PSCA rs2294008 Polymorphism with Increased Risk of Cancer

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Abstract

Background

Published data on the association between PSCA rs2294008 polymorphism and cancer risk have implicated inconclusive results. To determine the relationship and to precisely assess the effect size estimate of the association, we performed a meta-analysis.

Methods

We searched published literature in Embase and PubMed databases using the search terms “PSCA”, “prostate stem cell antigen”, “variants”, “polymorphism”, “polymorphisms”, and “cancer”. A total of 21 eligible articles were retrieved, with 27,197 cancer cases and 48,237 controls.

Results

On the whole, we found the association between PSCA rs2294008 polymorphism and cancer risk was statistically significant: TT vs CC: OR = 1.18, 95% CI, 1.10 to 1.27; TT + CT vs CC: OR = 1.08, 95% CI, 1.05 to 1.10; TT vs CT + CC: OR = 1.14, 95% CI, 1.07 to 1.21; T vs C: OR = 1.10, 95% CI, 1.06 to 1.14; CT vs CC: OR = 1.10, 95% CI, 1.06 to 1.13. Stratified analyses in cancer type and ethnicity showed similar results.

Conclusions

Based on the statistical evidence, we can draw a conclusion that the rs2294008 polymorphism of PSCA gene is likely to play a role in cancer carcinogenesis, especially in gastric cancer and bladder cancer.
Introduction

Genome-wide association studies (GWAS) concerning aetiology of cancer have established more than 150 regions associated with various specific cancers. The discoveries successfully expand the current understanding of carcinogenesis mechanisms [1]. Given the functional significance of genetic polymorphisms in cancer initiation and progression, it is of great importance to further explore the underlying pathophysiology of cancer at the gene level. Genetic variations, such as the alterations in sequence and aberrant organizations of the cellular genome ranging from single-nucleotide substitutions to gross chromosome, lead to cancer formation by biologically regulating a handful of molecular activities.

Prostate stem cell antigen (PSCA), located on chromosome 8q24.2, is a 123-amino-acid cell membrane glycoprotein which belongs to the LY-6/Thy-1 family of cell surface antigens. PSCA was reported as a cell surface marker to over-express in prostate cancer cell lines when compared to the normal tissues [2]. High expression of PSCA is significantly associated with adverse prognostic features including Gleason score, seminal vesicle invasion and capsular involvement [3], as well as cancer severity and metastasis [4]. In addition, PSCA is up-regulated in several solid tumors (pancreas, bladder, renal cell carcinoma and ovarian mucinous) [2,5], and down-regulated in esophage cancer, gastric cancer and gallbladder carcinoma [6–8]. However, there is no conclusive evidence for the role of PSCA expression in cancer carcinogenesis except a proposal that the expression of PSCA differs depending on cellular context [5].

Two recent GWAS based on the subjects with different ethnic origins showed rs2294008 polymorphism in PSCA is a significant risk factor for increased gastric cancer susceptibility in Caucasian population [9], while deceases gastric cancer risk in Asian population [10]. rs2294008 polymorphism in the first exon of PSCA gene may have notable influence on the variations in transcriptional activity of an upstream fragment of PSCA [8]. To date, although accumulating data have documented the association between PSCA rs2294008 polymorphism and cancer risk, the evidence regarding the role of the polymorphism as a genetic marker for cancer risk remains inconclusive [9–14]. Most of the studies focused on a single type of cancer with a relatively small sample size. As a result, the effects of PSCA rs2294008 polymorphism on cancer risk may be underestimated and less reliable. In this work, therefore, with an aim to determine the relationship between PSCA rs2294008 polymorphism and cancer risk and to precisely assess the effect size estimate of the association, we performed a meta-analysis using all available published data.

Materials and Methods

Search strategy

Studies examining the association between PSCA rs2294008 polymorphism and cancer risk were comprehensively searched in Embase and PubMed using the following subjects terms: “PSCA”, “prostate stem cell antigen”, “variants”, “polymorphism”, “polymorphisms”, and “cancer” by two independent investigators. No limitations of publication language or a minimum number of subjects were defined for this search. Additional published data were identified by reviewing the bibliographical references listed in each retrieved article.

Inclusion and exclusion criteria

In order to minimize heterogeneity and facilitate an appropriate interpretation of the findings, we selected the studies eligible for this meta-analysis based on the following criteria: (a) assessed the association between PSCA rs2294008 polymorphism and cancer risk using a case-control design; (b) provided available frequency for each genotype (CC, CT, TT) in both cases.
and controls to calculate odds ratios (ORs) and corresponding 95% confidence intervals (CIs). In a case that a same case series was subsequently used in a new article, we considered the largest one. The studies were excluded if they were: reviews, editorials, comments or animal studies.

Data extraction
The data extraction was completed by the two independent investigators responsible for the literature search. The information collected form each publication was as follows: first author’s name, year of publication, study country, ethnic origin of the included subjects (Caucasian or Asian), methods conducted for genotyping, source of controls (hospital- or population-based), type of cancer, total numbers of cases and controls, and frequency of PSCA rs2294008 genotypes between cases and control subjects. A consensus on the extracted items was reached by discussion between the two investigators.

Statistical analysis
In order to evaluate the association between PSCA rs2294008 polymorphism and cancer risk, the ORs and corresponding 95% CIs were summarized for each study in TT vs CC, TT + CT vs CC, TT vs CT + CC, T vs C and CT vs CC models. Subgroup analysis was performed according to ethnicity and cancer type (gastric cancer, bladder cancer and others when concerned by less than three studies).

Heterogeneity is the degree of variations among outcomes between different studies included in a same meta-analysis. Chi-square based Q-test was adopted to detect the heterogeneity across studies in this meta-analysis. \(P < 0.10\) was considered statistically significant. In this case, the pooled ORs were calculated by the random effects model (Der Simonian and Laird) [15]; otherwise, the fixed effects model (Mantel-Haenszel method) was used [16].

Sensitivity analysis was performed to identify the study that influenced homogeneity of the included studies when significant heterogeneity was indicated. Hardy-Weinberg equilibrium (HWE) in the control group was checked by chi-square test. Publication bias was examined by two commonly used analytic tools: funnel plot and Egger’s linear regression test [17].

The statistical analyses for the present study were done by using Stata software (version 12.0; StataCorp LP, College Station, TX, USA). All tests were two-sided and significance level was maintained at \(P < 0.10\).

Results
Study selection
We obtained 535 articles matching the subjects term used in the search strategy. After reviewing their titles and abstracts, we selected 30 articles in full text for eligibility evaluation. Among these, 9 were finally deleted for various reasons including inadequate data [18–22], review articles [23,24], with no control population [25] and research irrelevant to the currently studied polymorphism [26]. Therefore, 27, 197 cancer cases and 48, 237 controls from 21 articles with 24 studies were included in this meta-analysis [4,8–14,27–39] (Fig 1).

Characteristics of included studies
The basic characteristics of all included studies are listed in Table 1. A total of twenty four studies were eligible for this meta-analysis, among which eight were for Caucasian subjects and sixteen for Asian subjects. There was wide differences in the literature as to the number of
participants in each study, varying from 77 to 5,303 in case group and from 200 to 16,567 in control population. Only two studies deviated from the p values of HWE [10,33].

Quantitative synthesis

By pooling all eligible studies into one large dataset, we found the association between PSCA rs2294008 polymorphism and cancer risk was statistically significant. The association appeared more pronounced in TT vs CC and TT vs CT + CC: OR = 1.18, 95% CI, 1.10 to 1.27 (Fig 2); OR = 1.14, 95% CI, 1.07 to 1.21, respectively. We also noted a moderate increase using TT + CT vs CC (OR = 1.08, 95% CI, 1.05 to 1.10) (Fig 3), T vs C (OR = 1.10, 95% CI, 1.06 to 1.14), and CT vs CC (OR = 1.10, 95% CI, 1.06 to 1.13) (Table 2).

Stratification analyses for different cancer type showed similarly increased risk in gastric cancer and bladder cancer. When stratifying the populations according to ethnicity, both Asian and Caucasian populations indicated a tend to an increase in the risk of cancer (Table 2).

Heterogeneity and sensitivity analyses

Due to significant heterogeneity across studies (TT vs CC: \(P = 0.007\); TT vs CT + CC: \(P = 0.029\); T vs C: \(P = 0.007\)), sensitivity analysis by repeating the meta-analysis while omitting each study, one at a time, was conducted to identify the source. The results showed Matsuo
et al. [27] made major contributions to the notable heterogeneity. The exclusion of this study dramatically decreased the heterogeneity (TT vs CC: $P = 0.440$; TT vs CT + CC: $P = 0.710$; T vs C: $P = 0.245$). However, the combined results were not statistically influenced by excluding each study, including the study in disagreement with HWE. These data suggested that our results are stable and robust.

**Publication bias**

Begg’s funnel plot and Egger’s test were used to determine publication bias in this meta-analysis. There was no obvious asymmetry indicated in the plots. Egger’s test also provided supportive evidence for no significant publication bias in the meta-analysis (Begg: $P = 0.442$; Egger: $P = 0.316$; model: TT + CT vs CC) (Fig 4).

**Discussion**

PSCA as a prostate-specific antigen plays a key role in cell adhesion, proliferation, and survival [40]. The serum level was directly or indirectly associated with cancer progression. PSCA overexpression was initially reported in prostate cancer [2], followed by several other cancers, such as pancreatic cancer [41,42]. Investigations into the association between PSCA rs2294008 polymorphism and cancer risk have been frequently conducted in either a small or large population to identify the relationship. Currently, there is no consistent evidence supporting
this association. Some studies indicated the rs2294008 polymorphism of *PSCA* gene may have a significant role in bladder carcinogenesis and it could serve as a biomarker for genetic

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**Fig 2. Forest plot of cancer susceptibility associated with PSCA rs2294008 polymorphism under TT vs CC stratified according to cancer type.** For each study, the estimates of OR and its 95% CI were plotted with a box and a horizontal line. The symbol filled diamond indicates pooled OR and its 95% CI. Random effects meta-analysis shows a significant association.

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susceptibility to this cancer [37,38], while this finding contradicted a following replication study regarding gastric cancer in Japanese population, where a reduced risk of gastric cancer

Fig 3. Forest plot of cancer susceptibility associated with PSCA rs2294008 polymorphism under TT + CT vs CC stratified according to cancer type. For each study, the estimates of OR and its 95% CI were plotted with a box and a horizontal line. The symbol filled diamond indicates pooled OR and its 95% CI. Fixed effects meta-analysis shows a significant association.

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was suggested [10]. A most recent study, however, even demonstrated no genotypic association between PSCA rs2294008 polymorphism and the risk of colorectal cancer. In view of the relatively limited sample size, it is indefinite to determine a stable effect size of PSCA rs2294008 polymorphism in relation to cancer.

Table 2. Results of meta-analysis for PSCA rs2294008 C>T polymorphism and cancer. P, p value of Q test for heterogeneity.

| Study group | No. of studies | TT vs CC | TT + CT vs CC | TT vs CT + CC | T vs C | CT vs CC |
|-------------|----------------|----------|---------------|---------------|--------|---------|
|             |                | OR (95% CI) | P    | OR (95% CI) | P    | OR (95% CI) | P    | OR (95% CI) | P    |
| Total       | 24             |           |       |       |       |       |       |       |       |       |
| Cancer type |                |           |       |       |       |       |       |       |       |       |
| Gastric cancer | 15         | 1.21 (1.08, 1.36) | 0.001 | 1.09 (1.05, 1.13) | 0.384 | 1.17 (1.06, 1.29) | 0.004 | 1.12 (1.07, 1.18) | 0.004 | 1.12 (1.08, 1.18) | 0.536 |
| Bladder cancer | 5             | 1.16 (1.09, 1.23) | 0.723 | 1.07 (1.03, 1.11) | 0.628 | 1.10 (1.04, 1.17) | 0.699 | 1.08 (1.05, 1.11) | 0.481 | 1.08 (1.04, 1.13) | 0.673 |
| Others      | 4              | 0.99 (0.80, 1.24) | 0.574 | 0.99 (0.86, 1.12) | 0.511 | 1.04 (0.85, 1.27) | 0.909 | 1.00 (0.90, 1.11) | 0.475 | 0.97 (0.84, 1.13) | 0.351 |
| Ethnicity   |                |           |       |       |       |       |       |       |       |       |
| Asian       | 16             | 1.18 (1.06, 1.32) | 0.003 | 1.09 (1.06, 1.13) | 0.397 | 1.12 (1.02, 1.23) | 0.013 | 1.11 (1.06, 1.17) | 0.006 | 1.13 (1.08, 1.17) | 0.609 |
| Caucasian   | 8              | 1.17 (1.08, 1.26) | 0.309 | 1.06 (1.02, 1.10) | 0.655 | 1.13 (1.06, 1.20) | 0.367 | 1.08 (1.03, 1.12) | 0.245 | 1.07 (1.03, 1.11) | 0.473 |

Fig 4. Funnel plots of PSCA rs2294008 polymorphism and cancer risk (Begg: P = 0.442; Egger: P = 0.316; model: TT + CT vs CC). Each point represents an individual study for the indicated association.

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Meta-analysis has been widely accepted as a significant tool to analyze cumulative data from studies in which results with low statistical power were produced due to the limited study subjects [43]. In the present meta-analysis, composed of 27,197 cancer cases and 48,237 controls from 21 articles with 24 studies, comprehensively explored the association between PSCA rs2294008 polymorphism and cancer risk. The combined results suggested a statistical association with overall cancer risk. In the stratified analyses according to cancer type, elevated risks of gastric cancer and bladder cancer were indicated. Consistent with the findings in the former analyses, stratification analyses in ethnicity also showed PSCA rs2294008 polymorphism was associated with an increased risk of cancer in Asian as well as Caucasian populations.

This is the first study addressing cancer risk associated with PSCA rs2294008 polymorphism to date, although a number of meta-analyses have investigated the predisposition effects of PSCA rs2294008 polymorphism on gastric cancer [6,060 cases and 4,824 controls, 10,717 cases and 9,235 controls in the study conducted by Wang et al., Zhang et al. (Asian Pac J Cancer Prev), Zhang et al. (Exp Ther Med), respectively] [44–46]. All of these studies showed PSCA rs2294008 polymorphism is a risk factor for the development of gastric cancer, an observation consistent with the current work (55,363 more participants even compared to the largest study) which was expanded via the inclusion of several subsequently published studies. The reference to increased cancer susceptibility implies that variation of rs2294008 polymorphism leads to abnormal expression of PSCA, consequently promoting cancer progression regardless of cancer type or ethnic origin.

It is known that H. pylori infection represents a main and specific infectious cause of human cancer, gastric cancer in particular. Various lines of evidence have demonstrated the important role H. Pylori infection plays in gastric cancer. For example, Levi et al. reported that not only H. pylori infection itself acts as a susceptibility factor, but it may have additive effects on gastric carcinogenesis by combining with other confounding factors [47]. Almost at the same time, Wang et al. provided further evidence that persistent H. pylori infection and the infection-induced chronic inflammation may increase the likelihood of gastric cardia cancer in Chinese [48]. Also, Lunet et al. indicated that H. Pylori has a major impact with the effects varying extensively across geographical areas due to the distinct lifestyles and exposure to environmental carcinogens [49]. These reports seem to support our findings of slightly lower risk of cancer associated with rs2294008 genotypes, compared to that reported in a previous association study of H. pylori infection [36]. This difference indicates that rs2294008 polymorphism relative to other carcinogens, such as infection with H. pylori, contributes a less part to carcinogenesis. The aetiology of cancer is multifactorial and heterogeneous, further investigation is needed to identify the risk factors, thus facilitating an early detection and prevention.

There is significant between-study heterogeneity in this meta-analysis. Although no substantial change was found in the combined results when removing the study donating the heterogeneity, we can not rule out the potential influence and the current findings should be treated with caution. Furthermore, in terms of the moderate sample size in stratified analyses, it is still indecisive about the stable effect size of PSCA rs2294008 polymorphism in connection with cancer risk. Finally, departure from HWE was detected in two studies. By comparing the results between including and excluding them, we observed minor alternation in the results failing to reach the significant level. Nevertheless, in light of few significant effects as a result of the presence of heterogeneity and departure form HWE, our findings are reliable based on the statistical evidence.

In summary, this meta-analysis suggested that PSCA rs2294008 polymorphism was significantly associated with increased risk of cancer. Stratified analyses in cancer type and ethnicity showed similar results. However, it is worthwhile to carry out large studies in future to validate the present findings.
Supporting Information

S1 PRISMA Checklist. (DOC)

Author Contributions

Conceived and designed the experiments: PG JL NW. Performed the experiments: XZ YL. Analyzed the data: PG CL JO GX LX. Contributed reagents/materials/analysis tools: XZ YL. Wrote the paper: PG HL.

References

1. Chung CC, Chanock SJ. Current status of genome-wide association studies in cancer. Hum Genet. 2011; 130: 59–78. doi: 10.1007/s00439-011-1030-9 PMID: 21678065
2. Reiter RE, Gu Z, Watabe T, Thomas G, Szigeti K, Davis E, et al. Prostate stem cell antigen: a cell surface marker overexpressed in prostate cancer. Proc Natl Acad Sci U S A. 1998; 95: 1735–1740. PMID: 9465086
3. Han KR, Seligson DB, Liu X, Horvath S, Shintaku PI, Thomas GV, et al. Prostate stem cell antigen expression is associated with gleason score, seminal vesicle invasion and capsular invasion in prostate cancer. J Urol. 2004; 171: 1117–1121. PMID: 14767283
4. Wu X, Ye Y, Kiemeney LA, Sulem P, Rafnar T, Matullo G, et al. Genetic variation in the prostate stem cell antigen gene PSCA confers susceptibility to urinary bladder cancer. Nat Genet. 2009; 41: 991–995. doi: 10.1038/ng.421 PMID: 19648920
5. Saeki N, Gu J, Yoshida T, Wu X. Prostate stem cell antigen: a Jekyll and Hyde molecule? Clin Cancer Res. 2010; 16: 3533–3538. doi: 10.1158/1078-0432.CCR-09-3169 PMID: 20501618
6. Bahrenberg G, Brauers A, Joost HG, Jakse G. Reduced expression of PSCA, a member of the LY-6 family of cell surface antigens, in bladder, esophagus, and stomach tumors. Biochem Biophys Res Commun. 2000; 275: 783–788. PMID: 10973799
7. Ono H, Hiraoka N, Lee YS, Woo SM, Lee WJ, Choi IJ, et al. Prostate stem cell antigen, a presumable organ-dependent tumor suppressor gene, is down-regulated in gallbladder carcinogenesis. Genes Chromosomes Cancer. 2012; 51: 30–41. doi: 10.1002/gcc.20928 PMID: 21936014
8. Sakamoto H, Yoshimura K, Saeki N, Katai H, Shimoda T, Matsuno Y, et al. Genetic variation in PSCA is associated with susceptibility to diffuse-type gastric cancer. Nat Genet. 2008; 40: 730–740. doi: 10.1038/ng.152 PMID: 18488030
9. Wu X, Ye Y, Kiemeney LA, Sulem P, Rafnar T, Matullo G, et al. Genetic variation in the prostate stem cell antigen gene PSCA confers susceptibility to urinary bladder cancer. Nat Genet. 2009; 41: 991–995. doi: 10.1038/ng.421 PMID: 19648920
10. Wang P, Ye D, Guo J, Liu F, Jiang H, Gong J, et al. Genetic score of multiple risk-associated single nucleotide polymorphisms is a marker for genetic susceptibility to bladder cancer. Genes Chromosomes Cancer. 2014; 53: 99–105. doi: 10.1002/gcc.22121 PMID: 24155119
11. Rai R, Sharma KL, Misra S, Kumar A, Mittal B. PSCA gene variants (rs2294008 and rs2978974) confer increased susceptibility of gallbladder carcinoma in females. Gene. 2013; 530: 172–177. doi: 10.1016/j.gene.2013.08.058 PMID: 23988503
12. Wang P, Ye D, Guo J, Liu F, Jiang H, Gong J, et al. Genetic score of multiple risk-associated single nucleotide polymorphisms is a marker for genetic susceptibility to bladder cancer. Genes Chromosomes Cancer. 2014; 53: 99–105. doi: 10.1002/gcc.22121 PMID: 24155119
13. Kim SY, Yoo JY, Shin A, Kim Y, Lee ES, Lee YS. Prostate stem cell antigen single nucleotide polymorphisms influence risk of estrogen receptor negative breast cancer in Korean females. Asian Pac J Cancer Prev. 2012; 13: 41–48.
14. Smith C, Lochhead P, Basavaraju U, Hold GL, Fyle N, Murray GI, et al. Lack of association between the rs2294008 polymorphism in the prostate stem cell antigen gene and colorectal neoplasia: a case-control and immunohistochemical study. BMC Res Notes. 2012; 5: 371. doi: 10.1186/1756-0500-5-371 PMID: 22824379
15. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986; 7: 177–188. PMID: 3802833
16. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. 1959; 22: 719–748. PMID: 13695060
17. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ. 1997; 315: 629–634. PMID: 9310563
18. Hwang JY, Kim DH, Ji YI, Jin Go M, Heo L, Jin Kim Y, et al. Recapitulation of previous genome-wide association studies with two distinct pathophysiological entities of gastric cancer in the Korean population. J Hum Genet. 2013; 58: 233–235. doi: 10.1038/jhg.2012.158 PMID: 23389241
19. Abnet CC, Freedman ND, Hu N, Wang Z, Yu K, Shu XO, et al. A shared susceptibility locus in PLCE1 at 10q23 for gastric adenocarcinoma and esophageal squamous cell carcinoma. Nat Genet. 2010; 42: 764–767. doi: 10.1038/ng.649 PMID: 20729852
20. Shi Y, Hu Z, Wu C, Dai J, Li H, Dong J, et al. A genome-wide association study identifies new susceptibility loci for non-cardia gastric cancer at 3q13.31 and 5p13.1. Nat Genet. 2011; 43: 1215–1218. doi: 10.1038/ng.978 PMID: 22037551
21. Saeki N, Saito A, Choi IJ, Matsuo K, Ohnami S, Totsuka H, et al. A functional single nucleotide polymorphism in mucin 1, at chromosome 1q22, determines susceptibility to diffuse-type gastric cancer. Gastroenterology. 2011; 140: 892–902. doi: 10.1053/j.gastro.2010.10.058 PMID: 21070779
22. Wang M, Bai J, Tan Y, Wang S, Tian Y, Gong W, et al. Genetic variant in PSCA predicts survival of diffuse-type gastric cancer in a Chinese population. Int J Cancer. 2011; 129: 1207–1213. doi: 10.1002/ijc.25740 PMID: 21064099
23. Golka K, Selinski S, Lehmann ML, Blaszkewicz M, Marchan R, Ickstadt K, et al. Genetic variants in urinary bladder cancer: collective power of the "wimp SNPs". Arch Toxicol. 2011; 85: 539–554. doi: 10.1007/s00204-011-0676-3 PMID: 21380501
24. Saeki N, Ono H, Sakamoto H, Yoshida T. Genetic factors related to gastric cancer susceptibility identified using a genome-wide association study. Cancer Sci. 2013; 104: 1–8. doi: 10.1111/cas.12042 PMID: 23057512
25. Kohaar I, Porter-Gill P, Lenz P, Fu YP, Mumy A, Tang W, et al. Genetic variant as a selection marker for anti-prostate stem cell antigen immunotherapy of bladder cancer. J Natl Cancer Inst. 2013; 105: 69–73. doi: 10.1093/jnci/djs458 PMID: 23266392
26. Chan M, Ji SM, Liaw CS, Yap YS, Law HY, Yoon CS, et al. Association of common genetic variants with breast cancer risk and clinicopathological characteristics in a Chinese population. Breast Cancer Res Treat. 2012; 136: 209–220. doi: 10.1007/s10549-012-2234-y PMID: 22965832
27. Matsuo K, Tajima K, Suzuki T, Kawase T, Watanabe M, Shitara K, et al. Association of prostate stem cell antigen gene polymorphisms with the risk of stomach cancer in Japanese. Int J Cancer. 2009; 125: 1961–1964. doi: 10.1002/ijc.24519 PMID: 19582881
28. Wu C, Wang G, Yang M, Huang L, Yu D, Tan W, et al. Two genetic variants in prostate stem cell antigen and gastric cancer susceptibility in a Chinese population. Mol Carcinog. 2009; 48: 1131–1138. doi: 10.1002/mc.20565 PMID: 19554573
29. Ou J, Li K, Ren H, Bai H, Zeng D, Zhang C. Association and haplotype analysis of prostate stem cell antigen with gastric cancer in Tibetans. DNA Cell Biol. 2010; 29: 319–323. doi: 10.1089/dna.2009.0960 PMID: 20230293
30. Lu Y, Chen J, Ding Y, Jin G, Wu J, Huang H, et al. Genetic variation of PSCA gene is associated with the risk of both diffuse- and intestinal-type gastric cancer in a Chinese population. Int J Cancer. 2010; 127: 2183–2189. doi: 10.1002/ijc.25228 PMID: 20131315
31. Song HR, Kim HN, Piao JM, Kweon SS, Choi JS, Bae WK, et al. Association of a common genetic variant in prostate stem-cell antigen with gastric cancer susceptibility in a Korean population. Mol Carcinog. 2011; 50: 871–875. doi: 10.1002/mc.20796 PMID: 21538581
32. Zeng Z, Wu X, Chen F, Yu J, Xue L, Hao Y, et al. Polymorphisms in prostate stem cell antigen gene rs2294008 increase gastric cancer risk in Chinese. Mol Carcinog. 2011; 50: 353–358. doi: 10.1002/mc.20718 PMID: 21268123
33. Lochhead P, Frank B, Hold GL, Rabkin CS, Ng MT, Vaughan TL, et al. Genetic variation in the prostate stem cell antigen gene and upper gastrointestinal cancer in white individuals. Gastroenterology. 2011; 140: 435–441. doi: 10.1053/j.gastro.2010.11.001 PMID: 21070776
34. Zhao JD, Geng PL, Zhao JH, Wang LJ, Ji FX, Li JZ, et al. Relationship between the rs2294008 polymorphism of the PSCA gene and susceptibility to gastric cancer in Tibetans. World Chin J Digestology. 2012; 20: 418–421.
35. Li F, Zhong MZ, Li JH, Liu W, Li B. Case-control study of single nucleotide polymorphisms of PSCA and MUC1 genes with gastric cancer in a Chinese. Asian Pac J Cancer Prev. 2012; 13: 2593–2596. PMID: 22938426
36. Rizzato C, Kato I, Plummer M, Munoz N, Canzian F. Genetic variation in PSCA and risk of gastric advanced preneoplastic lesions and cancer in relation to Helicobacter pylori infection. PLoS One. 2013; 8: e73100. doi: 10.1371/journal.pone.0073100 PMID: 24023815
37. Wang S, Tang J, Wang M, Yuan L, Zhang Z. Genetic variation in PSCA and bladder cancer susceptibility in a Chinese population. Carcinogenesis. 2010; 31: 621–624. doi: 10.1093/carcin/bgp323 PMID: 20083643

38. Fu YP, Kohaar I, Rothman N, Earl J, Figueroa JD, Ye Y, et al. Common genetic variants in the PSCA gene influence gene expression and bladder cancer risk. Proc Natl Acad Sci U S A. 2012; 109: 4974–4979. doi: 10.1073/pnas.1202189109 PMID: 22416122

39. Ma Z, Hu Q, Chen Z, Tao S, Macnamara L, Kim ST, et al. Systematic evaluation of bladder cancer risk-associated single-nucleotide polymorphisms in a Chinese population. Mol Carcinog. 2013; 52: 916–921. doi: 10.1002/mc.21932 PMID: 22711262

40. Eshel R, Zanin A, Kapon D, Sagi-Assif O, Brakenhoff R, van Dongen G, et al. Human Ly-6 antigen E48 (Ly-6D) regulates important interaction parameters between endothelial cells and head-and-neck squamous carcinoma cells. Int J Cancer. 2002; 98: 803–810. PMID: 11948455

41. Oliveira-Cunha M, Byers RJ, Siriwardena AK. Poly(A) RT-PCR measurement of diagnostic genes in pancreatic juice in pancreatic cancer. Br J Cancer. 2011; 104: 514–519. doi: 10.1038/sj.bjc.6606047 PMID: 21245863

42. Grubbs EG, Abdel-Wahab Z, Tyler DS, Pruitt SK. Utilizing quantitative polymerase chain reaction to evaluate prostate stem cell antigens as a tumor marker in pancreatic cancer. Ann Surg Oncol. 2006; 13: 1645–1654. PMID: 16957968

43. Wu R, Li B. A multiplicative-epistatic model for analyzing interspecific differences in outcrossing species. Biometrics. 1999; 55: 355–365. PMID: 11318188

44. Wang T, Zhang L, Li H, Wang B, Chen K. Prostate stem cell antigen polymorphisms and susceptibility to gastric cancer: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev. 2012; 21: 843–850. doi: 10.1158/1055-9965.EPI-11-1176 PMID: 22426141

45. Zhang QH, Yao YL, Gu T, Gu JH, Chen L, Liu Y. Association of the PSCA rs2294008 C>T polymorphism with gastric cancer risk: evidence from a meta-analysis. Asian Pac J Cancer Prev. 2012; 13: 2867–2871. PMID: 22938475

46. Zhang T, Chen YN, Wang Z, Chen JQ, Huang S. Effect of PSCA gene polymorphisms on gastric cancer risk and survival prediction: A meta-analysis. Exp Ther Med. 2012; 4: 158–164. PMID: 23060941

47. Levi E, Sochacki P, Khoury N, Patel BB, Majumdar AP. Cancer stem cells in Helicobacter pylori infection and aging: Implications for gastric carcinogenesis. World J Gastrointest Pathophysiol. 2014; 5: 366–372. doi: 10.4291/wjgp.v5.i3.366 PMID: 25133037

48. Wang Y, Liu S, Zhang Y, Bi C, Xiao Y, Lin R, et al. Helicobacter pylori infection and gastric cardia cancer in Chaoshan region. Microbes Infect. 2014; 16: 840–844. doi: 10.1016/j.micinf.2014.06.009 PMID: 25038396

49. Lunet N, Barros H. Helicobacter pylori infection and gastric cancer: facing the enigmas. Int J Cancer. 2003; 106: 953–960. PMID: 12918076