Relationship between SRD5A2 rs9282858 polymorphism and the susceptibility of prostate cancer
A meta-analysis based on 20 publications
Cheng Fang, PhDa, Zhong-Qiang Guo, PhDb, Xiao-Yan Chen, MDb, Tong-Zu Liu, PhDb, Xian-Tao Zeng, PhDa, Xing-Huan Wang, PhDabc,

Abstract
The pathogenetic mechanism of prostate cancer (PCa) has not been understood completely, and gene polymorphisms have been demonstrated to play a critical role in the course. It has been reported that rs9282858 polymorphism of steroid 5-α-reductase type 2 (SRD5A2) may affect the susceptibility of PCa, but some researches showed different results. We therefore carried out a meta-analysis to clarify this relationship.

Relevant studies were identified through PubMed and Chinese National Knowledge Infrastructure databases concerning the association between SRD5A2 rs9282858 polymorphism and PCa. Odds ratios (ORs) with their 95% confidence intervals (95% CIs) were calculated to assess the strength of the association. Additionally, stratified analyses were performed based on ethnicity and source of control. Besides, heterogeneity test, sensitivity analysis, and publication bias evaluation were conducted in current meta-analysis as well.

Ultimately, 20 publications incorporating 30 case-control studies were included in this meta-analysis, involving a total of 7300 cases and 7952 controls. The overall results demonstrated that SRD5A2 rs9282858 polymorphism was remarkably associated with increased susceptibility of PCa (TT vs. AA: OR = 4.08, 95% CI = 1.11–1.47; TT vs. AA + AT: OR = 4.44, 95% CI = 2.12–9.27; allele T vs. allele A: OR = 1.34, 95% CI = 1.17–1.54). After subgroup analyses by ethnicity and source of control, we also observed a similar trend in Latinos, other-ethnicity, population-based, and hospital-based groups under corresponding genetic models.

Our findings indicate that SRD5A2 rs9282858 polymorphism may be a susceptible factor to PCa.

Abbreviations: 95% CIs = 95% confidence intervals, HWE = Hardy-Weinberg equilibrium, ORs = odds ratios, PCa = prostate cancer, SRD5A2 = steroid 5-α-reductase type 2.

Keywords: meta-analysis, PCa, polymorphism, SRD5A2

Editor: Xiaolin Zhu
CF and Z-QG are the co-first authors.

Author contributions: X-HW had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis; study concept and design: CF, ZQG, XHW; acquisition of data: CF, ZQG, XYC; analysis and interpretation of data: TZL, CF, ZQG; drafting of the manuscript: CF, ZQG, XHW; critical revision of the manuscript for important intellectual content: CF, ZQG, XHW; statistical analysis: XYC, XTZ; supervision: XHW.

The authors claim that none of the material in the paper has been published or is under consideration for publication elsewhere.
The authors report no conflicts of interest.

a Center for Evidence-Based and Translational Medicine, b Department of Urology, Zhongnan Hospital of Wuhan University, Wuhan, China.

Correspondence: Xing-Huan Wang, Department of Urology, Center for Evidence-Based and Translational Medicine, Zhongnan Hospital of Wuhan University, 169 Donghu Road, Wuchang District, Wuhan 430071, Hubei Province, China (e-mail: wangxinghuan1965@163.com).

© 2017 the Author(s). Published by Wolters Kluwer Health, Inc. This is an open access article distributed under the Creative Commons Attribution License 4.0 (CCBY), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Medicine (2017) 96:19(e6791)
Received: 10 January 2017 / Received in final form: 22 March 2017 / Accepted: 7 April 2017
http://dx.doi.org/10.1097/MD.0000000000006791

1. Introduction
Prostate cancer (PCa) is the most common malignancy in male reproductive system.[1] In Europe, PCa accounts for 12% of all male cancers, and 9% of tumor-related deaths in adult males.[2] It is estimated that there are approximately 238,590 newly diagnosed PCa patients and 29,720 deaths caused by it in America in 2013.[3] Although the occurrence rate of PCa has been at a low level for a long time in China, it is rising significantly in recent years as a result of the changes in dietary structure and environment, making PCa become the third malignancy of male urogenital system in the country nowadays.[4] It is well known that age and race are two of the most important risk factors to PCa.[5–6] Documents reveal that PCa is rare in men younger than 40 years, but its morbidity increases with age more rapidly than any other cancers in men.[6] As a public security issue all over the world,[7] this malignancy still threatens the health, even life, of aged males in spite of notable improvements in the techniques for the diagnosis and treatment.

Cancer is essentially a genetic disease, and its genesis and development involve a multistep, multistage, and polygenic process.[8] The occurrence and growth of PCa are induced by the changes of multiple genes and stimulation from environmental factors.[9] At present, researchers have paid close attention to
genetic association studies about the relationships of cancer with oncogenes, tumor-suppressor genes, and other genes involved in hormonal environment. Androgen reportedly plays a vital role in the canceration of prostate, so relevant genes involved in biosynthesis and metabolic pathway of androgen may influence the pathogenesis of this malignancy. As well known, there are 2 main types of androgen in humans and other mammals, namely, testosterone and dihydrotosterone (DHT). Steroid 5α-reductase can restore testosterone into stronger DHT, which has a significant impact on the growth and differentiation of prostate cells. Two types of steroid 5α-reductase have been identified so far, which are steroid 5α-reductase type 1 (SRD5A1) and steroid 5α-reductase type 2 (SRD5A2). Among them, SRD5A2 is highly expressed in androgen-sensitive tissues, such as prostate and testis. In addition, catalyzing SRD5A2 can remarkably enhance the biological activity of DHT and its affinity for androgen receptor (AR), thereby possibly affecting the onset risk of PCa.

A large number of researches have been performed to explore the effects of SRD5A2 polymorphisms on PCa susceptibility during the past decade, but the conclusions remained inconsistent. The keywords applied in searches were SRD5A2 polymorphism or mutation or variation. In this study, we searched all eligible publications to carry out a meta-analysis for a clearer perspective on the association of SRD5A2 rs9282858 polymorphism and the susceptibility of PCa.

2. Materials and methods

2.1. Literature search

This meta-analysis was conducted in accordance with the checklist of the Meta-analysis of Observational Studies in Epidemiology guidelines. The proposed checklist contains specifications for reporting of meta-analyses of observational studies in epidemiology, including background, search strategy, methods, results, discussion, and conclusions. The PubMed and Chinese National Knowledge Infrastructure databases were searched for all relevant publications about the association between SRD5A2 rs9282858 polymorphism and PCa. Language restrictions were imposed on literature search strategy. The keywords applied in searches were “steroid 5α-reductase type 2 or SRD5A2” in combination with “prostate cancer” and “polymorphism or mutation or variation.” Moreover, the references of all pertinent articles were manually checked to identify additional relevant studies. All analyses were based on previous published studies; thus, ethical approval was not necessary for this meta-analysis.

2.2. Inclusion and exclusion criteria

Studies included in the meta-analysis were required to fulﬁl the following criteria: they were designed as case-control studies; assessing the correlation between SRD5A2 rs9282858 polymorphism and PCa susceptibility; presenting adequate genotype data for calculating pooled odds ratios (ORs) and 95% conﬁdence intervals (95% CIs). Apart from articles not meeting the inclusion criteria, reviews, meta-analysis, and repeated publications were excluded.

2.3. Data extraction

Data extraction was completed by 2 investigators independently, and all the information was recorded in a standardized form. The results were compared and disagreements were resolved through discussion to reach a consensus. The following data were gathered from each relevant study: the first author’s name, year of publication, original country, ethnicity, control source, genotyping method, numbers of cases and controls, genotype frequencies in case and control groups, and P values for Hardy-Weinberg equilibrium (HWE) in controls.

2.4. Statistical analysis

The genetic relationship between SRD5A2 rs9282858 polymorphism and PCa susceptibility was examined through crude ORs and 95% CIs under TT vs. AA, TT+AT vs. AA, TT vs. AA+AT, allele T vs. allele A, and AT vs. AA contrasts. Subgroup analyses by ethnicity and source of control were performed subsequently. A χ2-based Q-statistic test was employed to explore statistical heterogeneity with P < 0.05 for statistical significance. A quantitative measure of between-study heterogeneity was also investigated using the I2 statistic, and the heterogeneity was defined as low, moderate, and high based on I2 values of 25%, 50%, and 75%, respectively. If significant heterogeneity existed (P < 0.05), the random-effects model was used to pool overall effects; otherwise, a fixed-effect model was selected. Sensitivity analysis was undertook by excluding each single study in turn to investigate the stability of results. Begg funnel plot and Egger test were adopted to detect any underlying publication bias in the meta-analysis. Finally, the distribution of genotypes in controls was tested for a departure from HWE using χ2 test. All statistical analyses in this study were implemented with STATA 12.0 software (Stata Corporation, College Station, TX).

3. Results

3.1. Study characteristics

In accordance with search strategy, 123 articles were searched from electronic databases originally. Apart from 14 duplicates, another 65 records were also deleted because of reviews (n = 6), without controls (n = 12) and irrelevant to the topic (n = 47), and 24 articles were removed because of republished data (n = 2), unsusable data (n = 5), meta-analysis (n = 4), and not involving rs9282858 polymorphism (n = 13). Ultimately, 20 articles incorporating 30 case-control studies were included in the meta-analysis, involving a total of 7300 cases and 7952 controls. The selection process and characteristics of eligible studies are displayed in Figure 1 and Table 1, respectively. The genotype distributions of the controls were consistent with HWE in all included studies (P > 0.05).

3.2. Meta-analysis results

Table 2 presents the main results of this meta-analysis. Overall, we found that there was a statistically significant relationship between SRD5A2 rs9282858 polymorphism and increased PCa susceptibility (TT vs. AA: OR = 4.08, 95% CI = 1.94–8.38 [Fig. 2]; TT+AT vs. AA: OR = 1.28, 95% CI = 1.11–1.47; TT vs. AA+AT: OR = 4.44, 95% CI = 2.12–9.27; allele T vs. allele A: OR = 1.34, 95% CI = 1.17–1.54 [Fig. 3]).

After subgroup analysis based on ethnicity, the susceptibility of PCa was notably enhanced in Latinos (TT vs. AA: OR = 64.82, 95% CI = 3.80–110.87; TT vs. AA+AT: OR = 46.44, 95% CI = 3.98–1110.33; allele T vs. allele A: OR = 1.61, 95% CI = 1.17–2.22 [Fig. 3]) and in other-ethnicity (TT+AT vs. AA: OR = 2.20, 95% CI = 1.43–3.37; allele T vs. allele A: OR = 1.86, 95% CI = 1.26–2.74 [Fig. 3]) groups.
What is more, after stratified analysis by source of control, similar results were observed in population-based (TT vs. AA: OR = 4.69, 95% CI = 2.09–10.51; Fig. 2); TT+AT vs. AA: OR = 1.27, 95% CI = 1.07–1.50; TT vs. AA+AT: OR = 5.10, 95% CI = 2.29–11.37; allele T vs. allele A: OR = 1.38, 95% CI = 1.17–1.62; AT vs. AA: OR = 1.27, 95% CI = 1.01–1.59) and hospital-based (allele T vs. allele A: OR = 1.46, 95% CI = 1.09–1.96) subgroups as well.

### 3.3. Heterogeneity test

As shown in Table 2, there was significant heterogeneity under AT versus AA model ($P = .041$), so we chose the random-effects model to calculate pooled results. Additionally, after stratification analysis by control source, we observed that studies enrolling controls from hospitals might be the source of significant heterogeneity.

Meanwhile, as no substantial heterogeneity was found under TT versus AA ($P = .159$), TT+AT versus AA ($P = .068$), TT versus AA+AT ($P = .127$), and allele T versus allele A ($P = .074$) comparisons, a fixed-effect model was therefore applied.

### 3.4. Sensitivity analysis and publication bias

Through removing one single included study each time, sensitivity analysis was completed, and no substantial change was observed during the whole course, reflecting that the results of this meta-analysis were stable and credible.

As for publication bias, the shapes of all funnel plots seemed symmetrical (Fig. 4), and statistical values from Egger test also supported these results (TT vs. AA: $P = .356$; TT+AT vs. AA: $P = .213$). 

---

### Table 1

Principal characteristics of the studies included in the meta-analysis.

| First author | Ethnicity | Control source | Genotyping method | Sample size | Case | Control |
|--------------|-----------|----------------|-------------------|-------------|------|---------|
| Li et al.[20] | Asian     | Population-based | RFLP-PCR | 302 302 | 0 0 | 604 604 |
| Pearce et al.[23] | Asian | Population-based | PCR | 430 430 | 0 0 | 860 860 |
| Rajender et al.[31] | Asian | Population-based | RFLP-PCR | 87 87 | 0 0 | 174 174 |
| Hsing et al.[27] | Asian | Population-based | AS PCR | 170 170 | 0 0 | 340 340 |
| Liu et al.[34] | Asian | Hospital-based | RFLP-PCR | 112 104 | 7 7 | 215 215 |
| Cicek et al.[29] | African | Family-based | RFLP-PCR | 38 38 | 0 0 | 76 76 |
| Fernandez et al.[30] | African | Hospital-based | SSCP-PCR | 25 18 | 0 0 | 82 82 |
| Fernandez et al.[30] | African | Hospital-based | SSCP-PCR | 75 75 | 0 0 | 150 150 |
| Makridakis et al.[33] | African | Population-based | SSCP-PCR | 216 203 | 9 9 | 415 415 |
| Pearce et al.[28] | African | Population-based | SSCP-PCR | 642 628 | 14 14 | 1270 1270 |
| Soderstrom et al.[11] | White | Population-based | PCR | 175 168 | 7 7 | 343 343 |
| Lambhari et al.[31] | White | Population-based | PCR | 300 279 | 21 21 | 579 579 |
| Hayes et al.[18] | White | Population-based | Mass array | 827 752 | 75 75 | 1579 1579 |
| Pearce et al.[23] | White | Population-based | SSCP-PCR | 432 406 | 25 25 | 837 837 |
| Margiotti et al.[19] | White | Population-based | SSCP-PCR | 106 103 | 3 3 | 209 209 |
| Forrest et al.[25] | White | Population-based | RFLP-PCR | 47 47 | 0 0 | 94 94 |
| Chang et al.[23] | White | Population-based | PCR | 213 203 | 10 10 | 416 416 |
| Giwercman et al.[24] | White | Population-based | AS PCR | 86 74 | 12 12 | 160 160 |
| Torkko et al.[17] | White | Population-based | TaqMan | 444 411 | 33 33 | 855 855 |
| Cicek et al.[29] | White | Family-based | RFLP-PCR | 397 370 | 26 26 | 766 766 |
| Fernandez et al.[30] | White | Hospital-based | PCR | 120 90 | 30 30 | 210 210 |
| Torkko et al.[17] | Hispanic | Population-based | TaqMan | 141 135 | 6 6 | 276 276 |
| Makridakis et al.[33] | Hispanic | Population-based | SSCP-PCR | 172 160 | 10 10 | 330 330 |
| Pearce et al.[29] | Latino | Population-based | SSCP-PCR | 585 566 | 19 19 | 1151 1151 |
| Paz-y-Mino et al.[31] | Latino | Population-based | RFLP-PCR | 114 33 | 60 60 | 212 212 |
| Fernandez et al.[30] | Mixed | Hospital-based | PCR | 207 120 | 87 87 | 327 327 |
| Salam et al.[25] | Mixed | Population-based | SSCP-PCR | 96 92 | 4 4 | 188 188 |
| Pearce et al.[23] | Native-Hawaiian | Population-based | SSCP-PCR | 66 66 | 0 0 | 132 132 |
| Mononen et al.[24] | White | Population-based | ASOH PCR | 449 422 | 27 27 | 588 588 |
| Lati et al.[18] | White | Population-based | RFLP-PCR | 226 219 | 7 7 | 156 156 |

As PCR = allele-specific polymerase chain reaction, HWE = Hardy-Weinberg equilibrium, PCR = polymerase chain reaction, RFLP-PCR = restriction fragment length polymorphism-PCR, SSCP = single-strand conformation analysis, SSCP-PCR = single-stranded conformational polymorphism-PCR, TaqMan = TaqManSNP.
Table 2  
SRD5A2 rs9282858 polymorphism and the susceptibility of PCa.

| Genetic comparison | Group/subgroup | OR (95% CI) | \( P_h \) |
|--------------------|----------------|-------------|---------|
| TT vs. AA          | Ethnicity       |             |         |
| Asian              | 2.34 (0.09, 58.19) | /          |         |
| African            | 5.06 (0.56, 45.66) | /          |         |
| White              | 1.05 (0.21, 5.22) | .620       |         |
| Hispanic           | 1.21 (0.17, 8.66) | /          |         |
| Latino             | 64.82 (3.80, 1106.87) | /        |         |
| Other              | 0.39 (0.02, 9.62) | /          |         |
| Source of control  | Population-based| 4.69 (2.09, 10.51) | .073 |
| Hospital-based     | 2.34 (0.09, 58.19) | /          |         |
| Family-based       | 1.09 (0.07, 17.43) | /          |         |
| Total              | 4.08 (1.94, 8.58) | .159       |         |
| TT + AT vs. AA     | Ethnicity       |             |         |
| Asian              | 0.78 (0.28, 2.16) | /          |         |
| African            | 1.31 (0.77, 2.23) | .069       |         |
| White              | 1.15 (0.96, 1.37) | .241       |         |
| Hispanic           | 1.45 (0.74, 2.83) | .282       |         |
| Latino             | 1.35 (0.68, 2.09) | .860       |         |
| Other              | 2.20 (1.43, 3.37) | .241       |         |
| Source of control  | Population-based| 1.27 (1.07, 1.50) | .243 |
| Hospital-based     | 1.21 (0.65, 2.28) | .034       |         |
| Family-based       | 0.81 (0.49, 1.36) | .570       |         |
| Total              | 1.28 (1.11, 1.47) | .068       |         |
| TT vs. AA + AT     | Ethnicity       |             |         |
| Asian              | 2.41 (0.10, 59.63) | /          |         |
| African            | 4.91 (0.54, 44.22) | /          |         |
| White              | 1.05 (0.21, 5.21) | .618       |         |
| Hispanic           | 1.16 (0.16, 8.36) | /          |         |
| Latino             | 66.45 (3.98, 1110.33) | /         |         |
| Other              | 0.37 (0.01, 9.22) | /          |         |
| Source of control  | Population-based| 5.10 (2.29, 11.37) | .056 |
| Hospital-based     | 2.41 (0.10, 59.63) | /          |         |
| Family-based       | 1.10 (0.07, 17.46) | /          |         |
| Total              | 4.44 (2.12, 9.27) | .127       |         |
| T vs. A            | Ethnicity       |             |         |
| Asian              | 0.89 (0.34, 2.35) | /          |         |
| African            | 1.26 (0.47, 3.38) | .037       |         |
| White              | 1.17 (0.97, 1.41) | .183       |         |
| Hispanic           | 1.40 (0.75, 2.64) | .333       |         |
| Latino             | 1.61 (1.17, 2.22) | .663       |         |
| Other              | 1.88 (1.26, 2.74) | .342       |         |
| Source of control  | Population-based| 1.38 (1.17, 1.62) | .158 |
| Hospital-based     | 1.46 (1.09, 1.96) | .096       |         |
| Family-based       | 0.83 (0.50, 1.36) | .567       |         |
| Total              | 1.34 (1.17, 1.54) | .074       |         |
| AT vs. AA          | Ethnicity       |             |         |
| Asian              | 0.68 (0.24, 1.96) | /          |         |
| African            | 1.12 (0.45, 2.81) | .120       |         |
| White              | 1.18 (0.91, 1.51) | .155       |         |
| Hispanic           | 1.49 (0.61, 3.64) | .227       |         |
| Latino             | 1.11 (0.72, 1.72) | .400       |         |
| Other              | 1.98 (0.44, 8.97) | .176       |         |
| Source of control  | Population-based| 1.27 (1.01, 1.59) | .178 |
| Hospital-based     | 1.17 (0.61, 2.27) | .026       |         |
| Family-based       | 0.81 (0.48, 1.37) | .574       |         |
| Total              | 1.24 (1.00, 1.59) | .041       |         |

\( CI = \) confidence interval, OR = odds ratio, PCa = prostate cancer, \( P_h = \) value of heterogeneity test.

*Represents values calculated with random-effects model.

\( P = .228; \) TT vs. AA + AT: \( P = .353; \) allele T vs. allele A: \( P = .282; \) AT vs. AA: \( P = .253),\) demonstrating that there was no significant publication bias.

### 4. Discussion

PCa is one of the common diseases in older men, frequently occurring in western countries in particular.\[^{11}\] Up to now, the pathogenesis of PCa has not been identified utterly, but a few risk factors have been recognized, including heredity, high-fat diet, low intake of isoflavone, and excessive intake of pickled meats.\[^{13-18}\] Recently, reduce of copy number in AR gene CAG repeat sequences is also proposed to possibly conduce to the occurrence of PCa.\[^{17}\]

Steroid 5α-reductase is a membrane protein in microsomal membrane and nuclear membrane principally, consisting of SRD5A1 and SRD5A2. The gene SRD5A2 coding for the latter is located at chromosome 2p23, containing 5 exons and encoding 254 oxyacids. Investigations have displayed that SRD5A2 SNPs may change the activity of 5α-reductase, so the rs9282858 SNPs may change the activity of 5α-reductase, so the rs9282858 SNPs may change the activity of 5α-reductase, so the rs9282858
polymorphism, among others, has attracted increasing attention from scholars for the past few decades. So far, numerous studies have been conducted on the relationship between \( SRD5A2 \) rs9282858 polymorphism and PCa susceptibility, but the conclusions are not unanimous. A few meta-analyses\(^{39-42} \) were also conducted to figure out the influence of \( SRD5A2 \) rs9282858 polymorphism on PCa susceptibility. However, because of different inclusive criteria and uneven sample sizes, these reports presented different conclusions. Among them, the most recent one\(^{42} \) was conducted in 2012 based on 17 case-control studies, including 13 in whites, 3 in Asians, and 1 in Africans. Thus, it is of great significance to perform a more comprehensive meta-analysis with the updated publications.

This meta-analysis, including 30 independent case-control studies with 7300 cases and 7952 controls, was strictly implemented from literature search to information abstract to data syntheses. Compared to the previous studies, this meta-analysis had several strengths. Most importantly, our relatively larger sample size provided the analysis results with strong statistical power, and subgroup analyses by ethnicity and control source also facilitated a more detailed interpretation of the impact of \( SRD5A2 \) rs9282858 polymorphism on PCa in specific populations. In this study, our findings revealed that \( SRD5A2 \) rs9282858 polymorphism increased PCa susceptibility under all but one comparison in total analysis. Furthermore, after stratified analyses by ethnicity and source of control, a similar association was also found in Latinos, other-ethnicity, population-based, and hospital-based subgroups under corresponding genetic models. Although in terms of Latino groups the data are distinguished between the studies of Pearce et al\(^{28} \) and Paz-y-Mino et al\(^{31} \), no substantial heterogeneity was found between the studies (Fig. 3). Since the selection criteria for study subjects varied among the

---

**Figure 2.** Forest plot of prostate cancer susceptibility associated with \( SRD5A2 \) rs9282858 polymorphism under TT vs. AA model after stratification analysis by control source. CI = confidence interval, OR = odds ratio.
studies, basic characteristics such as age period, pathological tumor stage, and lifestyles might be statistically different. Besides, the sample sizes in the studies were uneven and various genotype detection methods may also contribute to biased conclusions. Research by Uemura et al.\(^{[43]}\) indicated that steroid 5a-reductase is a culture medium of 11-deoxycorticosterone, and that it might contribute to the proliferation and differentiation of PCa cells via regulating AR pathway. The rs9282858 (A49T) is a common polymorphism site in the \(\text{SRD5A2}\) gene, which results in an alanine residue at codon 49 being replaced with threonine.\(^{[33]}\) Furthermore, in vitro experiments uncovered that the presence of rs9282858 missense mutation could increase the activity of steroid 5a-reductase by 5 times,\(^{[28,33]}\) thereby affecting the onset risk of PCa.

Despite certain advantages, some insurmountable limitations in this meta-analysis should be addressed. First, only published studies were included, and publication bias might have been generated, even though it was not detected in relevant tests. Second, although no language restrictions were imposed on literature search strategy, only articles written in English or
polymorphism in SRD5A2 work because of the lack of original information. We therefore did not evaluate the possible impacts of gene-gene and gene-environment interactions on the pathogenesis of PCA in this work because of the lack of original information. Taken together, the present meta-analysis offers additionally strong evidence for the association between the rs9282858 polymorphism in SRD5A2 and increased PCA susceptibility. It provides an important theoretical basis to reveal the rs9282858 polymorphism and the biological mechanism of developing PCA, which may be helpful to predict the occurrence of PCA. Importantly, more attention should be paid to the roles of polymorphisms in clinical aggressiveness and therapeutic response in future work. Considering the above-mentioned restrictions, more larger-scale and well-designed studies based on multiple ethnic populations are needed to confirm our results in future.

References

[1] Burgess EF, Raghavan D. Prostate cancer: what did we learn from the 2012 Annual Scientific Meeting of ASCO? Oncology (Williston Park) 2012;26:1216–21.
[2] Ferlay J, Parkin DM, Steliarova-Foucher E. Estimates of cancer incidence and mortality in Europe in 2008. Eur J Cancer 2010;46:765–81.
[3] Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. CA Cancer J Clin 2013;63:11–30.
[4] Matsuda T, Saika K. Comparison of time trends in prostate cancer incidence (1973–2002) in Asia, from cancer incidence in five continents, Vols IV–IX. Jpn J Clin Oncol 2009;39:468–9.
[5] Gronberg H. Prostate cancer epidemiology. Lancet 2003;361:859–64.
[6] Henderson BE, Feigelson HS. Hormonal carcinogenesis. Carcinogenesis 2000;21:427–33.
[7] Crawford ED. Understanding the epidemiology, natural history, and key pathways involved in prostate cancer. Urology 2009;73(5 suppl):S4–10.
[8] Dianat SS, Margreiter M, Eckersberger E, et al. Gene polymorphisms and prostate cancer: the evidence. BJU Int 2009;104:1360–72.
[9] DeMarino AM, Nelson WG, Isaacs WB, et al. Pathological and molecular aspects of prostate cancer. Lancet 2003;361:955–64.
[10] Marcelli M, Cunningham GR. Hormonal signaling in prostate hyperplasia and neoplasia. J Clin Endocrinol Metab 1999;84:3463–8.
[11] Wu Y, Godoy A, Azouz F, et al. Prostate cancer cells differ in testosterone accumulation, dihydrotestosterone conversion, and androgen receptor signaling response to steroid 5alpha-reductase inhibitors. Prostate 2013;73:1470–82.
[35] Lih FB, Titus MA, Mohler JL, et al. Atmospheric pressure photoionization tandem mass spectrometry of androgens in prostate cancer. Anal Chem 2010;82:6000–7.

[36] Donovan MJ, Hamann S, Clayton M, et al. Systems pathology approach for the prediction of prostate cancer progression after radical prostatectomy. J Clin Oncol 2008;26:3923–9.

[37] Donovan MJ, Osman I, Khan FM, et al. Androgen receptor expression is associated with prostate cancer-specific survival in castrate patients with metastatic disease. BJU Int 2010;105:462–7.

[38] Wang H, McKnight NC, Zhang T, et al. SOX9 is expressed in normal prostate basal cells and regulates androgen receptor expression in prostate cancer cells. Cancer Res 2007;67:528–36.

[39] Ntais C, Polycarpou A, Ioannidis JP. SRD5A2 gene polymorphisms and the risk of prostate cancer: a meta-analysis. Cancer Epidemiol Biomarkers Prev 2003;12:618–24.

[40] Li J, Coates RJ, Gwinn M, et al. Steroid 5-(alpha)-reductase Type 2 (SRD5a2) gene polymorphisms and risk of prostate cancer: a HuGE review. Am J Epidemiol 2010;171:1–3.

[41] Li X, Huang Y, Fu X, et al. Meta-analysis of three polymorphisms in the steroid-5-alpha-reductase, alpha polypeptide 2 gene (SRD5A2) and risk of prostate cancer. Mutagenesis 2011;26:371–83.

[42] Li Q, Zhu Y, He J, et al. Steroid 5-alpha-reductase type 2 (SRD5A2) V89L and A49T polymorphisms and sporadic prostate cancer risk: a meta-analysis. Mol Biol Rep 2013;40:5597–608.

[43] Uemura M, Honma S, Chung S, et al. SalphaDH-DOC (Salpha-dihydrodeoxycorticosterone) activates androgen receptor in castration-resistant prostate cancer. Cancer Sci 2010;101:1897–904.

[44] Zeng X, Zhang Y, Kwong JS, et al. The methodological quality assessment tools for preclinical and clinical studies, systematic review and meta-analysis, and clinical practice guideline: a systematic review. J Evid Based Med 2015;8:2–10.