Research Article

Cancer Epidemiology, Biomarkers & Prevention

Prostate Stem Cell Antigen Polymorphisms and Susceptibility to Gastric Cancer: A Systematic Review and Meta-analysis

Tao Wang[1,2], Lina Zhang[3,4], Haixin Li[1,3], Bangmao Wang[2], and Kexin Chen[1,3]

Abstract

Background: Many studies have reported that prostate stem cell antigen (*PSCA*) polymorphisms (rs2294008 and/or 2976392) are significantly associated with gastric cancer (GC) risk, although the published results are inconsistent. We conducted a systematic review and meta-analysis for relevant literatures to quantitatively evaluate the relationship between *PSCA* polymorphisms and GC susceptibility.

Methods: Extensive searches were conducted in three databases up to November 1, 2011. ORs and 95% CIs were used to assess the strength of the associations. The data were further stratified by ethnicity, histopathology, subsite, and study design. All of the associations were evaluated with dominant model and recessive model, respectively. Heterogeneity and publication bias were also assessed by Q test, I^2, and funnel plot accordingly.

Results: Nine articles including 11 case–control data sets were included, with 10,746 GC cases and 9,158 controls for rs2294008 and 6,060 cases and 4,824 controls for rs2976392. The results showed that risk allele carriers were significantly associated with GC risk compared with nonrisk allele homozygotes. In stratification analyses, these associations remained significant for majority of subgroups except for Caucasians and noncardia tumor in dominant model, and cardia tumor in both dominant and recessive model. Random model was used when heterogeneity among studies was detected. No publication bias was observed.

Conclusions: The two loci of *PSCA* (rs2294008 and rs2976392) were both significantly associated with GC susceptibility and in linkage disequilibrium.

Impact: More prospective studies on *PSCA* polymorphisms at multicenters with sufficient sample size and less heterogeneity will be needed for further validations. *Cancer Epidemiol Biomarkers Prev; 21(5); 843–50.*

Introduction

Gastric cancer (GC) is the fourth common cancer and the second leading cause of cancer-related death worldwide (1). It was estimated that there were 990,000 newly diagnosed cases and 738,000 cancer-related deaths in 2008 (2). The incidence rates of GC vary geographically throughout the world, and the areas with high incidence mainly include Eastern Asia, Eastern Europe, and South of America, whereas the low incidence mainly include North America and most parts of Africa, furthermore, more than 70% of new cases and deaths occur in developing countries (3).

The pathogenesis of stomach cancer is still unclear, which may partly account for its poor prognosis. In general, the established etiology involves *Helicobacter Pylori* (*H. Pylori*) infection, environmental factors, and genetic susceptibility. GC can histopathologically be classified into intestinal type adenocarcinomas and diffuse type ones. The 2 types of tumors are clinically different in their etiology, incidence trend, and prognosis. The common causes of intestinal type adenocarcinomas are excessive salt intake, alcohol consumption, and low intake of fresh fruit and vegetable in diet, while the diffuse type tumors are associated with gastroesophageal reflux disease and obesity (4, 5). *H. Pylori* infections are believed to be the common cause for them (6, 7) and genetic factor is more likely to be related to diffuse type adenocarcinomas. With the use of antibiotics for eradication of *H. Pylori* and improved dietary contents, the incidence of intestinal type adenocarcinoma has decreased over the past decades, but that of the diffuse type

Authors' Affiliations: Departments of [1]Epidemiology and Biostatistics and [2]Gastroenterology of General Hospital, Tianjin Medical University, Tianjin, China; [3]Key Laboratory of Breast Cancer Prevention and Therapy, Tianjin Medical University, Ministry of Education, Tianjin, China; and [4]Breast Oncology of Cancer Institute and Hospital, Tianjin, China

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Corresponding Author: Kexin Chen, Department of Epidemiology and Biostatistics, Tianjin Medical University Cancer Institute and Hospital, Tiyuanbei, Huanhuxi Road, Hexi District, Tianjin 300060, China. Phone: 86-22-23340123-6010; Fax: 86-22-23359984; E-mail: chenkexin1963@yahoo.com

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presents an increasing trend (5). Another cause for decreased incidence is population screening for early-stage GC and its precancerous lesions, especially in the countries with high incidence rates. Until now, GC is still a heavy public health burden for the majority of countries of the world, and early detection and intervention for GC may be practically the only way to improve the outcome.

To date, there is not an international consensus on screening and surveillance strategies for GC, which is mainly due to large incidence variation among different countries. The problem we are facing today is how to identify the individuals with high risk in the general population. In recent years, genome-wide association studies (GWAS) are found to have an important role in hypothesis-free risk assessment by identifying potential candidate single-nucleotide polymorphisms (SNP) using high-density SNP chips (8–10).

Prostate stem cell antigen (*PSCA*), locating on chromosome 8q24.2 with 30% homology to stem cell antigen 2, encodes a protein consisted of 123 amino acid residues (11). PSCA, a member of the LY-6/Thy-1 family of glycosylphosphatidylinositol-anchored cell surface proteins, was initially identified as a prostate-specific antigen, which is overexpressed in most of prostate cancer (11–13) and plays an important role in cell adhesion, proliferation, and survival (14). PSCA was also found to express abnormally in other types of malignancies, such as cancers of the bladder, pancreas, esophagus, and stomach (15–18). Many studies have explored the association between variant genotype of *PSCA* and risk for cancers of the prostate, bladder, and stomach (16, 19–21). Two loci in *PSCA*, rs2976392 and rs2294008, were first identified to be remarkably associated with risk of diffuse type GC based on a 2-stage GWAS study conducted by Sakamoto (21). The *in vitro* experiments revealed that the variant rs2294008T could reduce the transcriptional activity of an upstream fragment of *PSCA*, while the function of rs2976392 was unclear (21). Notably, PSCA was reported to express at the isthmus of gastric gland, in which proliferative precursor cells were enriched (21). Although the detailed mechanism of PSCA in gastric carcinogenesis has not been clarified, it may act as a tumor suppressor to inhibit cell proliferation on the basis of above reported findings. The relationship between these 2 SNPs in *PSCA* and GC risk was further validated with different stratified variables such as age, gender, ethnicity, histopathology, differentiation of cancer cell, tumor location, and stage of tumor (21–31). Because of various backgrounds and designs of the studies, some inconsistent results were produced. Meanwhile, these 2 susceptibility loci for GC showed a strong linkage disequilibrium (LD) in many studies on Japanese and Korean populations (21, 30), but some studies on Chinese populations reported quite different results (28, 29, 31). In this study, we carried out a systematic review to clarify the associations between these 2 SNPs and GC risk based on available published papers and unpublished data.

Materials and Methods

Literature source and search strategy

In this meta-analysis, we first conducted a search using the terms "*PSCA* polymorphism," "rs2976392," and "rs2294008" in combination with "gastric cancer," "gastric adenocarcinoma," "stomach cancer," and "stomach tumor" in the following electronic databases: PubMed, Elsevier Science Direct, China National Knowledge Infrastructure database (the last search was updated on November 1, 2011). No language restriction was set. In addition, the references of the selected articles were also reviewed. Conference abstracts were also included if they had complete data for the meta-analysis without subsequent publication. Our systematic review accorded with the standard of meta-analysis of observational studies in epidemiology (32).

Inclusion and exclusion criteria

The included studies had to meet the following criteria: (i) GWAS or SNP studies on the relationship between *PSCA* polymorphism rs2976392 and/or rs2294008 and GC risk; ii) case–control study design; (iii) for the duplicative or overlapping data, the publications with the largest sample size were included. The literatures with the following conditions were excluded: (i) studies without sufficient data of genotypes in cases and controls, ORs, and 95% CIs; (ii) not in accordance with Hardy–Weinberg equilibrium in control groups.

Data extraction

Literature search, selection, and data extraction were conducted independently by 2 reviewers (Tao Wang and Lina Zhang). Data were included if a consensus was reached. For controversial studies, the third reviewer (Haixin Li) was asked to repeat the evaluation, and the final decision was achieved by discussion among the 3 reviewers. The following informations were collected from each eligible study: the first author, name of journal, year of publication, country, ethnicity, demographics, design of study, total number of cases and controls, and genotype frequency of *PSCA* SNPs for both cases and controls.

Quantitative data synthesis

The overall strength of an association between *PSCA* polymorphisms (variant allele *T* for rs2294008, variant allele *A* for rs2976392) and GC risk was assessed by OR with its 95% CIs. The stratified assessments were further carried out for rs2294008 by ethnicity, histopathology, subsite, and study design separately. For the limited studies available, stratified analysis was not carried out for rs2976392. The ORs and 95% CIs were calculated to estimate GC risk in risk allele TT, CT with comparison to nonrisk allele CC, dominant model [(TT + CT) versus CC], recessive model [TT versus (CT + CC)] for rs2294008, and risk allele AA, AG with comparison with nonrisk allele GG, dominant model [(AA + AG) versus GG], recessive

model [AA versus (AG + GG)] for rs2976392 for each group or subgroup. The statistical significance for each OR value was evaluated by the *Z* test. Heterogeneity of the inclusive studies was measured by the *Q* test and I^2 statistic. Lack of heterogeneity among studies was indicated, when *P* value for *Q* test was beyond 0.10. The fixed model was used, if there was no significant heterogeneity; otherwise, the random model was used. The funnel plot and the Egger test were applied to evaluate publication bias. All of the statistical analyses were conducted with software Review Manager (version 5.1) and stata11.0. The statistical significance for all *P* values from 2-sided tests was defined as less than 0.05.

Results

Result of literature search and selection

A total of 21 articles were used to evaluate the relationship between *PSCA* polymorphisms and cancer risk, 5 of which (16, 19, 20, 33, 34) were excluded because studies were on urinary tumors. Four reviews (35–38) were also excluded. In addition, 3 studies (22, 24, 39) were excluded because of their unavailable or incomplete data. Finally, 9 articles (21, 23, 25–31) were included for our final meta-analysis, which consisted of 11 data sets because 2 multicenter studies, each including 2 data sets. No unpublished data were found. The consensus for all articles searched was reached by at least 2 reviewers.

Characteristics of studies

The characteristics of eligible studies are summarized in Table 1. All of the studies were case–control studies, 2 of which were multicenter studies. For rs2294008, there were 8 studies on Asian populations and 3 on Caucasian, while 6 studies on rs2976392 only involved Asian populations. Of the 11 studies, 6 were population-based case–control (PCC) studies and 5 were hospital-based case–control (HCC) ones. The genotype distribution among controls was in accordance with Hardy–Weinberg equilibrium (HWE), except for a subgroup control from Poland ($P = 0.011$).

Overall analyses of *PSCA* polymorphisms

For all of 11 data sets, the frequencies of risk *T* allele in rs2294008 and *A* allele in rs2976392 varied greatly among different control populations (Table 1 and Fig. 1). Japanese populations presented the highest frequencies of risk alleles of both 2 SNPs, whereas the lowest frequencies appeared in Chinese.

The overall associations of risk alleles with GC risk are shown in Table 2, section 1A–E, Table 3 and Supplementary Material. According to the pooled ORs and corresponding 95% CIs, the variant genotypes (T for rs2294008, A for rs2976392), compared with the wild-type genotypes, were associated with increased cancer risk. Generally, the OR values of homozygotes carrying risk alleles were remarkably higher than those of heterozygotes. All the variant genotypes for rs2976392 showed significant

Table 1. Characteristics of case–control studies on PSCA polymorphisms and GC risk

First author	Publication year	Country	Ethnicity	Study design	No. of cases/controls	Frequency of *T* allele in rs2294008	Frequency of *A* allele in rs2976392	*P* for HWE		Genotyping methods
								rs2294008	rs2976392	
Sakamoto H	2008	Japan	Asian	PCC	1,531/1,399	0.617	0.616	NA	NA	TaqMan SNP genotyping
		Korea	Asian	PCC	871/390	0.462	0.463	NA	NA	
Wu C	2009	China	Asian	HCC	1,736/1,020	0.284	0.295	NA	NA	PCR-RFLP
Matsuo K	2009	Japan	Asian	HCC	708/708	0.624	0.626	0.64	0.64	TaqMan SNP genotyping
Lu Y	2010	China	Asian	PCC	1,053/1,100	0.253	0.258	0.166	0.336	PCR-RFLP
Ou J	2010	China	Asian	HCC	196/246	0.268	0.264	NA	NA	PCR/LDR
Lochhead P	2011	Poland	Caucasian	PCC	312/383	0.518	—	0.011	—	TaqMan SNP genotyping
		United States	Caucasian	PCC	309/211	0.500	—	NA	—	
Zeng Z	2011	China	Asian	HCC	460/549	0.270	—	0.493	—	PCR-RFLP
Song HR	2011	Korea	Asian	HCC	3,245/1,700	0.516	—	0.13	—	PCR-RFLP
Sala N	2011	Europe	Caucasian	PCC	411/1,530	0.440	—	NA	—	Illumina SNP genotyping

Abbreviation: NA, not available.

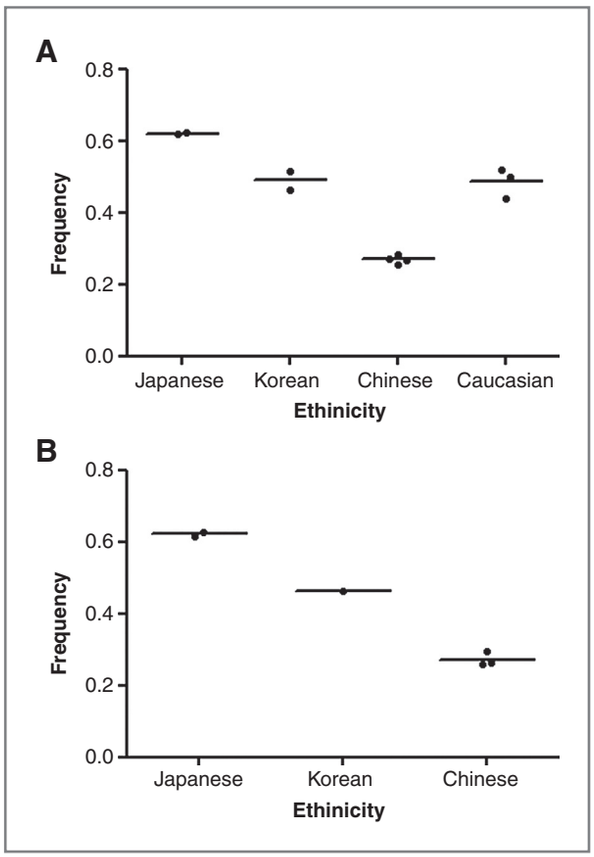

Figure 1. A, frequencies of *T* allele in rs2294008 among controls stratified by ethnicity. B, frequencies of *A* allele in rs2976392 among controls stratified by ethnicity.

correlation with GC. Although homozygous genotype showed the maximum correlation, the recessive model showed the least. Results of Cochran's Q test and I^2 values for all of comparisons indicated there were significant heterogeneities among studies used for the analysis (Table 2, section 1B–1E and Table 3 and Supplementary Material).

Heterogeneity and sensitivity analyses

Because of significant heterogeneities of overall analyses, stratified analyses of rs2294008 were further carried out by ethnicity, histopathology, subsite, and study design. The results of analyses and heterogeneity test are shown in Table 2 and Supplementary Material.

In the subsets for racial descent, 8 studies (21, 23, 26, 28–31) focused on Asians and 3 (25, 27) on Caucasians (Table 2, section 2A). Genotypes TT, CT (Table 2, section 2B, 2C), and 2 types of models (Table 2, section 2D, 2E) were significantly associated with higher GC risk in Asians, while only the TT homozygote (Table 2, section 2B) and recessive model (Table 2, section 2E) had a moderate association with GC risk in Caucasians. There was no evidence for associations between the CT or dominant model (Table 2, section 2C, 2D) and stomach cancer risk in Caucasians.

In the subsets divided by histopathology, there were 8 studies (21, 25–27, 29, 30) for each type, in which 5 (21, 26, 29, 30) were from Asians and 3 (25, 27) from Caucasians (Table 2, section 3A). In both intestinal type and diffuse type GC, genotype TT, CT, and both 2 models were all associated with significantly increased GC risk; moreover, the OR values of diffuse type were greatly higher than those of intestinal type GC for all above-mentioned genotypes (Table 2, section 3B-3E). Further stratification analyses for both 2 types of GC indicated that genotype CT had no effect on GC risk of intestinal type in Caucasians, nor on diffuse type (Table 2, section 3C).

In the subsets for subsite of stomach tumor, 5 studies (23, 25–27, 31) were detected (Table 2, section 5A). No significant associations were found between GC risk and all of variant genotypes in cardia GC (Table 2, section 5B–5E), nor were genotype CT and dominant model in noncardia GC (Table 2, section 5C, 5D). The recessive model had a moderate effect on noncardia GC risk (Table 2, section 5E).

The 11 studies were subdivided into PCC and HCC by study design, 6 (21, 25, 27, 29) of which were PCC, and 5 (23, 26, 28, 30, 31) were HCC (Table 2, section 4A). Each variant genotype for each of study designs presented statistically significant associations with GC risk. Notably, in corresponding genotype, a higher GC risk was observed in PCC than in HCC (Table 2, section 4B–4E).

All of the stratified analyses mentioned above were checked with Cochran's Q test for their heterogeneities. Results revealed that the studies in majority of stratification analyses had significant heterogeneity (Table 2, section 2B–5E and Supplementary Material).

Publication bias

Funnel plot was generated for each analysis. According to funnel plots, there was absence of obvious asymmetries for the distributions of ORs from individual studies with their corresponding SDs (Fig. 2). The results of the Egger test revealed that there was no significant publication bias among studies included in our meta-analysis ($P = 0.253$ for rs2294008 and 0.244 for rs2976392). Therefore, the publication bias, if any, had little effect on the results of our meta-analysis.

Discussion

Our meta-analysis analyzed the association of these 2 GC related SNPs in the *PSCA* gene with GC susceptibility. As a whole, both SNPs were statistically significantly associated with GC susceptibility, and the variant homozygotes of the 2 loci presented a stronger association with high-cancer risk than the heterozygotes. This result was consistent with almost all included studies, except for a study on Chinese by Lu and colleagues, in which there was significant association only between rs2976392 and stomach cancer risk but not for rs2294008 (29). Furthermore, some studies carried out the stratification analyses by different variables, such as ethnicity, histopathology,

Table 2. Overall and stratified analyses on the association of *T* allele in rs2294008 with GC risk and heterogeneity test

			TT vs. CC				CT vs. CC				Dominant model [(TT + CT) vs. CC]				Recessive model [TT vs. (CT + CC)]				
rs2294008	No. of study	No. of cases/ controls	OR (95% CI)	P^a	I^2	P^b	OR (95% CI)	P^a	I^2	P^b	OR (95% CI)	P^a	I^2	P^b	OR (95% CI)	P^a	I^2	P^b	
Overall	11	10,746/9,158	1.75 (1.40–2.18)	<0.00001	79	<0.00001	1.51 (1.28–1.79)	<0.00001	79	<0.00001	1.59 (1.33–1.90)	<0.00001	83	<0.00001	1.33 (1.22–1.45)	<0.00001	21	0.25	1
Ethnicity																			2
Asian	8	9,737/7,053	1.78 (1.34–2.36)	<0.0001	84	<0.00001	1.59 (1.33–1.91)	<0.00001	79	<0.0001	1.66 (1.35–2.05)	<0.00001	86	<0.00001	1.30 (1.17–1.44)	<0.00001	33	0.17	
Caucasian	3	1,009/2,105	1.68 (1.19–2.37)	0.003	53	0.12	1.24 (0.73–2.10)	0.43	84	0.002	1.37 (0.87–2.16)	0.18	81	0.005	1.44 (1.21–1.72)	<0.0001	0	0.53	
Histopathology																			3
Intestinal type	8	2,775/5,813	1.74 (1.32–2.31)	0.0001	65	0.006	1.49 (1.24–1.79)	<0.0001	48	0.06	1.58 (1.28–1.96)	<0.0001	66	0.005	1.34 (1.14–1.57)	0.0005	41	0.10	
Asian	5	2,377/3,708	1.77 (1.18–2.65)	0.005	77	0.002	1.53 (1.23–1.90)	0.0002	57	0.05	1.64 (1.24–2.16)	0.0005	76	0.002	1.31 (1.04–1.65)	0.02	60	0.04	
Caucasian	3	398/2,105	1.78 (1.27–2.51)	0.0009	12	0.32	1.38 (0.90–2.11)	0.14	50	0.14	1.50 (1.03–2.19)	0.04	45	0.16	1.39 (1.09–1.78)	0.008	0	0.43	
Diffuse type	8	2,218/5,823	2.39 (1.62–3.52)	<0.0001	74	0.0004	1.77 (1.18–2.67)	0.006	84	<0.00001	1.94 (1.29–2.92)	0.002	85	<0.00001	1.53 (1.29–1.80)	<0.00001	34	0.16	
Asian	5	1,947/3,678	2.44 (1.39–4.27)	0.002	83	<0.0001	2.00 (1.19–3.37)	0.009	88	<0.00001	2.10 (1.20–3.68)	0.010	91	<0.00001	1.43 (1.16–1.77)	0.0008	45	0.12	
Caucasian	3	271/2,145	2.24 (1.55–3.23)	<0.0001	0	0.62	1.35 (0.74–2.45)	0.32	58	0.09	1.59 (1.02–2.49)	0.04	38	0.20	1.80 (1.37–2.37)	<0.0001	0	0.39	
Study design																			4
PCC	6	4,427/4,960	1.85 (1.29–2.65)	0.0009	84	<0.00001	1.53 (1.09–2.16)	0.02	88	<0.00001	1.64 (1.15–2.34)	0.006	90	<0.00001	1.40 (1.23–1.58)	<0.00001	24	0.26	
HCC	5	6,319/4,198	1.60 (1.26–2.03)	<0.0001	56	0.06	1.42 (1.29–1.56)	<0.00001	0	0.50	1.47 (1.29–1.68)	<0.00001	39	0.16	1.26 (1.14–1.39)	<0.00001	0	0.48	
Subsite																			5
Cardia	5	1,269/4,967	1.06 (0.66–1.70)	0.80	72	0.007	1.03 (0.62–1.71)	0.92	89	<0.00001	1.03 (0.64–1.67)	0.90	89	<0.00001	1.01 (0.82–1.23)	0.94	0	0.74	
Noncardia	5	5,004/4,967	1.45 (1.08–1.95)	0.01	70	0.009	0.88 (0.54–1.45)	0.63	95	<0.00001	1.21 (0.87–1.68)	0.27	90	<0.00001	1.32 (1.07–1.63)	0.01	57	0.05	
		A		*B*				*C*				*D*				*E*			

[a]*P* value for OR.

[b]*P* value for I^2.

Table 3. Overall analyses on the association of *A* allele in rs2976392 with GC risk and heterogeneity test

					Significance (*Z* test)		Heterogeneity (*Q* test)	
rs2976392	No. of study	No. of cases	No. of controls	OR (95% CI)	*Z* value	*P*	I^2 (%)	*P*
AA vs. GG	6	6,060	4,824	1.81 (1.21–2.72)	2.86	0.004	87	<0.00001
AG vs. GG	6	6,060	4,824	1.62 (1.24–2.12)	3.50	0.0005	85	<0.00001
Dominant model	6	6,060	4,824	1.69 (1.24–2.31)	3.31	0.0009	90	<0.00001
Recessive model	6	6,060	4,824	1.31 (1.13–1.52)	3.66	0.0003	44	0.11

differentiation of cancer cell, tumor location, and stage of the tumor (21, 23, 25–27, 29–31). However, controversial conclusions were yielded from different stratification analyses. Sakamoto and colleagues (21) suggested that rs2294008 had far a more significant association with diffuse type GC than intestinal type. This effect was supported by case–control studies on Japanese, Korean, and Caucasian populations (23, 25, 30) and also consistent with our meta-analysis. While an opposite outcome was reported about the difference in associations of rs2294008 with 2 types of GC in a Chinese study (26). Another study on Caucasians showed that no significant difference was observed for association with rs2294008 between intestinal and diffuse type GC (27). In addition, in spite of the contradictory results on LD between the 2 loci for the association with GC (21, 28–31), the LD could be supported by our results.

It is likely that different genetic background and large variation in risk allele frequencies in ethnicities may mainly be responsible for the contradictory results. Variations of sample sizes and subject sources of different studies may also account for the observed inconsistency. In this large meta-analysis, we observed that risk rs2294008T allele had slightly greater effects on Asians than Caucasians, and the effect was statistically more significant in diffuse type than intestinal type GC. This phenomenon may be explained by the higher frequencies of risk *T* allele in Asians than in Caucasians. Some research also focused on the difference in tumor locations in the stomach. Majority of the related studies suggested that rs2294008 had a strong effect on risk of noncardia stomach tumors but little or no effect on risk of cardia tumors (25–27, 31), which was approximately consistent with our stratified analysis for subsite of GC. In contrast, Song and colleagues indicated that rs2294008 had a stronger association with risk of cardia tumors than noncardia ones in a Korean study (23). Fewer studies reported that significant interactions were observed between rs2294008 and female, poor differentiation of cancer cell and progressive tumor-node-metastasis (TNM) stage of tumors (26, 30, 31). Our stratified analysis on study design revealed that variant genotypes were slightly more prevalent in PCC studies than in HCC ones. These results may be caused by some bias in hospital-based patients' selection and specific geographic distribution of GC, which indicates that the effect of variants on GC susceptibility might be underestimated based on HCC compared with PCC.

Heterogeneity among inclusive studies was a crucial problem for our meta-analysis, which may at least

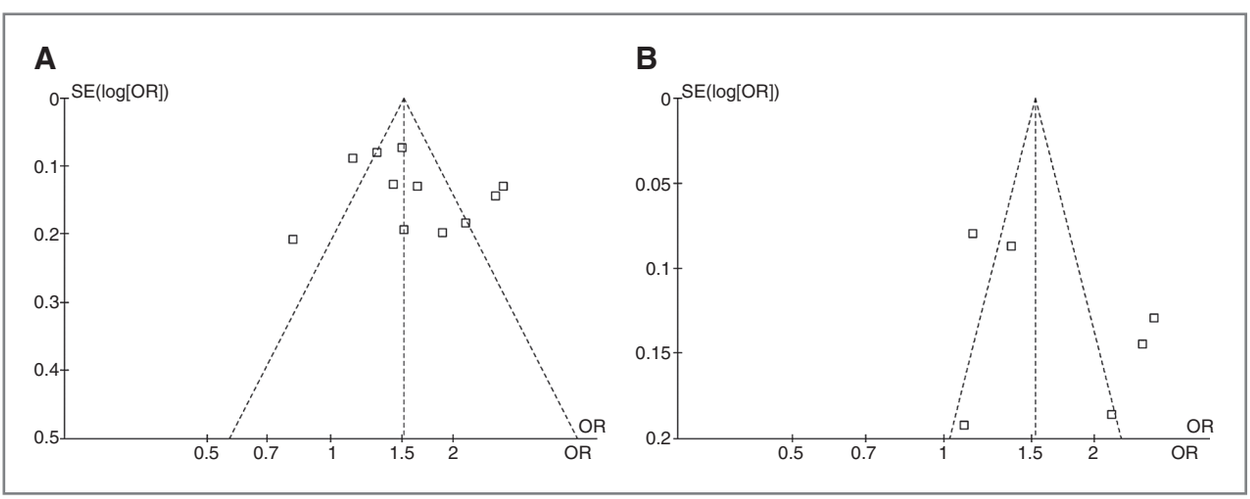

Figure 2. A, Funnel plot of rs2294008 for publication bias: $P = 0.253$. B, Funnel plot of rs2976392 for publication bias: $P = 0.244$.

partly account for the inconsistent results, especially in the stratification analyses. Inappropriate management for the heterogeneity may induce misleading statistical inference. In our meta-analysis, we adopted Q test and I^2 values to evaluate the scale of heterogeneity. Heterogeneity in present meta-analysis was mainly caused by the following. First, study populations were consisted of different racial descent sources, in which variant genotype distribution of *PSCA* varied greatly, particularly in Asians. Second, study designs varied remarkably. There were large differences in sample size, patient's source, and stratification criteria. Small sample size, single-center with HCC, vague strata criteria may result in statistical biases. Lastly, diagnosis standard applied for GC was different among inclusive studies. Even now, for example, the consensus for the histopathologic classification standard of GC has not been reached between eastern and western countries. In addition, the TNM stage of stomach tumor was carried out with different versions of the American Joint Committee on Cancer Guidelines. All of the factors that may interfere with statistical inference have been carefully paid attention to in our meta-analysis. Also, funnel plots were made to assess the publication bias, and no obvious asymmetry was observed in funnel plots.

GWAS is a powerful tool for high-risk population screening for many diseases in molecular epidemiology, and progressions of mass screening for several types of cancers have been achieved with the GWAS, including breast, prostate, colorectal, lung cancers (40–43). Although the advanced understanding of population-specific genetic variation by more and more GWAS studies, SNP chips technology has still not been clinically applicable so far. Large-scale studies will be needed for high-risk population screening, individualized prevention and treatment, and cost effectiveness evaluation in the future (44).

In conclusion, our meta-analysis suggested that 2 SNPs of *PSCA*, rs2294008 and rs2976392 were both associated with GC susceptibility and showed the LD. In addition, in dominant model, variant T genotypes of rs2294008 had a greater effect on diffuse type GC, Asians, and PCC than intestinal type GC, Caucasians, and HCC, respectively. Notably, controversial results were generated from various studies included in this meta-analysis. So, large prospective studies at multicenters with sufficient sample size and less heterogeneity will be needed for further validations.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: T. Wang, L. Zhang, K. Chen
Development of methodology: T. Wang, K. Chen
Acquisition of data: T. Wang, L. Zhang
Analysis and interpretation of data: T. Wang, H. Li, B. Wang
Writing, review, and/or revision of the manuscript: T. Wang, H. Li, K. Chen
Administrative, technical, or material support: L. Zhang, B. Wang
Study supervision: B. Wang, K. Chen

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