Contribution of prostate stem cell antigen variation rs2294008 to the risk of bladder cancer

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Abstract

Objective: Number of studies have been performed to evaluate the relationship between prostate stem cell antigen (PSCA) variation rs2294008 and bladder cancer risk, but the sample size was small and the results were conflicting. This meta-analysis was conducted to comprehensively evaluate the overall association.

Methods: Pubmed, Web of science, Embase, China biology medical literature database (CBM), China National Knowledge Infrastructure (CNKI), Wan Fang and Weipu databases were searched before June 30, 2018. The strength of associations was assessed using odds ratios (ORs) and 95% confidence intervals (CIs). All of the statistical analyses were conducted using Review Manager 5.3 and Stata 14.0.

Results: Ten studies involved 14,021 cases and 26,871 controls. Overall, significant association was observed between the PSCA gene variant rs2294008 polymorphism and bladder cancer (T vs C: OR = 1.16, 95%CI = 1.12–1.20; TT vs CC: OR = 1.32, 95%CI = 1.24–1.41; TT vs CT+CC: OR = 1.15, 95%CI = 1.09–1.22; TT+CT vs CC: OR = 1.27, 95%CI = 1.21–1.34). In subgroup analysis by ethnic group, a statistically significant association was observed in Asians (T vs C: OR = 1.23, 95%CI = 1.15–1.31) and Caucasians (T vs C: OR = 1.14, 95%CI = 1.10–1.18). The sensitivity analysis confirmed the reliability and stability of the meta-analysis.

Conclusion: Our meta-analysis supports that the PSCA gene variant rs2294008 polymorphism might contribute to individual susceptibility to bladder cancer.

Abbreviations: CBM = China biology medical literature database, CIs = confidence intervals, CNKI = China National Knowledge Infrastructure, HWE = Hardy–Weinberg equilibrium, NOS = Newcastle–Ottawa scale, ORs = odds ratios, PCR = polymerase chain reaction, PCR-RFLP = polymerase chain reaction-restriction fragment length polymorphism, PSCA = prostate stem cell antigen.

Keywords: bladder cancer, meta-analysis, polymorphism, PSCA

1. Introduction

Bladder cancer, the ninth most frequently-diagnosed cancer worldwide, is the leading cause of cancer-related morbidity and mortality among urological cancers.[11] The United States estimates suggested that approximately 76,960 new BC cases were diagnosed, and 16,390 patients died of bladder cancer in 2016.[12] At present, the etiology of bladder cancer is still largely unknown, multiple factors such as smoking, alcoholic consumption, genetic mutation, family history, and occupational exposure to carcinogens are risk factors for bladder cancer, and play essential roles in the pathogenesis and progression of bladder cancer.[13,14] In addition, current evidence indicates that PSCA gene variant rs2294008 polymorphism is associated with the risk of bladder cancer.[13,14]

PSCA gene is located in chromosome 8q24.2, and PSCA is a member of Ly-6/Thy-1 family of glycosylphosphatidyl-inositol-anchored cell-surface proteins, involved in cell adhesion, proliferation, and survival.[15–17] Previous studies showed that PSCA is over-expressed in serosal solid tumors, including gastric cancer, endometrial cancer, and bladder cancer.[18–21] Recently, the association of the PSCA rs2294008 C>T polymorphism and cancer susceptibility have been widely investigated.[13,14] However, though a number of studies have investigated the association between PSCA gene variant rs2294008 polymorphism and bladder cancer risk, the results remain controversial and previous studies have small patient sample sizes. Therefore, to derive a more precise estimation of the association, an updated meta-analysis based on 10 studies of PSCA gene variant rs2294008 polymorphism (14,021 cases and 26,871 controls) was performed.

2. Materials and methods

2.1. Searching strategy

All relevant publications were searched from Pubmed, Embase, Web of Science, China National Knowledge Infrastructure (CNKI), China biology medical literature database (CBM), VIP,
and Wan Fang databases (up to March 31, 2018) using the terms: “prostate stem cell antigen,” “PSCA,” “polymorphism, mutation, or variant,” “bladder cancer or bladder carcinoma or bladder tumor or bladder neoplasm.” In addition, references listed on reviews and retrieved articles were also searched to identify other relevant publications. The search strategy flowchart is shown in Figure 1. All analyses were based on previous published studies, thus no ethical approval and patient consent are required.

2.2. Inclusion criteria and exclusion criteria
The selected studies were required to meet the criteria as follows: first, studies with full text articles, published in English or Chinese; second, investigating the association between PSCA gene variant rs2294008 polymorphism and bladder cancer susceptibility; third, the study contained the complete data with genotype and allele frequencies for both cases and controls; fourth, case-control studies; fifth, sufficient genotype data were available for the estimation of odds ratios (ORs) and 95% confidence intervals (CIs). Studies were excluded for the following reasons: first, not case-control studies; second, duplicated publications, reviews, animal studies, abstracts, and comments; third, lack of sufficient data for calculating genotype frequency.

2.3. Quality assessment
The Newcastle–Ottawa scale was used to assess the quality of included studies by two authors. This scale assesses the quality of case-control studies included three areas: selection, comparability, and exposure. A star rating system was used to judge methodological quality. Scores range from 0 stars (worst) to 9 stars (best), and studies with a score ≥7 were defined as high quality. Discrepant opinions were resolved by discussion and consensus.

2.4. Data extraction strategy
All data were independently extracted from each study by two authors based on a standard protocol. The following information was extracted: first, the first author’s name, year of publication, country, source of control, genotyping method; second, sample size of the study case and control groups; third, results of the Hardy–Weinberg equilibrium test. Extracted data were checked
by a third author and disagreements were resolved by discussion between the three investigators.

2.5. Statistical analysis

Odds ratios with 95% CI were used to assess the strength of association between PSCA gene variant rs2294008 polymorphism and bladder cancer risk. The pooled ORs were performed for PSCA gene variant rs2294008 polymorphism under the allele comparison model (T vs C), additive model (TT vs CC), recessive model (TT vs CT+CC), and dominant model (TT+CT vs CC), respectively. The significance of the pooled OR was analyzed by the Z test, and \( P < 0.05 \) was considered statistically significant. The Chi-square-based \( Q \)-test and \( I^2 \) statistics were used to calculate heterogeneity among included studies. The \( P > 0.05 \) for \( Q \) test or \( I^2 < 50\% \) indicated a statistically significant degree of heterogeneity among studies, thus, a fixed effect model was used. In contrast, the random-effects model was used. All statistical analyses were performed by using Review Manager 5.3 and Stata 14.0. Publication bias was investigated with the funnel plot, Begg’s test, and Egger’s test. Sensitivity analysis was conducted to assess the stability of the results by sequentially omitted individual studies.

Table 1

| Author   | Year | Region    | Ethnicity | Source of control | Genotyping method | Case | Control | CC  | CT  | TT  | CC  | CT  | TT  | HWE |
|----------|------|-----------|-----------|-------------------|-------------------|------|---------|-----|-----|-----|-----|-----|-----|-----|
| Fu YP1   | 2012 | Finland   | Caucasian | PB                | GWAS              | 401  | 704     | 71  | 227 | 103 | 163 | 370 | 171 | >0.05 |
| Fu YP2   | 2012 | USA       | Caucasian | PB                | GWAS              | 685  | 726     | 162 | 365 | 158 | 209 | 363 | 154 | >0.05 |
| Fu YP3   | 2012 | USA       | Caucasian | PB                | GWAS              | 629  | 759     | 165 | 325 | 139 | 223 | 369 | 167 | >0.05 |
| Fu YP4   | 2012 | USA       | Caucasian | PB                | GWAS              | 691  | 1859    | 170 | 364 | 157 | 543 | 910 | 406 | >0.05 |
| Fu YP5   | 2012 | Spain     | Caucasian | PB                | GWAS              | 1103 | 1047    | 315 | 572 | 216 | 308 | 529 | 210 | >0.05 |
| Fu YP6   | 2012 | USA       | Caucasian | PB                | GWAS              | 968  | 957     | 234 | 500 | 234 | 302 | 456 | 199 | >0.05 |
| Fu YP7   | 2012 | USA       | Caucasian | PB                | GWAS              | 602  | 949     | 166 | 297 | 139 | 267 | 479 | 203 | >0.05 |
| Fu YP8   | 2012 | Eingland  | Caucasian | PB                | GWAS              | 314  | 325     | 80  | 154 | 80  | 92  | 169 | 62  | >0.05 |
| Lee      | 2014 | Korea     | Asian     | PB                | PCR               | 420  | 1700    | 79  | 222 | 119 | 414 | 818 | 468 | >0.05 |
| Ma ZC    | 2013 | China     | Asian     | PB                | PCR               | 175  | 942     | 84  | 80  | 11  | 543 | 335 | 64  | >0.05 |
| Matsuda K| 2014 | Japan     | Asian     | PB                | GWAS              | 530  | 5225    | 61  | 228 | 241 | 730 | 2416 | 2079 | >0.05 |
| Wang P   | 2013 | China     | Asian     | HB                | Real-time PCR     | 1210 | 1008    | 604 | 509 | 97  | 566 | 376 | 66  | >0.05 |
| Wang RJ  | 2014 | China     | Asian     | HB                | AS-PCR            | 358  | 434     | 120 | 189 | 49  | 189 | 211 | 34  | <0.05 |
| Wang SZ  | 2010 | China     | Asian     | HB                | Real-time PCR     | 581  | 580     | 272 | 259 | 50  | 316 | 220 | 44  | <0.05 |
| Wu XF    | 2009 | Multicenter| Caucasian | PB                | GWAS              | 5038 | 9365    | 1288| 2613| 1137| 2842| 4668| 1853| >0.05 |
| Yang JF  | 2016 | China     | Asian     | HB                | Real-time PCR     | 235  | 200     | 99  | 112 | 24  | 104 | 80  | 16  | >0.05 |
| Zhang XT | 2017 | China     | Asian     | HB                | PCR               | 81   | 95      | 26  | 38  | 17  | 42  | 41  | 12  | >0.05 |

GWAS = genome-wide association study, HB = hospital based, HWE = Hardy–Weinberg equilibrium, PB = population based, PCR = polymerase chain reaction.

Figure 2. Forest plot of studies assessing association between PSCA gene rs2294008 polymorphism and bladder cancer (Allelic model: T vs C).
3. Results

3.1. Study characteristics

According to the selection criteria, a total of 378 results were retrieved after first search in Pubmed, Embase, Web of Science, CNKI, CBM, VIP, and Wan Fang databases. Of these studies, after the first screening, 368 studies were excluded due to duplicates and obvious irrelevant information. Finally, after our careful selection, ten case-control studies considering 14,021 cases and 26,871 controls were included in this meta-analysis.\(^{[5,6,16–22]}\) The publication years of the assessed studies ranged from 2009 to 2017. Of these, there were two studies of Caucasian descendants considering 10,431 cases and 16,687 controls and eight studies of Asian descendants considering 3,590 cases and 15,184 controls. The characteristics of each of the included studies are shown in Table 1.

3.2. Meta-analysis of PSCA gene variant rs2294008 polymorphism in bladder cancer susceptibility

Ten studies involving a total of 40,892 individuals evaluated the influence of the PSCA gene variant rs2294008 polymorphism on bladder cancer susceptibility.\(^{[5,6,16–22]}\) The publication years of the assessed studies ranged from 2009 to 2017. Of these, there were two studies of Caucasian descendants considering 10,431 cases and 16,687 controls and eight studies of Asian descendants considering 3,590 cases and 15,184 controls. The characteristics of each of the included studies are shown in Table 1.
the risk of bladder cancer. Figures 2–5 show the meta-analysis results for the allele model, additive model, recessive model, and dominant model, for which the $I^2$ value was 9%, 0%, 0%, and 0%, respectively. Thus, the fixed effect model was used to synthesize the data. Overall, pooled risk estimates indicated that PSCA gene variant rs2294008 polymorphism was associated with an increased risk of bladder cancer (T vs C: OR = 1.16, 95% CI = 1.12–1.20; TT vs CC: OR = 1.32, 95% CI = 1.24–1.41; TT vs CT+CC: OR = 1.15, 95% CI = 1.09–1.22; TT+CT vs CC: OR = 1.27, 95% CI = 1.21–1.34). Subgroup analysis based on ethnicity indicated that PSCA gene variant rs2294008 polymorphism was associated with increased susceptibility to bladder cancer in both Asians (OR = 1.23, 95% CI = 1.15–1.31) and Caucasians (OR = 1.14, 95% CI = 1.10–1.18) (Table 2). Subgroup analysis was conducted based on source of control, the results showed similar significant associations of PSCA gene variant rs2294008 polymorphism with bladder cancer risk in both hospital based control group (OR = 1.25, 95% CI = 1.16–1.35) and the population based control group (OR = 1.14, 95% CI = 1.11–1.18) (Table 2).

3.3. Sensitivity analyses and publication bias

Funnel plot, Begg’s test, and Egger’s test were used to analyze the publication bias in above 4 models, and no significant publication bias was found, as shown in Figure 6 and Table 3. The sensitivity analyses were performed to investigate the pooled ORs through excluding one study each time, and the results showed no individual study had substantial influence on the overall pooled ORs in all genetic models (Fig. 7). That is to say, the results of this meta-analysis are relatively stable.

4. Discussion

Via a comprehensive meta-analysis with 10 studies involving 40,892 subjects, we evaluated the genetic association between PSCA gene variant rs2294008 polymorphism and bladder cancer susceptibility. The results showed that PSCA gene variant rs2294008 polymorphism was a moderate risk factor of bladder cancer in both Caucasian and Asian populations.

The etiology of bladder cancer is complicated, and several risk factors are involved in the development and progression.[1] In addition to environmental and lifestyle risk factors, genetic

| Ethnicity  | Case/control | T vs C (OR, 95%CI) | TT vs CC (OR, 95%CI) | TT+CT vs CC (OR, 95%CI) | TT vs CT+CC (OR, 95%CI) |
|-----------|--------------|--------------------|----------------------|-------------------------|-------------------------|
| Caucasian | 10431/16687  | 1.14 [1.10, 1.18]  | 1.29 [1.21, 1.39]    | 1.24 [1.17, 1.31]       | 1.14 [1.07, 1.21]       |
| Asian     | 3590/15184   | 1.23 [1.15, 1.31]  | 1.44 [1.24, 1.67]    | 1.37 [1.24, 1.50]       | 1.22 [1.09, 1.37]       |

Control selection

|         | Case/control | T vs C (OR, 95%CI) | TT vs CC (OR, 95%CI) | TT+CT vs CC (OR, 95%CI) | TT vs CT+CC (OR, 95%CI) |
|---------|--------------|--------------------|----------------------|-------------------------|-------------------------|
| PB      | 11556/24554  | 1.14 [1.11, 1.18]  | 1.30 [1.22, 1.39]    | 1.25 [1.19, 1.32]       | 1.14 [1.08, 1.21]       |
| HB      | 2465/2317    | 1.25 [1.16, 1.35]  | 1.56 [1.26, 1.94]    | 1.37 [1.22, 1.54]       | 1.36 [1.11, 1.67]       |
| Overall | 14021/26871  | 1.16 [1.12, 1.20]  | 1.32 [1.24, 1.41]    | 1.27 [1.21, 1.34]       | 1.15 [1.09, 1.22]       |

HB = hospital based, PB = population based.

Figure 5. Forest plot of studies assessing association between PSCA gene rs2294008 polymorphism and bladder cancer (Recessive model: TT vs CT+CC).
causes, such as single gene mutations, also play essential roles in bladder cancer. The PSCA gene rs2294008 polymorphism is one of the most commonly investigated single nucleotide polymorphisms (SNPs), which is located in chromosome 8q24.2. A previous study revealed that PSCA mRNA was expressed at a significantly higher level in the tumor tissue of T allele carriers compared with CC homozygous patients. The SNP can affect the transcriptional activity of the PSCA promoter in vitro.

There is an increasing evidence investigating the association between PSCA gene rs2736098 polymorphism and risk of different type of cancers. Several studies have evaluated the relationship of PSCA gene rs2736098 polymorphism and bladder cancer. Wang et al. conducted a hospital-based case–control study of 581 cases and 580 controls in China. They found that the rs2294008 polymorphism of PSCA gene may play a role in bladder cancer carcinogenesis in Chinese populations. Similarly, three genome-wide association studies identified a significant association between the PSCA rs2294008 (C>T) polymorphism and risk of bladder cancer in Caucasians and Asians, respectively. In the present meta-analysis, we included 10 publication studies involved with 14,021 bladder cancer patients and 26,871 controls. The overall results showed that PSCA gene rs2736098 polymorphism could increase the risk of bladder cancer (T vs C: OR = 1.16, 95%CI = 1.12–1.20; TT vs CC: OR = 1.32, 95%CI = 1.24–1.41; TT vs CT+CC: OR = 1.15, 95%CI = 1.09–1.22; TT +CT vs CC: OR = 1.27, 95%CI = 1.21–1.34). It reveals that individuals with the variant T allele may have a higher risk for bladder cancer than those carrying C homozygote. Subgroup analysis based on ethnicity and source of control showed consistent results. In our study, there is no evidence of heterogeneity across studies, even though we included populations from different countries.

**Table 3**

| Comparisons       | Coefficient | P value | 95% CI         | Begg test P value |
|-------------------|-------------|---------|----------------|-------------------|
| T vs C            | 0.583       | .282    | -0.530 to 1.696 | .044              |
| TT vs CC          | 0.295       | .551    | -0.735 to 1.325 | .108              |
| TT + CT vs CC     | 0.491       | .340    | -0.571 to 1.554 | .077              |
| TT vs CT + CC     | -1.373      | .612    | -7.031 to 4.285 | .537              |
Despite the significant findings, there are some limitations of the present study should be considered. First, we did not estimate the potential gene-gene and gene-environment interactions due to the lack of information available in the original studies. Second, other clinical data, such as subject age, smoking, and pathological patterns were not considered here due to a lack of information. Third, its OR values were nonadjusted data, due to the lack of data of smoking, alcoholic consumption, family history, age, and other environmental exposure factors.

5. Conclusion

This meta-analysis results suggest that the presence of PSCA gene variant rs2294008 polymorphism may increase the risk of bladder cancer. Nevertheless, more studies with larger sample, representative population-based cases and more accurate sample information are needed to investigate the relationships about gene-gene and gene-environment interactions in bladder carcinogenesis.

Author contributions

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