Association between 8q24 Gene Polymorphisms and the Risk of Prostate Cancer: A Systematic Review and Meta-Analysis

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Abstract

Though numerous studies have been conducted to investigate the associations between five 8q24 polymorphisms (rs6983267 T>G, rs1447295 C>A, rs16901979 C>A, rs6983561 A>C and rs10090154 C>T) and prostate cancer (PCa) risk, the available results remained contradictory. Therefore, we performed a comprehensive meta-analysis to derive a precise estimation of such associations. We searched electronic databases PubMed, EMBASE, Web of Science and Wan Fang for the relevant available studies up to February 1st, 2017, and 39 articles were ultimately adopted in this meta-analysis. All data were extracted independently by two investigators and recorded in a unified form. The strength of association between 8q24 polymorphisms and PCa susceptibility was evaluated by pooled odds ratios (ORs) with 95% confidence intervals (CIs). Subgroup analysis was conducted based on ethnicity, source of controls and genotypic method. Overall, a total of 39 articles containing 80 studies were adopted in this meta-analysis. The results of this meta-analysis indicated that five 8q24 polymorphisms above were all related to PCa susceptibility. Besides, in the subgroup analysis by ethnicity, all selected 8q24 polymorphisms were significantly associated with PCa risk in Asian population. In addition, stratification analysis by source of controls showed that significant results were mostly concentrated in the studies’ controls from general population. Moreover, when stratified by genotypic method, significant increased PCa risks were found by TaqMan method. Therefore, this meta-analysis demonstrated that 8q24 polymorphisms (rs6983267 T>G, rs1447295 C>A, rs16901979 C>A, rs6983561 A>C and rs10090154 C>T) were associated with the susceptibility to PCa, which held the potential biomarkers for PCa risk.

Key words: 8q24, Polymorphisms, Prostate cancer, Meta-analysis.

Introduction

Prostate cancer (PCa) is one of the most common non-cutaneous malignancies among men in developed country, with an estimated 161,360 new cases and 26,730 deaths in the United States in 2017 [1]. Many influencing factors have been proved to be associated with the risk of PCa, including advancing age, ethnicity, smoking and alcohol consumption, endocrine system, and genetic factors. However, the underlying etiology of PCa is still confusing [2]. Recently, genetic predisposition of PCa have gradually attracted investigators’ attention. Especially, it suggested that common genetic
polymorphisms such as single nucleotide polymorphic variants (SNPs) might be associated with sporadic cases of PCa [3]. In addition, several studies have identified the 8q24 polymorphisms increased the risk of PCa [4-6]. Therefore, we plan to study the etiology of PCa from the aspect of genetic predisposition.

Chromosomal region 8q24 has been proved to be associated with a wide spectrum of cancers, including cancers of the breast, prostate, bladder, colon, lung, ovaries and pancreas among different ethnicities [7-13]. A region on chromosome 8q24 was originally shown to confer PCa risk in a genome-wide linkage scan of 871 Icelandic men in 2006 [14]. In addition, 8q24 was considered as a gene-free region, flanked by the FAM84B and MYC genes on the centromeric and telomeric ends respectively [15]. Physical nearness might indicate the association between 8q24 and MYC proto-oncogene. As a highly conserved genomic region, three 8q24 regions (region 1: 128.54-128.62 Mb; region 2: 128.12-128.28 Mb; region 3: 128.47-128.54 Mb) have been identified to contain variants independently associated with PCa susceptibility [16]. Subsequently, multiple independent studies have been performed to extensively explore the roles of 8q24 SNPs in the risk of PCa. Thus, it was hypothesized that the genetic variations in the 8q24 region were likely to take effect in prostate carcinogenesis.

Genome-wide association studies (GWAS) have identified more than 100 common SNPs that were associated with the susceptibility of PCa. A large number of studies have explored the associations between these polymorphisms and the risk of PCa [17]. In previous studies, five 8q24 polymorphisms (rs6983267 T>G, rs1447295 C>A, rs16901979 C>A, rs6983561 A>C and rs10090154 C>T) among these SNPs might have strong associations with PCa susceptibility. Nevertheless, the results of these studies were inconsistent and inconclusive [4,18-20]. Hence, we conducted an updated meta-analysis including all eligible case-control studies to investigate the association between 8q24 gene polymorphisms and the risk of PCa.

Materials and Methods

We searched PubMed, EMBASE, Web of Science and Wan Fang databases comprehensively to obtain relevant studies published up to February 1st, 2017. The following searching keywords were utilized: “8q24”, “polymorphisms” or “mutations” or “variants”, and “prostate cancer” or “prostatic neoplasms”. Potential eligible articles were manually collected by searching from the reference lists of relevant literature and reviews. In addition, overlapping data from different articles were removed.

Then, all eligible articles were collected according the following inclusive criteria: (1) Independent case-control or cohort studies; (2) Possessing at least one of 8q24 polymorphisms (rs6983267 T>G, rs1447295 C>A, rs16901979 C>A, rs6983561 A>C and rs10090154 C>T); (3) Availability of genotype data of both cases and controls; (4) Enrolled patients with PCa confirmed by histopathological examination, and controls with no history of neoplasms. Meanwhile, the exclusive criteria were as follows: (1) No case-control study; (2) Duplicate or unavailable data; (3) Studies not related to 8q24 or prostate cancer.

Data extraction

All available data from the eligible studies identified were extracted independently by two investigators (Li R and Qin ZQ). If any disagreement appeared, a third investigator (Tang JY) would join in and make a better decision. All the extracted data were recorded in a unified form and the following items were collected: first author’ name, publication year, ethnicity, source of controls, genotypic method, the number of cases and controls, the number of 8q24 polymorphisms carriers and non-carriers respectively and the results of the Hardy-Weinberg equilibrium (HWE) test.

Statistical analysis

The Pearson’s goodness-of-fit chi-square test was adopted to access HWE in the control groups. Besides, P value was more than 0.05, which was regarded as significant equilibrium. The strength of associations between 8q24 polymorphisms and susceptibility to PCa were evaluated by the pooled odds ratios (ORs) with 95% confidence intervals (CIs) using five genetic comparison models: allele model, homozygous model, heterozygous model, dominant model and recessive model. Fixed effect model (a Mantel-Haenszel method) and random effect model (a DerSimonian-Laird method), as two common statistical models, were selected according to Cochrane Q test and Higgins I² statistic. If the heterogeneity is acceptable (I² < 50% suggested no obvious heterogeneity), the fixed effect model will be adopted; Otherwise, the random effect model will be performed to calculate the pooled ORs. Besides, the random effect model is a kind of method for disposing heterogeneous data, but it cannot replace the reason analysis of the source of heterogeneity. Normally, several reasons might induce the heterogeneity, including design scheme, measuring method, age, ethnicity and so on. In addition, subgroup analysis

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according to ethnicity, source of controls and genotypic method was further used to explore the source of heterogeneity. To examine the stability and reliability of the results in this meta-analysis, sensitive analysis was adopted to recalculate the pooled ORs following the sequential exclusion of a single study at a time. Moreover, Begg’s funnel plots and Egger’s linear regression test were used to check out the publication bias between all included studies, and P values were considered as a significantly selective bias when less than 0.05. STATA 12.0 software (State Corporation, College Station, TX, USA) was utilized to dispose all above statistical analyses.

Results

Studies characteristics

Based on the retrieve strategy above, a total of related 182 articles were initially collected by a primary search of databases and reference lists. According to the inclusive criteria, 39 articles consisting of 80 studies were ultimately adopted in the present meta-analysis for a further evaluation, which had been accrued between March 2007 and January 2015 [4-6, 18-53]. The details of the literature search and screening process were shown in Figure 1.

Among the eligible 80 studies, the distribution of genotypes in the controls was consistent with HWE, except three studies. In this meta-analysis, all of the baseline characteristics of the studies associated with the risk of PCa were listed in Table 1. These studies were conducted in Caucasians, Asians, Africans and Mixed. Furthermore, in order to distinguish between different sources of control group, investigators divided them into population-based group or hospital-based group in all studies. Besides, six genotypic methods were applied in these studies, such as Taqman, PCR-RFLP, iPLEX and so on.

Quantitative synthesis results

In general, the pooled ORs and 95% CIs were utilized to evaluate the strength of the association between 8q24 polymorphisms and PCa risk based on five genetic comparison models. Results of the association between 8q24 polymorphisms and PCa susceptibility were listed in Table 2. To explore the heterogeneity of these studies, stratification analysis by ethnicity, source of controls and genotypic method was conducted. Meanwhile, subgroups with less than three studies were excluded from further analysis to avoid the possible false associations.

Figure 1. The flowchart of literature search and selection procedure.
### Table 1. Characteristics of individual studies included in the meta-analysis.

| rs6983267(T>C) | Year | Surname | Ethnicity | SOC | Genotypic | Case (n) | Control (n) |
|----------------|------|---------|-----------|-----|-----------|----------|-------------|
|                | 2010 | Oskina  | Caucasian | PB  | TaqMan    | 389      | 341         |
|                | 2010 | Zhang   | Asian     | PB  | PCR-RFLP  | 124      | 133         |
|                | 2014 | Francesco| Caucasian | HB  | TaqMan    | 82       | 210         |
|                | 2013 | Chan     | Asian     | HB  | Illumina 1M chip | 288 | 144 |
|                | 2013 | Brankovia| Caucasian | HB  | PCR-RFLP  | 150      | 100         |
|                | 2013 | Zhao     | Asian     | PB  | PCR-RFLP  | 282      | 282         |
|                | 2012 | Ho       | Caucasian | PB  | PCR-RFLP  | 216      | 248         |
|                | 2012 | Joung    | Asian     | HB  | iPlex     | 194      | 166         |
|                | 2012 | Liu      | Asian     | PB  | PCR-RFLP  | 260      | 282         |
|                | 2011 | Okobia   | African   | HB  | TaqMan    | 345      | 426         |
|                | 2011 | Papapnikolopoulou | Caucasian | HB | TaqMan | 86  | 99          |
|                | 2011 | Liu      | Asian     | PB  | GWAS      | 792      | 1325        |
|                | 2011 | Liu      | Asian     | PB  | PCR-RFLP  | 40       | 40          |
|                | 2010 | Zheng    | Asian     | PB  | iPlex     | 282      | 152         |
|                | 2010 | Liu      | Asian     | HB  | TaqMan    | 391      | 323         |
|                | 2009 | Penney   | Caucasian | PB  | iPlex     | 1305     | 1402        |
|                | 2009 | Penney   | Caucasian | PB  | iPlex     | 377      | 249         |
|                | 2008 | Beuten   | Caucasian | PB  | Illumina 1M chip | 597 | 838 |
|                | 2008 | Terada   | Asian     | PB  | PCR-RFLP  | 507      | 511         |
|                | 2008 | Salinas  | Caucasian | PB  | PCR-RFLP  | 1258     | 1238        |
|                | 2008 | Cheng    | Caucasian | HB  | TaqMan    | 417      | 417         |
|                | 2008 | Cheng    | African   | HB  | TaqMan    | 89       | 89          |
|                | 2008 | Wokoloreczyk | Caucasian | PB | PCR-RFLP | 1885 | 1910 |
|                | 2007 | Zheng    | Caucasian | HB  | iPlex     | 1551     | 1573        |
|                | 2007 | Yeager   | Mixed     | PB  | GWAS      | 4206     | 4299        |
|                | 2007 | Haiman   | Mixed     | PB  | TaqMan    | 1047     | 857         |
|                | 2007 | Haiman   | Mixed     | PB  | TaqMan    | 708      | 718         |
| rs1447295(C>A) | Year | Surname | Ethnicity | SOC | Genotypic | Case (n) | Control (n) |
|                | 2014 | Zhang    | Asian     | PB  | PCR-RFLP  | 123      | 137         |
|                | 2014 | Oskina   | Caucasian | PB  | TaqMan    | 392      | 343         |
|                | 2014 | Cheryl   | African   | PB  | iPLEX     | 515      | 507         |
|                | 2014 | Francisco| Caucasian | HB  | TaqMan    | 83       | 21          |
|                | 2013 | Chan     | Asian     | HB  | Illumina 1M chip | 289 | 143 |
|                | 2013 | Brankovia| Caucasian | HB  | PCR-RFLP  | 150      | 100         |
|                | 2013 | Zhao     | Asian     | PB  | PCR-RFLP  | 277      | 287         |
|                | 2012 | Joung    | Asian     | PB  | iPLEX     | 195      | 168         |
|                | 2012 | Liu      | Asian     | PB  | PCR-RFLP  | 260      | 287         |
|                | 2011 | Okobia   | African   | HB  | TaqMan    | 354      | 348         |
|                | 2011 | Zeegers  | Caucasian | PB  | PCR-RFLP  | 281      | 267         |
|                | 2011 | Benford  | African   | HB  | TaqMan    | 189      | 523         |
|                | 2010 | Wokoloreczyk | Caucasian | PB | PCR-RFLP | 690  | 602 |
|                | 2010 | Zheng    | Asian     | PB  | iPLEX     | 284      | 151         |
|                | 2010 | Xie      | Asian     | PB  | PCR-RFLP  | 120      | 120         |
|                | 2009 | Liu      | Asian     | HB  | TaqMan    | 391      | 323         |
|                | 2009 | Chen     | Asian     | PB  | TaqMan    | 340      | 337         |
|                | 2008 | Terada   | Asian     | HB  | PCR-RFLP  | 507      | 387         |
|                | 2008 | Salinas  | Caucasian | PB  | TaqMan    | 1252     | 1233        |
|                | 2008 | Cheng    | Caucasian | HB  | TaqMan    | 417      | 417         |
|                | 2008 | Cheng    | African   | HB  | TaqMan    | 89       | 89          |
|                | 2007 | Schumacher | Caucasian | PB | TaqMan | 11466 | 12888 |
|                | 2007 | Zheng    | Caucasian | HB  | iPLEX     | 1546     | 571         |
|                | 2007 | Suurinimi| Caucasian | PB  | TaqMan    | 582      | 538         |
|                | 2007 | Severi   | Caucasian | PB  | TaqMan    | 821      | 732         |
|                | 2007 | Wang     | Caucasian | PB  | TaqMan    | 491      | 545         |
| rs16901879(C>A) | Year | Surname | Ethnicity | SOC | Genotypic | Case (n) | Control (n) |
|                | 2015 | Geraldine| African   | PB  | TaqMan    | 489      | 534         |
|                | 2014 | Cheryl   | African   | PB  | iPLEX     | 320      | 310         |
|                | 2013 | Joung    | Asian     | HB  | iPLEX     | 289      | 144         |
|                | 2012 | Joung    | Asian     | HB  | iPLEX     | 194      | 169         |
|                | 2011 | Okobia   | African   | HB  | TaqMan    | 338      | 426         |
|                | 2010 | Chen     | Asian     | HB  | TaqMan    | 331      | 335         |
|                | 2010 | Benford  | African   | HB  | TaqMan    | 192      | 512         |
|                | 2010 | Xie      | Asian     | PB  | PCR-RFLP  | 120      | 120         |
|                | 2010 | Zheng    | Asian     | PB  | iPLEX     | 283      | 145         |

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Rs6983267 T>G and PCa risk

Twenty-seven studies that met the inclusion criteria were retrieved, including 21,351 PCa cases and 17,190 controls. The pooled risk estimates indicated the significant association between rs6983267 T>G and PCa susceptibility under allele model (OR=1.14, 95% CI=1.06-1.22), dominant model (OR=1.18, 95% CI=1.06-1.30), heterozygous model (OR=1.13, 95% CI=1.03-1.23), homozygous model (OR=1.31, 95% CI=1.13-1.51) and recessive model (OR=1.21, 95% CI=1.10-1.34) (Figure 2). Furthermore, when stratified by ethnicity, the results were significant in both Caucasians and Asians. In the subgroup by source of control, the results were significant in both population-based controls and hospital-based controls. In addition, stratification analysis by genotypic method showed the significant association with PCa risk only in TaqMan under all genetic models, while no significant association was found using PCR-RFLP and iPLEX method.

Rs1447295 C>A and PCa risk

The current meta-analysis includes 22,142 PCa cases and 22,294 controls from a total of twenty-seven case-control studies on rs1447295 C>A polymorphism and PCa risk. The pooled ORs of these studies were 1.25 (95% CI: 1.13-1.39) for allele model, 1.29 (95% CI: 1.14-1.45) for dominant model, 1.27 (95% CI: 1.13-1.43) for heterozygote model, 1.40 (95% CI: 1.07-1.82) for homozygote model, and 1.36 (95% CI: 1.09-1.69) for recessive model, which indicated a strong association between rs1447295 mutation and the susceptibility to PCa (Figure 3). Moreover, in the subgroup by ethnicity, significant associations were observed in Asian population and Caucasian population. For the subgroup by source of control, the result was significant only in population-based controls under all genetic models, while no significant result was found in hospital-based controls. The significant association was more prominent among these studies using iPLEX than TaqMan under most of genetic models (e.g. iPLEX with allele model (OR=1.52, 95% CI=1.08-2.14); dominant model (OR=1.59, 95% CI=1.13-2.24); and heterogeneity model (OR=1.54, 95% CI=1.13-2.10) vs. TaqMan with allele model (OR=1.25, 95% CI=1.11-1.40); dominant model (OR=1.31, 95% CI=1.16-1.48); and heterogeneity model (OR=1.31, 95% CI=1.17-1.48).

Rs16901979 C>A and PCa risk

Significant differences were found between rs16901979 C>A polymorphism and susceptibility of PCa under allele model (OR=1.30, 95% CI=1.20-1.40), dominant model (OR=1.42, 95% CI=1.27-1.58), heterozygous model (OR=1.36, 95% CI=1.21-1.52), homozygous model (OR=1.64, 95% CI=1.39-1.92), recessive model (OR=1.36, 95% CI=1.18-1.57) (Figure 4). In the stratification analysis by ethnicity, the significant PCa risk effects were observed in African, Asian, Caucasian population under all genetic models. Besides, when stratified by source of control, the positive results were detected in population-based controls and hospital-based controls. In addition, in the subgroup analysis by genotypic method, the results of studies were significant in TaqMan and iPLEX rather than Illumina 1M chip and PCR-RFLP.
Table 2. Meta-analysis results for the included studies of the association between 8q24 polymorphisms (rs6983267 T>G, rs1447295 C>A, rs16901979 C>A, rs6983561 A>C and rs10090154 C>T) and risk of prostate cancer.

| Variables | No. of studies | Allele model | Dominant model | Heterozygous model | Homozygous model | Recessive model |
|-----------|----------------|--------------|----------------|-------------------|------------------|----------------|
|          |                | rs6983267 T>G |                |                   |                  |                |
|          |                | T vs G        | (TG+GG) vs TT  | TG vs TT          | CG vs TT         | GG vs (TG+TT)  |
| All      | 27             | 1.14 (1.06, 1.22) | <0.001 | 73.7 | 1.18 (1.06, 1.23) | <0.001 | 64.4 |
| Ethnicty |                |              |                  |                   |                  |                |
| Caucasian| 13             | 1.14 (1.01, 1.28) | 0.01 | 83.9 | 1.17 (0.98, 1.39) | <0.001 | 80.1 |
| Asian    | 10             | 1.11 (1.00, 1.22) | <0.001 | 39.9 | 1.13 (1.02, 1.26) | 1.23 | <0.001 |
| African  | 2              | 1.17 (0.81, 1.68) | <0.01 | 0.1 | 1.35 (0.14, 13.32) | 19.48 | 0.11 |
| Mixed    | 2              | 1.25 (1.19, 1.38) | <0.01 | 0.1 | 1.25 (1.13, 1.48) | 0.482 | <0.01 |
| Source of control |               |              |                  |                   |                  |                |
| PB       | 16             | 1.12 (1.03, 1.21) | <0.001 | 78.3 | 1.16 (1.03, 1.31) | <0.001 | 73.3 |
| HB       | 11             | 1.18 (1.02, 1.37) | 0.01 | 66.1 | 1.20 (0.99, 1.47) | 0.215 | 25.8 |
| Method of genotype |               |              |                  |                   |                  |                |
| TaqMan   | 9              | 1.24 (1.12, 1.35) | 0.02 | 126.3 | 1.32 (1.13, 1.53) | 0.215 | 25.8 |
| PCR-RFLP | 9              | 1.02 (0.88, 1.19) | <0.001 | 79.1 | 0.91 (0.90, 1.30) | 0.087 | 67.1 |
| Illumina 1M chip | 2       | 1.34 (1.14, 1.27) | <0.001 | 80.1 | 1.37 (0.94, 2.01) | 1.27 | <0.001 |
| iPLEX    | 5              | 1.06 (0.89, 1.27) | 0.01 | 79.2 | 1.01 (0.80, 1.01) | 0.002 | 25.3 |
| GWAS     | 2              | 1.18 (1.01, 1.37) | 0.02 | 59.8 | 1.24 (1.13, 1.36) | <0.001 | 70.1 |
| rs1447295 |                |                |                  |                   |                  |                |
| C>A      | 27             | 1.25 (1.13, 1.39) | <0.001 | 78.6 | 1.29 (1.14, 1.45) | <0.001 | 77.5 |
| Ethnicty |                |              |                  |                   |                  |                |
| Caucasian| 12             | 1.52 (1.22, 1.76) | <0.001 | 86.0 | 1.22 (1.01, 1.46) | <0.001 | 85.9 |
| African  | 4              | 0.97 (0.86, 1.09) | 0.01 | 59.8 | 0.97 (0.84, 1.14) | 0.049 | <0.1 |
| Source of control |               |              |                  |                   |                  |                |
| PB       | 15             | 1.32 (1.20, 1.47) | 0.005 | 55.3 | 1.37 (1.23, 1.54) | <0.001 | 55.8 |
| HB       | 12             | 1.16 (0.91, 1.47) | 0.005 | 86.7 | 1.13 (0.85, 1.51) | 0.004 | 86.5 |
| Method of genotype |               |              |                  |                   |                  |                |
| PCR-RFLP | 8              | 1.11 (0.79, 1.56) | <0.001 | 87.5 | 0.98 (0.63, 1.53) | <0.001 | 88.9 |
| TaqMan   | 14             | 1.25 (1.11, 1.40) | <0.001 | 70.7 | 1.31 (1.16, 1.48) | <0.001 | 64.4 |
| iPLEX    | 4              | 1.52 (1.08, 2.14) | <0.001 | 83.5 | 1.59 (1.13, 2.20) | 0.005 | 76.6 |
| Illumina 1M chip | 1       | 1.71 (1.71) | <0.001 | 0.1 | 1.71 (1.71) | 0.005 | 76.6 |
| rtas16901979 |               |                |                  |                   |                  |                |
| C>A      | 11             | 1.30 (1.20, 1.35) | 0.01 | 35.3 | 1.42 (1.17, 1.58) | 0.125 | 34.2 |
| Ethnicty |                |              |                  |                   |                  |                |
| African  | 5              | 1.29 (1.17, 1.42) | 0.351 | 9.7 | 1.45 (1.25, 1.68) | 0.661 | <0.1 |
| Asian    | 5              | 1.27 (1.13, 1.46) | 0.057 | 56.3 | 1.36 (1.12, 1.58) | 0.027 | 63.6 |
| Caucasian| 1              | 1.83 (1.10, 3.04) | 0.03 | - | 1.91 (1.13, 3.24) | 0.001 | 0.1 |
| Source of control |               |              |                  |                   |                  |                |
| PB       | 2              | 1.28 (1.14, 1.42) | 0.066 | 58.3 | 1.46 (1.24, 1.72) | 0.144 | 44.5 |
| HB       | 2              | 1.31 (0.18, 1.46) | 0.232 | 25.8 | 1.39 (1.12, 1.61) | 0.144 | 37.3 |
| Method of genotype |               |              |                  |                   |                  |                |
| TaqMan   | 6              | 1.35 (1.22, 1.49) | 0.551 | <0.1 | 1.46 (1.27, 1.69) | 0.585 | <0.1 |
| iPLEX    | 3              | 1.29 (1.12, 1.48) | 0.033 | 70.6 | 1.36 (1.28, 1.91) | 0.146 | 48.0 |
| Illumina 1M chip | 1       | 0.97 (0.72, 1.32) | <0.01 | 0.1 | 0.86 (0.58, 1.29) | 0.81 | <0.1 |
| PCR-RFLP | 1              | 1.13 (0.76, 1.69) | 0.001 | 0.1 | 1.14 (0.69, 1.66) | 0.11 | <0.1 |

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Seven studies that met the inclusion criteria were retrieved, including 2,666 PCa cases and 2,855 controls. Significant association between rs6983561 A>C and PCa risk was observed by the pooled risk estimates under allele model (OR=1.41, 95% CI=1.27-1.57), dominant model (OR=1.50, 95% CI=1.31-1.71), heterozygous model (OR=1.42, 95% CI=1.23-1.63), homozygous model (OR=1.93, 95% CI=1.50-2.49) and recessive model (OR=1.64, 95% CI=1.30-2.08) (Figure 5). For subgroups by ethnicity, the results of these studies in Asians indicated the significant association with PCa risk under all genetic models. Similarly, stratified analysis by source of control detected a significant association in both population-based controls and hospital-based controls. Moreover, since all of the study number less than three for genotypic method, further analysis is not necessary.

Rs6983561 A>C and PCa risk

Rs10090154 C>T and PCa risk

The pooled risk estimates indicated the significant association between rs10090154 C>T and the risk of PCa under allele model (OR=1.46, 95% CI=1.28-1.67), dominant model (OR=1.62, 95% CI=1.40-1.88), heterozygous model (OR=1.66, 95% CI=1.42-1.93). However, no significant association was found under homozygous model (OR=1.18, 95% CI=0.72-1.93), recessive model (OR=1.02, 95% CI=0.62-1.66) (Figure 6). Stratification analyses by ethnicity also detected that rs10090154 polymorphism increased PCa risk in Asians and Caucasians. Besides, increased PCa susceptibility associated with rs10090154 was observed only in population-based studies. Stratification analyses by genotypic method
found that the meta-analysis results were significant in TaqMan, PCR-RFLP and iPLEX method, instead of PCR-HRM.

**Sensitivity analysis**

Individual studies were consecutively omitted in the sensitivity analysis to detect the influence of each study on the pooled OR. The sensitivity analysis for the results of 8q24 genetic polymorphisms and PCa risk demonstrated that the obtained results were statistically robust and no individual study affected the pooled OR significantly (Figure 7).

**Publication bias**

The Begg’s funnel plot and Egger’s test were adopted to evaluate the publication bias of articles in this meta-analysis. As illustrated in Figure 8, the shapes of funnel plot were symmetric, suggesting that there was no evidence of publication bias under dominant model in this meta-analysis. Therefore, our results were reliable according to the included articles.

**Discussion**

Chromosomal region 8q24 is a risk locus for a wide spectrum of cancers, and it is a risk region for PCa which has been investigated extensively. On the basis of racial differences and the fine-mapping study, 8q24 region contains at least three independent risk regions for PCa. Region 1 (126.54–128.62 Mb) was initially identified through a study of Icelandic families, which indicated that this region might confer risk of PCa and contribute to a higher incidence of PCa in Africa-American men than men of European ancestry [14]. Region 2 (128.14–128.28 Mb) contains a 14-SNP haplotype that efficiently tags a relatively uncommon (2–4%) susceptibility variant in individuals of European descent, which happens to be very common (42%) in Africa-American [54]. And region 3 (128.47–128.54 Mb) is defined as a recombination hot-spot among European Americans [47, 55]. Moreover, 8q24 is considered as a gene-free region, flanked by the FAM84B and MYC genes on the centromeric and telomeric ends respectively [55]. Though its biological significance in PCa is still unclear, some evidence in vitro and vivo experiments indicated that risk loci at 8q24 might be tissue-specific enhancers of MYC [15]. Especially, rs6983267 represents Region 1/Block 4 at 8q24 could be associated with MYC expression and CARLo-5, one of the long noncoding RNAs (CARLos) in the 8q24 region, is significantly related to the rs6983267 allele associated with increased cancer susceptibility [56]. However, their association with MYC expression in PCa is not conclusive and others failed to find clear association between rs6983267 genotype and MYC expression. Hence, more significant studies should be conducted to explore the function of these risk loci in the development of PCa.
Figure 3. Forest plot of the association between the rs1447295 C>A and prostate cancer risk. A: allele model; B: dominant model; C: heterozygote model; D: homozygote model; E: recessive model.

Figure 4. Forest plot of the association between the rs16901979 C>A and prostate cancer risk. A: allele model; B: dominant model; C: heterozygote model; D: homozygote model; E: recessive model.
Figure 5. Forest plot of the association between the rs6983561 A>C and prostate cancer risk. A: allele model; B: dominant model; C: heterozygote model; D: homozygote model; E: recessive model.

Figure 6. Forest plot of the association between the rs10090154 C>T and prostate cancer risk. A: allele model; B: dominant model; C: heterozygote model; D: homozygote model; E: recessive model.
Figure 7. Sensitivity analysis under the dominant model. A: rs6983267 T>G; B: rs1447295 C>A; C: rs16901979 C>A; D: rs6983561 A>C; E: rs10090154 C>T.

Figure 8. Begg’s funnel plot of publication bias test under the dominant model. A: rs6983267 T>G; B: rs1447295 C>A; C: rs16901979 C>A; D: rs6983561 A>C; E: rs10090154 C>T.

Although previous meta-analysis has explored the associations between these 8q24 polymorphisms and PCA risk, we conducted a more detailed analysis with a larger sample size that included the most up-to-date research. To the best of our knowledge, this is the largest meta-analysis containing 80 studies to investigate associations between the selected 8q24 polymorphisms and PCA risk. During the past few years, many case-control studies have demonstrated the strong associations of 8q24 polymorphisms with...
the susceptibility to PCa. Nevertheless, the findings were controversial [2,4-6]. For example, no significant association between rs6983267 polymorphism at 8q24 and PCa risk was found reported by Ren et al. [57]. However, Li et al. suggested that there is a significant PCa risk associated with the rs6983267 polymorphism at 8q24 [16]. As a powerful tool, meta-analysis was performed to provide a more comprehensive understanding of such associations compared to a single study, especially in analyzing unexplained studies. We took advantages of meta-analysis to prove the associations between 8q24 polymorphisms with PCa. According to quantitative synthesis results, all selected 8q24 polymorphisms (rs6983267 T>G, rs1447295 C>A, rs16901979 C>A, rs6983561 A>C and rs10090154 C>T) were found significant associations with PCa risk under the most assumed genetic models in this meta-analysis.

When stratified by ethnicity, significant association was found between all selected risk loci and PCa risk in Asians. Studies in Caucasians found significant association between rs6983267 T>G and rs1447295 C>A polymorphisms and PCa risk. Meanwhile, significant association between the rs16901979 C>A polymorphism and PCa risk was found in Africans, but as for rs1447295 C>A, the result is contrary, which is consistent with the results as reported by Okobia et al. [58]. The ethnic-specific findings indicated that racial differences might have a relationship with the association between 8q24 polymorphisms and the susceptibility of PCa [59]. Though the exact mechanism was unclear, it was likely that different ethnic groups with various genetic backgrounds might have different gene polymorphisms risk in the development of PCa. The observation of highly variable PCa rates by ethnicities provided benefits to disease gene detection [60]. However, the related articles to explain these genetic differences were still scarce. More studies should be undertaken to investigate evolutionary and population genetics relationships across ethnicities.

In the subgroup analysis by source of controls, rs1447295 C>A polymorphism showed significant association with PCa risk in the population-based control studies under all genetic models. While, no significant results were found in the hospital-based control studies under all genetic models. The possible reason might be that hospital-based controls might not have the similar representativeness of general populations. Meanwhile, when we selected the controls from hospitals, inherent selection biases might happen inevitably. Especially, the risk factors of PCa susceptibility were complex. Some ignored risk factors might interfere the results of this meta-analysis.

After stratified analysis by method of genotype, the significant results were observed in these studies using TaqMan method for all selected risk loci, while no significant results were found in these studies by PCR-RFLP method for rs6983267 T>G, rs1447295 C>A and rs16901979 C>A polymorphisms. One possible reason for these discrepancies was that different genotypic methods had their own benefits in diverse aspects, which might lead to different statistical results. PCR-RFLP, as a traditional detecting technology of genetic polymorphisms, can only detect part of the SNP, which makes sequencing time-consuming and laborious. Besides, the two-level structure of DNA chain is also likely to cause artificial false and sequencing result deviation [61, 62]. However, the advantages of TaqMan are that since the reaction is carried out in the PCR process, the separation and elution process is not needed, thus reducing the possibility of PCR pollution [62]. Accordingly, only applying the same appropriate genotypic method would make the results more significant and reliable in the detection of the selected genetic polymorphisms.

To a certain extent, several limitations of this meta-analysis should be considered. (1) Some published studies involved in the 8q24 polymorphisms are not accord with the HWE, resulting in potential bias during control selection or genotypic errors; (2) The number of included studies in the stratified analyses was relatively small. Though we did not make further discussion in the subgroups with less than three studies to avoid the false associations, it might potentially also limit the enough statistical power to explore the real relationship; (3) Adjusted estimates could not be conducted in this meta-analysis. Due to inadequate information, we failed to adjust estimates by other covariates, such as age, obesity, smoking, lifestyle and so on; (4) PCa is a multifactorial disease and complex interactions between genetic and environment factors, which may affect the occurrence and development of PCa. The investigation of single gene region cannot interpret the association of PCa risk comprehensively. Therefore, more attention should be paid to interactions of SNP-SNP, gene-gene, and gene-environment in future large multicentric studies.

**Conclusion**

In summary, the results of this meta-analysis suggested that five 8q24 polymorphisms (rs6983267 T>G, rs1447295 C>A, rs16901979 C>A, rs6983561 A>C and rs10090154 C>T) had strong associations with the susceptibility to PCa. Therefore, the 8q24 polymorphisms might be considered the ideal markers in PCa diagnosis and therapy, which is
worthy to exploring extensively in the subsequent studies. In addition, more high-quality and multicentric studies with larger sample sizes are needed to confirm these real associations.

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Competing Interests

The authors declared that no competing interest exists.

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