)	0.052	0.68 (0.57-0.84) <sup>a</sup>	0.132	0.70 (0.62-0.80) <sup>a</sup>	0.496
Ethnicity											
Asian	7	0.88 (0.74-1.05)	0	0.71 (0.47-1.06)	0	1.05 (0.89-1.23)	0.014	0.93 (0.76-1.13)	0	0.67 (0.51-0.89) <sup>a</sup>	0
Chinese	4	0.94 (0.70-1.27)	0	0.83 (0.68-1.01)	0.41	1.07 (0.88-1.31)	0.74	0.94 (0.77-1.13)	0.566	0.79 (0.71-0.87) <sup>a</sup>	0.348

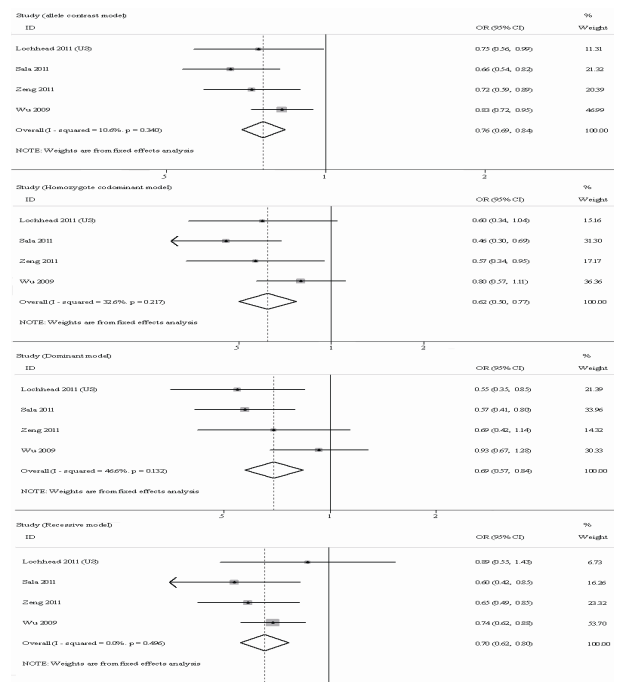
Ph P-value of overall effect test

**Figure 1. Forest Plot for the Association Between PSCA rs2294008 C > T and Gastric Cancer Risks in all Studies (for the homozygote codominant model and the recessive model).** The study is shown by the point estimate of the OR (the size of the square is proportional to the weight of each study) and 95% CI for OR; pooled OR and 95% CI have been appropriately derived from the random effects model

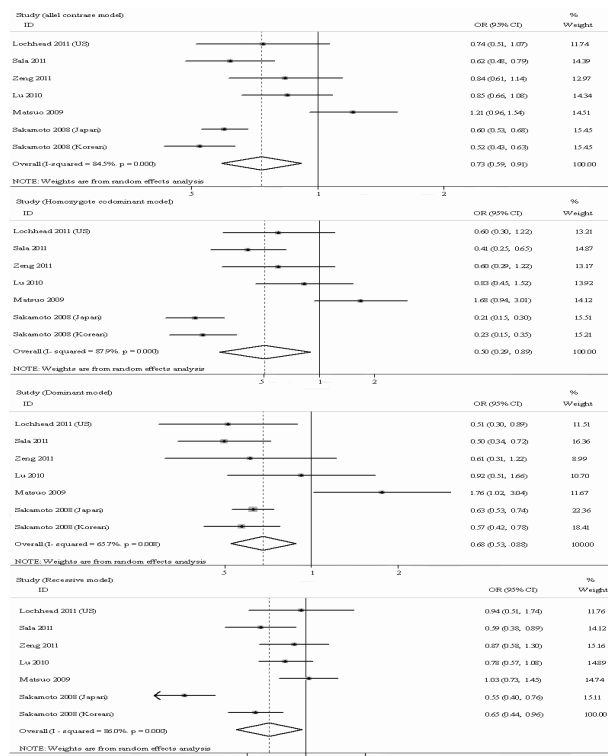
inclusion and exclusion criteria, 9 publications were included in the final meta-analysis (Sakamoto et al., 2008; Matsuo et al., 2009; Wu et al., 2009; Lu et al., 2010; Ou et al., 2010; Lochhead et al., 2011; Song et al., 2011; Zeng et al., 2011; Sala et al., 2012). Characteristics of studies focusing on PSCA rs2294008 C > T are summarized in Table 1. Genotypes and separate P values for PSCA rs2294008 polymorphism are listed in Table 2. When we conducted the above analysis, Lochhead's study about Polish was excluded due to its HWE disequilibrium ( $P = 0.01$ ) in controls.

#### Meta-analysis results

Table 3 lists the main results of pooled ORs for PSCA rs2294008 C > T polymorphism and gastric cancer risk. We observed that the PSCA rs2294008 C > T polymorphism was significantly correlated with gastric cancer risk when all studies were pooled into the meta-analysis (the homozygote codominant model: OR = 0.70, 95% CI = 0.50-0.97,  $P = 0.28$  for heterogeneity; the recessive model: OR = 0.70, 95% CI = 0.55-0.89,  $P = 0.13$  for heterogeneity, Figure 1). Further subgroup analysis showed that rs2294008 C > T polymorphism is

**Figure 2. Forest Plot for the Association Between PSCA rs2294008 C > T and Diffuse Gastric Cancer Risks (for the allele contrast model, the homozygote codominant model, the dominant model and the recessive model).** The study is shown by the point estimate of the OR (the size of the square is proportional to the weight of each study) and 95% CI for OR; pooled OR and 95% CI have been appropriately derived from the fixed effects model

associated with diffuse (the allele contrast model: OR = 0.73; 95% CI = 0.59-0.91,  $P = 0.07$  for heterogeneity; the homozygote codominant model: OR = 0.50; 95% CI = 0.29-0.89,  $P = 0.51$  for heterogeneity; the dominant model: OR = 0.68; 95% CI = 0.53-0.88,  $P = 0.07$  for heterogeneity; the recessive model: OR = 0.65; 95% CI = 0.44-0.95,  $P = 0.22$  for heterogeneity, Figure 2) and noncardia gastric cancer (the allele contrast model: OR = 0.76; 95% CI = 0.69-0.84,  $P = 0.34$  for heterogeneity; the homozygote codominant model: OR = 0.62; 95% CI = 0.50-0.77,  $P = 0.22$  for heterogeneity; the dominant model: OR = 0.68; 95% CI = 0.57-0.84,  $P = 0.13$  for heterogeneity; the recessive model: OR = 0.70; 95% CI = 0.62-0.80,  $P = 0.50$  for heterogeneity, Figure 3). In the stratified analysis by ethnicity, significant associations were observed in Asian (the recessive model: OR = 0.67; 95% CI = 0.51-0.89,  $P = 0.14$  for heterogeneity, Figure 4) and Chinese population (the recessive model: OR = 0.79;



**Figure 3. Forest Plot for the Association Between PSCA rs2294008 C > T and Noncardia Gastric Cancer Risks (for the allele contrast model, the homozygote codominant model, the dominant model and the recessive model).** The study is shown by the point estimate of the OR (the size of the square is proportional to the weight of each study) and 95% CI for OR; pooled OR and 95% CI have been appropriately derived from the random effects model

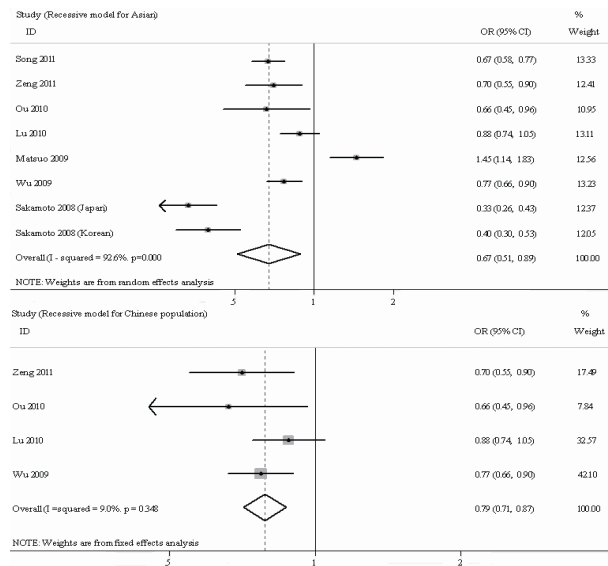
95% CI = 0.71–0.87, P = 0.35 for heterogeneity, Figure 4).

**Publication bias**

We performed Begg’s funnel plot and Egger’s test to assess the publication bias of literatures. The results did not show any evidence of publication bias in all the comparisons. Also, the results of Egger’s test still did not suggest any evidence of publication bias (P = 0.679 for T vs G; P = 0.134 for GT vs GG; P = 0.104 for TC vs. TT, respectively).

**Discussion**

PSCA was initially identified as a prostate-specific cell-surface antigen (Argani et al., 2001). PSCA is largely expressed in normal prostate and overexpressed in a majority of prostate cancer. Meanwhile, PSCA is highly expressed in other non-prostatic malignancies, including bladder cancer, pancreatic cancer, and gastric cancer (Elsamman et al., 2006; Grubbs et al., 2006). Recently studies have reported that its expression is different in these tumor and adjacent normal tissues, but its gene polymorphisms are significant discrepancies (Elsamman et al., 2006; Feng et al., 2008). Among these variants, rs2294008 C > T and rs2976392 G > A are explicit, while these significant relationships were observed in several but not all studies, especially in gastric cancer (Ou et



**Figure 4. Forest Plot for the Association Between PSCA rs2294008 C > T and Gastric Cancer Risks In Asian And Chinese Population (for the recessive model).** The study is shown by the point estimate of the OR (the size of the square is proportional to the weight of each study) and 95% CI for OR; pooled OR and 95% CI have been appropriately derived from the random and fixed effects model, respectively

al., 2010). The rs2294008 was shown to be functionally associated with downregulation of PSCA and to increase the risk of gastric cancer,

The aim of our study was to demonstrate the role of PSCA rs2294008 C > T polymorphism in the relationship with gastric cancer risk using the meta-analysis. In present study, we observed significant differences among the two major types GC. The effect of the rs2294008 C > T polymorphism was greater in diffuse than in intestinal-type gastric cancer, consistent with previous reports. The genetic susceptibility factors may contribute more to diffuse-type gastric cancer development compared to intestinal-type gastric cancer (Lao-Sirieix et al., 2010), so genetic variations appear to be associated with an increased risk for diffuse-type gastric cancer.

Interestingly, we also observed that PSCA rs2294008 C > T was significantly correlated with risk for noncardia gastric cancer rather than cardia gastric cancer. As well known, H. pylori is the explicit risk factor for gastric cancer, and play an important role in the process of gastritis, intestinal metaplasia, gastric ulcers, and gastric cancer (Tan et al., 2011). Previous researches have reported that rs2294008 C > T polymorphism is a predisposing genetic variant for H. pylori positive gastric cancer. H. pylori infection was strongly associated with the risk of noncardia gastric cancer, but was inversely associated with the risk of cardia gastric cancer (Kamangar et al., 2006). Similar to these studies, our study is shown that PSCA rs2294008 C > T polymorphism is correlated with noncardia gastric cancer, but is not interrelated with cardia gastric cancer, for several genetic model, such as for allele contrast model, homozygote codominant model, dominant model and recessive model.

Simultaneously there was an evidence to indicate that PSCA rs2294008 C > T polymorphism was associated with increased risk of gastric cancer in Asian and Chinese

population only for recessive genetic model.

In summary, our study shows a genetic association between PSCA rs2294008 C > T variant increases susceptibility to GC, whereas we need to be further warranted to verify these findings in large population-based prospective studies with ethnically diverse populations, as well as biologically functional studies.

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