

Review Article

Prostate stem cell antigen polymorphism rs2294008 and cancer risk: a meta-analysis

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Abstract: Prostate stem cell antigen (PSCA) is a cell surface protein, which has a cell-proliferation inhibition and/or cell-death induction activity. Multiple studies have reported the association between PSCA rs2294008 polymorphism and cancer risk, which showed inconclusive results. This meta-analysis based on 39 studies involving 36,742 cases and 64,756 controls was performed to address this issue. We assessed the strength of the association, using odds ratios (ORs) with 95% confidence intervals (CIs). The statistical heterogeneity between studies was checked by χ^2 -based Q-test. Overall, the individuals with the TT/TC genotypes were associated with higher cancer risk than those with the CC genotype (TT/TC vs. CC: OR = 1.27, 95% CI = 1.17-1.39, $P_{\text{heterogeneity}} < 0.001$). In the stratified analyses, there was a significantly increased risk of gastric cancer (TT vs. CC: OR = 1.42, 95% CI = 1.16-1.73, $P_{\text{heterogeneity}} < 0.001$; TC vs. CC: 1.40, 1.27-1.55, $P_{\text{heterogeneity}} < 0.001$) and bladder cancer (TT vs. CC: 1.30, 1.22-1.39, $P_{\text{heterogeneity}} = 0.417$; TT vs. TC/CC: 1.14, 1.08-1.20, $P_{\text{heterogeneity}} = 0.458$) in all genetic models except recessive model. Moreover, significant effects were observed in both Asians and Caucasian populations (TT vs. CC: 1.21, 1.01-1.44, $P_{\text{heterogeneity}} < 0.001$; TT/TC vs. CC: 1.28, 1.14-1.43, $P_{\text{heterogeneity}} < 0.001$ for Asians and TT vs. CC: 1.46, 1.23-1.74, $P_{\text{heterogeneity}} < 0.001$; TT/TC vs. CC: 1.25, 1.09-1.44, $P_{\text{heterogeneity}} < 0.001$ for Caucasians). These findings supported that PSCA rs2294008 polymorphism may contribute to the susceptibility of cancers, especially among gastric cancer and bladder cancer.

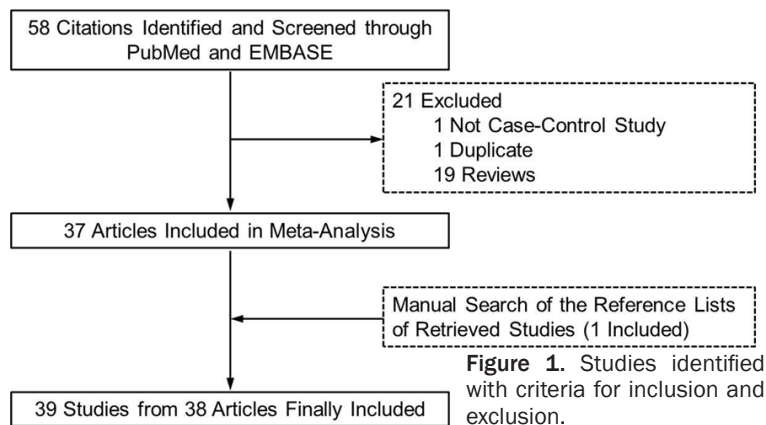
Keywords: PSCA, genetic variation, cancer susceptibility, GWAS, meta-analysis

Introduction

Cancer is a long-term multi-process disease that results from complex interactions between genetic and environmental factors [1]. Among the causations of cancer, inherited genetic factors accounted for 1%-53% [2]. In the past few years, the genome-wide association study (GWAS) has been successful in exploring a number of cancer-associated loci, thus advanced our knowledge of the genetic architecture of cancer [3, 4]. Recently, a couple of unexpected, exciting findings from two separate GWAS identified a significant association of a functional single nuclear polymorphism (SNP) in the prostate stem cell antigen (PSCA) gene, rs2294008 (C > T), with the risk of gastric cancer and bladder cancer at a genome-wide significant level ($P < 1 \times 10^{-7}$) [4, 5].

The PSCA gene consisting of 3 exons and 2 introns maps approximately 15 Mb distal to *Myc* oncogene on chromosome 8q24, which is one of the most frequently amplified regions in human cancers [6]. It encodes a small, glycosylphosphatidylinositol-anchored cell surface protein PSCA belonging to the Thy-1/LY-6 family [7]. The function of PSCA in normal cellular processes or carcinogenesis is unknown, but PSCA is detected to be overexpressed in a large proportion of prostate cancers and abnormally expressed in lots of malignancies including gastric cancer, esophageal cancer, bladder cancer, clear cell renal cell carcinoma and pancreatic cancer [8-11]. The investigations on PSCA before have been largely focusing on its potential application as a cancer biomarker and therapeutic target [7, 11].

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In recent years, an increasing number of studies have investigated the association between *PSCA* rs2294008 and cancer risk in human. Most focused on gastric and bladder cancer, and to a less extent on the cancers of prostate, colorectal, esophageal, breast and cervical [9, 12-19]. The rs2294008 polymorphism denotes a C > T transition in exon 1 of the *PSCA* gene, at the presumed translation-initiating codon. It is reported that the T allele of rs2294008 resulted in a significant reduction in transcriptional activity of the *PSCA* promoter *in vitro* [4]. Recently, Wang *et al.* conducted a meta-analysis to assess the association between *PSCA* polymorphisms and risk of gastric cancer, and they found an increased risk for gastric and bladder cancer associated with rs2294008 T allele, which is in consistent with the results of other meta-analyses [20-25]. However, more studies on *PSCA* rs2294008 and different cancer risk have been published and the results remain conflicting rather than conclusive. Given the biological functions of *PSCA* protein involved in cancer incidences such as cell-proliferation inhibition and/or cell-death induction activity [4], we performed a meta-analysis on all published case-control studies to estimate the overall cancer risk of this rs2294008 polymorphism and to quantify heterogeneity between the individual studies.

Materials and methods

Publication search

In order to identify the relative papers on *PSCA* rs2294008 C > T polymorphism and cancer risk, we carried out a search in PubMed and EMBASE databases, using the following key

words: “*PSCA*” or “prostate stem cell antigen”, “polymorphism” and “cancer” (the last search update was 30 July 2016). In addition, references of all included articles were also identified by a manual search and studies matching the eligible criteria were retrieved.

Inclusion criteria

Studies included in the current meta-analysis have to meet the following inclusion

criteria: (1) use an independent case-control design, (2) evaluation of the association between *PSCA* rs2294008 C > T polymorphism and cancer risk, and (3) provide complete information about all genotype frequency.

Data extraction and quality assessment

Two of the authors extracted all data independently according to the inclusion criteria listed above and reached a consensus on all the items. For each study, the following basic information was collected: the first author’s last name, publication date, country of origin, ethnicity, cancer type, source of controls (population- or hospital-based controls), genotyping methods and numbers of genotyped cases and controls. Different ethnic descents were categorized as Asian and Caucasian. For study including subjects of different cancer types, data were extracted separately whenever possible. The study quality was assessed according to the quality assessment criteria (Supplementary Table 1), which was developed for genetic association studies [26]. Total scores range from 0 (worst) to 12 (best).

Statistical analysis

The departure of frequencies of *PSCA* rs2294008 C > T polymorphism from expectation under Hardy-Weinberg equilibrium (HWE) was assessed by χ^2 test in controls. Odds ratios (ORs) corresponding to 95% confidence intervals (CIs) were used to assess the strength of association between *PSCA* rs2294008 C > T polymorphism and cancer risk. The statistical significance of the summary OR was determined with the Z-test. We first estimated the

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Table 1. Characteristics of eligible studies included in the meta-analysis

First author	Year	Country	Ethnicity	Cancer types	Source of controls	Genotyping method	Genotype (N)								HWE	Quality score
							Case				Control					
							Total	TT	TC	CC	Total	TT	TC	CC		
Qiu	2016	China	Asian	Gastric	PB	Taqman	1124	98	489	537	1192	146	383	663	< 0.01	7
Wang S	2016	China	Asian	Cervical	HB	Taqman	1126	48	469	609	1237	92	527	618	0.16	8
Wang M	2016	China	Asian	Breast	HB	MassARRAY	560	56	231	273	583	37	247	299	0.14	9
Mou	2015	China	Asian	Gastric	HB	Multiplex PCR	198	49	126	23	130	91	34	5	0.43	2
Maria	2015	Spain	Caucasian	Gastric	PB	Taqman	603	147	302	154	675	130	346	199	0.35	9
Sun	2015	China	Asian	Gastric	HB	Taqman	702	61	309	332	774	72	297	405	0.11	9
Kupcinskask	2015	Latvia	Caucasian	Colorectal	HB	Taqman	191	54	77	60	377	88	189	100	0.94	8
Ichikawa	2015	Japan	Asian	Gastric	HB	PCR-RFLP	193	65	104	24	266	95	119	52	0.19	10
Zhang	2015	China	Asian	Gastric	HB	MassARRAY	475	41	207	227	480	36	183	261	0.62	8
Wang	2014	China	Asian	Bladder	PB	Taqman	1210	97	509	604	1008	66	376	566	0.74	9
Sun	2014	USA	Caucasian	Gastric	HB	Taqman	130	17	64	49	125	30	63	32	0.93	9
Dai	2014	China	Asian	Esophageal	PB	Taqman	2083	127	724	1232	2220	147	851	1222	0.94	9
Lee	2014	Korea	Asian	Bladder	HB	HRM	411	119	222	70	1700	468	818	414	0.13	8
Matsuda	2014	Japan	Asian	Bladder	HB	Multiplex PCR	530	241	228	61	5225	2079	2416	730	0.51	9
Kupcinskask	2014	Lithuania	Caucasian	Gastric	HB	Taqman	251	102	116	33	243	56	123	64	0.83	10
Ali	2013	Pakistan	Asian	Bladder	PB	PCR-RFLP	200	9	142	49	200	3	126	71	< 0.01	6
Rai	2013	India	Asian	Gallbladder	PB	Taqman	405	68	233	104	247	42	126	79	0.49	9
Rizzato	2013	Germany	Caucasian	Gastric	HB	Taqman	178	69	86	23	1057	319	507	231	0.27	10
Ono	2013	Japan	Asian	Gallbladder	HB	Taqman	44	12	23	9	173	68	75	30	0.24	8
Zhao	2013	China	Asian	Gastric	PB	DHPLC	717	100	342	275	951	85	401	465	0.91	9
Ma	2013	China	Asian	Bladder	PB	MassARRAY	175	11	80	84	962	64	355	543	0.56	10
Smith	2012	Scotland	Caucasian	Colorectal	PB	TaqMan	77	13	39	25	804	130	387	287	0.98	10
Kim	2012	Korea	Asian	Breast	PB	MassARRAY	451	116	216	119	459	106	240	113	0.32	7
Li	2012	China	Asian	Gastric	PB	MassARRAY	300	35	141	124	300	21	111	168	0.65	9
Fu	2012	USA	Caucasian	Bladder	PB	Multiplex PCR	5393	1226	2804	1363	7324	1572	3645	2107	0.95	9
Tanikawa	2012	Japan	Asian	Gastric	HB	Multiplex PCR	2300	1030	1073	197	16567	6620	7587	2360	0.01	8
Sala	2011	European countries	Caucasian	Gastric	HB	Multiplex PCR	409	118	198	93	1515	310	714	491	0.09	9
Song	2011	Korea	Asian	Gastric	PB	PCR-RFLP	3245	1049	1620	576	1700	468	818	414	0.13	10
Zeng	2011	China	Asian	Gastric	PB	PCR-RFLP	460	42	216	202	549	37	223	289	0.49	9
Joung	2011	Korea	Asian	Prostate	HB	MassARRAY	192	49	98	45	168	37	84	47	0.96	10
Lochhead	2011	Scotland	Caucasian	Gastric	PB	TaqMan	600	196	272	132	590	164	276	150	0.12	9
		Scotland	Caucasian	Esophageal	PB	TaqMan	158	34	63	61	208	49	110	49	0.40	9
Ou	2010	China	Asian	Gastric	PB	PCR-LDR	196	18	93	85	246	18	96	132	0.92	8
Lu	2010	China	Asian	Gastric	PB	PCR-RFLP	1023	72	404	547	1069	77	387	605	0.17	11

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Wang	2010	China	Asian	Bladder	HB	PCR-RFLP	581	50	259	272	580	44	220	316	0.50	10
Wu	2009	USA	Caucasian	Bladder	Combined	Multiplex PCR	5038	1137	2613	1288	9363	1853	4668	2842	0.42	9
Matsuo	2009	Japan	Asian	Gastric	HB	TaqMan	708	49	329	330	708	97	338	273	0.64	9
Wu C	2009	China	Asian	Gastric	PB	PCR-RFLP	1710	132	819	759	995	77	412	506	0.30	10
Sakamoto	2008	Japan	Asian	Gastric	HB	Multiplex PCR	2395	728	700	96	1396	536	650	210	0.57	9
		Korea	Asian	Gastric	HB	Multiplex PCR	871	277	461	133	390	92	176	122	0.07	

PCR-RFLP, Polymerase chain reaction-restriction fragment length polymorphism; LDR, Ligase detection reaction; PB, Population-based; HB, Hospital-based; Combined, studies conducted on both population-based and hospital-based control group; HWE, *P* value in the control group for Hardy-Weinberg Equilibrium.

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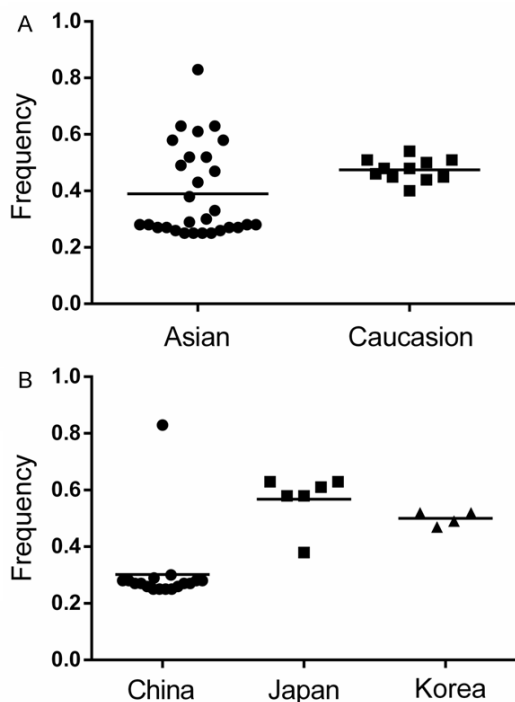


Figure 2. A. Frequencies of the variant alleles (T allele) among controls stratified by ethnicity. B. Frequencies of the variant alleles (T allele) among controls stratified by countries in Asian. Black triangle ● ■ ▲ represents each included study.

risk of the TT or TC genotype on cancers, compared with the wild-type CC homozygote, and then evaluated the risks of TT/TC vs. CC and TT vs. TC/CC on cancers, assuming dominant and recessive effects of the variant T allele, respectively. Stratified analyses were also performed by cancer types (if one cancer type contained one individual study, it was combined into other cancer group), ethnicity, source of controls and sample size (subjects > 500 in both cases and controls or not).

Heterogeneity assumption was checked by the χ^2 -based Q-test [27]. A P -value ≤ 0.10 for the Q-test indicated a lack of heterogeneity among the studies, and then random-effects model (DerSimonian and Laird method) was used to calculate the summary OR estimate of each study [28]. Otherwise, the fixed-effects model (the Mantel-Haenszel method) was used [29]. If the P value is more than 0.05, then the genotype distributions among controls were in accordance with HWE. Sensitivity analyses were performed to assess the stability of the results, namely, a single study in the meta-analysis was deleted each time to reflect the influ-

ence of the individual data set to the pooled OR. To evaluate the publication bias, Funnel plots and Egger's linear regression test was applied [30]. All analyses were carried out with Stata software (version 8.2; StataCorp LP, College Station, TX, USA), using two-sided P values.

Results

Study characteristics

There were 59 articles relevant to the search words, including one in manual search (**Figure 1**). Among these, 38 articles with 39 studies involving 36,742 cases and 64,756 controls met our inclusion criteria and were subjected to further examination. Remarkably, the article by Lochhead *et al.* analyzed the association of rs2294008 polymorphism with two types of cancer, and hence we included it as two different studies [15]. We excluded 21 studies (19 were reviews, 1 was duplication and 1 was not a case-control study). Characteristics of the selected studies are summarized in **Table 1**. Among the 39 case-control studies, there were 28 groups of Asians [4, 9, 12, 13, 16-19, 31-50], and 11 groups of Caucasians [5, 14, 15, 51-57]. Controls were mainly matched for sex and age, of which 18 were hospital-based [4, 13, 18, 32, 35, 38-42, 44, 45, 48, 52, 54-57], 20 were population-based [9, 12, 14-17, 19, 31, 33, 34, 36, 37, 43, 46, 47, 49-51, 53] and 1 study was conducted on both hospital-based and population-based control group [5]. Cancers were confirmed histologically or pathologically in most studies. All studies were case-control studies, including 21 gastric cancer studies [4, 12, 15, 17, 19, 31-36, 39-42, 49, 52, 53, 55-57], 8 bladder cancer studies [5, 9, 37, 44-46, 50, 51] and the others were categorized into the "other cancers" group [13, 14, 16, 18, 38, 43, 47, 48, 54]. The distribution of genotypes in the controls of all studies was not deviated from the HWE except four studies [4, 19, 32, 46].

Quantitative synthesis

The frequency of T allele was found to be statistically significant among the controls across different ethnicities ($P = 0.018$). For Caucasian populations, the T allele frequency was 0.48 (95% CI = 0.45-0.50), a little bit higher than that in Asian populations (0.39, 95% CI = 0.33-

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Table 2. Meta-analysis of the PSCA rs2294008 C > T polymorphism on cancer risk

Variables	N ^a	TT vs. CC			TC vs. CC			TT/TC vs. CC (dominant)			TT vs. TC/CC (recessive)		
		OR (95% CI)	Heterogeneity		OR (95% CI)	Heterogeneity		OR (95% CI)	Heterogeneity		OR (95% CI)	Heterogeneity	
			I ²	P		I ²	P		I ²	P		I ²	P
Total	39	1.29 (1.14-1.46) ^b	83.0%	< 0.001	1.26 (1.16-1.36) ^b	78.2%	< 0.001	1.27 (1.17-1.39) ^b	83.1%	< 0.001	1.10 (1.00-1.21) ^b	79.7%	< 0.001
Cancer type													
Gastric	21	1.42 (1.16-1.73) ^b	86.3%	< 0.001	1.40 (1.27-1.55) ^b	68.5%	< 0.001	1.42 (1.26-1.60) ^b	80.7%	< 0.001	1.11 (0.95-1.30) ^b	86.7%	< 0.001
Bladder	8	1.30 (1.22-1.39)	1.7%	0.417	1.24 (1.18-1.31)	5.8%	0.385	1.26 (1.20-1.32)	0.0%	0.446	1.14 (1.08-1.20)	0.0%	0.458
Other	10	0.95 (0.74-1.20) ^b	62.0%	0.005	0.91 (0.79-1.05) ^b	53.4%	0.023	0.93 (0.80-1.07) ^b	55.9%	0.015	0.99 (0.81-1.22) ^b	57.9%	0.011
Ethnicity													
Asian	28	1.21 (1.01-1.44) ^b	85.1%	< 0.001	1.29 (1.16-1.44) ^b	80.9%	< 0.001	1.28 (1.14-1.43) ^b	85.4%	< 0.001	1.01 (0.88-1.15) ^b	82.9%	< 0.001
Caucasian	11	1.46 (1.23-1.74) ^b	75.8%	< 0.001	1.17 (1.02-1.34) ^b	68.0%	0.001	1.25 (1.09-1.44) ^b	75.2%	< 0.001	1.30 (1.16-1.47) ^b	63.5%	0.002
Source of controls													
Population-based	20	1.25 (1.10-1.42) ^b	65.2%	< 0.001	1.24 (1.12-1.37) ^b	76.3%	< 0.001	1.25 (1.14-1.38) ^b	77.3%	< 0.001	1.13 (1.03-1.24) ^b	48.8%	0.008
Hospital-based	18	1.28 (0.98-1.67) ^b	88.9%	< 0.001	1.29 (1.09-1.52) ^b	81.5%	< 0.001	1.30 (1.07-1.57) ^b	87.7%	< 0.001	1.04 (0.86-1.25) ^b	88.5%	< 0.001
Combined	1	1.35 (1.23-1.50)	-	-	1.24 (1.14-1.34)	-	-	1.27 (1.18-1.37)	-	-	1.18 (1.09-1.28)	-	-
Sample size ^c													
> 500	19	1.23 (1.05-1.43) ^b	88.2%	< 0.001	1.23 (1.12-1.36) ^b	85.4%	< 0.001	1.24 (1.12-1.38) ^b	88.7%	< 0.001	1.09 (0.99-1.20) ^b	78.3%	< 0.001
< 500	20	1.37 (1.08-1.73) ^b	72.6%	< 0.001	1.30 (1.12-1.50) ^b	60.7%	< 0.001	1.32 (1.13-1.54) ^b	69.4%	< 0.001	1.12 (0.89-1.41) ^b	81.7%	< 0.001

^aNumber of comparisons. ^bRandom-effects model was used when P value for heterogeneity test < 0.10; otherwise, fix-effects model was used. ^cStratified according to subjects > 500 in both case and control groups or not.

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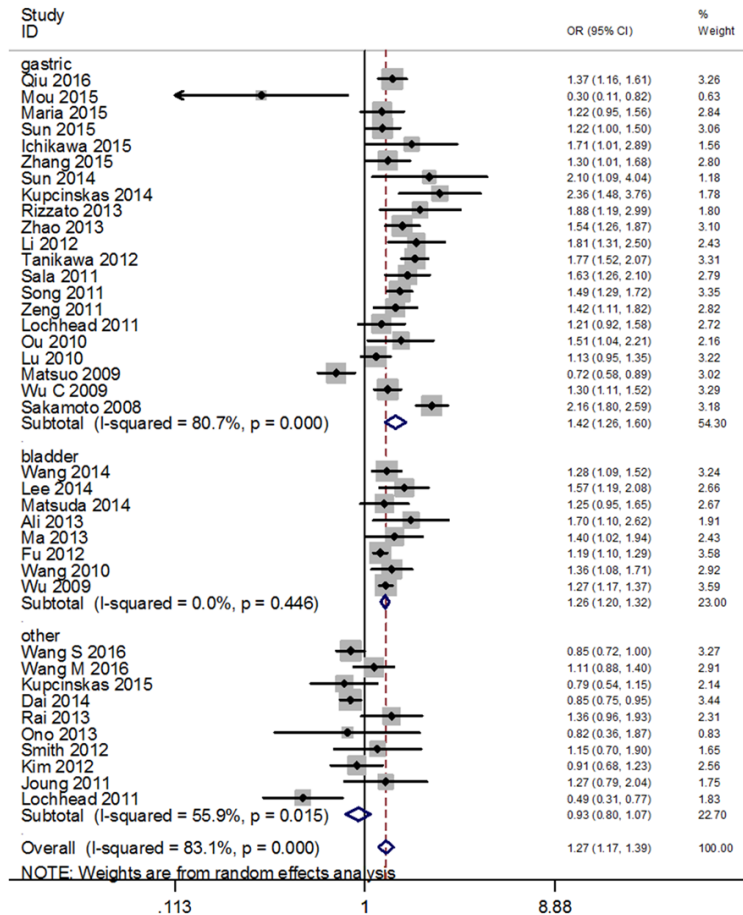


Figure 3. Forest plot of cancer risk associated with the PSCA rs2294008 polymorphism (dominant model) stratified by cancer type. The squares and horizontal lines correspond to the study-specific OR and 95% CI. The area of the squares reflects the weight (inverse of the variance). The diamond represents the summary OR and 95% CI.

0.46). There was a wide variation of the T allele frequency in different countries of Asian, ranging from 0.31 to 0.57. The allele frequency was the lowest in Chinese populations and was the highest in Japanese populations (0.31, 95% CI = 0.23-0.38, vs. 0.57, 95% CI = 0.47-0.67; **Figure 2**), which is very close to that obtained from the HapMap Project (0.26 for CHB and 0.67 for JPT). The difference among the three country groups was statistically significant ($P < 0.001$).

The evaluations of the association between PSCA rs2294008 polymorphism and cancer risk are shown in **Table 2**. Overall, when all the eligible studies were pooled into the meta-analysis, the individuals with variant genotypes had an increased risk of cancer in all genetic model (TT vs. CC: OR = 1.29, 95% CI = 1.14-

1.46, $P_{\text{heterogeneity}} < 0.001$; TC vs. CC: 1.26, 1.16-1.36, $P_{\text{heterogeneity}} < 0.001$; TT/TC vs. CC: 1.27, 1.17-1.39, $P_{\text{heterogeneity}} < 0.001$; TT vs. TC/CC: 1.10, 1.00-1.21, $P_{\text{heterogeneity}} < 0.001$; **Table 2**). In terms of stratified analysis by cancer type, significantly increased risk was observed in gastric cancer in all genetic models tested except the recessive model (TT vs. CC: OR = 1.42, 95% CI = 1.16-1.73, $P_{\text{heterogeneity}} < 0.001$; TT vs. TC/CC: 1.11, 0.95-1.30, $P_{\text{heterogeneity}} < 0.001$) and all the four genotypic model were found to significantly associated with increased risk in bladder cancer (TT vs. CC: 1.30, 1.22-1.39, $P_{\text{heterogeneity}} = 0.417$; TT vs. TC/CC: 1.14, 1.08-1.20, $P_{\text{heterogeneity}} = 0.458$), but not in “other cancers” (**Table 2**; **Figure 3** of dominant model).

We then evaluated the effects of PSCA rs2294008 polymorphism according to ethnicity and source of controls. Significant effects were observed in both Asian and Caucasian populations in all genetic models except for the recessive model for Asian

(TT vs. CC: OR = 1.21, 95% CI = 1.01-1.44, $P_{\text{heterogeneity}} < 0.001$; TT vs. TC/CC: 1.01, 0.88-1.15, $P_{\text{heterogeneity}} < 0.001$ for Asians and TT vs. CC: 1.46, 1.23-1.74, $P_{\text{heterogeneity}} < 0.001$; TT vs. TC/CC: 1.30, 1.16-1.47, $P_{\text{heterogeneity}} = 0.002$ for Caucasians) (**Table 2**).

Test of heterogeneity, sensitivity and publication bias

There was significant heterogeneity in all genetic models. Therefore, we assessed the source of heterogeneity for homozygote comparison by cancer type, ethnicity, source of controls, and sample size (participants more than 500 in both cases and controls). As a result, only cancer type ($P = 0.009$) was found to contribute to the substantial heterogeneity. Sensitivity analyses indicated that the results of this meta-anal-

protein [32]. Therefore, the genetic variation in PSCA could have considerable effect on the biological function of the PSCA protein by altering its subcellular localization and stability. Sakamoto *et al.* found that the rs2294008 T allele resulted in a significant reduction in transcriptional activity of the PSCA promoter in gastric cell lines [4]. In concordance with Sakamoto *et al.* observations, Wu *et al.* reported that the T allele reduced the transcriptional activity of the PSCA promoter in bladder cell lines as well [36]. However, it is perplexing that the risk allele is the same and the reduced transcriptional activity is consistent in both gastric and bladder cancers, even though the PSCA gene is down-regulated in gastric cancer but up-regulated in bladder cancer. Further efforts are needed to determine the physiological function of the functional consequence of PSCA rs2294008 polymorphism *in vivo*.

In the analysis stratified by cancer type, significantly elevated risks were more pronounced among gastric cancer and bladder cancer. However, rs2294008 polymorphism had no effects on other cancers composed of six different tumor studies. As heterogeneity among different cancers may interfere the authenticity of result in “other cancers”, the inverse result of esophageal cancer study need to be paid more attention. This difference may be due to limited statistical power as a result of the small sample size as well as possibly diverse carcinogenic mechanisms underlying the etiology.

Subsequently, we found that the association was more significant among studies using the population-based controls than the hospital-based controls. This may indicate that the hospital-based studies have inherent selection biases due to the fact that such controls may not be representative of the study population or the general population, particularly when the genotypes under investigation were associated with the disease-related conditions the hospital-based controls may have. In addition, we observed that risk rs2294008 T allele had slightly greater effects on Caucasians than Asians, suggesting a possible role of ethnic differences in genetic background and the environment they lived in [60].

To identify the source of heterogeneity, we stratified the studies according to cancer type, ethnicity, source of controls, and sample size.

Results showed the sources of heterogeneity were from cancer type, suggesting that certain effects of genetic variant were cancer specific.

Our meta-analysis had some advantages. First, substantial number of cases and controls were pooled from different studies, which significantly increased statistical power of the analysis. Second, the quality of case-control studies included in our present meta-analysis strictly met our selection criteria. Third, we did not detect any publication bias indicating that the whole pooled result may be unbiased. Furthermore, on the basis of our study, functional variants of PSCA might be conducted and replicate these observations, so that it might find a novel mechanism to predict the risk of cancer. However, some limitations in this meta-analysis should be addressed. First, we pooled the data based on unadjusted information, while a more precise analysis needs to be conducted if individual data are available. Second, lack of the original data of the reviewed studies limited our further evaluation of potential interactions, because the gene-environment or gene-gene interaction may modulate cancer risk.

In conclusion, our meta-analysis suggested that the rs2294008 polymorphism in PSCA may contribute to genetic susceptibility for increased cancer risk, especially in the subgroup of gastric cancer and bladder cancer. Therefore, additional larger studies of other cancers are warranted to validate our findings. Future functional studies focusing on polymorphism rs2294008 and cancer risk are still needed.

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Disclosure of conflict of interest

None.

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Supplementary Table 1. Criteria for quality assessment of genetic associations of PSCA polymorphism rs2294008 and cancer risk

Criteria	Quality score
<i>Representativeness of cases</i>	
A. Consecutive/randomly selected from case population with clearly defined random frame	2
B. Consecutive/randomly selected from case population without clearly defined random frame or with extensive inclusion criteria	1
C. Method of selection not described	0
<i>Representativeness of controls</i>	
D. Controls were consecutive/randomly drawn from the same area (ward/community) as cases with the same criteria	2
E. Controls were consecutive/randomly drawn from a different area than cases	1
F. Not described	0
<i>Ascertainment of cancer cases</i>	
G. Clearly described objective criteria for diagnosis of cancer	1
H. Not described	0
<i>Ascertainment of controls</i>	
I. Clinical examinations were performed on controls to prove that controls did not have cancer	2
J. Article merely stated that controls were subjects who did not have cancer; no proof provided	1
K. Not described	0
<i>Ascertainment of genotyping examination</i>	
L. Genotyping done under "blind" conditions	1
M. Unblinded or not mentioned	0
<i>Test for Hardy-Weinberg equilibrium</i>	
N. Hardy-Weinberg equilibrium in control group	2
O. Hardy-Weinberg disequilibrium in control group	1
P. Hardy-Weinberg equilibrium not checked	0
<i>Association assessment</i>	
Q. Assessed association between genotypes and cancer with appropriate statistic and adjusting confounders	2
R. Assessed association between genotypes and cancer with appropriate statistic without adjusting confounders	1
S. Inappropriate statistic used	0