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Predictive performance of prostate cancer risk in Chinese men using 33 reported prostate cancer risk-associated SNPs

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Abstract

Background—Genome-wide association studies (GWAS) have identified more than 30 single nucleotide polymorphisms (SNPs) that were reproducibly associated with prostate cancer (PCa) risk in populations of European descent. In aggregate, these variants have shown potential to predict risk for PCa in European men. However, their utility for PCa risk prediction in Chinese men is unknown.

Methods—We selected 33 PCa risk-related SNPs that were originally identified in populations of European descent. Genetic scores were estimated for subjects in a Chinese case-control study (1,108 cases and 1,525 controls) based on these SNPs. To assess the performance of the genetic score on its ability to predict risk for PCa, we calculated Area under the curve (AUC) of the receiver operating characteristic (ROC) in combination with 10-fold cross-validation.

Results—The genetic score was significantly higher for cases than controls ($P = 5.91 \times 10^{-20}$), and was significantly associated with risk of PCa in a dose-dependent manner (P for trend: 4.78×10^{-18}). The AUC of the genetic score was 0.604 for risk prediction of PCa in Chinese men. When ORs derived from this Chinese study population were used to calculate genetic score, the AUCs were 0.631 for all 33 SNPs and 0.617 when using only the 11 significant SNPs.

Conclusion—Our results indicate that genetic variants related to PCa risk may be useful for risk prediction in Chinese men. Prospective studies are warranted to further evaluate these findings.

Keywords

Genetic score; Cumulative risk; Prostate cancer; AUC; Risk prediction; Susceptibility; Chinese

Introduction

Prostate cancer (PCa) is the most common noncutaneous tumor in developed countries. In contrast to the U.S., where PCa screening is routinely conducted [1], PCa screening is rare in China, thus contributing to a low incidence of PCa among Chinese men. However, the incidence rate has increased sharply in China [2].

Family history is one of well-established risk factors for PCa in US [1,3]. However, family history of PCa is rarely reported in Chinese men and thus this factor contributes very little to risk prediction. Therefore, it is important to identify additional risk factors for PCa that are specific to China, that may allow for identification of high-risk individuals in order to facilitate prevention, screening and early diagnosis.

Genome-wide association studies (GWAS) have identified more than 30 single nucleotide polymorphisms (SNPs) that are reproducibly associated with prostate cancer (PCa) risk in populations of European descent [4-14]. Each of these genetic markers confers a modest effect size [15] and is unlikely to have significant utility for risk prediction. However, we have shown that these genetic markers can be combined to identify men at high risk for this disease [16] and we have evaluated their use in identifying men for diagnostic biopsies [17]. However, to our knowledge, no report has focused on the utility of combining these genetic markers for risk prediction of PCa in Chinese men. Therefore, the cumulative effect of 33 SNPs that had been previously identified as associated with increased PCa risk in populations of European descent, was evaluated in this case-control study of 1,108 Chinese cases and 1,525 Chinese controls.

Patients and Methods

Study Population

The subjects included in this study were previously described in detail [18]. Briefly, 820 pathology confirmed PCa patients were recruited in 2010 from 8 hospitals in the Southern and Eastern areas of China. Controls include 1,370 men randomly selected from a community in Taizhou, Jiangsu Province (South-East China). In addition, an existing case-control study with 288 PCa patients and 155 controls from Shanghai, China was also included; details of the Shanghai case-control study were described previously [19]. In total, 1,108 cases and 1,525 controls were available and included in this study. This study was approved by the Institutional Review Board at Fudan University, the Shanghai Cancer Institute, and each participating hospital.

SNP Selection and Genotyping

As described previously [16, 18], a total of 33 SNPs that were independently associated with PCa risk in men of European descent were selected for genotyping. Samples from all 2,633 subjects included in this study were genotyped on the MassARRAY iPLEX (Sequenom, Inc., San Diego, CA) platform. Technicians that performed the genotyping were blinded to the case-control status of all subjects. For genotyping quality control, duplicates from two subjects and two water samples (negative controls) were included in each 96-well plate. The overall concordance rate was above 99% for these 33 SNPs among the 58 duplicate samples, and all water samples were negative.

Statistical Methods

Genetic scores for each subject were first estimated based on the genotype frequencies of each genetic variant in the HapMap Chinese population and the allelic odds ratio (OR) from the meta-analysis of external studies among populations of European descent (Supplemental Table 1) that were reported previously [15]. Genetic scores were also calculated based on the allelic ORs based on the association results of this population. First, the relative risk of genotypes was estimated according to allelic OR for each SNP. Then the relative risk was converted to the relative risk in the population by multiplying the allelic OR of the SNP with its genotype frequency. Finally, the genetic score for each subject was derived by multiplying the relative risk to the population by each individual SNP carried by the individual. T-tests were used to evaluate differences in the genetic scores (log-transformed to satisfy assumptions of normality) between case and control groups. Logistic regression was employed to test for association between the genetic scores and PCa risk. The performance of genetic scores in correctly discriminating between PCa cases and controls was evaluated using the area under the receiver operating characteristic (ROC) curve (AUC), known as a concordance (i.e., c) statistic. Ten-fold cross-validation was performed with 100 iterations of simulation for each model of genetic score. A nonparametric U test was used to compare the performance (AUC) between different risk models [20]. We used 3 kinds of genetic score to generate AUCs for the Chinese population: one based on external ORs of all 33 SNPs (Supplemental Table 1), and the other two based on ORs in this case-control study of all 33 SNPs or only the 11 SNPs that we subsequently found to be significantly associated with PCa risk, respectively. All analyses were performed using Statistical Analysis System (SAS) software (version 9.2; SAS Institute, Cary, NC).

Results

Figure 1 shows the distribution of genetic scores among cases and controls, as estimated based on the ORs of 33 SNPs from external meta-analysis in studies among populations of European descent. After the data were log-transformed to approach normal distribution, the

genetic score for cases (1.20) was significant higher than in controls 0.86) ($P = 5.91 \times 10^{-20}$). When the subjects were grouped by quartile of genetic score (Table 1), the proportion of cases (32.6%) was significantly higher than proportion of controls (19.5%) in the highest quartile group, while the proportion of cases (18.9%) was significantly lower than proportion of controls (29.5%) in the lowest quartile ($P = 1.15 \times 10^{-16}$). Compared to individuals with the lowest quartile of genetic score, those with genetic scores in the second, third or fourth quartiles had significantly increased risk of PCa (ORs of 1.28 (95%CI: 1.02-1.61), 1.68 (95%CI: 1.34-2.11) and 2.58 (95%CI: 2.07-3.24), respectively) which increased in a dose-dependent manner (P for trend: 4.78×10^{-18}).

As shown in Figure 2, we calculated AUCs to evaluate the performance of genetic score in the identification of PCa cases among Chinese men. The AUC was 0.604 for the genetic score that had been derived from the ORs of external meta-analysis in studies among populations of European descent (CEU SNP33). To compare the performance of genetic score derived from effects (ORs) observed in European and Chinese populations, AUCs were estimated using ORs in the current case-control study based on all 33 SNPs (CHN SNP33) as well as the 11 SNPs (CHN SNP11) that were found to be significantly associated with PCa (Supplemental Table 1). Both risk models, CHN SNP33 and CHN SNP11, resulted in higher AUCs of 0.631 and 0.617, respectively. Of note, CHN SNP33 had the best ability to discriminate PCa cases from controls when compared to either CEU SNP33 ($P = 0.0005$) and CHN SNP 11 ($P = 0.0047$). The AUCs changed little when we performed ten-fold cross-validation to test the stability of the genetic models (Table 2).

Discussion

In this study, we evaluated the clinical utility of genetic markers in PCa risk prediction for Chinese men. Using 33 SNPs identified in populations of European descent, we demonstrated that the genetic markers were effective in discriminating Chinese PCa cases from Chinese controls, with AUCs above 0.60. Although these results need to be confirmed, our study shows these genetic markers may be useful for PCa risk prediction in Chinese men and might be informative for guiding prevention and screening of PCa in China.

In contrast to the traditional risk factors for PCa, such as family history, or biomarkers such as serum prostate specific antigen levels, genetic scores derived from inherited genetic variations have an advantage in that the genetic variants are stable throughout the life of the individuals. Family history information may change over time, and is strongly dependent on other factors including family size, age of relatives, healthcare access within the family, and the level of family communication. PSA levels change over time, and must be measured repeatedly.

With the cost of genotyping declining, genetic testing represents a cost-efficient method to predict PCa risk. Further efficiency can be obtained by simultaneously estimating the risk of multiple diseases, based on a single sample of DNA obtained from blood or saliva, by integrating multiple disease risk prediction markers. In addition, it is important to stress that the potential benefit of using genetic markers in PCa risk prediction may be stronger in Chinese men than western men for at least two reasons: 1) family history of PCa is very rare among the Chinese population, thus precluding its utility for PCa risk prediction in Chinese men; 2) the majority of PCa cases in Chinese men have advanced stage disease because most PCa diagnoses in China are based on symptoms rather than PSA screening.

We calculated AUCs based on ORs from studies of populations of European descent as well as from the association results observed in subjects of the current study. We used the European ORs because estimates of ORs based on a large Chinese population for those 33

SNPs were not available. As expected, the AUC was higher for either model that we developed based on ORs from all 33 SNPs or just the 11 significant SNPs in these Chinese cases and controls, compared with a lower AUC when using the risk model derived from ORs in the European population. However, at this time, we are not able to conclude that the risk model derived from Chinese ORs actually performed better than that derived from European ORs; over-fitting of the genetic models might have occurred because we used the effect sizes that were calculated from the same set of subjects. In addition, a higher AUC was observed for all 33 SNPs than for the 11 significant SNPs, which suggests the SNPs that were not significantly associated with PCa risk in this study contribute additional information to the prediction model. Further studies with larger sample sizes may be helpful to confirm our results and further refine the list of SNPs related to PCa risk in Chinese men.

Given the substantial heterogeneity of genetic determinants between populations of Chinese (relatively homogenous) versus those of European descent (relatively heterogeneous), it may be imprecise to assess the performance of 33 SNPs on risk prediction in Chinese men based on the SNP effects (ORs) estimated from studies among populations of European descent. In fact, if the effect sizes of the 33 SNPs were not available in this Chinese population, then ORs for 33 SNPs from the European population might be an alternative approach for the assessment of the genetic markers. At least two factors may support our approach. First, in populations of European descent these 33 SNPs were all identified from GWAS and have been reproducibly replicated [4-14]; these SNPs might be causal or good surrogates for their respective causal variants. In populations of non-European descent, these genetic markers, might be modifiers for PCa risk. At least 11 of these 33 loci were observed to be significantly associated with PCa risk in our study of 1,108 cases and 1,525 controls. In addition, suggestive evidence for association with PCa risk was also found for 6 additional SNPs for which the reported risk alleles were more common in cases than controls ($P < 0.20$). Second, some of these SNPs may be important in European populations but not in Chinese populations. We recognize that such loci might have resulted in noise for the genetic risk model and therefore may have decreased the efficiency of this study. However, such noise should be random and have a net neutral effect, and thus should not substantially increase or decrease the performance of the genetic model.

Limitations of this study should be noted. First, utilization of an existing case-control study was a cost-efficient approach to build and evaluate the risk prediction model, although potential bias may have been introduced. It is also challenging to assess the value of genetic markers in addition to PSA for PCa risk prediction. Further prospective cohort studies are required to formally evaluate the findings of this study. Second, we did not obtain detailed epidemiologic information from all participants, which limited our ability to compare the genetic model versus risk prediction models based on family history. Finally, this study was focused on the SNPs identified in populations of European descent. Additional genetic risk factors, particularly those unique to the Chinese population, need to be identified and evaluated in future studies, and may further improve the discriminatory accuracy of risk prediction based on genotyping data.

In summary, our results show that genetic scores, an aggregate measure of the combined effect of multiple genetic risk factors, based on PCa risk variants identified in populations of European descent are potential predictors for PCa risk in Chinese men. This study extends the previous findings from European populations to the Chinese population and provides additional support for the clinical utility of genetic markers. Although the genetic risk scores had moderate discriminatory accuracy, they showed promise for assessing PCa risk in Chinese men, and this may help identify men who would obtain the most benefit from PCa prevention and screening strategies. Nevertheless, further efforts should be focused on the

discovery of genetic risk variants that are specific to the Chinese population, so they may be used as risk predictors to improve the discriminatory accuracy of genetic risk models.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.
The distributions of prostate cancer cases and controls among different scales of genetic score

Figure 2.

Receiver operating characteristic (ROC) curves for genetic models. The straight line indicates the null discrimination. Black curve shows the ROC based on the ORs of 33 SNPs from external meta-analysis in studies of European descent (CEU 33); Red curve shows the ROC based on the ORs of 33 SNPs in 1,108 cases and 1,525 controls in the current study (CHN 33); Blue curve shows the ROC based on the ORs of 11 significant SNPs in 1,108 cases and 1,525 controls in the current study (CHN 11). And the AUCs for CEU 33, CHN 33, and CHN 11 (0.604, 0.631 and 0.617, respectively) are presented in parentheses in the key.

Table 1
Distribution of genetic score and association with PCa risk in Chinese population

Genetic score *	Cases (n=1,108)		Controls (n=1,525)		OR(95%CI)	P
	N	%	N	%		
≤ 0.5752	210	18.9	448	29.5	1.00(Ref.)	
0.5759-0.9453	247	22.3	411	26.9	1.28(1.02-1.61)	0.032
0.9476-1.5316	290	26.2	368	24.1	1.68(1.34-2.11)	5.96×10 ⁻⁶
≥ 1.5333	361	32.6	298	19.5	2.58(2.07-3.24)	1.15×10 ⁻¹⁶

* Genetic score was estimated using 33 SNPs with allele frequency in the HapMap Chinese population and ORs from external meta-analysis reported in studies of European descent [15].

Table 2
Performance characteristics of risk prediction models

Models [*]	Overall AUC	Cross validation [†]	
		Testing set	Fitting set
CEU33	0.604	0.604	0.604
CHN33	0.631	0.631	0.631
CHN11	0.617	0.617	0.616

* Genetic models were derived from the ORs of 33 SNPs from populations of European descent (CEU33), 33 SNPs in the current cases-controls (CHN33), and 11 significant SNPs in the current cases-controls (CHN11).

[†] 10-fold cross-validation was performed with 100 iterations of simulation for each model.