RESEARCH

Association between the PSCA rs2294008 C>T polymorphism and the risk of gastric cancer: A meta-analysis

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ABSTRACT

Gastric cancer (GC) is one of the most frequently diagnosed cancers around the world, and is the second leading cause of cancer related deaths. Several epidemiological studies associated the *Helicobacter pylori* infection with the risk of GC. However, cancer initiation and progression is a complex and multifactorial involving both genetic and environmental factors. Prostate stem cell antigen (PSCA) plays an important role in cell adhesion, proliferation and tumor progression. A strong association between *PSCA* rs2294008 C > T polymorphism and the risk of gastric cancer was observed in a previous genome wide association study. However, subsequent association studies yielded inconsistent results. The aim of this meta-analysis is to evaluate the association between *PSCA* rs2294008 C > T polymorphism and susceptibility to gastric cancer. A literature search was conducted on PubMed, Embase and Google Scholar till December 30th, 2018 as the publication date. For this meta-analysis analysis, a total of 26 eligible case-control (15676 cases and 16087 controls) studies were taken. Meta-analysis showed that the *PSCA* rs2294008 C>T is associated with increased risk of gastric cancers. Sub-group analysis by ethnicity revealed that the increased risk of gastric cancers was found only in Asians but not in Caucasians. Further, rs2294008 C>T polymorphism revealed significant heterogeneity between studies. There was no evidence of publication bias in this study. In conclusion, this meta-analysis provides strong evidence that rs2294008 C>T polymorphism is associated with increased risk of gastric cancers and may serve as a genetic biomarker of gastric cancers in Asians.

KEYWORDS: Gastric cancer, PSCA, rs2294008, prostate stem cell antigen, meta-analysis.

Citation: Verma HK et al. (2019). Association between the PSCA rs2294008 C>T polymorphism and the risk of gastric cancer: a meta-analysis. Polymorphism 2;42-50.

INTRODUCTION

Gastric cancer (GC) is one of the most frequently diagnosed cancers around the world, and is the second leading cause of cancer related deaths (Qiu et al., 2016b, Sun et al., 2015). According to the Global Burden of Disease (GBD), about 17.5 million new cancer cases and 8.7 million deaths were estimated in 2015 in global population (Kupcinskas et al., 2014a). From them, more than 70% number of new cases and deaths occurred in the developing countries, such as South America, Eastern Asia and Europe (Kupcinskas et al., 2014a). Among developing countries, China has almost 3 times higher incidence rates of GC (Wolpin et al., 2014). Several epidemiological studies associated the high intake of tobacco, smoking, low fruit and vegetable intake, high meat and salt intake, the lack of food refrigeration and *Helicobacter pylori* infection with the risk of GC (Kupcinskas et al., 2014b, Zheng et al., 2013). However, the accurate mechanism of GC development is not yet fully understood (Song et al., 2017). Cancer initiation and progression is a complex and multifactorial process involving several genetic as well as environmental risk factors (Wang et al., 2011). Over the past decade, hundreds of cancer-associated genetic markers have been identified by case-control, cohort and genome wide association studies (Hishida et al., 2019).

Prostate stem cell antigen (PSCA) is a glycosylphosphatidylinositol-anchored protein related to cell proliferation, inhibition and/or cell death induction activity and is overexpressed in prostate cancer cell lines. In addition, PSCA plays an important role in cell adhesion and proliferation, which may support tumor progression (Li et al., 2017). The gene coding for *PSCA* is located on chromosome 8q24.2 and consists of 3 exons (Reiter et al., 1998). The *PSCA* gene is over-expressed in prostate, renal, and ovarian tumors and is down regulated in esophageal, bladder and gastric cancers (Elsamman et al., 2006). Strong association between *PSCA* rs2294008 C > T polymorphism and the risk of gastric cancer was observed in GWAS (Sakamoto et al., 2008b). Subsequent replication studies with this locus showed association mainly in Asians, and for rest of the populations, the results are largely inconclusive (Qiu et al., 2016a, Cai et al., 2017a, Turdikulova et al., 2016, Mou et al., 2015, García-González et al., 2015, Sun et al., 2015, Ichikawa et al., 2015, Zhang et al., 2015, Sun et al., 2014, Kupcinskas et al., 2014a, Rizzato et al., 2013, Zhao et al., 2013, Li et al., 2012, Sala et al., 2012, Song et al., 2011, Zeng et al., 2011, Lochhead et al., 2011, Ou et al., 2010, Lu et al., 2010, Matsuo et al., 2009, Wu et al., 2009, Sakamoto et al., 2008a). Therefore, to further assess the association, a meta-analysis was performed on the previously published studies that have investigated the association between PSCA rs2294008 polymorphism and gastric cancer risk.

MATERIALS AND METHODS

Search strategy

Research papers examining the association between PSCA rs2294008 C>T polymorphism and gastric cancer risk were extracted from databases such as PubMed, EMBASE and Google scholar. The following MeSH index search terms were used "PSCA/prostate stem cell antigen" or "rs2294008", or "bladder cancer" "stomach cancer" or "carcinoma of bladder. All published papers with available full text matching the eligible criteria were retrieved. The last search was updated at end of the December 2018.

Inclusion and exclusion criteria

In order to reduce heterogeneity, the following criteria were used for the selection of eligible studies: 1) original case–control studies exploring the association between PSCA rs2294008 polymorphism and gastric cancer risk; 2) articles with detailed genotyping data for both cases and controls; 3) full-text published in English language. The exclusion criteria were: 1) duplicate studies 2) reviews, editorials, comments or animal studies. Further, discrepancies were resolved by discussion.

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Data extraction and quality assessment

Two authors (HKV and SL) independently extracted genotypes from 26 eligible case-control (16551 cases and 16320 controls) studies. For each study, first author's name, publication year, country of origin and ethnicity, method of genotyping, numbers of genotyped cases and controls were collected.

Statistical analysis

The association between the PSCA rs2294008 C>T polymorphism and gastric cancer risk was evaluated for each study by the crude odds ratios (ORs) with 95% confidence intervals (CIs). For each study, HWE was assessed by the chi-square goodness of fit test. For all studies, we estimated the association under three different models [Allele contrast (C vs T), dominant model (CC+CT vs TT), and recessive model (CC vs CT + TT)]. Statistical heterogeneity between studies was assessed by Cochran's Q test and I-square > 50% indicated the significance (Higgins & Thompson, 2002). To calculate the OR and make inference for each study, we used a random effects model or fixed-effect model. Sensitivity analyses were conducted by omitting any single study, which predisposed the observed heterogeneity excessively. To detect possible publication bias, both a funnel plot and the Egger's test were used. All statistical analyses were performed in the MetaGenyo online Statistical Analysis System software (Martorell-Marugan et al., 2017).

RESULTS

Of the 26 case-controls studies (15676 cases and 16087 controls) included in this meta-analysis, nineteen were conducted on Asians and seven on Caucasian populations. Genotype distribution, ethnicity, genotyping method used for each study are documented in Table 1.

Quantitative Synthesis

Quantitative synthesis of eligible studies in different genetic models using random effects method is documented in Table 2 and Figure 1. By pooling all the studies, we found statistically significant association between PSCA rs2294008 C>T polymorphism and gastric cancer risk (Dominant model: pooled OR=1.39, 95% CI: 1.22–1.58; recessive model: pooled OR=1.05, 95% CI: 0.87–1.26; allele model: pooled OR=1.17, 95% CI: 1.05–1.29). Stratification analyses by ethnicity revealed significant association between this locus and cancer risk only in Asian populations (Dominant model: OR=1.47, 95% CI: 1.27–1.69; recessive model: OR=1.00, 95% CI: 0.80–1.25; allele model: OR=1.18, 95% CI: 1.05–1.32), but not in Caucasian populations (dominant model: OR=1.17, 95% CI: 0.83–1.64; recessive model: OR=1.17, 95% CI: 0.83–1.65; allele model: OR=1.12, 95% CI: 0.87–1.43).

Heterogeneity and sensitivity analysis

In all comparison models, a significant heterogeneity was observed (Table 2). Sensitivity analysis revealed that there is no change in the pooled ORs by omitting individual studies (Figure 2). This further suggests that the results are robust.

Table 1: PSCA rs2294008 polymorphism genotype distribution in cases and controls

Study	Country	Ethnicity	Genotyping	Gastric Cancer			Control			HWE p-value
				TT	TC	CC	TT	TC	CC	
Cai et al. 2017	China	Asian	PCR (KASP)	45	225	215	47	173	268	0.017
Qiu et al. 2016	China	Asian	Taqman	98	489	537	146	383	663	0.000
Turdikulova et al. 2016	Uzbekistan	Asian	PCR-RFLP	0	190	78	20	109	119	0.472
Mou et al. 2015	China	Asian	DHPLC	49	126	23	91	34	5	0.426
Garcia-Gonzalez et al. 2015	Spain	Caucasian	Taqman	147	302	154	130	346	199	0.350
Sun et al. 2015	China	Asian	Taqman	61	309	332	72	297	405	0.105
Ichikawa et al. 2015	Japan	Asian	PCR-RFLP	65	104	24	95	119	52	0.185
Zhang et al. 2015	China	Asian	Sequenom	41	207	227	36	183	261	0.618
Sun et al. 2014	USA	Caucasian	Taqman	17	64	49	30	63	32	0.926
Kupcinskas et al. 2014	Lithuania	Caucasian	Taqman	102	116	33	56	123	64	0.834
Rizzato et al. 2013	Germany	Caucasian	Taqman	69	86	23	319	507	231	0.269
Zhao et al. 2013_1	Tibet-China	Asian	DHPLC	23	103	93	19	113	154	0.777
Zhao et al. 2013_2	Hui-China	Asian	DHPLC	49	112	72	41	145	129	0.980
Zhao et al. 2013_3	Han-China	Asian	DHPLC	28	127	110	25	143	182	0.667
Li et al. 2012	China	Asian	Mass array	35	141	124	21	111	168	0.650
Sala et al. 2012	European	Caucasian	Taqman	118	198	93	310	714	491	0.088
Song et al. 2011	China	Asian	PCR-RFLP	1049	1620	576	468	818	414	0.131
Zeng et al. 2011	China	Asian	PCR-RFLP	42	216	202	37	223	289	0.493
Lochhead et al. 2011_1	USA	Caucasian	Taqman	85	129	94	49	110	49	0.405
Lochhead et al. 2011_2	Poland	Caucasian	Taqman	47	143	102	101	166	115	0.011
Ou et al. 2010	China	Asian	PCR/LDR	18	93	85	18	96	132	0.924
Lu et al. 2010	China	Asian	PCR-RFLP	72	404	547	77	387	605	0.166
Matsuo et al. 2009	Japan	Asian	Taqman	49	329	330	97	338	273	0.638
Wu et al. 2009	China	Asian	PCR-RFLP	84	492	440	77	412	506	0.587
Sakamoto et al. 2008_1	Japan	Asian	GWAS	728	700	96	536	650	210	0.574
Sakamoto et al. 2008_2	Korea	Asian	Taqman	277	461	133	92	176	122	0.069

Publication bias

In all comparison models, the shape of funnel plots (standard error and precision) did not reveal any evidence for asymmetry (Figure 3). Hence there is no publication bias and each included study was symmetrically distributed around the underlying true effect size. Egger's test also did not show any evidence of publication bias (TT+TC vs. CC; Egger: P = 0.954) in the meta-analysis (Table 2).

DISCUSSION

The present meta-analysis evaluated the association between PSCA rs2294008 C>T polymorphism and gastric cancer risk by pooling twenty-six studies. The results of the present meta-analysis revealed that the variant (T allele) is associated with an increased risk of gastric cancer. Our results are consistent with the previous meta-analyses that investigated the association of the PSCA rs2294008 polymorphism in gastric cancer risk (Wang et al., 2012, Zhang et al., 2012, Zhao et al., 2014, Gu et al., 2015, Qin et al., 2017).

The PSCA plays a major role in multiple cellular events such as cell adhesion, cell-proliferation inhibition, apoptosis and survival (Bradley et al., 2013). PSCA expression was found in non-prostatic malignancies including diffuse type gastric cancer (Sakamoto et al., 2008b). The over-expression of PSCA was reported in prostate cancer (Link et al., 2017, Saeki et al., 2010). Further, its high expression is related to poor prognosis and seminal vesicle invasion (Kim et al., 2016, Zhigang & Wenlv, 2004). Hence, PSCA has been considered as a biomarker for diagnosis and prognosis of prostate cancer

(Madu & Lu, 2010). The rs2294008 C > T is located in exon 1 and is associated with reduced transcriptional activity of an upstream fragment of PSCA in vitro (Higgins & Thompson, 2002). A significant association of PSCA rs2294008 polymorphism with gastric cancer was observed in the Asian populations (Chandra et al., 2016). A replication study using environmental risk factors and GWAS identified loci in Chinese population demonstrated that the interaction between rs2294008 polymorphism and H. pylori infection and/or alcohol consumption increased the gastric cancer risk (Cai et al., 2017b).

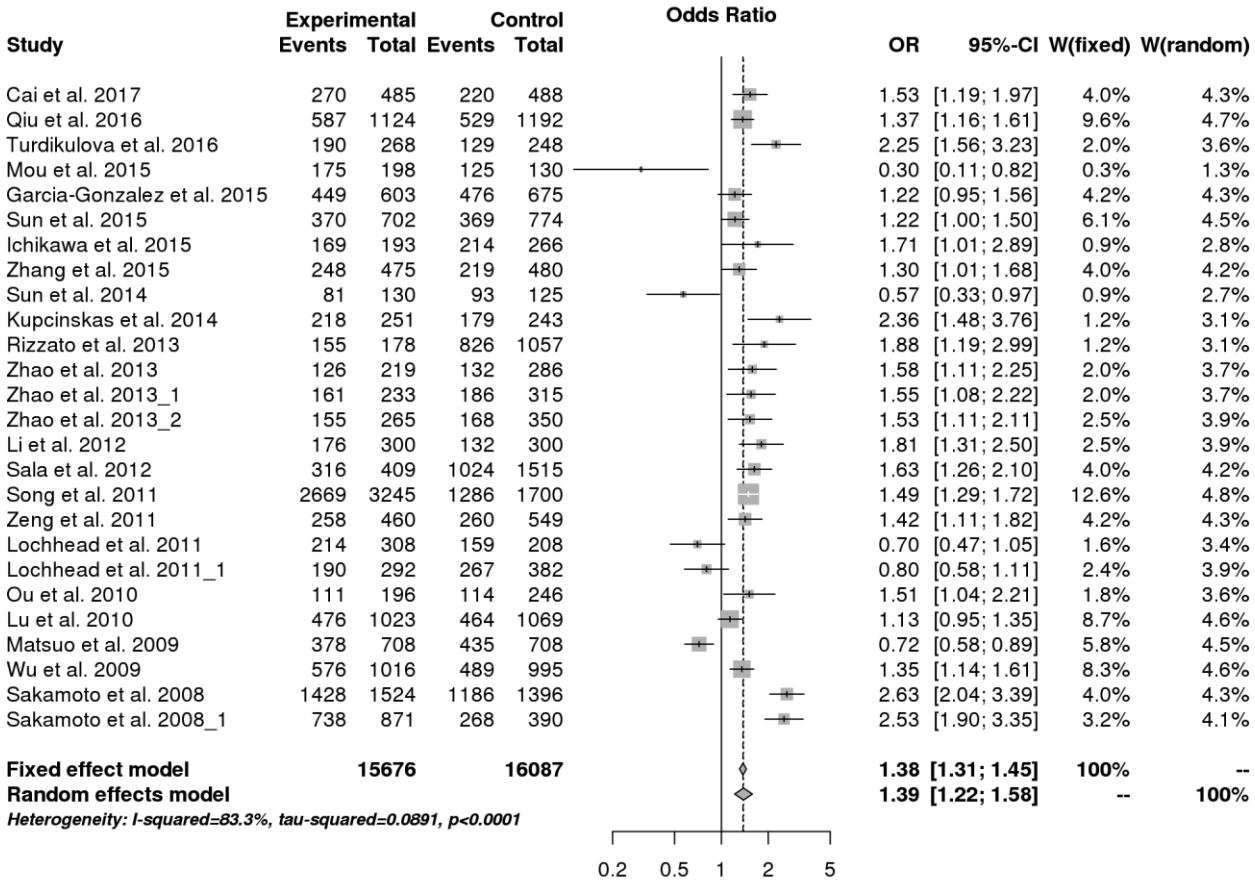

Figure 1: Meta-analysis pooled estimates of the association between PSCA rs2294008 (Dominant model: TT+TC vs. CC) and gastric cancer

Table 2: Overall meta-analysis and subgroup analysis by ethnicity for PSCA rs2294008 polymorphism

Genetic Model	Number of studies	Test of association			Heterogeneity			Egger's test p-value
		OR	95% CI	p-value	Model	p-value	I^2	
Overall								
Allele contrast (T vs. C)	26	1.17	1.05-1.29	0.003	Random	<0.001	0.88	0.273
Recessive model (TT vs. TC+CC)	26	1.05	0.87-1.26	0.611	Random	<0.001	0.87	0.089
Dominant model (TT+TC vs. CC)	26	1.39	1.22-1.58	<0.001	Random	<0.001	0.83	0.954
Caucasian								
Allele contrast (T vs. C)	7	1.12	0.87-1.43	0.371	Random	<0.001	0.89	0.377
Recessive model (TT vs. TC+CC)	7	1.17	0.83-1.65	0.377	Random	<0.001	0.85	0.229
Dominant model (TT+TC vs. CC)	7	1.17	0.83-1.64	0.367	Random	<0.001	0.84	0.691
Asian								
Allele contrast (T vs. C)	19	1.18	1.05-1.32	0.004	Random	<0.001	0.88	0.460
Recessive model (TT vs. TC+CC)	19	1.00	0.80-1.25	0.977	Random	<0.001	0.88	0.131
Dominant model (TT+TC vs. CC)	19	1.47	1.27-1.69	<0.001	Random	<0.001	0.83	0.499

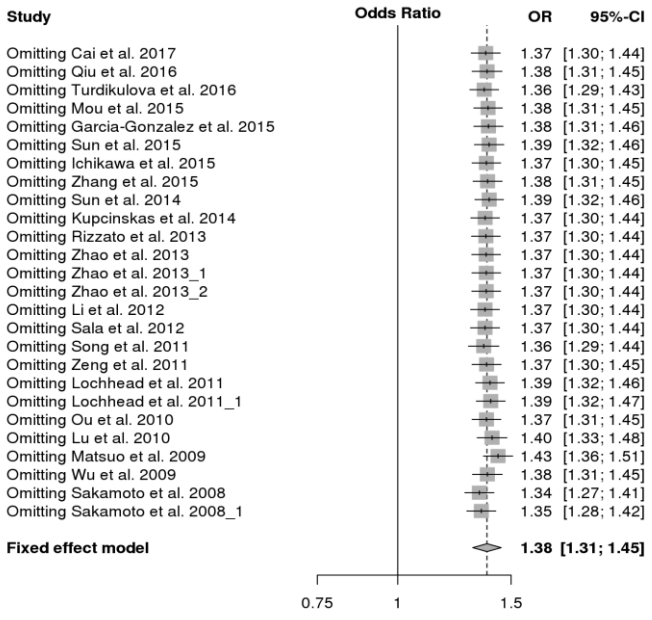

Figure 2. Sensitivity analysis of the meta-analysis of the association of the PSCA rs2294008 polymorphism (Dominant model: TT+TC vs. CC) with gastric cancer risk.

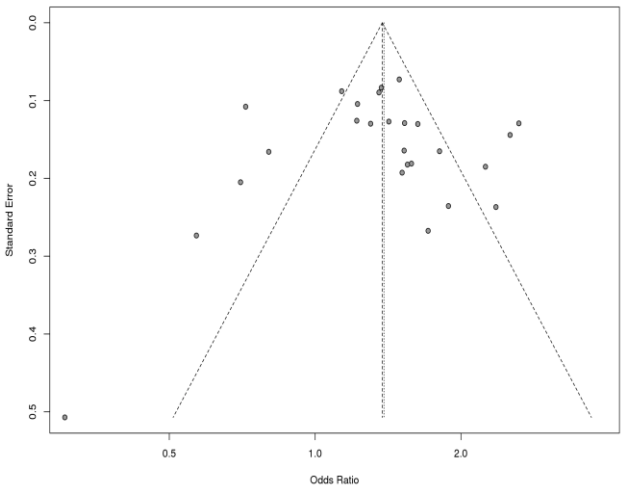

Figure 3. Funnel plot to assess the publication bias of the meta-analysis in dominant genetic model.

Non-availability of the data limited the present meta-analysis to evaluate the potential interactions, like interaction between PSCA rs2294008 polymorphism and H. pylori infection, alcohol consumption and smoking. Owing to inadequate data, the impact of multiple confounders such as age, gender, lifestyle and habits were not considered for subgroup analysis. However, our meta-analysis results demonstrated that the PSCA rs2294008 C >T polymorphism is a risk factor for gastric cancer in Asians populations. Additional investigations of the combined effects of gene and environment should be used to provide a comprehensive understanding of the association between the PSCA polymorphisms and gastric cancer risk.

Conflict of interest statement

The author has declared that no competing or conflict of interests exists. The funders had no role in study design, writing of the manuscript and decision to publish.

Authors' contributions

BVKSL designed the study, proposed the search terms, managed the work, reviewed data extraction and wrote the manuscript. HKV and SL searched the databases and participated in title, abstract screening, full text screening, data extraction, data analysis and manuscript writing. All authors have critically reviewed the manuscript and provided approval.

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