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Evaluation of Reported Prostate Cancer Risk-Associated SNPs From Genome-Wide Association Studies of Various Racial Populations in Chinese Men

Rong Na¹, Fang Liu^{1,2,3}, Penyin Zhang^{2,3}, Dingwei Ye^{4,5}, Chuanliang Xu⁶, Qiang Shao⁷, Jun Qi⁸, Xiang Wang¹, Zhiwen Chen⁹, Meilin Wang^{10,11}, Dalin He¹², Zhong Wang¹³, Fangjian Zhou^{14,15}, Jianlin Yuan¹⁶, Xin Gao¹⁷, Qiang Wei¹⁸, Jin Yang¹⁹, Yang Jiao⁸, Jun Ou-Yang²⁰, Yao Zhu^{4,5}, Qijun Wu²¹, Hongyan Chen^{2,3}, Daru Lu^{2,3}, Rong Shi²², Xiaoling Lin^{1,2,3}, Haowen Jiang¹, Zhong Wang²³, Deke Jiang^{2,3}, Jielin Sun²³, S. Lilly Zheng²³, Qing Ding¹, Zengnan Mo^{24,25}, Yinghao Sun^{6,*}, and Jianfeng Xu^{1,2,3,23,**}

¹Fudan Institute of Urology, Huashan Hospital, Fudan University, Shanghai, PR China

²State Key Laboratory of Genetic Engineering, School of Life Sciences, Fudan University, Shanghai, PR China

³Center for Genetic Epidemiology, School of Life Sciences, Fudan University, Shanghai, PR China

⁴Department of Urology, Fudan University Shanghai Cancer Center, Shanghai, PR China

⁵Department of Oncology, Shanghai Medical College, Fudan University, Shanghai, PR China

⁶Department of Urology, Shanghai Changhai Hospital, Second Military Medical University, Shanghai, PR China

⁷Department of Urology, Suzhou Municipal Hospital, Suzhou, PR China

⁸Department of Urology, Xinhua Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, PR China

⁹Urology Institute of PLA, Southwest Hospital, Third Military Medical University, Chongqing, PR China

¹⁰Department of Molecular and Genetic Toxicology, The Key Laboratory of Modern Toxicology of Ministry of Education, School of Public Health, Nanjing Medical University, Nanjing, PR China

¹¹State Key Laboratory of Reproductive Medicine, Nanjing Medical University, Nanjing, PR China

¹²Department of Urology, The First Affiliated Hospital of Medical College of Xi'an Jiaotong University, Xi'an, PR China

¹³Department of Urology, Ninth People's Hospital, School of Medicine, Shanghai Jiaotong University, Shanghai, PR China

¹⁴State Key Laboratory of Oncology in Southern China, Guangzhou, PR China

¹⁵Department of Urology, Cancer Center, Sun Yat-Sen University, Guangzhou, PR China

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*Correspondence to: Yinghao Sun, Department of Urology, Shanghai Changhai Hospital, Second Military Medical University, 168 Changhai Road, Shanghai, PR China. sunyh@medmail.com.cn. **Correspondence to: Jianfeng Xu, Fudan Institute of Urology, Huashan Hospital, Fudan University, 12 Mid-Wulumuqi Road, Shanghai, PR China. jxu@wakehealth.edu. Rong Na, Fang Liu, and Penyin Zhang contributed equally to this work.

Additional supporting information may be found in the online version of this article.

¹⁶Department of Urology, Xijing Hospital, The Fourth Military Medical University, Xi'an, PR China

¹⁷Department of Urology, The Third Affiliated Hospital, Sun Yat-sen University, Guangzhou, PR China

¹⁸Department of Urology, West China Hospital, Sichuan University, Chengdu, Sichuan, PR China

¹⁹Department of Cell Biology, Third Military Medical University, Chongqing, PR China

²⁰Department of Urology, First People's Hospital, Suzhou University, Suzhou, PR China

²¹State Key Laboratory of Oncogene and Related Genes, Shanghai Cancer Institute, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, PR China

²²School of Public Health, Shanghai Jiaotong University, Shanghai, PR China

²³Center for Cancer Genomics, Wake Forest School of Medicine, Winston-Salem, North Carolina

²⁴Center for Genomic and Personalized Medicine, Guangxi Medical University, Nanning, Guangxi, PR China

²⁵Department of Urology and Nephrology, The First Affiliated Hospital of Guangxi Medical University, Nanning, Guangxi, PR China

Abstract

BACKGROUND—Several genome-wide association studies (GWAS) of prostate cancer (PCa) have identified many single nucleotide polymorphisms (SNPs) that are significantly associated with PCa risk in various racial groups. The objective of this study is to evaluate which of these SNPs are associated with PCa risk in Chinese men and estimate their strength of association.

METHODS—All SNPs that were reported to be associated with PCa risk in GWAS from populations of European, African American, Japanese, and Chinese descent were evaluated in 1,922 PCa cases and 2,175 controls selected from the Chinese Consortium for Prostate Cancer Genetics (ChinaPCa). A logistic regression analysis was used to estimate allelic odds ratios (ORs) of these SNPs for PCa.

RESULTS—Among the 53 SNPs, 50 were polymorphic in the Chinese population. Of which, 10 and 24 SNPs were significantly associated with PCa risk in Chinese men at $P < 0.001$ and < 0.05 , respectively. These 24 significant SNPs included 17, 5, and 2 SNPs that were originally discovered in European, Japanese, and Chinese descent, respectively. The estimated ORs ranged from 1.10 to 1.49 and the direction of association was consistent with previous studies. When ORs were estimated separately for PCa with Gleason score 7 and 8, a marginally significant difference in ORs was found only for two of the 24 SNPs ($P = 0.02$ and 0.04).

CONCLUSION—About half of PCa risk-associated SNPs identified in GWAS of various populations are associated with PCa risk in Chinese men. Information on PCa risk-associated SNPs and their ORs may facilitate risk assessment of PCa risk in Chinese men.

Keywords

prostate cancer; SNPs; genome-wide association; Chinese

INTRODUCTION

With an estimated 914,000 new cases and 258,000 deaths every year globally [1], prostate cancer (PCa) is a major public health concern worldwide. The highest incidence and mortality rates are found in the Western developed countries, whereas the lowest incident and mortality rates are reported in Asians. In China, while the incidence is relatively low, it

is increasing rapidly, especially in developed metropolitan areas [2]. For instance, in Shanghai, the incidence of PCa rose from 1.6/100,000 person-years in 1972 to 7.7/100,000 person-years in 2000 [3].

The etiology of PCa is largely unknown and is likely to be multifactorial. Genetic susceptibility is a major risk factor for PCa, estimated to account for 42% variation of the disease [4]. Since 2006, more than 50 genomic regions that harbor inherited variants associated with PCa risk have been identified from multiple genome-wide association studies (GWAS) in populations of European, African American, Japanese, and Chinese descent [5–26]. These PCa risk-associated variants are common in respective populations and typically confer modest to moderate risk, with estimated odd ratios (ORs) ranging from 1.04 to 1.82. However, they have a stronger cumulative effect on PCa risk [27–30]. Risk assessment using combinations of these genetic variants are able to significantly discriminate individual's risk to PCa, independent of family history and levels of prostate specific antigen (PSA). Several studies have demonstrated the clinical utility of these genetic variants in predicting outcomes of initial and repeat prostate biopsies in populations of European descent [31–32].

The clinical utility of genetic variants in assessing genetic risk to PCa relies strongly on the validity of PCa risk associated single nucleotide polymorphisms (SNPs) and their magnitude of risk to PCa. While PCa risk-associated SNPs and their ORs are well established in populations of European descent, there is limited information regarding these two critical components in the Chinese population. The objective of this study is to evaluate which of the ~50 known PCa risk-associated SNPs identified from various populations are associated with PCa risk in Chinese men and to estimate their strength of association.

METHODS

Study Subjects

The subjects included in this study are part of a Chinese Consortium for Prostate Cancer Genetics (ChinaPCa), which was initiated in 2010 and was designed to understand genetic determinants of PCa risk in Chinese men. Due to relatively low incidence of PCa in China and the lack of a national cancer registry, a consortium effort to recruit PCa patients was necessary to achieve a sufficiently large sample size. Any hospital in China that was interested in joining ChinaPCa and was approved by the Institutional Ethic Review Board was welcomed to the consortium. Inclusion criteria were pathology confirmation of PCa (prevalent or incident cases), availability of blood samples, and Han Chinese ethnicity. Because PSA screening for PCa is uncommon in China, most of the PCa patients were diagnosed due to PCa related symptoms. The ChinaPCa also included control subjects from two community-based studies, including male subjects from Taizhou, Jiangsu Province and the Pudong District in Shanghai. Both populations are located in the South-East of China. Control subjects were defined as men without a diagnosis of PCa. Age and other factors were not matched for PCa patients. Serum levels of prostate-specific antigen (PSA) are available for all control subjects.

This study was approved by the Institutional Review Board at Fudan University and each participating hospital.

SNP Selection and Genotyping

All established PCa risk-associated SNPs from published GWAS of PCa in populations of European, African American, Japanese, and Chinese descent were selected for study. They include 42, 1, 8, and 2 PCa risk-associated SNPs in populations of European [5–22], African

[23], Japanese descent [24–25], and Chinese descent [26], respectively. The information of these SNPs is presented in Supplementary Table I.

Two subsets of cases and controls from ChinaPCa were evaluated for these SNPs. The first subset included 1,417 cases and 1,008 controls from Pudong District, Shanghai, as part of a GWAS using Illumina Human OmniExpress Bead Chips [26]. For SNPs that were not included in the GWAS chip, they were imputed based on haplotype data from the 1000 Genomes Project CHB + JPT subjects (Phase I integrated data version 3, released Mar 2012) using the IMPUTE2.2.2 computer program. A posterior probability of >0.90 was applied to call imputed genotypes. Genotype data were not available for three of the targeted SNPs (rs16902094, rs620861, and rs5945619) in this subset of subjects because they were not included in the GWAS chip and were not successfully imputed.

The second subset included 505 PCa cases and 1,167 controls from Taizhou, Jiangsu Province. SNP genotyping in this subset was performed using MassARRAY iPLEX (Sequenom, Inc., San Diego, CA) at the Fudan-VARI Center for Genetic Epidemiology at Fudan University. Duplicates from two subjects and two water samples (negative controls) were included in each 96-well plate for genotyping quality control. Four SNPs (rs10993994, rs7127900, rs130067, and rs10936632) were not evaluated in this subset of subjects because they failed quality control (missing data $>5\%$ or Hardy–Weinberg equilibrium P -value <0.001).

Statistical Methods

The allelic ORs and 95% confidence intervals (CI) for each SNP were estimated first in each of the two subsets of cases and controls using a logistic regression analysis assuming an additive model. A meta-analysis was then performed to obtain the pooled estimate of OR and its CI. Heterogeneity of OR between the two subsets was tested using the Q-statistic for heterogeneity and the I^2 statistic, which measures the proportion of total variance in estimated ORs due to heterogeneity. The I^2 statistic provides the degree of heterogeneity while the Q-statistic only provides the presence or absence of heterogeneity. A value of the I^2 statistic $>50\%$ indicates a high degree of heterogeneity in estimated ORs between study populations. If there was evidence for heterogeneity in OR estimates ($P < 0.05$ for Q-statistic or I^2 statistic $>50\%$), a random effect was used for meta-analysis to calculate the pooled OR and 95% CI; otherwise, a fixed effect was used. Forest plots are provided to visually present the OR and 95% CI for each SNP. Two criteria were used to determine the significance of SNPs in this study. The first is a P of 0.001 to ensure a Type I error of 5% in the study when taking 50 independent tests into consideration. The second is a liberal criterion, with P of 0.05.

OR and 95% CI were also estimated separately for cases with Gleason score 7 and 8 by comparing to the control subjects.

All analyses and forest plots in this study were performed using R software.

RESULTS

The characteristics of study subjects in the two subsets are presented in Table I. Most of the PCa patients (79.8%) in this study had clinically significant disease, defined as serum PSA levels ≥ 20 ng/ml, T3 or higher, N+, M+, or Gleason score ≥ 8 . In control subjects, 49 (2%) had serum PSA ≥ 4 ng/ml; they were not included in the association test.

Among the 53 SNPs, three SNPs were not polymorphic (rs7210100 reported from African descent, rs4962416 and rs5919432 reported from the European descent) and therefore were

not tested for their association with PCa risk. For the 50 polymorphic SNPs, 10 were significantly associated with PCa risk in Chinese men at $P < 0.001$ (Table II); they included five SNPs originally reported in subjects of European descent, three SNPs originally reported in subjects of Japanese descent, and two SNPs originally reported in subjects of Chinese descent. In addition, 14 additional SNPs were significantly associated with PCa risk in Chinese men at $P < 0.05$ (Table II); they included 12 SNPs originally reported in subjects of European descent and two SNPs originally reported in subjects of Japanese descent.

The OR of each SNP for PCa was estimated for the risk alleles identified in previous studies. For the 24 significant SNPs, the estimated ORs in the Chinese population were all >1.0 (i.e., consistent with previous studies) and ranged from 1.10 to 1.49 (Table II and Fig. 1). The top three SNPs that confer the strongest risk for PCa in the Chinese population were rs16901979 at 8q24 (Region 2), OR = 1.48, 95% CI: 1.34–1.63, P -value = 2.33×10^{-14} , rs1447295 at 8q24 (Region 1), OR = 1.48, 95% CI: 1.31–1.67, P -value = 1.54×10^{-10} , and rs817826 at 9q31, OR = 1.49, 95% CI: 1.27–1.75, P -value = 8.26×10^{-7} . For the remaining 26 SNPs that were not significantly associated with PCa risk in the Chinese population, all but two SNPs had OR estimates >1.0 .

We also estimated ORs for PCa separately for high-grade PCa (Gleason score ≥ 8) and for low-grade PCa (Gleason score ≤ 7 ; Table III and Fig. 2). For the 24 SNPs that were significantly associated with PCa risk in the meta-analysis, significantly different ORs between the two types of PCa were found only for two SNPs ($P < 0.05$). One of these two SNPs was rs620861 at 8q24 (Region 4), in which the association was stronger for PCa of Gleason Score ≥ 7 (OR = 1.53, 95% CI: 1.21–1.92) than that of Gleason score ≤ 8 (OR = 1.10, 95% CI: 0.86–1.41), $P = 0.04$. The other SNP was rs10875943 at 12q13, in which the association was stronger for PCa of Gleason Score ≥ 8 (OR = 1.25, 95% CI: 1.04–1.50) than that of Gleason score ≤ 7 (OR = 0.98, 95% CI: 0.84–1.13, $P = 0.02$).

DISCUSSION

Genetic susceptibility to PCa is well established [4]. GWAS of PCa in the past 5 years have identified more than 50 regions in the genome that were associated with PCa risk in various racial populations [6–26]. The potential clinical utility of these PCa risk-associated SNPs in predicting outcomes of initial and repeat prostate biopsy have been reported in populations of European descent [31–32]. However, such utility in the Chinese population has not been established, largely due to a lack of information on PCa risk-associated SNPs in Chinese and the degree of risk they confer. This study attempted to fill the gap by cataloging SNPs that are associated with PCa risk and the OR of these SNPs in Chinese. With the information of the 24 PCa risk-associated SNPs and their ORs, it is now possible to calculate a genetic score based on these SNPs for Chinese men and to assess their genetic risk for PCa.

Risk assessment of PCa using inherited genetic markers may be particularly important in Chinese men because family history of PCa, a commonly used marker for genetic risk to PCa in western countries, is essentially uninformative in China. The percentage of men with family history of PCa is extremely low in China because the disease was rarely detected in this country in past decades, likely due to low adoption of PSA screening and low life expectancy. Other issues such as small family size due to the family planning policies in China may further limit the value of family history in the future. Genetic score derived from PCa risk-associated SNPs, on the other hand, does not rely on information from relatives and therefore may overcome these limitations.

Several papers in the last 2 years reported PCa risk-associated SNPs in Chinese men. In a case–control study of Chinese men (1,108 cases and 1,525 controls) selected from the

ChinaPCa, Liu et al. [33] studied the first 33 PCa risk-associated SNPs initially discovered from GWAS of European descent and found 11 of them were associated with PCa risk at $P < 0.05$. Eight of these 11 were also implicated in the current study. The statistical evidence for association of the other three SNPs was weaker in our current study of larger sample size. In another case-control study of Chinese men (1,524 cases and 2,169 controls) also selected from the ChinaPCa, Wang and colleagues assessed association of the first five PCa risk-associated SNPs identified from GWAS of a Japanese population and found three of which were associated with PCa risk at $P < 0.05$ [34]. These three SNPs were also implicated in this current study. Finally, in a multi-stage GWAS of PCa in Chinese men, Xu et al. [26] identified two SNPs that were significantly associated with PCa risk at a genome-wide significance level. This Chinese GWAS also reported significant associations of 12 SNPs initially reported from GWAS of European descent ($N = 8$) and Japanese descent ($N = 4$) in subjects of the first-stage GWAS (1,417 cases and 1,008 controls). All 12 of these SNPs were implicated in this current study. It is noted that the study subjects between the current study and the previous three studies overlapped; therefore, the findings are not completely independent and the similarities are not surprising. The current study, however, represents the most comprehensive analysis for all established PCa risk-associated SNPs to date from various racial populations in a larger number of Chinese men. As a result, it provided evidence for the largest number of PCa risk-associated SNPs in Chinese.

Although only 10 of the 50 tested SNPs were significantly associated with PCa at $P < 0.001$ and exceeded study-wise significance after Bonferroni correction, 14 additional SNPs that were associated with PCa risk at $P < 0.05$ may also be considered as good candidates for risk assessment among Chinese men. These SNPs likely represent true PCa associations because of their statistical evidence and the fact that the direction of association was consistent with previous studies. They may be used for assessment of individual risk for PCa. Although it is possible that some of these SNPs represent false positives, it is known that inclusion of false positive SNPs in risk assessment will not improve or reduce the predictive performance.

Among the 24 SNPs that were significantly associated with PCa risk in Chinese men, 13 were located within known genes, including *NXX3.1* (rs1512268 at 8p21), *LILRA3* (rs103294 at 19q13), *RFX6* (rs339331 at 6q22), *HNF1B* (rs4430796 and rs11649743 at 17q12), *THADA* (rs1465618 at 2p21), *ZBTB38* (rs6763931 at 3q23), *EHBPI* (rs721048 at 2p15), *ITGA6* (rs12621278 at 2q31), *BIK* (rs5759167 at 22q13), *JAZF1* (rs10486567 at 7p15), *LMTK2* (rs6465657 at 7q21), and *SLC22A3* (rs9364554 at 6q25). The exact molecular mechanisms of these genetic variants are unknown. Additional functional studies are warranted.

In addition to common PCa risk associated SNPs discovered from GWAS, a rare but recurrent PCa risk-associated mutation, G84E of *HOXB13*, was noticed [35]. This gene was also evaluated in 1,518 cases and 1,536 controls selected from ChinaPCa. Although we did not observe the G84E mutation, we found a novel mutation (G125E) in five PCa cases but not in any of the controls [36]. We did not include the mutation in this current study because of its low frequency. However, this high-penetrance mutation should most likely be incorporated into PCa risk assessment for Chinese men.

There are several important limitations in this study. First, the sample size of this study remains limited, which affected statistical power to identify PCa risk-associated SNPs in Chinese men. However, this study nevertheless represents the largest collection of PCa cases in China. Due to the relatively low detection rate of PCa and the lack of a national cancer registry in China, it is a daunting effort to recruit case subjects. We intend to address this limitation by expanding ChinaPCa. Second, due to the open nature of this consortium, the

clinical characterization of PCa patients was not consistent across hospitals in this study, which limited our ability to conduct an in-depth analysis based on clinical phenotypes. Third, most of PCa risk-associated SNPs implicated in this study did not distinguish aggressive from indolent disease. This limitation has been commonly encountered in prior genetic studies of PCa as well as other common cancers [37]. More effort should be devoted to the identification of SNPs that are associated with aggressive but not indolent PCa using case–case study designs. Such SNPs would be helpful to address over-diagnosis of indolent PCa.

In conclusion, by systematically evaluating PCa risk-associated SNPs identified from GWAS of various populations in this large Chinese study, we identified 24 PCa risk-associated SNPs in Chinese men and provided estimates of their risk. The information may facilitate risk assessment of PCa in Chinese men for targeted PCa screening, early detection of PCa, and possible chemoprevention.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Fig. 1. Forest plots of PCa risk-associated SNPs identified from GWAS of various populations with PCa risk in Chinese men.

Fig. 2. Forest plots of PCa risk-associated SNPs identified from GWAS of various populations with risk to PCa of Gleason score ≤ 7 and ≥ 8 in Chinese men.

TABLE I

Characteristics of Study Subjects

Variables	Subset 1 (GWAS)		Subset 2	
	Cases (N = 1,417)	Controls (N = 1,008)	Cases (N = 505)	Controls (N = 1,167)
Age, mean (SD), year ^a	71.3 (8.1)	62.1 (10.0)	70.6 (8.3)	67.0 (6.6)
PSA levels, # (%), ng/ml ^b				
0–3.99	54 (4.0)	965 (95.9)	7 (1.9)	1,141 (99.3)
4–9.99	187 (14.0)	32 (3.2)	52 (13.8)	6 (0.5)
10–19.99	305 (22.8)	6 (0.6)	74 (19.7)	2 (0.2)
20–49.99	312 (23.3)	3 (0.3)	71 (18.9)	0
50–99.99	187 (14.0)	0	42 (11.2)	0
100	292 (21.9)	0	130 (34.6)	0
Missing	80	2	129	18
T-stage, # (%)				
T1	180 (14.7)	N/A	20 (6.7)	N/A
T2	547 (44.7)	N/A	151 (52.2)	N/A
T3	359 (29.4)	N/A	85 (29.4)	N/A
T4	137 (11.2)	N/A	33 (11.4)	N/A
TX	194	N/A	216	N/A
N-stage, # (%)				
N0	786 (68.1)	N/A	229 (76.3)	N/A
N+	369 (31.9)	N/A	71 (23.7)	N/A
NX	262	N/A	205	N/A
M-stage, # (%)				
M0	832 (65.4)	N/A	217 (62.4)	N/A
M+	440 (34.6)	N/A	131 (37.6)	N/A
MX	145	N/A	157	N/A
Gleason score, # (%)				
7	809 (60.1)	N/A	184 (55.4)	N/A
8	537 (39.9)	N/A	148 (44.6)	N/A
Missing	71	N/A	173	N/A

^a Age at diagnosis for cases or at recruitment for controls.

^b Serum PSA levels were measured at diagnosis for cases or obtained at recruitment for controls.

Results of Association Test in Chinese Men for Reported PCa Risk-Associated SNPs From Genome-Wide Association Studies of Populations in European, African, Japanese, and Chinese Descent

TABLE II

Origin of GWAS	Chr	SNPs	BP	Alleles	Risk alleles	Subset1			Subset 2			Meta-analysis					
						Allele frequency			Allele frequency			P for Q statistic	I ²	OR	P-value		
						Cases	Controls	OR ^d	P-value	Cases	Controls					OR	
European	8q24 (Region 2)	rs16901979	128,194,098	C/A	A	0.336	0.265	1.4 (1.23–1.59)	2.74E–07	0.359	0.256	1.63 (1.38–1.91)	4.84E–09	0.1506	51.6	1.48 (1.34–1.63)	2.33E–14
European	8q24 (Region 1)	rs1447295	128,554,220	C/A	A	0.196	0.147	1.44 (1.23–1.68)	5.45E–06	0.218	0.153	1.55 (1.28–1.87)	4.60E–06	0.5543	0	1.48 (1.31–1.67)	1.54E–10
European	8q24 (Region 3)	rs6983267	128,482,487	T/G	G	0.467	0.411	1.28 (1.14–1.44)	3.71E–05	0.519	0.428	1.44 (1.24–1.67)	1.25E–06	0.211	36.08	1.34 (1.22–1.47)	4.55E–10
European	8p21	rs1512268	23,582,408	G/A	T	0.324	0.277	1.27 (1.12–1.44)	2.42E–04	0.351	0.271	1.46 (1.24–1.71)	3.42E–06	0.1873	42.48	1.34 (1.21–1.48)	8.26E–09
Chinese	19q13.4	rs103294	59,489,660	T/C	C	0.301	0.242	1.36 (1.2–1.56)	3.64E–06	0.292	0.241	1.3 (1.1–1.53)	2.03E–03	0.6465	0	1.34 (1.21–1.48)	3.15E–08
Chinese	9q31.2	rs817826	109,196,121	T/C	C	0.107	0.075	1.53 (1.24–1.89)	5.52E–05	0.112	0.081	1.44 (1.13–1.84)	3.64E–03	0.6982	0	1.49 (1.27–1.75)	8.26E–07
Japanese	5p15	rs12653946	1,948,829	C/T	T	0.410	0.362	1.23 (1.09–1.39)	6.70E–04	0.421	0.358	1.31 (1.12–1.52)	5.63E–04	0.5472	0	1.26 (1.15–1.38)	1.54E–06
Japanese	13q22	rs9600079	72,626,140	G/T	T	0.487	0.444	1.19 (1.06–1.33)	3.96E–03	0.510	0.437	1.34 (1.15–1.55)	1.17E–04	0.2073	37.1	1.24 (1.13–1.36)	3.5E–06
Japanese	6q22	rs339331	117,316,745	T/C	T	0.687	0.635	1.28 (1.13–1.44)	9.20E–05	0.685	0.653	1.16 (0.99–1.35)	7.42E–02	0.332	0	1.23 (1.12–1.35)	2.91E–05
European	17q12	rs4430796	33,172,153	T/C	A	0.744	0.725	1.12 (0.98–1.28)	9.29E–02	0.766	0.706	1.36 (1.15–1.62)	4.08E–04	0.0733	68.81	1.2 (1.08–1.33)	5.15E–04
European	8q24 (Region 4)	rs620861	128,335,673	G/A	G	0.744	0.714	1.18 (1.04–1.35)	1.35E–02	0.757	0.551	1.28 (1.1–1.48)	1.63E–03	1	0	1.28 (1.1–1.48)	1.63E–03
European	2p21	rs1465618	43,407,453	A/G	T	0.744	0.714	1.18 (1.04–1.35)	1.35E–02	0.757	0.730	1.15 (0.97–1.36)	1.17E–01	0.7909	0	1.17 (1.05–1.3)	3.54E–03
European	3q23	rs6763931	142,585,523	C/T	A	0.367	0.336	1.13 (1–1.28)	4.64E–02	0.371	0.334	1.18 (1.01–1.37)	3.80E–02	0.6844	0	1.15 (1.04–1.26)	4.38E–03
Japanese	10q26	rs2252004	122,834,699	G/T	C	0.768	0.739	1.19 (1.02–1.37)	2.23E–02	0.752	0.723	1.16 (0.98–1.37)	8.71E–02	0.8402	0	1.17 (1.05–1.31)	4.42E–03
European	2p15	rs721048	62,985,235	G/A	A	0.038	0.028	1.37 (0.98–1.9)	6.58E–02	0.039	0.027	1.44 (0.96–2.16)	7.85E–02	0.8458	0	1.39 (1.08–1.8)	1.14E–02
European	2q31	rs12621278	173,019,799	A/G	A	0.749	0.724	1.14 (1–1.3)	5.60E–02	0.743	0.717	1.14 (0.96–1.35)	1.29E–01	0.9806	0	1.14 (1.03–1.26)	1.47E–02
European	17q12	rs11649743	33,149,092	C/T	G	0.687	0.671	1.09 (0.97–1.24)	1.60E–01	0.683	0.652	1.15 (0.98–1.34)	9.14E–02	0.6438	0	1.11 (1.01–1.23)	3.15E–02
European	22q13	rs5759167	41,830,156	G/T	G	0.730	0.710	1.1 (0.97–1.25)	1.54E–01	0.717	0.688	1.15 (0.97–1.35)	1.01E–01	0.6862	0	1.12 (1.01–1.23)	3.29E–02
European	12q13	rs10875943	47,962,277	T/C	C	0.853	0.850	1.06 (0.9–1.24)	4.95E–01	0.887	0.852	1.36 (1.08–1.7)	7.69E–03	0.0774	67.93	1.15 (1.01–1.31)	3.56E–02
European	19q13	rs887391	46,677,464	T/C	T	0.605	0.595	1.05 (0.93–1.18)	4.60E–01	0.627	0.581	1.21 (1.04–1.41)	1.42E–02	0.1408	53.9	1.1 (1.01–1.21)	3.66E–02
Japanese	2p24	rs13385191	20,751,746	G/A	G	0.461	0.438	1.1 (0.98–1.23)	1.14E–01	0.471	0.447	1.1 (0.95–1.28)	2.04E–01	0.9775	0	1.1 (1–1.21)	4.17E–02
European	7p15	rs10486567	27,943,088	T/C	G	0.148	0.127	1.19 (1–1.41)	4.89E–02	0.144	0.134	1.09 (0.88–1.35)	4.39E–01	0.5313	0	1.15 (1–1.31)	4.29E–02
European	7q21	rs6465657	97,654,263	C/T	C	0.875	0.859	1.15 (0.97–1.37)	1.00E–01	0.863	0.849	1.13 (0.91–1.39)	2.68E–01	0.8744	0	1.14 (1–1.31)	4.77E–02
European	6q25	rs9364554	160,753,654	C/T	C	0.678	0.657	1.11 (0.98–1.26)	8.86E–02	0.685	0.667	1.09 (0.93–1.27)	3.04E–01	0.824	0	1.1 (1–1.21)	4.83E–02
European	10q11	rs10993994	51,219,502	T/C	T	0.511	0.484	1.12 (1–1.26)	5.89E–02					1	0	1.12 (1–1.26)	5.89E–02
European	11p15	rs7127900	2,190,150	G/A	G	0.895	0.878	1.19 (0.99–1.43)	6.17E–02					1	0	1.19 (0.99–1.43)	6.17E–02
European	8q24 (Region 5)	rs10086908	128,081,119	T/C	T	0.830	0.820	1.06 (0.91–1.23)	4.85E–01	0.847	0.818	1.23 (1.01–1.5)	4.40E–02	0.2365	28.63	1.12 (0.99–1.26)	7.61E–02
European	4q24	rs7679673	106,280,983	A/C	C	0.211	0.186	1.16 (1–1.34)	5.02E–02	0.203	0.198	1.03 (0.86–1.24)	7.63E–01	0.3293	0	1.11 (0.99–1.24)	8.39E–02

Origin of GWAS	Subset1										Subset 2				Meta-analysis			
	Chr	SNPs	BP	Alleles	Risk alleles	Allele frequency			OR ^a	P-value	Allele frequency			P-value	P for Q statistic	I ²	OR	P-value
						Cases	Controls	OR ^a			Cases	Controls	OR					
European	2p11	rs10187424	85,647,808	A/G	T	0.626	0.612	1.05 (0.93–1.18)		4.28E–01	0.654	0.627	1.12 (0.96–1.31)	1.41E–01	0.4944	0	1.08 (0.98–1.18)	1.29E–01
European	6p21	rs130067	31,226,490	T/G	G	0.328	0.307	1.1 (0.97–1.24)		1.40E–01					1	0	1.1 (0.97–1.24)	1.40E–01
European	11q13	rs10896449	68,751,243	A/G	G	0.097	0.084	1.16 (0.95–1.43)		1.43E–01	0.000	0.038	NA	4.32E–04	1	0	1.16 (0.95–1.43)	1.43E–01
Japanese	6p21	rs1983891	41,644,405	C/T	T	0.345	0.332	1.06 (0.93–1.2)		3.89E–01	0.330	0.313	1.08 (0.92–1.27)	3.55E–01	0.8522	0	1.07 (0.96–1.18)	2.13E–01
European	3q26	rs10936632	171,612,796	A/C	A	0.269	0.253	1.09 (0.94–1.27)		2.59E–01					1	0	1.09 (0.94–1.27)	2.59E–01
European	5p12	rs2121875	44,401,302	T/G	A	0.483	0.473	1.03 (0.91–1.15)		6.50E–01	0.413	0.495	0.72 (0.58–0.89)	1.93E–03	0.0034	88.33	0.94 (0.85–1.05)	2.72E–01
European	19q13	rs8102476	43,427,453	A/G	C	0.374	0.360	1.08 (0.96–1.22)		2.08E–01	0.382	0.380	1.01 (0.87–1.18)	8.85E–01	0.5046	0	1.05 (0.96–1.16)	2.84E–01
European	3q21	rs10934853	129,521,063	C/A	A	0.441	0.428	1.05 (0.93–1.18)		4.54E–01	0.434	0.421	1.06 (0.91–1.23)	4.79E–01	0.9295	0	1.05 (0.96–1.15)	3.04E–01
European	8p21	rs2928679	23,494,920	G/A	A	0.134	0.120	1.15 (0.96–1.37)		1.24E–01	0.124	0.129	0.95 (0.76–1.19)	6.65E–01	0.1982	39.61	1.07 (0.93–1.23)	3.45E–01
Japanese	11q12	rs1938781	58,671,686	T/C	G	0.328	0.309	1.08 (0.95–1.22)		2.50E–01	0.322	0.322	1 (0.86–1.18)	9.72E–01	0.4936	0	1.05 (0.95–1.16)	3.51E–01
European	8q24.21	rs16902094	128,320,346	A/G	A						0.726	0.713	1.07 (0.9–1.26)	4.55E–01	1	0	1.07 (0.9–1.26)	4.55E–01
European	3p12	rs2660753	87,193,364	C/T	T	0.310	0.287	1.09 (0.96–1.24)		1.88E–01	0.290	0.299	0.96 (0.81–1.13)	6.07E–01	0.2229	32.7	1.04 (0.94–1.15)	4.67E–01
European	17q24	rs1859962	66,620,348	T/G	G	0.426	0.399	1.12 (1–1.27)		5.20E–02	0.394	0.420	0.9 (0.77–1.04)	1.57E–01	0.0209	81.27	1.03 (0.94–1.13)	5.07E–01
European	9q33	rs1571801	123,467,194	G/T	T	0.053	0.050	1.09 (0.83–1.42)		5.40E–01	0.054	0.051	1.05 (0.75–1.46)	7.93E–01	0.8587	0	1.07 (0.87–1.32)	5.23E–01
European	11q13	rs12418451	68,691,995	G/A	A	0.052	0.049	1.05 (0.8–1.37)		7.43E–01	0.053	0.065	0.8 (0.58–1.1)	1.67E–01	0.2061	37.45	0.93 (0.76–1.15)	5.24E–01
Japanese	3p11.2	rs2055109	87,550,022	C/T	C	0.080	0.069	1.18 (0.94–1.47)		1.44E–01	0.064	0.073	0.87 (0.65–1.17)	3.60E–01	0.1083	61.22	1.06 (0.89–1.26)	5.33E–01
European	12q13	rs902774	51,560,171	G/A	G	0.993	0.993	1 (0.49–2.04)		9.94E–01	0.991	0.988	1.41 (0.66–2.99)	3.69E–01	0.5188	0	1.18 (0.7–1.97)	5.36E–01
European	2q37.3	rs2292884	238,107,965	A/G	A	0.717	0.714	0.99 (0.87–1.13)		9.25E–01	0.735	0.718	1.09 (0.92–1.29)	3.19E–01	0.3988	0	1.03 (0.93–1.14)	5.96E–01
European	4q22	rs17021918	95,781,900	C/T	C	0.662	0.653	1.04 (0.92–1.17)		5.60E–01	0.663	0.661	1.01 (0.86–1.18)	9.10E–01	0.787	0	1.03 (0.93–1.13)	5.96E–01
European	19q13	rs2735839	56,056,435	G/A	A	0.391	0.384	1.01 (0.9–1.14)		8.22E–01	0.382	0.377	1.02 (0.88–1.19)	7.70E–01	0.9285	0	1.02 (0.93–1.12)	7.18E–01
European	Xp11	rs5945619	51,241,672	A/G	T						0.932	0.931	1.02 (0.67–1.55)	9.17E–01	1	0	1.02 (0.67–1.55)	9.17E–01
European	22q13	rs9623117	38,782,065	T/C	C	0.040	0.035	1.13 (0.83–1.54)		4.38E–01	0.032	0.038	0.83 (0.55–1.26)	3.86E–01	0.2471	25.36	1.01 (0.79–1.3)	9.18E–01
European	10q26	rs4962416	126,686,862	A/G	G						Not polymorphic							
African	17q21.32	rs7210100	44,791,748	G/A	A						Not polymorphic							
European	Xq12	rs5919432	66,938,275	A/G	A						Not polymorphic							

^a Allelic odds ratio (OR) and 95% confidence interval (95% CI).

TABLE III

Estimated OR for PCa With Gleason Score 7 or 8 in Chinese Men

Origin of GWAS	Chr	SNP	BP	Risk allele	Allele frequency			Risk for PCa of Gleason score 7		Risk for PCa of Gleason score 8		P for different ORs
					Controls (N = 2,126)	Gleason score 7 (N = 993)	Gleason score 8 (N = 684)	OR ^a	P-value	OR	P-value	
European	8q24 (Region 2)	rs16901979	128,194,098	A	0.26	0.34	0.34	1.47 (1.31–1.66)	5.67E–11	1.48 (1.29–1.68)	7.03E–09	9.86E–01
European	8q24 (Region 1)	rs1447295	128,554,220	A	0.15	0.20	0.20	1.43 (1.25–1.65)	3.20E–07	1.45 (1.24–1.69)	3.39E–06	9.11E–01
European	8q24 (Region 3)	rs6983267	128,482,487	G	0.42	0.48	0.48	1.26 (1.14–1.41)	1.80E–05	1.31 (1.16–1.48)	0.00001526	6.15E–01
European	8p21	rs1512268	23,582,408	T	0.27	0.33	0.33	1.29 (1.15–1.45)	1.37E–05	1.31 (1.14–1.49)	0.00007238	8.98E–01
Chinese	19q13.4	rs103294	59,489,660	C	0.24	0.29	0.31	1.29 (1.15–1.46)	2.68E–05	1.45 (1.27–1.66)	4.83E–08	1.29E–01
Chinese	9q31.2	rs817826	109,196,121	C	0.08	0.10	0.11	1.4 (1.17–1.69)	2.56E–04	1.52 (1.24–1.86)	4.10E–05	4.72E–01
Japanese	5p15	rs12653946	1,948,829	T	0.36	0.42	0.40	1.28 (1.15–1.43)	9.79E–06	1.2 (1.06–1.36)	4.05E–03	3.81E–01
Japanese	13q22	rs9600079	72,626,140	T	0.44	0.50	0.49	1.26 (1.13–1.4)	2.33E–05	1.21 (1.07–1.37)	2.11E–03	5.81E–01
Japanese	6q22	rs339331	117,316,745	T	0.64	0.69	0.69	1.23 (1.1–1.38)	3.91E–04	1.22 (1.07–1.39)	2.76E–03	9.25E–01
European	17q12	rs4430796	33,172,153	A	0.71	0.75	0.75	1.2 (1.06–1.35)	4.04E–03	1.19 (1.04–1.37)	1.35E–02	9.77E–01
European	8q24 (Region 4)	rs620861	128,335,673	G	0.55	0.65	0.58	1.53 (1.21–1.92)	2.90E–04	1.1 (0.86–1.41)	4.34E–01	4.36E–02
European	2p21	rs1465618	43,407,453	T	0.72	0.73	0.76	1.04 (0.92–1.18)	4.87E–01	1.21 (1.05–1.39)	9.94E–03	7.94E–02
European	3q23	rs6763931	142,585,523	A	0.34	0.37	0.36	1.16 (1.04–1.3)	7.99E–03	1.13 (0.99–1.28)	5.98E–02	6.99E–01
Japanese	10q26	rs2252004	122,834,699	C	0.73	0.77	0.76	1.23 (1.08–1.4)	2.18E–03	1.19 (1.03–1.39)	2.23E–02	7.37E–01
European	2p15	rs721048	62,985,235	A	0.03	0.04	0.05	1.29 (0.96–1.74)	9.60E–02	1.73 (1.27–2.37)	4.52E–04	9.36E–02
European	2q31	rs12621278	173,019,799	A	0.72	0.76	0.74	1.2 (1.06–1.35)	3.72E–03	1.11 (0.97–1.28)	1.32E–01	3.56E–01
European	17q12	rs11649743	33,149,092	G	0.66	0.69	0.69	1.14 (1.02–1.28)	2.23E–02	1.13 (0.99–1.28)	7.51E–02	8.47E–01
European	22q13	rs5759167	41,830,156	G	0.70	0.74	0.71	1.2 (1.06–1.35)	3.08E–03	1.05 (0.92–1.2)	4.74E–01	9.36E–02
European	12q13	rs10875943	47,962,277	C	0.85	0.85	0.88	0.98 (0.84–1.13)	7.60E–01	1.25 (1.04–1.5)	1.53E–02	1.62E–02
European	19q13	rs887391	46,677,464	T	0.59	0.61	0.60	1.11 (0.99–1.24)	6.87E–02	1.06 (0.93–1.2)	3.84E–01	5.21E–01
Japanese	2p24	rs13385191	20,751,746	G	0.44	0.46	0.47	1.06 (0.95–1.18)	2.69E–01	1.1 (0.98–1.25)	1.18E–01	5.97E–01
European	7p15	rs10486567	27,943,088	G	0.13	0.16	0.13	1.22 (1.05–1.42)	1.03E–02	1.01 (0.84–1.21)	8.99E–01	6.63E–02
European	7q21	rs6465657	97,654,263	C	0.85	0.88	0.87	1.24 (1.06–1.46)	7.51E–03	1.12 (0.94–1.34)	2.01E–01	3.38E–01
European	6q25	rs9364554	160,753,654	C	0.66	0.67	0.69	1.05 (0.94–1.18)	4.09E–01	1.17 (1.02–1.33)	2.10E–02	1.57E–01
European	10q11	rs10993994	51,219,502	T	0.48	0.51	0.51	1.11 (0.97–1.27)	1.26E–01	1.12 (0.97–1.3)	1.28E–01	8.73E–01

Origin of GWAS	Chr	SNP	BP	Risk allele	Allele frequency			Risk for PCa of Gleason score 7		Risk for PCa of Gleason score 8		P for different ORs
					Controls (N = 2,126)	Gleason score 7 (N = 993)	Gleason score 8 (N = 684)	OR ^a	P-value	OR	P-value	
European	11p15	rs7127900	2,190,150	G	0.88	0.90	0.89	1.22 (0.99–1.51)	6.19E–02	1.14 (0.9–1.45)	2.67E–01	5.99E–01
European	8q24 (Region 5)	rs10086908	128,081,119	T	0.82	0.83	0.84	1.09 (0.95–1.26)	2.25E–01	1.12 (0.95–1.32)	1.64E–01	7.64E–01
European	4q24	rs7679673	106,280,983	C	0.19	0.20	0.22	1.07 (0.94–1.22)	3.29E–01	1.15 (0.99–1.34)	6.91E–02	4.01E–01
European	2p11	rs10187424	85,647,808	T	0.62	0.63	0.63	1.03 (0.93–1.15)	5.56E–01	1.05 (0.93–1.19)	4.30E–01	8.07E–01
European	6p21	rs130067	31,226,490	G	0.31	0.32	0.35	1.06 (0.92–1.22)	4.46E–01	1.22 (1.04–1.43)	1.42E–02	8.71E–02
European	11q13	rs10896449	68,751,243	G	0.08	0.09	0.09	1.14 (0.91–1.43)	2.66E–01	1.19 (0.92–1.52)	1.79E–01	7.44E–01
Japanese	6p21	rs1983891	41,644,405	T	0.32	0.35	0.34	1.13 (1.01–1.28)	3.53E–02	1.07 (0.93–1.22)	3.27E–01	4.47E–01
European	3q26	rs10936632	171,612,796	A	0.25	0.27	0.25	1.11 (0.93–1.32)	2.57E–01	1.01 (0.83–1.22)	9.50E–01	3.52E–01
European	5p12	rs2121875	44,401,302	A	0.49	0.48	0.48	0.97 (0.87–1.09)	6.32E–01	0.97 (0.86–1.11)	6.81E–01	9.99E–01
European	19q13	rs8102476	43,427,453	C	0.37	0.38	0.38	1.05 (0.94–1.18)	3.50E–01	1.03 (0.91–1.17)	6.14E–01	7.83E–01
European	3q21	rs10934853	129,521,063	A	0.42	0.44	0.44	1.05 (0.95–1.17)	3.46E–01	1.06 (0.94–1.2)	3.48E–01	9.19E–01
European	8p21	rs2928679	23,494,920	A	0.12	0.14	0.13	1.1 (0.94–1.29)	2.29E–01	1.08 (0.9–1.29)	4.10E–01	8.41E–01
Japanese	11q12	rs1938781	58,671,686	G	0.32	0.32	0.33	1.03 (0.92–1.16)	5.75E–01	1.08 (0.95–1.23)	2.33E–01	5.37E–01
European	8q24.21	rs16902094	128,320,346	A	0.71	0.69	0.74	0.91 (0.72–1.15)	4.29E–01	1.15 (0.88–1.52)	3.08E–01	1.69E–01
European	3p12	rs2660753	87,193,364	T	0.30	0.32	0.30	1.13 (1.01–1.27)	3.32E–02	1.01 (0.88–1.15)	9.35E–01	1.18E–01
European	17q24	rs1859962	66,620,348	G	0.41	0.44	0.40	1.11 (1–1.24)	5.18E–02	0.95 (0.84–1.08)	4.41E–01	2.91E–02
European	9q33	rs1571801	123,467,194	T	0.05	0.04	0.06	0.89 (0.69–1.15)	3.64E–01	1.23 (0.94–1.59)	1.28E–01	4.04E–02
European	11q13	rs12418451	68,691,995	A	0.06	0.05	0.05	0.81 (0.63–1.04)	1.00E–01	0.83 (0.62–1.1)	1.88E–01	9.24E–01
Japanese	3p11.2	rs2055109	87,550,022	C	0.07	0.07	0.08	1.05 (0.85–1.29)	6.52E–01	1.19 (0.95–1.49)	1.23E–01	3.19E–01
European	12q13	rs902774	51,560,171	G	0.99	0.99	0.99	1.31 (0.73–2.37)	3.69E–01	1.7 (0.79–3.62)	1.67E–01	5.57E–01
European	2q37.3	rs2292884	238,107,965	A	0.72	0.71	0.72	0.98 (0.87–1.1)	7.53E–01	1 (0.88–1.15)	9.60E–01	7.73E–01
European	4q22	rs17021918	95,781,900	C	0.66	0.68	0.64	1.1 (0.98–1.23)	1.11E–01	0.93 (0.82–1.06)	2.80E–01	2.82E–02
European	19q13	rs2735839	56,056,435	A	0.38	0.38	0.40	0.98 (0.88–1.09)	6.82E–01	1.08 (0.96–1.23)	2.16E–01	1.58E–01
European	Xp11	rs5945619	51,241,672	T	0.93	0.92	0.95	0.84 (0.47–1.48)	5.38E–01	1.48 (0.67–3.28)	3.28E–01	2.19E–01
European	22q13	rs9623117	38,782,065	C	0.04	0.04	0.04	1.02 (0.77–1.35)	9.19E–01	1.04 (0.75–1.43)	8.21E–01	9.04E–01
European	10q26	rs4962416	126,686,862					Not polymorphic				
African	17q21.32	rs7210100	44,791,748					Not polymorphic				
European	Xq12	rs5919432	66,938,275					Not polymorphic				

^a Allelic odds ratio (OR) and 95% confidence interval (95% CI).