# Meta-Analysis of Genome-Wide and Replication Association Studies on Prostate Cancer

Hong Liu,[1] Bo Wang,[2] and Chunsheng Han[1]*

[1]State Key Laboratory of Reproductive Biology, Institute of Zoology, Chinese Academy of Sciences, Beijing, China
[2]Health Science Popularization Research Center, Chinese Academy of Medical Science, Beijing, China

**BACKGROUND.** Genome-wide and replication association studies (GWAs) have identified multiple loci at which common variants modestly influence the risk of developing prostate cancer (PCa). To enhance the power to identify loci associated with PCa, we constructed a meta-analysis of GWAs on PCa.

**METHODS.** Articles evaluating the effects of genome-wide SNPs on PCa were identified by searching the PubMed database. After extraction of relevant data, main and subgroup meta-analyses were performed to assess the effects of relevant SNPs on PCa.

**RESULTS.** 21 eligible articles containing 71 subgroups were included in this meta-analysis. Significant associations were found between 31 SNPs and PCa. They were rs445114, rs620861, rs983085, rs1016343, rs1447295, rs1859962, rs2660753, rs2710646, rs2735839, rs3760511, rs4242382, rs4430796, rs4962416, rs5945572, rs5945619, rs6470494, rs6501455, rs6983267, rs6983561, rs7000448, rs7214479, rs7501939, rs7920517, rs7931342, rs9364554, rs9623117, rs10090154, rs10486567, rs10896449, rs10993994, and rs16901979. The weighted odds ratios for above SNPs ranged between 0.64 and 1.88 (all $P < 0.05$). Subgroup analysis further indicated that the significant associations of some SNPs existed only in specific ancestry population ($P < 10^{-5}$).

**CONCLUSIONS.** The current meta-analysis demonstrated the moderate effects of above 31 SNPs on PCa and 14 independent PCa risk loci were identified. *Prostate 71: 209–224, 2011.* © 2010 Wiley-Liss, Inc.

*KEY WORDS:* **genome-wide association; prostate cancer; meta-analysis**

## INTRODUCTION

In developed countries, prostate cancer (PCa) is the most common noncutaneous malignancy in men [1]. Age, African ancestry, and a positive family history of disease are the only established risk factors [1]. Twin studies and epidemiologic observations have suggested a substantial genetic contribution to disease development [2]. Linkage, admixture mapping, and genome-wide studies have identified variants with moderate effects on PCa risk at multiple loci in the 8q24 region [3–7]. These loci account for a proportion of the increased risk for relatives of individuals with PCa which suggest that additional loci exist [8].

Genome-wide association studies (GWAs) are not inspecting on prior information relating to candidate genes or pathways, and thus are able to identity important variants in genes not reported so far. On the other hand, the effect sizes of individual variants, the need for strict thresholds for statistical significance, and financial constraints on numbers of variants that can be followed up limit study power unavoidably. To enhance the power to detect PCa risk loci, we conducted a meta-analysis of genome-wide and replication case–control association studies on PCa.

Grant sponsor: National Basic Research Program of China; Grant numbers: 2005CB522502, 2006CB944004.

*Correspondence to: Chunsheng Han, PhD, Division of Bioinformatics, State Key Laboratory of Reproductive Biology, Institute of Zoology, Chinese Academy of Sciences, Beijing 100101, China.
E-mail: hancs@ioz.ac.cn

Received 26 March 2010; Accepted 18 June 2010
DOI 10.1002/pros.21235
Published online 5 August 2010 in Wiley Online Library (wileyonlinelibrary.com).

## METHODS

### Criteria of Considering Studies for This Review

Studies were selected for analysis according to the following criteria:

**Types of studies.** We included genome-wide association studies. We excluded genome-wide linkage studies.

**Types of participants.** Participants involved any population in which PCa were epidemic. We defined ''PCa case'' referring to American Cancer Society guidelines, that is a digital rectal exam (DRE) and a serum prostate-specific antigen (PSA) >4 ng/ml [9,10]. We defined ''control'' as those who were free of PCa.

**Types of effect measures.** We included studies that used odds ratio (OR) as the measure of effects. Also, the included studies should provide genotype or allele frequency and sample size in case and control groups so that the allele-based OR value for each study could be calculated.

### Search Strategy for Identification of Studies

We searched the medical literature for genome-wide association studies on PCa. We searched PubMed database (National Library of Medicine, Bethesda, MD). Only published articles reported in English were considered. We did not specify any limitation on country, race, or publication year.

### Methods of the Review

First, we searched genome-wide association studies through title or abstract if needed. Then, based on the inclusion and exclusion criteria, eligible studies were screened out through abstract or full text when necessary.

The summary results and characteristics of included studies were tabled for analysis. The estimate of the principal effect was defined as OR of minor allele over major allele. In order to compute the pooled effects, each study was assigned a weight defined as the reciprocal of its variance.

Estimates of the ORs and 95% CIs (confidence intervals) were calculated using fixed-effect models or random-effect models according to the results of the heterogeneity tests. We presented the results of random-effect models if the tests for heterogeneity were significant. Otherwise, the results of fixed-effect models were presented.

The assumption of heterogeneity may suggest that the association of a SNP with PCa could be resulted from the diversity in ethnic origin, age, and family disease history. To validate this hypothesis, we further administered a subgroup analyses based on ethnic background. Finally, we checked publication bias by applying the funnel plots of the SE (standard error) against their relevant effect size. We employed RevMan 4.2 software (Cochrane Collaboration, Oxford, UK) to undertake heterogeneity tests and meta-analysis.

## RESULTS

### Characteristics of Included Studies

Though comprehensive searching we found 80 original articles. 59 articles that did not meet the inclusion criteria were excluded. We therefore performed a meta-analysis consisted of 21 eligible articles [5,7,11–29]. Table I shows the selected characteristics of the 21 studies that met the inclusion criteria. These articles included 71 subgroups according to participant cohort. Of all subgroups, 2 were executed in Asian descent populations (Chinese and Japanese American), 4 in African origin populations, and 65 in European descents. Eligible subgroups included 24 genome-wide association studies and 47 replication case–control studies. The ages of participants of included studies ranged from 8 to 105 years.

### Main Meta-Analysis

There were 37 SNPs in all reported in more than one included studies and were analyzed in this review (Table II). Using data from all PCa cases and controls of included studies, we obtained weighted OR and 95% CI, and associated *P*-value for each SNP. 31 SNPs, rs445114, rs620861, rs983085, rs1016343, rs1447295, rs1859962, rs2660753, rs2710646, rs2735839, rs3760511, rs4242382, rs4430796, rs4962416, rs5945572, rs5945619, rs6470494, rs6501455, rs6983267, rs6983561, rs7000448, rs7214479, rs7501939, rs7920517, rs7931342, rs9364554, rs9623117, rs10090154, rs10486567, rs10896449, rs10993994, and rs16901979, had statistical significance. The weighted ORs for above SNPs were ranged from 0.64 to 1.88 (all $P < 0.05$).

Figure 1 presented the weighted ORs (95% CIs) across the subgroups and the weights assigned to each subgroup for the 31 SNPs which showed significant associations with PCa in Table II. From the pooled samples, the weighted ORs for 9 SNPs of rs10486567, rs10486469, rs2735839, rs4430796, rs445114, rs620861, rs6983267, rs7931342, and rs983085 were ranged from 0.64 to 0.88 (all $P < 0.05$), therefore, these SNPs were significantly associated with PCa. And individuals carried minor allele of these SNPs may have a less risk to develop PCa compared with those major allele carriers. For the remaining 22 SNPs, the weighted ORs were ranged from 1.11 to 1.88 (all $P < 0.05$). So the

**TABLE I. Characteristics of Included Studies**

| Refs. | Cohort | Study name | General setting | Number of subjects | | Median age (range) | | Genotyping platform |
|---|---|---|---|---|---|---|---|---|
| | | | | Case | Control | Case | Control | |
| Gudmundsson et al. [5] | Iceland | Prostate, Lung, Colon and Ovarian Cancer Screening (PLCO) | Population-based case and control; GWA study | 1,453 | 3,064 | 71 (40–96) | 62 (22–97) | Illumina HumanHap300 SNP chip |
| Gudmundsson et al. [5] | The Netherlands | Nijmegen Biomedical Study | Population-based controls; Replication study | 367 | 1302 | 63 (49–83) | Match[a] | Centaurus (Nanogen) |
| Gudmundsson et al. [5] | Spain | Zaragoza Hospital Study | Hospital-based cases and controls; Replication study | 385 | 892 | 71 (45–83) | —[b] | Centaurus (Nanogen) |
| Gudmundsson et al. [5] | Chicago | Prostate Cancer Specialized Program of Research Excellence (SPORE) | Population-based controls; Replication study | 458 | 251 | 59 (39–77) | — | Centaurus (Nanogen) |
| Gudmundsson et al. [5] | Baltimore | The African American study | Hospital-based cases and controls; Replication study | 373 | 372 | 56 (36–74) | — | Centaurus (Nanogen) |
| Thomas et al. [11] | U.S. White | American Cancer Society Cancer Prevention Study II Nutrition Cohort (ACS) | Population-based controls; GWA study | 1,760 | 1,775 | 63 (40–92) | Match | iSelect Infinium assay (Illumina) |
| Thomas et al. [11] | Finland Caucasian | Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (ATBC) | Population-based cases and controls; GWA study | 929 | 921 | 50–69 | Match | iSelect Infinium assay (Illumina) |
| Thomas et al. [11] | French Paris, Brest, Nancy | French Prostate Cancer Case–Control Study (FPCC) | Population-based controls; GWA study | 656 | 657 | — | — | iSelect Infinium assay (Illumina) |
| Thomas et al. [11] | United States | Health Professional Follow -up Study (HPFS) | Population-based cases and controls; GWA study | 596 | 611 | 40–75 | Match | iSelect Infinium assay (Illumina) |
| Yeager et al. [7] | White, non-Hispanics European population | Prostate, Lung, Colon and Ovarian Cancer Screening (PLCO) | Population-based case and control; GWA study | 1,172 | 1,157 | 55–74 | Match | HumanHap 300; HumanHap 240; (Illumina) |
| Yeager et al. [7] | White U.S. | American Cancer Society Cancer Prevention Study II Nutrition Cohort (ACS) | Population-based cases and controls; Replication study | 1,150 | 1,151 | 63 (40–92) | Match | TaqMan |
| Yeager et al. [7] | Southwestern Finland | Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (ATBC) | Population-based cases and controls; Replication study | 896 | 894 | 50–69 | Match | TaqMan |

(*Continued*)

**TABLE I. (*Continued*)**

| Refs. | Cohort | Study name | General setting | Number of subjects | | Median age (range) | | Genotyping platform |
|---|---|---|---|---|---|---|---|---|
| | | | | Case | Control | Case | Control | |
| Yeager et al. [7] | French Paris, Brest, Nancy | French Prostate Cancer Case–Control Study (FPCC) | Population-based controls; Replication study | 455 | 459 | — | Match | TaqMan |
| Yeager et al. [7] | United States | Health Professional Follow-up Study (HPFS) | Population-based cases and controls; Replication study | 625 | 636 | 40–75 | Match | TaqMan |
| Gudmundsson et al. [12] | Iceland | Prostate, Lung, Colon and Ovarian Cancer Screening (PLCO) | population-based case and control; GWA study | 1,501 | 11,289 | 71 (40–96) | 67 (22–102) | Illumina Infinium HumanHap300 SNP Chip |
| Gudmundsson et al. [12] | Nijmegen, The Netherlands | Nijmegen Biomedical Study | Population-based controls; Replication study | 997 | 1,464 | 63 (43–83); 66 (43–75) | Match | Centaurus (Nanogen) |
| Gudmundsson et al. [12] | Zaragoza, Spain | Zaragoza Hospital Study | Hospital-based cases and controls; Replication study | 456 | 1,078 | 70 (44–83) | — | Centaurus (Nanogen) |
| Gudmundsson et al. [12] | Chicago | Prostate Cancer Specialized Program of Research Excellence (SPORE) | Population-based controls; Replication study | 536 | 514 | 59 (39–87) | — | Centaurus (Nanogen) |
| Duggan et al. [13] | Sweden | Cancer of the prostate in Sweden (CAPS) | Population-based cases and control; GWA study | 498 | 494 | — | Match | HumanHap500 Array set (Affymetrix) |
| Duggan et al. [13] | Iceland | Prostate, Lung, Colon and Ovarian Cancer Screening (PLCO) | Population-based case and control; GWA study | 737 | 1,105 | — | Match | HumanHap300 Bead Chip (Illumina) |
| Duggan et al. [13] | European American (JHH-EA) | Johns Hopkins Hospital Study (JHH) | Hospital-based cases and controls; Replication study | 1,558 | 1,142 | — | Match | MassyArray (Sequenom) |
| Duggan et al. [13] | African American (JHH-AA) | Johns Hopkins Hospital Study (JHH) | Hospital-based cases and controls; Replication study | 363 | 692 | — | Match | MassyArray (Sequenom) |
| Eeles et al. [14] | UK | UK Genetic Prostate Cancer Study (UK GPCS); ProtecT study; | Population-based cases and controls; GWA study | 1,854 | 1,894 | 36–88 | 50–71 | Illumina Infinium HumanHap550 array |
| Eeles et al. [14] | UK; Australia | Melbourne Collaborative Cohort Study (MCCS); Risk Factor for Prostate Cancer Study (RFPCS); Early Onset Prostate Cancer Study (EOPCS) | Population-based cases and controls; GWA study | 3,650 | 3,940 | 36–89 | Match | Illumina iSELECT |

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Eeles et al. [14] | Multiethnic studies | 21 | PRostate cancer AssoCiation group To Investigate Cancer Associated alterations in the genome (PRACTICAL Consortium) | Population- and Hospital-based; Replication study | 16,229 | 14,821 | — | — | TaqMan |
| Kote-Jarai et al. [15] | Multiethnic studies | 21 | PRostate cancer AssoCiation group To Investigate Cancer Associated aLterations in the genome (PRACTICAL Consortium) | Population- and Hospital-based; Replication study | 5,742 | 7,370 | — | — | TaqMan; Iplex Sequenon MassArray; SNPLex Genotyping System; |
| Hsu et al. [16] | Sweden | | The Cancer of the Prostate in Sweden (CAPS) | Population-based cases andcontrol; GWA study | 2,899 | 1,722 | — | Match | HumanHap500 Array set (Affymetrix) |
| Hsu et al. [16] | European descent | | Johns Hopkins Hospital Study (JHH) | Hospital-based case andcontrol; Replication study | 1,527 | 482 | — | — | iPLEX (Sequenom) |
| Hsu et al. [16] | Finland Caucasian | | Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (ATBC) | Population-based cases andcontrols; Replication study | 924 | 917 | 50–69 | Match | TaqMan |
| Hsu et al. [16] | French Paris, Brest, Nancy | | French Prostate Cancer Case–Control Study(FPCC) | Population-based controls; Replication study | 656 | 656 | — | Match | TaqMan |
| Hsu et al. [16] | United States | | Health Professional Follow-up Study (HPFS) | Population-based cases and controls; Replication study | 594 | 610 | 40–75 | Match | TaqMan |
| Hsu et al. [16] | Iceland | | Prostate, Lung, Colon and Ovarian Cancer Screening (PLCO) | Population-based case andcontrol; GWA study | 1,175 | 1,100 | 71 (40–96) | 62 (22–97) | Illumina HumanHap300 SNP chip |
| Hsu et al. [16] | White U.S. | | American Cancer Society Cancer Prevention Study II Nutrition Cohort (ACS) | Population-based cases andcontrols; Replication study | 1,759 | 1,774 | 63 (40–92) | Match | TaqMan |
| Yeager et al. [17] | European ancestry | | Cancer Genetic Markers of Susceptibility Project (CGEMS) | Population-based cases and controls; GWA study | 10,286 | 9,135 | 71 (40–96) | 62 (22–97) | Illumina HumanHap300 SNP chip |
| Eeles et al. [18] | UK | | UK Genetic Prostate Cancer Study (UK GPCS); | Population-based cases and controls; GWA study | 1,854 | 1,894 | 36–88 | 50–71 | Illumina Infinium HumanHap550 array |
| Eeles et al. [18] | UK | | UK Genetic Prostate Cancer Study (UK GPCS); ProtecT study; | Population-based cases and controls; GWA study | 1,960 | 2,104 | 36–89 | Match | TaqMan |

(*Continued*)

**TABLE I. (*Continued*)**

| Refs. | Cohort | Study name | General setting | Number of subjects | | Median age (range) | | Genotyping platform |
|---|---|---|---|---|---|---|---|---|
| | | | | Case | Control | Case | Control | |
| Eeles et al. [18] | Australia | Melbourne Collaborative Cohort Study (MCCS); Risk Factor for Prostate Cancer Study (RFPCS); Early Onset Prostate Cancer Study (EOPCS) | Population-based cases and controls; GWA study | 1,308 | 1,262 | 38–80 | Match | TaqMan |
| Gudmundsson et al. [19] | Iceland | Icelandic Cancer Registry (ICR) | Population-based cases and controls; GWA study | 1,968 | 35,227 | 40–96 | 8–105 | Infinium II assay; Sentrix HumanHap 300BeadChip; Centaurus |
| Gudmundsson et al. [19] | Chicago | Prostate Cancer Specialized Program of Research Excellence (SPORE) | Population-based controls; Replication study | 1,077 | 1,003 | 59(39–87) | — | — |
| Gudmundsson et al. [19] | Finland | Tampere University Hospital | Population-based controls; Replication study | 2,638 | 1,716 | 43.1–94.9 | — | — |
| Gudmundsson et al. [19] | The Netherlands | The Nijmegen Biomedical Study | Population-based control; Replication study | 1,084 | 1,827 | 43–83 | Match | — |
| Gudmundsson et al. [19] | Nashville | Vanderbilt University Medical Center; VA Tennessee Valley Healthcare System | Family-based cases and controls; Replication study | 596 | 687 | 60.3 | 63.0 | — |
| Gudmundsson et al. [19] | Spain | Zaragoza University Hospital | Hospital-based cases and controls; Replication study | 811 | 1,605 | 70 (44–83) | — | — |
| Gudmundsson et al. [19] | White U.S. | American Cancer Society Cancer Prevention Study II Nutrition Cohort (ACS) | Population-based cases andcontrols; Replication study | 1,758 | 1,775 | 63 (40–92) | Match | TaqMan |
| Gudmundsson et al. [19] | Finland Caucasian | Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (ATBC) | Population-based cases and controls; Replication study | 928 | 921 | 50–69 | Match | TaqMan |
| Gudmundsson et al. [19] | French Paris, Brest, Nancy | French Prostate Cancer Case–Control Study (FPCC) | Population-based controls; Replication study | 654 | 657 | — | Match | TaqMan |
| Gudmundsson et al. [19] | United States | Health Professional Follow-up Study (HPFS) | Population-based cases and controls; Replication study | 595 | 609 | 40–75 | Match | TaqMan |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| Gudmundsson et al. [19] | Iceland | Prostate, Lung, Colon and Ovarian Cancer Screening (PLCO) | Population-based case and control; GWA study | 1,167 | 1,093 | 71 (40–96) | 62 (22–97) | Illumina HumanHap300 SNP chip |
| Gudmundsson et al. [19] | Sweden | The Cancer of the Prostate in Sweden (CAPS) | Population-based cases and control; GWA study | 498 | 494 | — | Match | HumanHap500 Array set (Affymetrix) |
| Nam et al. [20] | Caucasian descent | Prostate Centers at the University of Toronto | Population-based cases and control; Replication study | 1,088 | 1,072 | | Match | Sequenom MassArray System |
| Sun et al. [21] | Sweden | The Cancer of the Prostate in Sweden (CAPS) | Population-based case and control; GWA study; Replication study | 2,836 | 1,678 | — | Match | Human Mapping 500K Array; Sequenom Iplex |
| Sun et al. [21] | European Americans | Johns Hopkins Hospital Study (JHH) | Hospital-based case and control; Replication study | 1,449 | 462 | — | Match | Sequenom Iplex |
| Sun et al. [21] | Finland Caucasian | Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (ATBC) | Population-based cases and controls; Replication study | 747 | 920 | 50–69 | Match | TaqMan |
| Sun et al. [21] | French Paris, Brest, Nancy | French Prostate Cancer Case–Control Study (FPCC) | Population-based controls; Replication study | 656 | 655 | — | Match | TaqMan |
| Sun et al. [21] | United States | Health Professional Follow-up Study (HPFS) | Population-based cases and controls; Replication study | 507 | 610 | 40–75 | Match | TaqMan |
| Sun et al. [21] | European descent | Prostate, Lung, Colon and Ovarian Cancer Screening (PLCO) | Population-based case and control; GWA study | 1,175 | 1,100 | 71 (40–96) | 62 (22–97) | HumanHap300; HumanHap240 assays (Illumina) |
| Sun et al. [21] | White U.S. | American Cancer Society Cancer Prevention Study II Nutrition Cohort (ACS) | Population-based cases and controls; Replication study | 1,595 | 1,775 | 63 (40–92) | Match | TaqMan |
| Olama et al. [22] | UK | UK Genetic Prostate Cancer Study (UK GPCS); ProtecT study; | Population-based cases and controls; GWA study | 1,854 | 1,894 | 36–88 | 50–71 | Illumina Infinium 550K array |
| Olama et al. [22] | UK; Australia | Melbourne Collaborative Cohort Study (MCCS); Risk Factor for Prostate Cancer Study (RFPCS); Early Onset Prostate Cancer Study (EOPCS) | Population-based cases and controls; GWA study | 3,650 | 3,940 | 36–89 | Match | Illumina Infinium array |
| Waters et al. [23] | African Americans | The Multiethnic Cohort Study | Population-based cases and controls; Replication study | 860 | 575 | 44–78 | 45–77 | Genomic DNA sample |
| Waters et al. [23] | European Americans | The Multiethnic Cohort Study | Population-based cases and controls; Replication study | 468 | 419 | 44–78 | 45–77 | Genomic DNA sample |

(*Continued*)

**TABLE I. (*Continued*)**

| Refs. | Cohort | Study name | General setting | Number of subjects | | Median age (range) | | Genotyping platform |
|---|---|---|---|---|---|---|---|---|
| | | | | Case | Control | Case | Control | |
| Waters et al. [23] | Latinos | The Multiethnic Cohort Study | Population-based cases and controls; Replication study | 603 | 572 | 44–78 | 45–77 | Genomic DNA sample |
| Waters et al. [23] | Japanese Americans | The Multiethnic Cohort Study | Population-based cases and controls; Replication study | 725 | 684 | 44–78 | 45–77 | Genomic DNA sample |
| Waters et al. [23] | Native Hawaiians | The Multiethnic Cohort Study | Population-based cases and controls; Replication study | 112 | 109 | 44–78 | 45–77 | Genomic DNA sample |
| Pal et al. [24] | European ancestry | Washington University School of Medicine | Population-based control; Replication study | 596 | 567 | 40–91 | Match | Applied Biosystem SNPlex; TaqMan |
| Ghoussaini et al. [25] | United Kingdom (UK) | UK Genetic Prostate Cancer Study (UK GPCS) | Population-based cases and control; Replication study | 1,854 | 1,894 | 36–88 | 50–71 | TaqMan |
| Hooker et al. [26] | African American | Howard University Hospital in Washingtin | Hospital-based cases and controls; Replication study | 454 | 301 | 40–85 | Match | Sequenom Iplex; Illumina GoldenGate |
| Zheng et al. [27] | Shanghai, China | Shanghai Cancer Institute | Population-based case and control; Replication study | 288 | 155 | >18 | Match | MassARRAY iPLEX (Sequenom) |
| Sun et al. [28] | European Americans | Johns Hopkins Hospital | Hospital-based cases and controls; Replication study | 1,563 | 576 | — | >55 | Sequenom Iplex |
| Sun et al. [28] | African Americans | Johns Hopkins Hospital | Hospital-based cases and controls; Replication study | 364 | 353 | — | >55 | Sequenom Iplex |
| Meyer et al. [29] | German | Hannover Medical School | Hospital-based cases and controls; Replicationn study | 488 | 462 | 42–82 | 20–71 | TaqMan |

[a]Match with control.
[b]No related information obtained from the original article.

**TABLE II. Summary of Results for 37 SNPs in Included GWA Studies on PCa**

| | | | | No. | Location | Allele | | GWA meta | | Replication meta | | All meta | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| ID | SNP name | Region[a] | Chr. | (study) | (bp) | Maj/Min | MAF[b] | OR (95% CI) | *P* | OR (95% CI) | *P* | OR (95% CI) | *P* | $P_{het}$[c] |
| 1 | rs10090154 | *8q24* | 8 | 3 | 128,081,119 | C/T | 0.088 | 1.72 (1.58,1.87) | <0.001 | 1.73 (1.19,2.51) | 0.004 | 1.72 (1.58,1.86) | <0.001 | 0.380 |
| 2 | rs1016343 | *8q24* | 8 | 4 | 128,162,479 | C/T | 0.196 | 1.30 (1.09,1.56) | 0.004 | 1.47 (1.19,1.83) | <0.001 | 1.36 (1.19,1.56) | <0.001 | 0.010 |
| 3 | rs10486567 | *JAZF1* | 7 | 12 | 27,749,803 | G/A | 0.254 | 0.72 (0.63,0.83) | <0.001 | 0.65 (0.53,0.81) | <0.001 | 0.68 (0.60,0.77) | <0.001 | <0.001 |
| 4 | rs10896469 | *11q13* | 11 | 6 | 68,751,243 | G/A | 0.475 | 0.64 (0.60,0.68) | <0.001 | 0.71 (0.57,0.87) | 0.001 | 0.64 (0.60,0.68) | <0.001 | 0.490 |
| 5 | rs10993994 | *MSMB* | 10 | 16 | 51,219,502 | C/T | 0.391 | 1.54 (1.09,1.27) | 0.010 | 1.28 (1.17,1.40) | <0.001 | 1.37 (1.19,1.58) | <0.001 | <0.001 |
| 6 | rs11649743 | *17q12* | 17 | 7 | — | G/A | 0.202 | 0.92 (0.84,1.00) | 0.060 | 1.08 (0.95,1.24) | 0.230 | 1.04(0.92,1.18) | 0.540 | 0.010 |
| 7 | rs13254738 | *8q24* | 8 | 2 | 128,173,525 | A/C | 0.330 | — | — | 1.20 (0.60,2.42) | 0.610 | 1.20 (0.60,2.42) | 0.610 | <0.001 |
| 8 | rs1447295 | *8q24* | 8 | 15 | 128,554,220 | C/A | 0.110 | 1.60 (1.49,1.71) | <0.001 | 1.46 (1.28,1.67) | <0.001 | 1.50 (1.36,1.64) | <0.001 | <0.001 |
| 9 | rs16901979 | *8q24* | 8 | 9 | 41,343,095 | C/A | 0.045 | 1.80 (1.61,2.00) | <0.001 | 1.68 (1.50,1.89) | <0.001 | 1.74 (1.60,1.88) | <0.001 | 0.160 |
| 10 | rs1859962 | *17q24.3* | 17 | 13 | 3,035,025 | T/G | 0.452 | 1.16 (1.10,1.22) | <0.001 | 1.17(1.11,1.23) | <0.001 | 1.16 (1.12,1.21) | <0.001 | 0.340 |
| 11 | rs2659056 | *KLK15/3* | 19 | 4 | 56,027,755 | A/G | 0.231 | 1.33 (1.20,1.48) | <0.001 | 0.97 (0.90,1.05) | 0.410 | 1.07 (0.88,1.31) | 0.490 | <0.001 |
| 12 | rs2660753 | *3P12.1* | 3 | 12 | 87,193,364 | C/T | 0.112 | 1.29 (0.96,1.75) | 0.100 | 1.12(1.04,1.21) | 0.003 | 1.15 (1.07,1.25) | <0.001 | 0.001 |
| 13 | rs2710646 | *EHBP1* | 2 | 2 | 63,046,530 | C/A | 0.202 | 1.13 (1.05,1.23) | 0.002 | 0.99 (0.59,1.68) | 0.980 | 1.13 (1.04,1.22) | 0.002 | 0.630 |
| 14 | rs2735839 | *KLK2/3* | 19 | 12 | 56,056,435 | G/A | 0.151 | 0.70 (0.44,1.11) | 0.130 | 0.88(0.78,0.99) | 0.040 | 0.85 (0.74,0.96) | 0.009 | <0.001 |
| 15 | rs3760511 | *17q12* | 17 | 6 | 1,380,465 | T/C | 0.334 | 1.17 (1.08,1.26) | <0.001 | 1.17 (1.09,1.26) | <0.001 | 1.17 (1.11,1.23) | <0.001 | 0.340 |
| 16 | rs4242382 | *8q24* | 8 | 6 | 128,586,755 | G/A | 0.138 | 2.18 (1.57,3.02) | <0.001 | 1.33 (1.02,1.72) | 0.030 | 1.88 (1.43,2.49) | <0.001 | <0.001 |
| 17 | rs4430796 | *HNF1B* | 17 | 18 | 33,172,153 | A/G | 0.485 | 0.67(0.57,0.80) | <0.001 | 0.79 (0.72,0.88) | <0.001 | 0.75 (0.68,0.82) | <0.001 | <0.001 |
| 18 | rs445114 | *8q24* | 8 | 9 | 128,392,363 | T/C | 0.341 | 0.86 (0.83,0.89) | <0.001 | 0.89 (0.85,0.94) | <0.001 | 0.87 (0.85,0.90) | <0.001 | 0.220 |
| 19 | rs4962416 | *CTBP2* | 10 | 7 | 126,686,862 | T/C | 0.225 | 1.28 (1.09,1.52) | 0.004 | 1.02 (0.77,1.35) | 0.880 | 1.25 (1.07,1.46) | 0.004 | <0.001 |
| 20 | rs5945572 | *NUDT10/11* | X | 7 | 51,062,719 | G/A | 0.357 | 1.22 (1.14,1.3) | <0.001 | 1.46 (1.33,1.59) | <0.001 | 1.38 (1.25,1.52) | <0.001 | 0.080 |
| 21 | rs5945619 | *NUDT11* | X | 6 | 51,258,412 | T/C | 0.349 | 1.45 (1.32,1.59) | <0.001 | 1.32 (1.13,1.54) | <0.001 | 1.35 (1.20,1.52) | <0.001 | <0.001 |
| 22 | rs620861 | — | — | 3 | 128,404,855 | C/T | 0.374 | 0.85 (0.79,0.92) | <0.001 | — | — | 0.85 (0.79,0.92) | <0.001 | 0.010 |
| 23 | rs6465657 | *LMTK2* | 7 | 12 | 97,654,263 | T/C | 0.451 | 1.16 (0.94,1.44) | 0.160 | 1.05 (0.92,1.21) | 0.440 | 1.08 (0.97,1.20) | 0.160 | <0.001 |
| 24 | rs6470494 | *8q24* | 8 | 2 | 128,157,086 | C/T | 0.280 | 1.14 (1.10,1.20) | <0.001 | 1.00 (0.83,1.20) | 0.990 | 1.14 (1.09,1.19) | <0.001 | 0.170 |
| 25 | rs6501455 | *17q24.3* | 17 | 6 | 3,128,083 | T/A | 0.512 | 1.16 (1.07,1.25) | <0.001 | 1.09 (0.96,1.23) | 0.190 | 1.11 (1.01,1.21) | 0.030 | 0.020 |
| 26 | rs6983267 | *8q24* | 8 | 15 | 128,482,487 | G/T | 0.463 | 0.68(0.59,0.77) | <0.001 | 0.76 (0.65,0.89) | <0.001 | 0.71 (0.65,0.78) | <0.001 | <0.001 |
| 27 | rs6983561 | *8q24* | 8 | 4 | 128,176,062 | A/C | 0.034 | 1.71 (1.49,1.96) | <0.001 | 2.04 (1.70,2.45) | <0.001 | 1.82 (1.63,2.03) | <0.001 | 0.350 |
| 28 | rs7000448 | *8q24* | 8 | 2 | 128,510,352 | G/A | 0.356 | — | — | 1.40 (1.28,1.53) | <0.001 | 1.40 (1.28,1.53) | <0.001 | 0.500 |
| 29 | rs721048 | *EHBP1* | 2 | 7 | 63,043,382 | G/A | 0.086 | — | — | 0.99 (0.74,1.33) | 0.960 | 0.99 (0.74,1.33) | 0.960 | <0.001 |
| 30 | rs7214479 | *17q24.3* | 17 | 6 | 3,117,221 | C/T | 0.413 | 1.16 (1.07,1.25) | <0.001 | 1.17 (1.09,1.25) | <0.001 | 1.16 (1.11,1.23) | <0.001 | 0.960 |
| 31 | rs7501939 | *HNF1B* | 17 | 7 | 33,175,269 | T/C | 0.575 | 1.17 (1.08,1.26) | <0.001 | 1.21 (1.13,1.29) | <0.001 | 1.19 (1.13,1.25) | <0.001 | 0.350 |
| 32 | rs7920517 | *MSMB* | 10 | 4 | 3,117,221 | A/G | 0.475 | 1.40(1.28,1.54) | <0.001 | 1.18(1.06,1.31) | 0.003 | 1.23 (1.10,1.38) | <0.001 | 0.009 |
| 33 | rs7931342 | *11q13.2* | 11 | 10 | 68,751,073 | G/T | 0.497 | 0.79 (0.72,0.86) | <0.001 | 0.85(0.71,1.01) | 0.070 | 0.84 (0.72,0.97) | 0.020 | <0.001 |
| 34 | rs902774 | *CpG* | 12 | 4 | 51,560,171 | G/A | 0.140 | 1.39 (1.23,1.57) | <0.001 | 1.02 (0.89,1.16) | 0.810 | 1.09 (0.89,1.33) | 0.400 | <0.001 |
| 35 | rs9364554 | *SLC22A3* | 6 | 12 | 160,804,075 | C/T | 0.297 | 1.14 (1.07,1.20) | <0.001 | 1.18 (1.13,1.23) | <0.001 | 1.17 (1.13,1.20) | <0.001 | 0.240 |
| 36 | rs9623117 | *22q13* | 22 | 8 | — | T/C | 0.208 | 1.12 (0.98,1.27) | 0.090 | 1.13 (1.03,1.24) | 0.010 | 1.12 (1.05,1.21) | 0.001 | 0.040 |
| 37 | rs983085 | *17q24.3* | 17 | 3 | 66,723,656 | A/C | 0.497 | 0.87 (0.81,0.94) | <0.001 | 0.90 (0.80,1.01) | 0.060 | 0.88 (0.83,0.94) | <0.001 | 0.680 |

[a]SNPs are included in the region of a gene if they are located within 20 kb of its transcription start site or within 10 kb from its last exon.
[b]MAF, minor allele frequency in controls (minor allele are defined based on European populations).
[c]*P*-value for heterogeneity test.

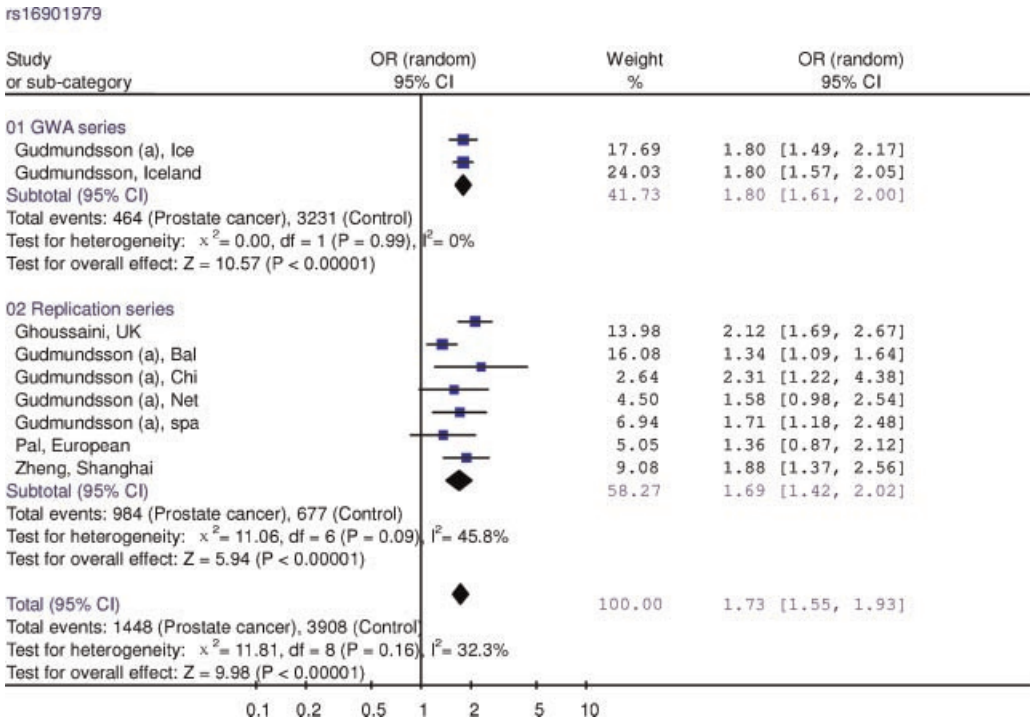


**Fig. 1.** Forest plots of effect size and direction for SNPs associated with prostate cancer. Boxes denote allelic OR point estimate, their areas being proportional to the inverse variance weight of the estimate. Horizontal lines represent 95% CIs. The diamond represents the summary OR computed under a random-effect model or fixed-effect model, with the 95% CI given by its width. The unbroken vertical line is at the null value (OR = 1.0).

minor alleles of these SNPs may be a risk factor for PCa development.

### Subgroup Analysis

Since the associations between some SNPs examined in this review and PCa risk showed evidence of between-study heterogeneity (heterogeneity tests, all $P < 0.10$), subgroup analysis were executed. Table III summarized the pooled estimates of weighted ORs in subgroups according to included participants' ethnicity origin. The associations of rs5945572, rs5945619, and rs6983267 with PCa were not found to be significant in Asian decent group (all $P > 0.05$). The associations of rs10993994, rs1447295, rs2735839, and rs4242382 were not significant in African descent populations (all $P > 0.05$), and the associations of rs2660753, rs4430796, rs4962416, and rs7920517 were only significant in European origin participants (all $P < 0.05$). The association between rs6501455 and PCa development disappeared in ethnicity subgroup analysis ($P > 0.05$).

### Publication Bias

The funnel plots (data not shown) showed that the ORs for SNPs examined here seemed to be symmetry which suggested that the effects of publication bias were perhaps negligible in the current meta-analysis.

## DISCUSSION

By combining data from published GWAs and replication case–control studies, we have confirmed 31 SNPs (namely rs10090154, rs1016343, rs10486567, rs10896449, rs10993994, rs1447295, rs16901979, rs1859962, rs2660753, rs2710646, rs2735839, rs3760511, rs4242382, rs4430796, rs5945572, rs5945619, rs620861, rs6470494, rs6501455, rs6983267, rs6983561, rs7000448, rs7214479, rs7501939, rs7920517, rs7931342, rs9364554, rs9623117, and rs983085) impacting PCa susceptibility which have significance to public health. When we combined all of the original data according to participants' ethnic origin, the associations of some SNPs with PCa were evident in different ethnic groups. This suggested more that the variation may play a role in PCa development whereas it would be restricted to some ethnic group, rather than having a wide effect, as was also supported by the evidence that ethnicity is a confirmed impact factor of PCa [1]. The funnel plots analysis suggested that the effects of publication bias were probably minimal in current meta-analysis. Hence, the effects of these variations on PCa were

**TABLE III. The Pooled Estimates of OR Based on Subgroup of Ethnicity**

| Variables | Asian descent | | | | African descent | | | | European descent | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Study | OR (95% CI) | *P*-value | $P_{het}$ [a] | Study | OR (95% CI) | *P*-value | $P_{het}$ [a] | Study | OR (95% CI) | *P*-value | $P_{het}$ [a] |
| rs1016343 | 1 | 1.69 (1.27,2.25) | <0.001 | — | — | — | — | — | 3 | 1.31 (1.15,1.50) | <0.001 | 0.020 |
| rs10486567 | 2 | 0.50 (0.29,0.85) | 0.010 | 0.020 | 2 | 0.83 (0.72,0.95) | 0.007 | 0.390 | 8 | 0.70 (0.63,0.79) | <0.001 | <0.001 |
| rs10993994 | 2 | 1.50 (1.26,1.80) | <0.001 | 0.220 | 2 | 1.10 (0.97,1.25) | 0.130 | 0.560 | 11 | 1.40 (1.14,1.73) | 0.001 | <0.001 |
| rs13254738 | 1 | 1.74 (1.27,2.39) | 0.006 | — | — | — | — | — | 1 | 0.85 (0.77,0.94) | 0.002 | — |
| rs1447295 | 1 | 1.56 (1.08,2.25) | 0.020 | — | 1 | 1.01 (0.81,1.26) | 0.940 | — | 13 | 1.45 (1.33,1.58) | <0.001 | 0.010 |
| rs2660753 | 2 | 1.22 (0.85,1.75) | 0.290 | 0.030 | 2 | 0.99 (0.87,1.13) | 0.910 | 0.290 | 7 | 1.20 (1.08,1.32) | <0.001 | 0.050 |
| rs2735839 | 2 | 0.78 (0.65,0.92) | 0.004 | 0.240 | 2 | 1.05 (0.60,1.84) | 0.870 | <0.001 | 7 | 0.80 (0.68,0.94) | 0.008 | <0.001 |
| rs4242382 | 1 | 1.58 (1.11,2.25) | 0.010 | — | 1 | 1.20 (0.96,1.50) | 0.110 | — | 4 | 2.18 (1.57,3.02) | <0.001 | <0.001 |
| rs4430796 | 2 | 0.93 (0.81,1.07) | 0.340 | 0.800 | 3 | 0.87 (0.72,1.05) | 0.160 | 0.050 | 13 | 0.70 (0.64,0.78) | <0.001 | <0.001 |
| rs4962416 | 1 | 1.89 (0.39,9.18) | 0.430 | — | 1 | 1.00 (0.76,1.33) | 0.990 | — | 5 | 1.28 (1.09,1.52) | 0.004 | <0.001 |
| rs5945572 | 1 | 1.28 (0.99,1.66) | 0.060 | — | 2 | 1.52 (1.32,1.74) | <0.001 | 0.950 | 4 | 1.26 (1.19,1.34) | <0.001 | 0.170 |
| rs5945619 | 1 | 1.54 (0.88,2.69) | 0.130 | — | 1 | 1.34 (1.08,1.65) | 0.007 | — | 3 | 1.28 (1.11,1.47) | <0.001 | 0.002 |
| rs6501455 | — | — | — | — | 1 | 1.10 (0.88,1.38) | 0.400 | — | 5 | 1.10 (1.00,1.22) | 0.060 | 0.009 |
| rs6983267 | 1 | 0.89 (0.68,1.18) | 0.430 | — | — | — | — | — | 13 | 0.72 (0.65,0.79) | <0.001 | <0.001 |
| rs7920517 | — | — | — | — | 1 | 0.94 (0.74,1.20) | 0.630 | — | 3 | 1.21 (1.03,1.43) | 0.020 | 0.003 |
| rs7931342 | 1 | 2.30 (1.87,2.82) | <0.001 | — | 2 | 0.85 (0.73,0.98) | 0.030 | 0.670 | 6 | 0.74 (0.66,0.83) | <0.001 | <0.001 |

[a]*P*-value for heterogeneity test.

ethnically heterogeneous indeed. However, it was possible that the data obtained may have been inadequate to detect an association due to the small number of included studies as only 4 subgroups were executed in African descent population and 2 in Asian origins. For example, in subgroup analysis, the association of SNP rs6501455 with PCa did not reach the statistical significance ($P > 0.05$), while it was significant in pooled analysis [weighted OR = 1.11 (1.01, 1.21), $P = 0.03$].

Table II indicated that there were 14 independent risk loci for PCa risk. The locus and the corresponding SNPs are as follows.

| Locus | SNP |
|---|---|
| *8q24* | rs10090154, rs1016343, rs1447295, rs16901979, rs4242382, rs445114, rs6470494, rs6983267, rs6983561, rs7000448 |
| *17q24.3* | rs1859962, rs6501455, rs7214479, rs983085 |
| *11q13* | rs10896469, rs7931342 |
| *MSMB* | rs10993994, rs7920517 |
| *HNF1B* | rs4430796, rs7501939 |
| *NUDT10/11* | rs5945572, rs5945619 |
| *17q12* | rs3760511 |
| *KLK2/3* | rs2735839 |
| *JAZF1* | rs10486567 |
| *3p12.1* | rs2660753 |
| *EHBP1* | rs2710646 |
| *CTBP2* | rs4962416 |
| *SLC22A3* | rs9364554 |
| *22q13* | rs9623117 |

8q24 is the most frequently gained chromosomal region in prostate tumors [30]. rs1447295 is the most reported SNP on 8q24. rs6983267 is 70 kb centromeric to rs1447295, but they are not linkage disequilibrium (LD) [7]. rs16901979 and rs1447295 are separated by about 300 kb in the genome and are located in distinct LD blocks [5]. rs16901979 and rs6983561 are highly correlated, rs7000448 is weakly correlated with rs6983267 and rs1447295, rs10090154 is perfectly correlated with rs1447295 [25]. rs4242382 is in strong LD with rs1447295 [3–7]. rs1016343 and rs6983561 are weakly correlated [22]. rs4242382 and rs6983267 are LD [11]. r6470494 and rs1016342 are of the 14 SNP HapC, while HapC is located in a different LD block about 300 kb upstream from rs1447295, rs16901979 is strongly correlated with HapC [5].

The known genes that are closest to 8q24 are *FAM84B* and *c-MYC*. rs1447295 is 263 kb telomeric to the oncogene *c-MYC*. Overexpression of *c-MYC* occurs in both breast and PCa [31–33], and reduction of *c-MYC* expression inhibits tumor growth both in vivo and in vitro [34]. FAM84B is a breast cancer

membrane-associated protein, little is known about its function [32]. Although SNPs located in the *c-MYC* and *FAM84B* genes were not found to be associated with PCa [3–5,35], it is possible that the risk variant modifies *c-MYC* regulation by predisposing to genomic instability or altering long-range regulation of expression. Several other genes were predicted to exist in 8q24 [3,36], although there is no evidence for any protein-coding transcripts. One is a pseudogene of transcription factor POU5F1P1. Study has confirmed the expression of this transcript in cancer tissues, including colon cancer, although its physiological role is unknown [37]. rs445114 is correlated with the breast cancer variant rs13281615 [35]. rs445114 show very little correlation with any of the previously published prostate[3,5–7], colon [36–39] or bladder cancer [39] risk variants on 8q24 [19]. Tuupanen et al. [40] showed that rs6983267 affects a binding site for TCF4 and may enhance Wnt signaling, suggesting that other mechanisms may be important.

Gain in 8q24 region has been associated with aggressive tumors, hormone independence, and poor prognosis [41]. Although this region is frequently amplified in prostate tumors, it covered few known or predicted genes [33,42]. Hence, either there are multiple functional variants in the region, or these alleles are in strong LD with a presently unknown risk variant. Further work are needed to identify common and uncommon variants to determine the optimal candidates for functional studies designed to confirm the causal variants in the 8q24 region.

The SNP rs10486567 located on chromosome 7 is in the second intron of the JAZF zinc finger 1 gene (*JAZF1*). *JAZF1* encodes a three C2-H2-type zinc finger protein that is a transcriptional repressor of *NR2C2* (a nuclear orphan receptor that is highly expressed in prostate tissue) and interacts with the androgen receptor. *JAZF1* is a component of a fusion gene with *SUZ12* (also known as *JJAZ1*) which was found in endometrial stromal tumors [43].

rs10993994 and rs7920517 lie in a ~100-kb LD block on chromosome 10 which contains the microseminoprotein beta gene (*MSMB*). rs10993994 resides 2 bp upstream of the transcription start site of *MSMB* and functionally alters gene expression in vitro [44]. *MSMB* encodes PSP94, a 10.7-kDa nonglycosylated cysteine-rich protein that is a member of the immunoglobulin binding factor family synthesized by epithelial cells in the prostate and secreted into seminal plasma. Loss of expression of PSP94 is associated with recurrence after radical prostatectomy [45]. PSP94 and PSPBP (its binding protein in serum) are potential serum markers for early detection of high-grade PCa [45,46]. *MSMB* can be silenced by *EZH2* (transcriptional repressor) in advanced, androgen-insensitive PCa [47]. So variants in *MSMB* may predispose to PCa by altered gene expression.

SNP rs2735839 lies between the *KLK2* (encoding hK2) and *KLK3* (encoding PSA protein [18,48]) genes which have been reported to influence PCa risk [49,50]. PSA is a serine protease that liquefies semen and is used as a serum marker in screening and disease monitoring. There are also evidence that hK2 may also be useful for screening and prognosis [51,52]. Multiple SNPs in the promoter region of *KLK3* have been associated with PSA concentrations [49,53], and some have been suggested to be associated with risk of PCa [49,50].

rs4430796 and rs7501939 on 17q12 are located in the first and second intron of the *HNF1B* (a transcription factor, *TCF2*) gene, respectively. A third SNP rs3760511 lays ~1.2 kb upstream of the first exon of *TCF2*. rs7501939 and rs3760511 are in weak LD. Although sequence variants in *TCF2* have not been implicated in the risk of PCa, more than 50 different exonic *TCF2* mutations have been reported in individuals with renal cysts, maturity-onset diabetes of the young type 5 (MODY5), pancreatic atrophy, and genital tract abnormalities [54,55].

rs4962416 is in the fifth intron of *CTBP2* which encodes a member of the C-terminal binding protein (CTBP) family that known to be transcriptional co repressors activated under metabolic stress. CTBP2 is highly expressed in prostate tissue, and its expression is associated with decreased *PTEN* expression and activation of the phosphatidylinositol 3-kinase pathway [56].

rs5945619 and rs5945572 are highly correlated [19]. rs5945619 is in a ~2-Mb LD block on Xp between *NUDT10* and *NUDT11* (nucleoside diphosphate linked moiety X-type motif 11) that is about 2 kb upstream of the latter. Eeles et al. [18] observed a weaker association with PSA concentrations, again in the same direction of PCa. rs5945572 located downstream of the *NUDT11* gene which was associated with increased PCa risk. These genes encode isoforms of diphosphoinositol polyphosphate phosphohydrolase that determine the rate of phosphorylation in DNA repair, stress responses, and apoptosis [57].

rs9364554 is in intron 5 of *SLC22A3*, one of the solute carrier family 22 (organic cation transporter, OCT) genes, and OCTs are critical for elimination of some drugs and environmental toxins.

rs9623117 is less than 2 kb from rs7291619 on 22q13 and is in strong LD with it. The two SNPs are within the *TNRC6B* gene. TNRC6B (trinucleotide repeat-containing gene 6b), a RNA recognition motif (RRM)-containing protein, were localized to the mRNA-degrading cytoplasmic P bodies, is functionally required to mediate miRNA-guided mRNA cleavage [58]. TNRC6B is expressed in many normal

tissues, including the prostate. TNRC6B expression was suppressed in hormone-refractory metastatic PCa compared to prostate carcinoma. Alteration in *TNRC6B* gene expression due to genetic variations might perturb the levels of mRNA species normally under its control and therefore contribute to carcinogenesis.

rs10896469 and rs7931342 lie in an LD block of 70 kb on chromosome 11 that is a gene desert [11,18]. The closest gene from rs10896449 is *MYEOV*, located ~67 kb away, and its expression has been shown to be unfavorable in multiple myeloma [59].

rs1859962, rs6501455, rs7214479, and rs983085 fall within a strong LD block on 17q24.3. rs3760511 is in weak LD with rs7501939. The two loci on 17q12 and 17q24.3 are separated by approximately 33 Mb and no LD were observed between them [12]. rs2660753 is in a gene-poor region on chromosome 3. SNP rs2710647 is within the *EHBP1* gene on 2p15 [14]. The next work should be to confirm the true causal variants or find other more SNPs related with PCa on these loci.

There are three limitations deserving consideration in our systematic review. First, the results of meta-analysis in this review came from heterogeneous data obtained from GWAs. Discrepancy in study characteristics, such as age group, ethnicity, and family disease history, might have contributed to heterogeneity among included studies. But, we believed that it was feasible and proper to integrate data from heterogeneous studies in random-effect meta-analyses because each study answered the same question of genome-wide SNPs' effects on PCa. We also undertook subgroup analyses to explore whether ethnicity factor contributed to heterogeneity or not. Second, because included studies did not examined uniform set of SNPs, we could only combine data from the studies which reported results for the same SNP to assess the effect of each SNP on PCa. Third, most of all included studies were implemented in developed countries, and only a few studies were executed in Asian and African descent populations. Much more studies are required to confirm the associations of the SNPs examined in this review with PCa in other groups other than in European descent only.

From Table II, we can see that a high proportion of the population carried at-risk alleles, whereas individual alleles afford only small effects, much larger risks are seen in carriers of multiple risk alleles [8]. Therefore, the SNPs validated here potentially have public health purport when more susceptibility loci are identified. Additional researches are required to characterize genetic variations at these loci and ascertain their relationships with the functional consequences that leading to PCa. Further efforts to broaden the scale of GWAs meta-analyses, involved both sample size and SNP coverage, and to increase the number of SNP applied to large-scale replication, may identify additional variants for PCa.

## CONCLUSION

The current meta-analysis, using GWAs and replication studies, displayed significant associations of 31 SNPs (rs445114, rs620861, rs983085, rs1016343, rs1447295, rs1859962, rs2660753, rs2710646, rs2735839, rs3760511, rs4242382, rs4430796, rs4962416, rs5945572, rs5945619, rs6470494, rs6501455, rs6983267, rs6983561, rs7000448, rs7214479, rs7501939, rs7920517, rs7931342, rs9364554, rs9623117, rs10090154, rs10486567, rs10896449, rs10993994, rs16901979) with PCa. However, the associations of some SNPs with PCa were significant only in specific descent population. Thus, the pooled results supported the hypothesis that the effect of genetic factor on PCa may be heterogeneous among different ethnic populations. We also confirmed 14 independent PCa risk loci which are *8q24*, *MSMB*, *HNF1B*, *NUDT10/11*, *KLK2/3*, *JAZF1*, *CTBP2*, *SLC22A*, *EHBP1*, *33p12.1*, *11q13*, *17q24.3*, *17q12*, and *22q13*.

## ACKNOWLEDGMENTS

We thank Pro Yonghua Hu (School of Public Health, Peking University, China) and Pro Siyan Zhan (School of Public Health, Peking University, China) for consultation and assistance in this system review. None of the authors had any conflicts of interest. This study was supported by the National Basic Research Program of China (2005CB522502 and 2006CB944004).

## REFERENCES

1. Crawford ED. Epidemiology of prostate cancer. Urology 2003;62(6 Suppl 1):3–12.
2. Steinberg GD, Carter BS, Beaty TH, Childs B, Walsh PC. Family history and the risk of prostate cancer. Prostate 1990;17(4):337–347.
3. Amundadottir LT, Sulem P, Gudmundsson J, Helgason A, Baker A, Agnarsson BA, Sigurdsson A, Benediktsdottir KR, Cazier JB, Sainz J, Jakobsdottir M, Kostic J, Magnusdottir DN, Ghosh S, Agnarsson K, Birgisdottir B, Le Roux L, Olafsdottir A, Blondal T, Andresdottir M, Gretarsdottir OS, Bergthorsson JT, Gudbjartsson D, Gylfason A, Thorleifsson G, Manolescu A, Kristjansson K, Geirsson G, Isaksson H, Douglas J, Johansson JE, Balter K, Wiklund F, Montie JE, Yu X, Suarez BK, Ober C, Cooney KA, Gronberg H, Catalona WJ, Einarsson GV, Barkardottir RB, Gulcher JR, Kong A, Thorsteinsdottir U, Stefansson K. A common variant associated with prostate cancer in European and African populations. Nat Genet 2006;38(6):652–658.
4. Freedman ML, Haiman CA, Patterson N, McDonald GJ, Tandon A, Waliszewska A, Penney K, Steen RG, Ardlie K, John EM, Oakley-Girvan I, Whittemore AS, Cooney KA, Ingles SA, Altshuler D, Henderson BE, Reich D. Admixture mapping identifies 8q24 as a prostate cancer risk locus in African-American men. Proc Natl Acad Sci USA 2006;103(38):14068–14073.

5. Gudmundsson J, Sulem P, Manolescu A, Amundadottir LT, Gudbjartsson D, Helgason A, Rafnar T, Bergthorsson JT, Agnarsson BA, Baker A, Sigurdsson A, Benediktsdottir KR, Jakobsdottir M, Xu J, Blondal T, Kostic J, Sun J, Ghosh S, Stacey SN, Mouy M, Saemundsdottir J, Backman VM, Kristjansson K, Tres A, Partin AW, Albers-Akkers MT, Godino-Ivan Marcos J, Walsh PC, Swinkels DW, Navarrete S, Isaacs SD, Aben KK, Graif T, Cashy J, Ruiz-Echarri M, Wiley KE, Suarez BK, Witjes JA, Frigge M, Ober C, Jonsson E, Einarsson GV, Mayordomo JI, Kiemeney LA, Isaacs WB, Catalona WJ, Barkardottir RB, Gulcher JR, Thorsteinsdottir U, Kong A, Stefansson K. Genome-wide association study identifies a second prostate cancer susceptibility variant at 8q24. Nat Genet 2007;39(5):631–637.

6. Haiman CA, Patterson N, Freedman ML, Myers SR, Pike MC, Waliszewska A, Neubauer J, Tandon A, Schirmer C, McDonald GJ, Greenway SC, Stram DO, Le Marchand L, Kolonel LN, Frasco M, Wong D, Pooler LC, Ardlie K, Oakley-Girvan I, Whittemore AS, Cooney KA, John EM, Ingles SA, Altshuler D, Henderson BE, Reich D. Multiple regions within 8q24 independently affect risk for prostate cancer. Nat Genet 2007;39(5):638–644.

7. Yeager M, Orr N, Hayes RB, Jacobs KB, Kraft P, Wacholder S, Minichiello MJ, Fearnhead P, Yu K, Chatterjee N, Wang Z, Welch R, Staats BJ, Calle EE, Feigelson HS, Thun MJ, Rodriguez C, Albanes D, Virtamo J, Weinstein S, Schumacher FR, Giovannucci E, Willett WC, Cancel-Tassin G, Cussenot O, Valeri A, Andriole GL, Gelmann EP, Tucker M, Gerhard DS, Fraumeni JF, Jr., Hoover R, Hunter DJ, Chanock SJ, Thomas G. Genome-wide association study of prostate cancer identifies a second risk locus at 8q24. Nat Genet 2007;39(5):645–649.

8. Schaid DJ. The complex genetic epidemiology of prostate cancer. Hum Mol Genet 2004;13 (Spec No 1):R103–R121.

9. Smith RA, Cokkinides V, Eyre HJ. American Cancer Society guidelines for the early detection of cancer, 2003. CA Cancer J Clin 2003;53(1):27–43.

10. Carroll P, Coley C, McLeod D, Schellhammer P, Sweat G, Wasson J, Zietman A, Thompson I. Prostate-specific antigen best practice policy—Part I: Early detection and diagnosis of prostate cancer. Urology 2001;57(2):217–224.

11. Thomas G, Jacobs KB, Yeager M, Kraft P, Wacholder S, Orr N, Yu K, Chatterjee N, Welch R, Hutchinson A, Crenshaw A, Cancel-Tassin G, Staats BJ, Wang Z, Gonzalez-Bosquet J, Fang J, Deng X, Berndt SI, Calle EE, Feigelson HS, Thun MJ, Rodriguez C, Albanes D, Virtamo J, Weinstein S, Schumacher FR, Giovannucci E, Willett WC, Cussenot O, Valeri A, Andriole GL, Crawford ED, Tucker M, Gerhard DS, Fraumeni JF, Jr., Hoover R, Hayes RB, Hunter DJ, Chanock SJ. Multiple loci identified in a genome-wide association study of prostate cancer. Nat Genet 2008;40(3):310–315.

12. Gudmundsson J, Sulem P, Steinthorsdottir V, Bergthorsson JT, Thorleifsson G, Manolescu A, Rafnar T, Gudbjartsson D, Agnarsson BA, Baker A, Sigurdsson A, Benediktsdottir KR, Jakobsdottir M, Blondal T, Stacey SN, Helgason A, Gunnarsdottir S, Olafsdottir A, Kristinsson KT, Birgisdottir B, Ghosh S, Thorlacius S, Magnusdottir D, Stefansdottir G, Kristjansson K, Bagger Y, Wilensky RL, Reilly MP, Morris AD, Kimber CH, Adeyemo A, Chen Y, Zhou J, So WY, Tong PC, Ng MC, Hansen T, Andersen G, Borch-Johnsen K, Jorgensen T, Tres A, Fuertes F, Ruiz-Echarri M, Asin L, Saez B, van Boven E, Klaver S, Swinkels DW, Aben KK, Graif T, Cashy J, Suarez BK, van Vierssen Trip O, Frigge ML, Ober C, Hofker MH, Wijmenga C, Christiansen C, Rader DJ, Palmer CN, Rotimi C, Chan JC, Pedersen O, Sigurdsson G, Benediktsson R, Jonsson E, Einarsson GV, Mayordomo JI, Catalona WJ, Kiemeney LA, Barkardottir RB, Gulcher JR, Thorsteinsdottir U, Kong A, Stefansson K. Two variants on chromosome 17 confer prostate cancer risk, and the one in TCF2 protects against type 2 diabetes. Nat Genet 2007;39(8):977–983.

13. Duggan D, Zheng SL, Knowlton M, Benitez D, Dimitrov L, Wiklund F, Robbins C, Isaacs SD, Cheng Y, Li G, Sun J, Chang BL, Marovich L, Wiley KE, Balter K, Stattin P, Adami HO, Gielzak M, Yan G, Sauvageot J, Liu W, Kim JW, Bleecker ER, Meyers DA, Trock BJ, Partin AW, Walsh PC, Isaacs WB, Gronberg H, Xu J, Carpten JD. Two genome-wide association studies of aggressive prostate cancer implicate putative prostate tumor suppressor gene DAB2IP. J Natl Cancer Inst 2007;99(24):1836–1844.

14. Eeles RA, Kote-Jarai Z, Al Olama AA, Giles GG, Guy M, Severi G, Muir K, Hopper JL, Henderson BE, Haiman CA, Schleutker J, Hamdy FC, Neal DE, Donovan JL, Stanford JL, Ostrander EA, Ingles SA, John EM, Thibodeau SN, Schaid D, Park JY, Spurdle A, Clements J, Dickinson JL, Maier C, Vogel W, Dork T, Rebbeck TR, Cooney KA, Cannon-Albright L, Chappuis PO, Hutter P, Zeegers M, Kaneva R, Zhang HW, Lu YJ, Foulkes WD, English DR, Leongamornlert DA, Tymrakiewicz M, Morrison J, Ardern-Jones AT, Hall AL, O'Brien LT, Wilkinson RA, Saunders EJ, Page EC, Sawyer EJ, Edwards SM, Dearnaley DP, Horwich A, Huddart RA, Khoo VS, Parker CC, Van As N, Woodhouse CJ, Thompson A, Christmas T, Ogden C, Cooper CS, Southey MC, Lophatananon A, Liu JF, Kolonel LN, Le Marchand L, Wahlfors T, Tammela TL, Auvinen A, Lewis SJ, Cox A, FitzGerald LM, Koopmeiners JS, Karyadi DM, Kwon EM, Stern MC, Corral R, Joshi AD, Shahabi A, McDonnell SK, Sellers TA, Pow-Sang J, Chambers S, Aitken J, Gardiner RA, Batra J, Kedda MA, Lose F, Polanowski A, Patterson B, Serth J, Meyer A, Luedeke M, Stefflova K, Ray AM, Lange EM, Farnham J, Khan H, Slavov C, Mitkova A, Cao G, Easton DF. Identification of seven new prostate cancer susceptibility loci through a genome-wide association study. Nat Genet 2009;41(10):1116–1121.

15. Kote-Jarai Z, Easton DF, Stanford JL, Ostrander EA, Schleutker J, Ingles SA, Schaid D, Thibodeau S, Dork T, Neal D, Donovan J, Hamdy F, Cox A, Maier C, Vogel W, Guy M, Muir K, Lophatananon A, Kedda MA, Spurdle A, Steginga S, John EM, Giles G, Hopper J, Chappuis PO, Hutter P, Foulkes WD, Hamel N, Salinas CA, Koopmeiners JS, Karyadi DM, Johanneson B, Wahlfors T, Tammela TL, Stern MC, Corral R, McDonnell SK, Schurmann P, Meyer A, Kuefer R, Leongamornlert DA, Tymrakiewicz M, Liu JF, O'Mara T, Gardiner RA, Aitken J, Joshi AD, Severi G, English DR, Southey M, Edwards SM, Al Olama AA, Eeles RA. Multiple novel prostate cancer predisposition loci confirmed by an international study: The PRACTICAL Consortium. Cancer Epidemiol Biomarkers Prev 2008;17(8):2052–2061.

16. Hsu FC, Sun J, Wiklund F, Isaacs SD, Wiley KE, Purcell LD, Gao Z, Stattin P, Zhu Y, Kim ST, Zhang Z, Liu W, Chang BL, Walsh PC, Duggan D, Carpten JD, Isaacs WB, Gronberg H, Xu J, Zheng SL. A novel prostate cancer susceptibility locus at 19q13. Cancer Res 2009;69(7):2720–2723.

17. Yeager M, Chatterjee N, Ciampa J, Jacobs KB, Gonzalez-Bosquet J, Hayes RB, Kraft P, Wacholder S, Orr N, Berndt S, Yu K, Hutchinson A, Wang Z, Amundadottir L, Feigelson HS, Thun MJ, Diver WR, Albanes D, Virtamo J, Weinstein S, Schumacher FR, Cancel-Tassin G, Cussenot O, Valeri A, Andriole GL, Crawford ED, Haiman CA, Henderson B, Kolonel L, Le Marchand L, Siddiq A, Riboli E, Key TJ, Kaaks R, Isaacs W, Isaacs S, Wiley KE, Gronberg H, Wiklund F, Stattin P, Xu J, Zheng SL, Sun J, Vatten LJ, Hveem K, Kumle M, Tucker M, Gerhard DS, Hoover RN, Fraumeni JF, Jr., Hunter DJ, Thomas G, Chanock SJ. Identification of a new prostate cancer susceptibility locus on chromosome 8q24. Nat Genet 2009;41(10):1055–1057.

18. Eeles RA, Kote-Jarai Z, Giles GG, Olama AA, Guy M, Jugurnauth SK, Mulholland S, Leongamornlert DA, Edwards SM, Morrison J, Field HI, Southey MC, Severi G, Donovan JL, Hamdy FC, Dearnaley DP, Muir KR, Smith C, Bagnato M, Ardern-Jones AT, Hall AL, O'Brien LT, Gehr-Swain BN, Wilkinson RA, Cox A, Lewis S, Brown PM, Jhavar SG, Tymrakiewicz M, Lophatananon A, Bryant SL, Horwich A, Huddart RA, Khoo VS, Parker CC, Woodhouse CJ, Thompson A, Christmas T, Ogden C, Fisher C, Jamieson C, Cooper CS, English DR, Hopper JL, Neal DE, Easton DF. Multiple newly identified loci associated with prostate cancer susceptibility. Nat Genet 2008;40(3):316–321.
19. Gudmundsson J, Sulem P, Gudbjartsson DF, Blondal T, Gylfason A, Agnarsson BA, Benediktsdottir KR, Magnusdottir DN, Orlygsdottir G, Jakobsdottir M, Stacey SN, Sigurdsson A, Wahlfors T, Tammela T, Breyer JP, McReynolds KM, Bradley KM, Saez B, Godino J, Navarrete S, Fuertes F, Murillo L, Polo E, Aben KK, van Oort IM, Suarez BK, Helfand BT, Kan D, Zanon C, Frigge ML, Kristjansson K, Gulcher JR, Einarsson GV, Jonsson E, Catalona WJ, Mayordomo JI, Kiemeney LA, Smith JR, Schleutker J, Barkardottir RB, Kong A, Thorsteinsdottir U, Rafnar T, Stefansson K. Genome-wide association and replication studies identify four variants associated with prostate cancer susceptibility. Nat Genet 2009;41(10):1122–1126.
20. Nam RK, Zhang WW, Loblaw DA, Klotz LH, Trachtenberg J, Jewett MA, Stanimirovic A, Davies TO, Toi A, Venkateswaran V, Sugar L, Siminovitch KA, Narod SA. A genome-wide association screen identifies regions on chromosomes 1q25 and 7p21 as risk loci for sporadic prostate cancer. Prostate Cancer Prostatic Dis 2008;11(3):241–246.
21. Sun J, Zheng SL, Wiklund F, Isaacs SD, Li G, Wiley KE, Kim ST, Zhu Y, Zhang Z, Hsu FC, Turner AR, Stattin P, Liu W, Kim JW, Duggan D, Carpten J, Isaacs W, Gronberg H, Xu J, Chang BL. Sequence variants at 22q13 are associated with prostate cancer risk. Cancer Res 2009;69(1):10–15.
22. Al Olama AA, Kote-Jarai Z, Giles GG, Guy M, Morrison J, Severi G, Leongamornlert DA, Tymrakiewicz M, Jhavar S, Saunders E, Hopper JL, Southey MC, Muir KR, English DR, Dearnaley DP, Ardern-Jones AT, Hall AL, O'Brien LT, Wilkinson RA, Sawyer E, Lophatananon A, Horwich A, Huddart RA, Khoo VS, Parker CC, Woodhouse CJ, Thompson A, Christmas T, Ogden C, Cooper C, Donovan JL, Hamdy FC, Neal DE, Eeles RA, Easton DF. Multiple loci on 8q24 associated with prostate cancer susceptibility. Nat Genet 2009;41(10):1058–1060.
23. Waters KM, Le Marchand L, Kolonel LN, Monroe KR, Stram DO, Henderson BE, Haiman CA. Generalizability of associations from prostate cancer genome-wide association studies in multiple populations. Cancer Epidemiol Biomarkers Prev 2009;18(4):1285–1289.
24. Pal P, Xi H, Guha S, Sun G, Helfand BT, Meeks JJ, Suarez BK, Catalona WJ, Deka R. Common variants in 8q24 are associated with risk for prostate cancer and tumor aggressiveness in men of European ancestry. Prostate 2009;69(14):1548–1556.
25. Ghoussaini M, Song H, Koessler T, Al OlamaAA, Kote-Jarai Z, Driver KE, Pooley KA, Ramus SJ, Kjaer SK, Hogdall E, DiCioccio RA, Whittemore AS, Gayther SA, Giles GG, Guy M, Edwards SM, Morrison J, Donovan JL, Hamdy FC, Dearnaley DP, Ardern-Jones AT, Hall AL, O'Brien LT, Gehr-Swain BN, Wilkinson RA, Brown PM, Hopper JL, Neal DE, Pharoah PD, Ponder BA, Eeles RA, Easton DF, Dunning AM. Multiple loci with different cancer specificities within the 8q24 gene desert. J Natl Cancer Inst 2008;100(13):962–966.
26. Hooker S, Hernandez W, Chen H, Robbins C, Torres JB, Ahaghotu C, Carpten J, Kittles RA. Replication of prostate cancer risk loci on 8q24, 11q13, 17q12, 19q33, and Xp11 in African Americans. Prostate 2010;70(3):270–275.
27. Zheng SL, Hsing AW, Sun J, Chu LW, Yu K, Li G, Gao Z, Kim ST, Isaacs WB, Shen MC, Gao YT, Hoover RN, Xu J. Association of 17 prostate cancer susceptibility loci with prostate cancer risk in Chinese men. Prostate 2010;70(4):425–432.
28. Sun J, Purcell L, Gao Z, Isaacs SD, Wiley KE, Hsu FC, Liu W, Duggan D, Carpten JD, Gronberg H, Xu J, Chang BL, Partin AW, Walsh PC, Isaacs WB, Zheng SL. Association between sequence variants at 17q12 and 17q24.3 and prostate cancer risk in European and African Americans. Prostate 2008;68(7):691–697.
29. Meyer A, Schurmann P, Ghahremani M, Kocak E, Brinkhaus MJ, Bremer M, Karstens JH, Hagemann J, Machtens S, Dork T. Association of chromosomal locus 8q24 and risk of prostate cancer: A hospital-based study of German patients treated with brachytherapy. Urol Oncol 2009;27(4):373–376.
30. Baudis M, Cleary ML. Progenetix.net: An online repository for molecular cytogenetic aberration data. Bioinformatics 2001;17(12):1228–1229.
31. Sears RC. The life cycle of C-myc: From synthesis to degradation. Cell Cycle 2004;3(9):1133–1137.
32. Buttyan R, Sawczuk IS, Benson MC, Siegal JD, Olsson CA. Enhanced expression of the c-myc protooncogene in high-grade human prostate cancers. Prostate 1987;11(4):327–337.
33. Nupponen NN, Kakkola L, Koivisto P, Visakorpi T. Genetic alterations in hormone-refractory recurrent prostate carcinomas. Am J Pathol 1998;153(1):141–148.
34. Wang YH, Liu S, Zhang G, Zhou CQ, Zhu HX, Zhou XB, Quan LP, Bai JF, Xu NZ. Knockdown of c-Myc expression by RNAi inhibits MCF-7 breast tumor cells growth in vitro and in vivo. Breast Cancer Res 2005;7(2):R220–R228.
35. Easton DF, Pooley KA, Dunning AM, Pharoah PD, Thompson D, Ballinger DG, Struewing JP, Morrison J, Field H, Luben R, Wareham N, Ahmed S, Healey CS, Bowman R, Meyer KB, Haiman CA, Kolonel LK, Henderson BE, Le Marchand L, Brennan P, Sangrajrang S, Gaborieau V, Odefrey F, Shen CY, Wu PE, Wang HC, Eccles D, Evans DG, Peto J, Fletcher O, Johnson N, Seal S, Stratton MR, Rahman N, Chenevix-Trench G, Bojesen SE, Nordestgaard BG, Axelsson CK, Garcia-Closas M, Brinton L, Chanock S, Lissowska J, Peplonska B, Nevanlinna H, Fagerholm R, Eerola H, Kang D, Yoo KY, Noh DY, Ahn SH, Hunter DJ, Hankinson SE, Cox DG, Hall P, Wedren S, Liu J, Low YL, Bogdanova N, Schurmann P, Dork T, Tollenaar RA, Jacobi CE, Devilee P, Klijn JG, Sigurdson AJ, Doody MM, Alexander BH, Zhang J, Cox A, Brock IW, MacPherson G, Reed MW, Couch FJ, Goode EL, Olson JE, Meijers-Heijboer H, van den Ouweland A, Uitterlinden A, Rivadeneira F, Milne RL, Ribas G, Gonzalez-Neira A, Benitez J, Hopper JL, McCredie M, Southey M, Giles GG, Schroen C, Justenhoven C, Brauch H, Hamann U, Ko YD, Spurdle AB, Beesley J, Chen X, Mannermaa A, Kosma VM, Kataja V, Hartikainen J, Day NE, Cox DR, Ponder BA. Genome-wide association study identifies novel breast cancer susceptibility loci. Nature 2007;447(7148):1087–1093.
36. Zanke BW, Greenwood CM, Rangrej J, Kustra R, Tenesa A, Farrington SM, Prendergast J, Olschwang S, Chiang T, Crowdy E, Ferretti V, Laflamme P, Sundararajan S, Roumy S, Olivier JF, Robidoux F, Sladek R, Montpetit A, Campbell P, Bezieau S, O'Shea AM, Zogopoulos G, Cotterchio M, Newcomb P, McLaughlin J, Younghusband B, Green R, Green J, Porteous ME, Campbell H, Blanche H, Sahbatou M, Tubacher E, Bonaiti-Pellie C, Buecher B, Riboli E, Kury S, Chanock SJ, Potter J, Thomas G, Gallinger S, Hudson TJ, Dunlop MG. Genome-wide association scan identifies a colorectal cancer susceptibility locus on chromosome 8q24. Nat Genet 2007;39(8):989–994.

37. Tomlinson I, Webb E, Carvajal-Carmona L, Broderick P, Kemp Z, Spain S, Penegar S, Chandler I, Gorman M, Wood W, Barclay E, Lubbe S, Martin L, Sellick G, Jaeger E, Hubner R, Wild R, Rowan A, Fielding S, Howarth K, Silver A, Atkin W, Muir K, Logan R, Kerr D, Johnstone E, Sieber O, Gray R, Thomas H, Peto J, Cazier JB, Houlston R. A genome-wide association scan of tag SNPs identifies a susceptibility variant for colorectal cancer at 8q24.21. Nat Genet 2007;39(8):984–988.
38. Haiman CA, Le Marchand L, Yamamato J, Stram DO, Sheng X, Kolonel LN, Wu AH, Reich D, Henderson BE. A common genetic risk factor for colorectal and prostate cancer. Nat Genet 2007; 39(8):954–956.
39. Kiemeney LA, Thorlacius S, Sulem P, Geller F, Aben KK, Stacey SN, Gudmundsson J, Jakobsdottir M, Bergthorsson JT, Sigurdsson A, Blondal T, Witjes JA, Vermeulen SH, Hulsbergen-van de Kaa CA, Swinkels DW, Ploeg M, Cornel EB, Vergunst H, Thorgeirsson TE, Gudbjartsson D, Gudjonsson SA, Thorleifsson G, Kristinsson KT, Mouy M, Snorradottir S, Placidi D, Campagna M, Arici C, Koppova K, Gurzau E, Rudnai P, Kellen E, Polidoro S, Guarrera S, Sacerdote C, Sanchez M, Saez B, Valdivia G, Ryk C, de Verdier P, Lindblom A, Golka K, Bishop DT, Knowles MA, Nikulasson S, Petursdottir V, Jonsson E, Geirsson G, Kristjansson B, Mayordomo JI, Steineck G, Porru S, Buntinx F, Zeegers MP, Fletcher T, Kumar R, Matullo G, Vineis P, Kiltie AE, Gulcher JR, Thorsteinsdottir U, Kong A, Rafnar T, Stefansson K. Sequence variant on 8q24 confers susceptibility to urinary bladder cancer. Nat Genet 2008;40(11):1307–1312.
40. Tuupanen S, Turunen M, Lehtonen R, Hallikas O, Vanharanta S, Kivioja T, Bjorklund M, Wei G, Yan J, Niittymaki I, Mecklin JP, Jarvinen H, Ristimaki A, Di-Bernardo M, East P, Carvajal-Carmona L, Houlston RS, Tomlinson I, Palin K, Ukkonen E, Karhu A, Taipale J, Aaltonen LA. The common colorectal cancer predisposition SNP rs6983267 at chromosome 8q24 confers potential to enhanced Wnt signaling. Nat Genet 2009;41(8):885–890.
41. El Gedaily A, Bubendorf L, Willi N, Fu W, Richter J, Moch H, Mihatsch MJ, Sauter G, Gasser TC. Discovery of new DNA amplification loci in prostate cancer by comparative genomic hybridization. Prostate 2001;46(3):184–190.
42. Cher ML, Bova GS, Moore DH, Small EJ, Carroll PR, Pin SS, Epstein JI, Isaacs WB, Jensen RH. Genetic alterations in untreated metastases and androgen-independent prostate cancer detected by comparative genomic hybridization and allelotyping. Cancer Res 1996;56(13):3091–3102.
43. Koontz JI, Soreng AL, Nucci M, Kuo FC, Pauwels P, van Den Berghe H, Dal Cin P, Fletcher JA, Sklar J. Frequent fusion of the JAZF1 and JJAZ1 genes in endometrial stromal tumors. Proc Natl Acad Sci USA 2001;98(11):6348–6353.
44. Buckland PR, Hoogendoorn B, Coleman SL, Guy CA, Smith SK, O'Donovan MC. Hoogendoorn B, Coleman SL, Guy CA, Smith SK, O'Donovan MC. Strong bias in the location of functional promoter polymorphisms. Hum Mutat 2005;26(3):214–223.
45. Reeves JR, Dulude H, Panchal C, Daigneault L, Ramnani DM. Prognostic value of prostate secretory protein of 94 amino acids and its binding protein after radical prostatectomy. Clin Cancer Res 2006;12(20 Pt 1):6018–6022.
46. Nam RK, Reeves JR, Toi A, Dulude H, Trachtenberg J, Emami M, Daigneault L, Panchal C, Sugar L, Jewett MA, Narod SA. A novel serum marker, total prostate secretory protein of 94 amino acids, improves prostate cancer detection and helps identify high grade cancers at diagnosis. J Urol 2006;175(4):1291–1297.
47. Beke L, Nuytten M, Van Eynde A, Beullens M, Bollen M. The gene encoding the prostatic tumor suppressor PSP94 is a target for repression by the Polycomb group protein EZH2. Oncogene 2007;26(31):4590–4595.
48. Ahn J, Berndt SI, Wacholder S, Kraft P, Kibel AS, Yeager M, Albanes D, Giovannucci E, Stampfer MJ, Virtamo J, Thun MJ, Feigelson HS, Cancel-Tassin G, Cussenot O, Thomas G, Hunter DJ, Fraumeni JF, Jr., Hoover RN, Chanock SJ, Hayes RB. Variation in KLK genes, prostate-specific antigen and risk of prostate cancer. Nat Genet 2008;40(9):1032–1034. Author reply 1035–1036.
49. Lai J, Kedda MA, Hinze K, Smith RL, Yaxley J, Spurdle AB, Morris CP, Harris J, Clements JA. PSA/KLK3 AREI promoter polymorphism alters androgen receptor binding and is associated with prostate cancer susceptibility. Carcinogenesis 2007; 28(5):1032–1039.
50. Severi G, Hayes VM, Neufing P, Padilla EJ, Tilley WD, Eggleton SA, Morris HA, English DR, Southey MC, Hopper JL, Sutherland RL, Boyle P, Giles GG. Variants in the prostate-specific antigen (PSA) gene and prostate cancer risk, survival, and circulating PSA. Cancer Epidemiol Biomarkers Prev 2006;15(6):1142–1147.
51. Steuber T, Helo P, Lilja H. Circulating biomarkers for prostate cancer. World J Urol 2007;25(2):111–119.
52. Steuber T, Vickers AJ, Haese A, Becker C, Pettersson K, Chun FK, Kattan MW, Eastham JA, Scardino PT, Huland H, Lilja H. Risk assessment for biochemical recurrence prior to radical prostatectomy: Significant enhancement contributed by human glandular kallikrein 2 (hK2) and free prostate specific antigen (PSA) in men with moderate PSA-elevation in serum. Int J Cancer 2006;118(5):1234–1240.
53. Cramer SD, Chang BL, Rao A, Hawkins GA, Zheng SL, Wade WN, Cooke RT, Thomas LN, Bleecker ER, Catalona WJ, Sterling DA, Meyers DA, Ohar J, Xu J. Association between genetic polymorphisms in the prostate-specific antigen gene promoter and serum prostate-specific antigen levels. J Natl Cancer Inst 2003;95(14):1044–1053.
54. Bellanne-Chantelot C, Clauin S, Chauveau D, Collin P, Daumont M, Douillard C, Dubois-Laforgue D, Dusselier L, Gautier JF, Jadoul M, Laloi-Michelin M, Jacquesson L, Larger E, Louis J, Nicolino M, Subra JF, Wilhem JM, Young J, Velho G, Timsit J. Large genomic rearrangements in the hepatocyte nuclear factor-1beta (TCF2) gene are the most frequent cause of maturity-onset diabetes of the young type 5. Diabetes 2005;54(11):3126–3132.
55. Edghill EL, Bingham C, Ellard S, Hattersley AT. Mutations in hepatocyte nuclear factor-1beta and their related phenotypes. J Med Genet 2006;43(1):84–90.
56. Paliwal S, Kovi RC, Nath B, Chen YW, Lewis BC, Grossman SR. The alternative reading frame tumor suppressor antagonizes hypoxia-induced cancer cell migration via interaction with the COOH-terminal binding protein corepressor. Cancer Res 2007;67(19):9322–9329.
57. Hidaka K, Caffrey JJ, Hua L, Zhang T, Falck JR, Nickel GC, Carrel L, Barnes LD, Shears SB. An adjacent pair of human NUDT genes on chromosome X are preferentially expressed in testis and encode two new isoforms of diphosphoinositol polyphosphate phosphohydrolase. J Biol Chem 2002;277(36):32730–32738.
58. Meister G, Landthaler M, Peters L, Chen PY, Urlaub H, Luhrmann R, Tuschl T. Identification of novel argonaute-associated proteins. Curr Biol 2005;15(23):2149–2155.
59. Specht K, Haralambieva E, Bink K, Kremer M, Mandl-Weber S, Koch I, Tomer R, Hofler H, Schuuring E, Kluin PM, Fend F, Quintanilla-Martinez L. Different mechanisms of cyclin D1 overexpression in multiple myeloma revealed by fluorescence in situ hybridization and quantitative analysis of mRNA levels. Blood 2004;104(4):1120–1126.