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Prediction of Prostate Cancer From Prostate Biopsy in Chinese Men Using a Genetic Score Derived From 24 Prostate Cancer Risk-Associated SNPs

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Abstract

BACKGROUND.—Twenty-four prostate cancer (PCa) risk-associated single nucleotide polymorphisms (SNPs) in Chinese men have been cataloged. We evaluated whether these SNPs can independently predict outcomes of prostate biopsy, and improve the predictive performance of existing clinical variables.

METHODS.—Three hundred eight consecutive patients that underwent prostate biopsy for detection of PCa at Huashan Hospital, Shanghai, China between April 2011 and August 2012 were recruited. Clinical variables such as serum prostate-specific antigen (PSA) levels and peripheral blood samples were collected prior to a 10-core biopsy. A genetic score based on these 24 PCa associated SNPs was calculated for each individual.

RESULTS.—Among 308 patients underwent prostate biopsy, 141 (45.8%) were diagnosed with PCa. Genetic score was significantly higher in patients with PCa (median = 1.30) than without (median = 0.89), $P = 3.81 \times 10^{-6}$. The difference remained significant after adjusting for age and total PSA, $P = 0.007$. The PCa detection rate increased with increasing genetic score; 26.3%, 43.2%, and 60.0% for men with lower (<0.5), average (0.5–1.5), and higher (>1.5) genetic score, respectively, $P_{\text{trend}} = 0.0003$. For patients with moderately elevated PSA levels (1.6–20 ng/ml), the PCa detection rate was 31.2% overall and was 16.7%, 31.2%, and 40.9% for men with lower (<0.5), average (0.5–1.5), and higher (>1.5) genetic score, respectively, $P_{\text{trend}} = 0.03$. For patients with PSA ≥ 20 ng/ml, however, the PCa detection rates were high (>69%) regardless of genetic score.

CONCLUSION.—A genetic score based on PCa risk-associated SNPs is an independent predictor of prostate biopsy outcomes in Chinese men and may be helpful to determine the need for prostate biopsy among patients within a “gray zone” of PCa risk.

Keywords

ChinaPCa; SNPs; risk assessment; PSA

INTRODUCTION

Prostate cancer (PCa) is typically considered uncommon in China, although the incidence has been increasing rapidly in recent decades, especially in developed metropolitan areas [1]. 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 [2]. The exact reasons for the increase are unclear but are likely due to a combination of several factors, including increased life expectancy, life style and dietary change, and increasing adoption of prostate-specific antigen (PSA) screening for PCa. The increasing adoption of PSA screening for PCa in China has also led to changes in the characteristics of patients under-going prostate biopsy; the proportion of biopsy patients with a total PSA level between 4 and 20 ng/ml has increased considerably in the past decade [3]. As a result, prostate over-biopsy is becoming a challenging clinical matter and public health concern where more patients undergo prostate biopsy every year and a smaller proportion of PCa is detected from these biopsies.

Several strategies have been taken in western developed countries to address the issue of prostate over-biopsy, from not recommending the practice of PSA screening for PCa to incorporating additional biomarkers to refine the indication for prostate biopsy [4-9]. These additional biomarkers include serum levels of [-2]proPSA (p2PSA), prostate health index (phi), urine mRNA levels of PCA3 and fusion genes such as TMPRESS-ERG, as well as genetic score derived from multiple PCa risk-associated single nucleotide polymorphisms (SNPs). Multiple studies have demonstrated that these biomarkers improve the predictive performance of total PSA levels for PCa [10-14]. However, the clinical utility of these additional biomarkers in Chinese patients has not been assessed.

In this study, we tested whether inherited PCa risk-associated SNPs can be used to improve the performance of PSA in predicting biopsy outcomes in Chinese men, especially among patients with moderately elevated PSA levels. This study is now feasible because 24 PCa risk-associated SNPs have been cataloged in the Chinese population [15].

METHODS

Study Subjects

The subjects included in this study were consecutive patients that underwent prostate biopsy for detection of PCa at Huashan Hospital, a tertiary hospital in Shanghai, China between April 2011 and August 2012. Therefore, the subjects in this study are representative of prostate biopsy patients in metropolitan areas of Southeast China. The indications for prostate biopsy at Huashan Hospital were: (1) total PSA level >4.0 ng/ml, (2) free-to-total PSA ratio < 0.16, (3) PSA density (PSAD) > 0.15, or (4) presence of prostate nodules detected by digital rectal examination (DRE) or ultrasound. Transrectal ultrasound (TRUS)-guided biopsy using a 10-core scheme was performed. All biopsy specimens were reviewed at the Pathology Department of Huashan Hospital. Demographic and clinical variables prior to biopsy were collected for these patients, including total PSA levels, free-to-total PSA ratio (% free PSA), DRE, and prostate volume (measured by transrectal ultrasound). In addition, peripheral blood was collected for DNA isolation. Written informed consent was obtained from each patient. This study was approved by the Institutional Review Board of Huashan Hospital, Fudan University, Shanghai, China.

PCa Risk-Associated SNPs and Genotyping

Twenty-four SNPs that are associated with PCa risk in Chinese men were selected for genotyping [10]. They include 17, 5, and 2 SNPs originally discovered in genome-wide association studies (GWAS) in populations of European, Japanese, and Chinese descent, respectively. SNP genotyping was performed using MassARRAY iPLEX (Sequenom, Inc., San Diego, CA) at the Fudan 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. The call rate was >98% for each of these SNPs and the overall concordance rate was 99.9% among duplicates.

Statistical Methods

A genetic score was calculated for each subject based on their genotype at these 24 SNPs and weighted by ORs [16]. Briefly, (1) the allelic OR for each SNP was obtained from an external study [15], (2) the genotypic OR of each SNP was estimated from the allelic OR assuming a multiplicative model, (3) the risk relative to the average risk in the population was calculated for each genotype based on genotypic OR and genotype frequency in the Chinese population [15], and (4) genetic score was obtained by multiplying the risks relative to the population of all SNPs. Therefore, a genetic score of 1.0 indicates an average risk in the general population.

Difference in mean between two groups of subjects was tested using the *t*-test when variables were normal distributed (age and free PSA). For variables that were not normally distributed (PSA, prostate volume, and genetic score), two tests were performed; (1) Wilcoxon signed rank test for different medians between two groups and (2) *t*-tests for different means between two groups after log-transformation. For binary variables (positive vs. negative for prostate nodules), a chi-square test of the proportion was performed.

RESULTS

Among 308 patients underwent prostate biopsy for detection of PCa at Huashan Hospital, 141 (45.8%) were diagnosed with PCa, 146 (47.4%) had histology that was consistent with benign prostatic hyperplasia (BPH), and 21 (6.8%) were diagnosed with other conditions such as high-grade prostatic intraepithelial neoplasia (PIN) and inflammation. Compared to patients diagnosed with conditions other than PCa, patients diagnosed with PCa were older (mean: 73.86 and 69.36 years, respectively, $P = 5.76 \times 10^{-6}$), had higher total PSA levels (median: 22.3 and 10.83 ng/ml, respectively, $P = 6.66 \times 10^{-16}$), lower free to total PSA ratio (mean: 0.12 and 0.17, respectively, $P = 0.0004$), smaller prostate volume (median: 37.5 and 51.0 ml, $P = 7.09 \times 10^{-8}$), and a higher proportion of these men were positive for nodules in the prostate (64.03% and 35.76%, respectively, $P = 8.97 \times 10^{-7}$; Table I). In addition, patients diagnosed with PCa had significantly higher genetic scores than those not diagnosed with PCa (median: 1.30 and 0.89, respectively, $P = 3.81 \times 10^{-6}$). The difference remained statistically significant after adjusting for age and total PSA levels ($P = 0.007$; Table I).

The genetic score derived from the 24 known PCa risk-associated SNPs was informative in this prostate biopsy cohort with a wide distribution, ranging from 0.16 to 7.04 (Fig. 1). Although the distributions of genetic score overlapped considerably between patients diagnosed with PCa or with other conditions, higher proportion of patients diagnosed with PCa (39%) were in the higher risk group (genetic score >1.5) than those non-PCa patients (19%). Compared with men in the average risk group (genetic score of 0.5–1.5), men in the lower risk group (genetic scores <0.5) had a lower risk of being diagnosed with PCa (RR = 0.61, 95% CI: 0.35–1.06), while men in the higher risk group (genetic scores > 1.5) had significantly higher risk of being diagnosed with PCa (RR = 1.39, 95% CI: 1.09–1.76; Table

II). The trend of increasing PCa risk with increasing genetic score was statistically significant, $P_{\text{trend}} = 0.0003$.

To explore the potential clinical utility of genetic score in decision making for prostate biopsy, we calculated the detection rate of PCa among men within different estimated genetic score groups, alone or in combination with total PSA levels. The detection rate of PCa increased with increasing genetic score and was estimated at 26.3%, 43.2%, and 60.0% for men in the lower (<0.5), average ($0.5-1.5$), and higher (>1.5) genetic score groups, respectively. The trend of increasing PCa detection rate with increasing genetic score was statistically significant, $P_{\text{trend}} = 0.0003$ (Fig. 2).

When the analysis was stratified by total PSA levels, considerably different results were found in patients with moderately or greatly elevated PSA levels. The PCa detection rates were 31.2% and 76.6%, respectively, for 202 patients with moderately elevated PSA levels ($1.6-20$ ng/ml) and 94 patients with greatly elevated PSA levels (≥ 20 ng/ml; Fig. 3a). In patients with total PSA levels <20 ng/ml, the PCa detection rate was 16.7%, 31.2%, and 40.9% for men within the lower (<0.5), average ($0.5-1.5$), and higher (>1.5) genetic score groups, respectively. The trend of increasing PCa detection rate with increasing genetic score was statistically significant, $P_{\text{trend}} = 0.03$ (Fig. 3b). On the other hand, in patients with total PSA levels ≥ 20 ng/ml, the PCa detection rate was consistently high among all three genetic score groups; they were 71.4%, 69.4%, and 86.8% for men at lower (<0.5), average ($0.5-1.5$), and higher (>1.5) genetic score groups, respectively. The trend was not statistically significant, $P = 0.09$ (Fig. 3c).

We also considered the added value of genetic score to a more comprehensive clinical assessment of PCa risk based on total PSA levels, prostate volume, DRE result, and age. A model with these variables was first developed using a logistic regression. The model was well fit with the observed data ($P = 0.26$ for the Hosmer–Lemeshow Goodness-of-Fit test). The PCa detection rates were 13.6% and 79.1% for patients with lower (defined as predicted probability <0.5 from the logistic model, $N = 154$ [54.4%]) and higher risk (defined as predicted probability ≥ 0.5 , $N = 129$ [45.6%]; Fig. 4a). The difference of PCa detection rate between the higher and lower risk groups was larger using this comprehensive model ($79.1-13.6\% = 65.4\%$) than that based on total PSA levels alone ($76.6-31.2\% = 45.4\%$), suggesting better discrimination of biopsy outcomes using the combined clinical variables. In patients with lower clinical risk based on the clinical model, the PCa detection rate was 4.0%, 16.7%, and 26.5% for men at lower (<0.5), average ($0.5-1.5$), and higher (>1.5) genetic score groups, respectively; the trend was statistically significant, $P_{\text{trend}} = 0.03$ (Fig. 4b). In patients with higher clinical risk, the PCa detection rates were consistently high among all three genetic score groups; they were 75.0%, 80.0%, and 89.1% for men at lower (<0.5), average ($0.5-1.5$), and higher (>1.5) genetic score groups, respectively; the trend was not statistically significant, $P = 0.15$ (Fig. 4c).

Finally, we assessed the performance of genetic score in predicting high-grade PCa from prostate biopsy. Among the 308 patients that underwent prostate biopsy, 35 (11.4%) were diagnosed with high-grade PCa (Gleason score ≥ 8). Patients diagnosed with PCa of Gleason score ≥ 8 had significantly higher genetic scores (median: 1.47) than other subjects, including patients with a negative biopsy and patients whose Gleason score < 8 (median: 1.02), $P = 0.002$. The difference remained statistically significant after adjusting for age and total PSA level, $P = 0.03$. The detection rate of PCa with Gleason score ≥ 8 was 5.3%, 9.7%, and 17.7%, for men at lower (<0.5), average ($0.5-1.5$), and higher (>1.5) genetic score groups, respectively. $P_{\text{trend}} = 0.02$. However, genetic score did not differentiate high-grade from low-grade disease among patients diagnosed with PCa; the median genetic score was 1.47 and 1.21 in PCa patients with Gleason ≥ 8 and < 8 , respectively, $P = 0.18$.

DISCUSSION

Twenty-four PCa risk-associated SNPs have been previously identified and confirmed in the Chinese population [15]. The intent of this study was not to perform another confirmation study of these SNPs, but rather to assess the clinical utility of these established SNPs in predicting a diagnosis of PCa in a cohort of patients that underwent prostate biopsy using a historically prospective design. We first calculated the genetic score for each patient based on genotypes of these 24 known PCa risk-associated SNPs and odds ratios of these SNPs obtained from an external study. We then evaluated correlations between their genetic score and outcomes of prostate biopsy. We demonstrated that the genetic score, with a broad range in the patient cohort, was informative in estimating individual risk to PCa. We found that increasing genetic score was associated with significantly increased risk of being diagnosed with PCa. We also found that genetic score can improve the performance of existing clinical predictors such as total PSA levels, prostate volume, DRE result, and age in predicting PCa, especially in patients with modest and moderate risk for PCa based on existing clinical variables.

The added value of genetic score in predicting PCa may have some potential clinical utility. One of the most direct applications is to use genetic score to better determine the need for prostate biopsy for detection of PCa. Decisions regarding invasive prostate biopsy represent a major challenge in developed countries, where a large number of men are found to have modestly or moderately elevated PSA levels through PSA screening. This issue is emerging in China, where PSA screening through routine physical examination has become a more common practice, especially in metropolitan areas. Due to the limited specificity of PSA tests for PCa and the sampling issues of needle biopsy, only about one-third of these patients are diagnosed with PCa through biopsy. In our study, about 68% patients that underwent prostate biopsy had PSA levels of <20 ng/ml and the PCa detection rate was 31.2% in these patients. Additional information is urgently needed to better assess the likelihood that these patients having PCa. Several biomarkers such as p2PSA, PCA3, fusion genes, and inherited risk-associated SNPs have been recently evaluated for their ability to predict PCa in the Western developed countries [5-14]. This current study examined the prediction performance of genetic score derived from 24 known PCa risk-associated SNPs in Chinese men. A careful examination of our results suggests that genetic score can further differentiate the risk for PCa among patients with modest or moderately elevated PSA levels (<20 ng/ml). The observed detection rate was low (16.7%) among those with a lower genetic score (<0.5) and increased to 31.2% and 40.9% if they have average (0.5–1.5) or higher genetic scores (>1.5), respectively. Based on this observation, we may consider performing biopsies for men with higher (or average) genetic scores while continuing to observe those patients with lower genetic score. If our results are confirmed in independent and large studies, this strategy may help to reduce the number of unnecessary prostate biopsy (therefore, avoiding potential side effects and financial costs) while increasing the likelihood of early diagnosis of PCa in others. On the other hand, for patients that have greatly elevated PSA levels (≥20 ng/ml), genetic score contributes little to further differentiate their risk. The observed detection rates of PCa for these patients were high enough (>69%) to warrant prostate biopsy, regardless of their genetic scores.

Improved assessment of PCa risk was also observed when genetic score was added to a more comprehensive clinical model that includes total PSA levels, prostate volume, DRE result, and age. For patients who were considered as lower risk based on the model (rv54.4% in our study), the PCa detection rate was 13.6% overall. The genetic score can further differentiate their risk to PCa; those with lower genetic score had an extremely low PCa detection rate (4.0%) while those with higher genetic score still had a concerning level of PCa detection rate (26.5%). Two interpretations may be made from these observations: (1) a

comprehensive clinical model performs better than total PSA level alone in predicting PCa risk and (2) patients with lower clinical risk based on the comprehensive model and lower genetic score could be encouraged not to undergo prostate biopsy.

Although the cutoff values used in this study to define high or low genetic score were subjective, the trend of increased PCa risk with increasing genetic score was also evident from a more objective statistical test when the genetic score was treated as a continuous variable, alone ($P = 3.81 \times 10^{-6}$) or adjusting for total PSA levels and age ($P = 0.007$). It is noted that these results were obtained simply by genotyping these 24 known PCa risk-associated SNPs in Chinese and utilizing OR estimates of these SNPs from an external study. The highly significant association between PCa risk and genetic score was consistent with two published studies in the Caucasian population, although different and ethnicity-specific sets of PCa risk-associated SNPs were used. In a cohort of patients that underwent prostate biopsy in Stockholm, Sweden ($N = 5,241$), Aly et al. [13] found a genetic score derived from 35 PCa risk-associated SNPs was a significant predictor of being diagnosed with PCa, $P < 0.0001$ in both univariate analysis or multivariate analysis that adjusted for other known clinical variables. Utilizing a Phase III clinical trial population, the randomized Reduction by Dutasteride of Prostate Cancer Events (REDUCE), Kader et al. [14] found genetic score derived from 33 PCa risk-associated SNPs was significantly associated with PCa diagnosis within 4 years. Together, all the results published to date consistently demonstrate the clinical validity of genetic score in predicting PCa risk.

Another potential application of genetic score is to identify high-risk men for targeted PSA screening. This is supported by the consistent association of genetic score with PCa risk and the fact that it can be measured long before any measurable biomarkers and clinical measurements of PCa such as elevated PSA levels. Men with higher genetic scores may be recommended for early PSA screening at higher frequency while men with lower genetic scores may delay and/or reduce the frequency of PSA testing. This approach may better take advantage of the benefits of PSA testing while reducing the problems seen with too much PSA screening. The clinical utility and cost-effectiveness of this genomic-targeted PSA screening approach, however, needs to be directly assessed in evidence-based studies.

Both genetic score and family history of PCa measure the inherent likelihood of developing PCa. However, genetic score may be a more objective and accurate measurement of inherited PCa risk than family history [13-14]. Family history, while does not require a laboratory test, is influenced by family size, age and survival status of male relatives, and may change from negative to positive. Family history is also influenced by the incidence of PCa in the population. This is a particularly important limitation 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. Therefore, genetic score is a more widely applicable measurement of inherent risk for PCa, especially in China.

PCa risk-associated SNPs in Chinese men were evaluated in several studies, including a genome-wide association study [16-19]. In particular, an association between a genetic score derived from PCa risk-associated SNPs and PCa risk in Chinese men was reported previously [20]. However, there were several important differences between the previous and current study. In the previous study, the genetic score was derived from 33 PCa risk-associated SNPs reported from populations of European descent, regardless whether they were confirmed in the Chinese population. In contrast, the genetic score in this study was calculated from 24 PCa risk-associated SNPs confirmed in the Chinese population [15].

Another major difference was study designs. The previous study was based on a PCa case-control design in the Chinese Consortium for PCa Genetics (ChinaPCa) while the current study was based on a historical prospective design in a cohort of prostate biopsy patients.

There are several important limitations in this study. First, the sample size of this study is relatively small. Although a highly significant association between genetic score and PCa risk was observed even with this small study, the limited sample size may affect the estimate of its association and the statistical power for subset analyses. Larger studies are needed to better understand interaction effect of genetic score with other clinical variables on PCa risk. Second, there were high proportions of missing data for some clinical variables in this study, which limit the ability to develop comprehensive clinical models for risk assessment. For example, free PSA level was missing in 31% subjects, which prevented us from including free PSA in the comprehensive clinical model. Third, we did not evaluate the added value of other novel biomarkers in predicting PCa in this study. It is expected that a combination of biomarkers, including p2PSA, PCA3, fusion genes, and PCa risk-associated SNPs may further improve the performance of risk assessment. Finally, although we found that increasing genetic score was significantly associated with a diagnosis of high-grade PCa (Gleason score 2: 8), the genetic score did not significantly distinguish risk between high-grade and low-grade PCa. This latter finding could be due to the small sample size and low detection rate of high-grade PCa (N = 35, 11.4%) in this study. It is also noted that none of these 24 PCa risk associated SNPs was significantly associated with Gleason score of PCa in Chinese [15], a similar finding to that of Caucasians [21]. More effort should be devoted to the identification of SNPs that are associated with aggressive but not indolent PCa. Such SNPs would be helpful to identify patients at high risk for aggressive PCa, and thus in guiding biopsy decisions.

In conclusion, this historical prospective study demonstrated that genetic score based on PCa risk-associated SNPs is an independent predictor of prostate biopsy outcomes in Chinese men and may be helpful to determine the need for prostate biopsy among patients in the “gray zone” of risk for PCa.

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Fig. 1. Histogram (a) and box-plot (b) of genetic score derived from 24 known PCa risk-associated SNPs in patients with and without a diagnosis of prostate cancer.

Fig. 2.
Prostate cancer detection rate among patients with low, average, and high genetic score.

Fig. 3. Prostate cancer detection rate among patients with various PSA levels and genetic score: **(a)** based on PSA levels, **(b)** based on genetic score among patients with moderately elevated PSA levels, and **(c)** based on genetic score among patients with greatly elevated PSA levels.

Fig. 4.

Prostate cancer detection rate among patients with various risks for PCa defined by a comprehensive clinical model and genetic score: (a) based on estimated low or high risk for PCa, (b) based on genetic score among patients with low PCa risk, and (c) based on genetic score among patients with low PCa risk.

TABLE I

Key Characteristics of Biopsy Subjects at Huashan Hospital

Variables	Biopsy outcomes			Univariate <i>P</i> -value
	All	PCa	Non-PCa	
No (%). of subjects	308 (100%)	141 (45.78%)	167 (54.22%)	
Age (N = 296)				
Mean (SD), year	71.44 (8.74)	73.86 (7.62)	69.36 (9.11)	5.76E-06
Total PSA level (N = 296)				
Median (Q1–Q3), ng/ml	13.85(8.83)	22.3(13.38–73.4)	10.83 (6.54–14.84)	6.66E-16
Mean (SD), ng/ml	18.09(3.28)	33.18(4.03)	10.88 (1.88)	4.17E-15
% of free PSA (N = 214)				
Mean (SD)	0.15 (0.10)	0.12 (0.10)	0.17 (0.10)	0.0004
Prostate volume (N = 303)				
Median (Q1–Q3)	45 (33–64)	37.5 (28–54)	51 (39–74)	7.09E-08
Mean (SD), ml	45.94 (1.58)	39.48 (1.57)	52.14 (1.54)	9.34E-08
Positive nodule (N = 304) %	148 (48.68%)	89 (64.03%)	59 (35.76%)	8.97E-07
Genetic score (N = 308)				
Median (Q1–Q3)	1.08 (0.67–1.59)	1.30 (0.85–2.03)	0.89 (0.57–1.41)	3.81E-06
Mean (SD)	1.06 (1.94)	1.30 (1.92)	0.89 (1.88)	7.41E-07

t-test was performed for different means between two groups when the variable is normal distributed (age and % free PSA). For variables that were not normally distributed (PSA, prostate volume, and genetic score), two tests were performed; (1) tests for different medians between two groups were performed using a Wilcoxon signed rank test, (2) *t*-tests for different means between two groups were performed after log-transformation. For % of positive nodule, chi-square test was performed.

TABLE II

Genetic Score and Risk for Detection of Prostate Cancer From Prostate Biopsy

Genetic score	<u>No. of patients diagnosed with</u>		RR	95% CI	P-value
	PCa	Non-PCa			
<0.5	10	28	0.61	0.35–1.06	0.07
0.5–1.5	80	105	Reference		
>1.5	51	34	1.39	1.09–1.76	0.01

PCa, prostate cancer; RR, relative risk; 95% CI, 95% confidence interval.