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Plateau Effect of Prostate Cancer Risk-Associated SNPs in Discriminating Prostate Biopsy Outcomes

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Abstract

BACKGROUND—Additional prostate cancer (PCa) risk-associated single nucleotide polymorphisms (SNPs) continue to be identified. It is unclear whether addition of newly identified SNPs improves the discriminative performance of biopsy outcomes over previously established SNPs.

METHODS—A total of 667 consecutive patients that underwent prostate biopsy for detection of PCa at Huashan Hospital and Changhai Hospital, Shanghai, China were recruited. Genetic scores were calculated for each patient using various combinations of 29 PCa risk-associated SNPs. Performance of these genetic scores for discriminating prostate biopsy outcomes were compared using the area under a receiver operating characteristic curve (AUC).

RESULTS—The discriminative performance of genetic score derived from a panel of all 29 SNPs (24 previous and 5 new) was similar to that derived from the 24 previously established SNPs, the AUC of which were 0.60 and 0.61, respectively ($P = 0.72$). When SNPs with the strongest effect on PCa risk (ranked based on contribution to the total genetic variance from an external study) were sequentially added to the models for calculating genetic score, the AUC gradually increased and peaked at 0.62 with the top 13 strongest SNPs. Under the 13-SNP model, the PCa detection rate was 21.52%, 36.74%, and 51.98%, respectively for men with low (<0.5), intermediate (0.5–1.5), and high (>1.5) genetic score, P-trend = 9.91×10^{-6}.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article at the publisher's website.

TABLE SI Prostate Cancer Risk-Associated SNPs Confirmed in the Chinese Population

TABLE SII Contribution of SNPs to Genetic Variance

CONCLUSION—Genetic score based on PCa risk-associated SNPs implicated to date is a significant predictor of biopsy outcome. Additional small-effect PCa risk-associated SNPs to be discovered in the future are unlikely to further improve predictive performance.

Keywords

prostate; SNPs; genetic score; ChinaPCa; biopsy; AUC

INTRODUCTION

Prostate cancer (PCa) is the most common cancer affecting men in western developed countries and its incidence has been gradually increasing in many other countries, such as in China [1]. The etiology of PCa and the different incidence rates among countries, races, and geographic regions are largely unknown. It is hypothesized that a combination of factors such as prevalence of PCa screening using prostate-specific antigen (PSA), life expectancy, dietary and environmental exposures, and genetic factors may contribute to differential risks to PCa.

Genetic susceptibility to PCa is well established [2]. Men with a positive family history of PCa have increased risk for the disease [3–5]. More importantly, about four dozen PCa risk-associated single nucleotide polymorphisms (SNPs) have been identified during the past 7 years with the use of genome-wide association studies (GWAS) among populations of European, African-American, Japanese, and Chinese descent [6–27]. PCa risk-associated variants of these SNPs 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; men whom inherited a greater number of PCa risk-associated variants have several-fold higher risk than those inheriting fewer risk-associated variants [28]. As a result, genetic scores derived from multiple PCa risk-associated SNPs are able to significantly discriminate an individual's risk to PCa [29–36]. Several studies have further demonstrated the clinical utility of genetic scores in discriminating outcomes of initial and repeat prostate biopsies in populations of European descent [37,38] and Chinese descent [39].

With the increasing sample size utilized in GWAS through combined or meta-analysis, more PCa risk-associated SNPs are expected to be identified. For example, 23 novel PCa risk-associated SNPs were recently discovered after evaluating 211,155 SNPs across the genome among 25,074 PCa cases and 24,272 controls from the international PRACTICAL Consortium [40]. The effect of these SNPs on PCa risk was relatively smaller compared to most prior SNPs, with ORs in the range of 1.06–1.15. This observation could be expected, as stronger PCa risk-associated SNPs were more likely to have been detected in prior studies with smaller sample sizes. However, an outstanding question is whether these newly discovered and smaller-effect PCa risk-associated SNPs can improve the discriminative performance of genetic score of previously established PCa risk-associated SNPs.

In this study, we aimed to explore this question by comparing the discriminative performance of genetic scores derived from previously established PCa risk-associated SNPs versus genetic scores based on the addition of newly implicated PCa risk-associated SNPs in a biopsy cohort from two hospitals in Shanghai, China.

METHODS

Study Subjects

The subjects included in this study were 667 consecutive patients that underwent prostate biopsy for detection of PCa at Huashan Hospital and Changhai Hospital, both of which are tertiary care hospitals in Shanghai, China. Therefore, the subjects in this study are representative of prostate biopsy patients in metropolitan areas of Southeast China. The time period for recruitment was both between April 2011 and August 2012 at Huashan Hospital and Changhai Hospital. The typical indications for prostate biopsy at these two hospitals 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 was both performed using a 10-core scheme at Huashan Hospital and Changhai Hospital. All biopsy specimens were reviewed at the Pathology Department of both hospital. Demographic and clinical variables prior to biopsy were collected for these patients, including age, total PSA levels, and free-to-total PSA ratio (% free PSA) (Table I). 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 both hospitals.

PCa Risk-Associated SNPs in Han Chinese

In a previous study of 1,922 PCa cases and 2,175 controls selected from the Chinese Consortium for Prostate Cancer Genetics (ChinaPCa), Na et al. [41] evaluated 53 PCa risk-associated SNPs reported prior to the end of 2012 from PCa GWAS in populations of European, Japanese, and Chinese descent, leading to the confirmation of 24 SNPs in Han Chinese at $P < 0.05$. The estimated ORs for these 24 SNPs ranged from 1.10 to 1.49 in Han Chinese. When a similar analysis was extended to the 23 new PCa risk-associated SNPs recently reported from PCa GWAS of the international PRACTICAL Consortium [40], five more SNPs were confirmed in the ChinaPCa (unpublished data). The OR ranged from 1.14 to 1.21 for these five SNPs. These 29 SNPs are estimated to account for 18% of the genetic variance in the Chinese population. The association results for all 29 PCa risk-associated SNPs in the ChinaPCa study are presented in Supplementary Table SI.

Genotyping of SNPs

The 29 SNPs that are associated with PCa risk in Han Chinese were selected for genotyping in 667 patients that underwent prostate biopsy. 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 genotypes at these 29 SNPs and weighted by ORs of these SNPs derived from an external study using a method described by Pharoah et al. [42] Briefly, (1) the allelic OR for each SNP was obtained from an external study (ChinaPCa, Supplementary Table SI), (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 HapMap CHB population, 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.

A genetic score was also calculated for each subject based on the 24 PCa risk-associated SNPs that were previously confirmed in ChinaPCa [41]. The performance of these two genetic scores in discriminating biopsy outcomes (PCa or non-PCa) was compared using the area under the receiver operating characteristic (ROC) curve (AUC). A nonparametric test was used to test different AUC's of these two genetic scores [43].

To evaluate the model fitting and discriminative performance of genetic scores derived from various numbers of PCa risk-associated SNPs for biopsy outcomes, we first ranked these 29 SNPs based on their effect on PCa risk in the Chinese population, as measured by proportion of genetic variance explained by the SNP (Supplementary Table SII) [42]. We then calculated a series of genetic scores sequentially using the top n SNPs, where n is from 1 to 29. Finally, we fit a series of logistic regression models where in each model the dependent variable was biopsy outcome and independent variable was each genetic score. Other covariates known to be associated with biopsy outcomes such as age and total PSA levels were also included as independent variables. The Akaike information criterion (AIC) was used to compare the model fit for these genetic scores and AUC was used to compare the discriminative performance of these genetic scores.

The *t*-test was used to test the difference in mean of normally distributed variables between two groups (PCa and non-PCa). For variables that were not normally distributed (PSA and genetic score), two tests were performed; (1) a nonparametric method using the Wilcoxon rank sum test, and (2) *t*-tests for different means between two groups after log-transformation. For binary variables, a chi-square test of the proportion was performed.

RESULTS

The detection rate of PCa was 38.98% overall in this biopsy cohort and was significantly higher among patients with higher total PSA levels or older ages (Fig. 1). The detection rate of PCa was 19.37%, 35.10%, and 70.68% among patients with total PSA levels <10, 10–20, and >20 ng/ml, respectively, P-trend = 1.77×10^{-27}, and was 24.19%, 42.61%, and 55.94% among patients with age <65, 65–75, and >75, respectively, P-trend = 3.45×10^{-10}.

The median genetic score based on the 29 PCa risk-associated SNPs, including 24 previously implicated SNPs and 5 newly implicated SNPs, was significantly higher among patients diagnosed with PCa (1.09) than that among patients without PCa (0.88), $P = 6.05 \times 10^{-6}$ (Table II). Compared to men with a genetic score <1.0, men with a higher genetic score (≥1.0) had a significantly higher risk to be diagnosed with PCa, OR = 1.76, 95% confidence interval (CI): 1.39–2.23, $P = 2.75 \times 10^{-6}$. The performance of the genetic score to discriminate PCa cases from subjects without PCa, measured by AUC, was 0.60. The PCa detection rate increased with genetic score, and was 29.52%, 36.10%, and 50.85% in men with low (<0.5), intermediate (0.5–1.5), and high (>1.5) genetic score, respectively, P-trend = 0.0001.

As a comparison, we also calculated genetic score based on only the 24 previously implicated SNPs. We found the association and discriminative performance of this genetic score was similar to that based on the 29 SNPs (Table II). The median genetic score based on the 24 SNPs was 1.19 and 0.88 for patients diagnosed with PCa and those without PCa, respectively, $P = 5.61 \times 10^{-7}$. The OR of the genetic score for a PCa diagnosis was 1.92 (95% CI: 1.49–2.45), $P = 3.20 \times 10^{-7}$, slightly higher than that of 29 SNPs. Similarly, the AUC of this genetic score to discriminate PCa from non-PCa was 0.61, also slightly higher than that of 29 SNPs (0.60), although the difference between these two AUCs was not statistically significant, $P = 0.72$. The detection rate of PCa increased with genetic score;

30.95%, 34.96%, and 52.32% in men with low (<0.5), intermediate (0.5–1.5), and high (>1.5) genetic score, respectively, *P*-trend = 9.14×10^{-5}.

To further explore the impact of number of SNPs on the predictive performance of genetic score, we systematically evaluated model fitting (AIC) and discriminative performance (AUC) of genetic scores derived from the top n highest impact PCa risk-associated SNPs based on the contribution of SNPs to the total genetic variance, where n is from 1 to 29 SNPs (Supplementary Table SII). The AIC of these genetic scores decreased gradually first, reached a bottom for the genetic score derived from the top 13 highest impact SNPs (i.e., best fit), then increased slightly and finally stabilized when the remaining SNPs were included (Fig. 2A). Correspondingly, the AUC increased gradually and reached a peak of 0.62 for the genetic score derived from the top 13 highest impact SNPs, then decreased slightly and stabilized at ~0.60 when more SNPs were added (Fig. 2B).

Considering that the genetic score derived from the top 13 highest impact SNPs was the best fitting and most discriminative model in this biopsy cohort, we evaluated the discriminative performance of this model in the entire cohort as well as in subsets of patients based on their PSA level and age. In the entire cohort, the detection rate of PCa increased significantly with increasing genetic score; 21.52%, 36.74%, and 51.98% for men with low (<0.5), intermediate (0.5–1.5), and high (>1.5) genetic score, respectively, *P*-trend = 1.21×10^{-6} (Fig. 3). The association of increasing PCa detection rate with higher genetic score was consistently observed in all subgroups based on tPSA levels or age (Fig. 3). Detailed results of PCa detection rates by genetic score in each of these subgroups, as well as AUC of the genetic score, are presented in Table III.

Finally, we assessed the performance of the genetic score derived from the top 13 SNPs in predicting high-grade PCa from prostate biopsy. Among the 667 patients that underwent prostate biopsy, 77 (11.54%) were diagnosed with high-grade PCa (Gleason score ≥8). Patients diagnosed with high-grade PCa had significantly higher genetic scores (median: 1.13) than other subjects, including patients with a negative biopsy and patients whose Gleason score <8 (median: 0.96), $P = 0.04$. The detection rate of PCa with Gleason score ≥8 was 6.49%, 11.60%, and 14.20%, for men in the low (<0.5), intermediate (0.5–1.5), and high (>1.5) genetic score groups, respectively. *P*-trend = 0.09. However, genetic score did not differentiate high-grade from low-grade disease among patients diagnosed with PCa; the median genetic score was 1.13 and 1.19 in PCa patients with Gleason ≥8 and ≤7, respectively, $P = 0.67$.

DISCUSSION

About 70 PCa risk-associated SNPs have been discovered throughout the genome since 2007, using GWAS in European, African American, Japanese, and Chinese populations [6–27,40]. Several studies have consistently demonstrated that genetic score calculated based on these risk-associated SNPs outperforms family history in measuring inherited risk for PCa [44] and is an independent predictor of biopsy outcome [37–39]. It is also expected that additional PCa risk-associated variants, including common SNPs and rare variants, will be identified with the use of larger sample sizes and sequencing and genotyping technologies that have a better genome coverage. An outstanding question, however, is whether these additional PCa risk-associated SNPs will further improve the overall performance in measuring genetic risk [45].

In the current study, we performed two analyses in a prostate biopsy cohort from China to explore this question. In the first analysis, we directly compared the performance of two genetic scores in predicting biopsy outcomes; one was based on 24 previously implicated

PCa risk-associated SNPs, and the other was based on the 24 SNPs and 5 recently implicated PCa risk-associated SNPs. Results from this analysis revealed that the performance was similar between these two genetic scores. In fact, the performance was slightly worse, although not statistically significant, for the genetic score based on 29 SNPs. This comparison was relevant because it reflected the reality of these sequentially discovered PCa risk-associated SNPs, where each of the five new PCa risk-associated SNPs generally confers lower risk (OR from 1.14 to 1.21) than each of the 24 previously implicated SNPs (OR from 1.10 to 1.49). In the second analysis, we firstly ranked each of these discovered PCa risk-associated SNPs by its contribution to the total genetic variance and then systematically evaluated the predictive performance of genetic scores derived from the top highest impact SNPs. Interestingly, the analysis revealed that the predictive performance reached a peak when the top 13 highest impact PCa risk-associated SNPs were included in calculating the genetic score. Considering that PCa risk-associated variants with higher impact (stronger OR and higher frequency) have likely been discovered, results from these two analyses suggest that lower impact PCa risk-associated SNPs to be discovered in the future are unlikely to further improve the performance of genetic score in measuring inherited risk to PCa.

A similar result was reported previously in a population-based case–control study in Sweden, including 2,899 PCa cases and 1,722 controls [32]. When a set of genetic scores were calculated based on 28 ordered PCa risk-associated SNPs, from highest to lowest contribution to the total genetic variance, their positive predictive value of PCa increased gradually and reached a plateau when the top 11 SNPs were included in calculating genetic score. In addition, we observed the similar finding from the REduction by DUtasteride of Prostate Cancer Events (REDUCE) trial, a randomized chemoprevention trial of PCa using dutasteride (unpublished data). Genotype data of 64 known PCa risk-associated SNPs were available among 1,654 Caucasian men in the placebo arm of the REDUCE. We performed a similar analysis as the current study. When SNPs with the strongest effect on PCa risk (ranked based on contribution to the total genetic variance from an external study) were sequentially added to the models for calculating genetic score, the AUC gradually increased, peaked at 0.62 with the top 43 strongest SNPs, and then gradually decreased to 0.61. These additional data suggest the reported phenomenon of the current study is not limited to this Chinese population and maybe a general finding.

The plateau effect is also reported in simulated data and other diseases. In a simulation study evaluating factors affecting the predictive performance (AUC) of risk-associated SNPs discovered from GWAS, including the number of SNPs (20, 50, 100, 200, 300, and 400 most significant SNPs), sample size (500, 1,000, 2,000, 5,000, and 10,000), and classification algorithms (logistic regression, risk-score, and support vector machine), Kang et al. [46] found that the risk-score logistic regression model with 20–50 SNPs provided the best performance when the ORs of these SNPs were moderate (median OR was 1.31). These ORs were similar to that discovered for PCa. In that same paper, Kang et al. also evaluated the predictive performance of risk-associated SNPs for Crohn’s disease in a GWAS study of 547 cases and 549 controls. They evaluated the predictive performance of the top 2, 10, 20, 50, and 100 most significant SNPs using a risk-score and found the best performance was observed when the top 20 SNPs were included in the model.

Results from this study provide evidence that genetic score calculated from PCa risk-associated SNPs may help to supplement PSA levels to better determine the need for prostate biopsy which is used to diagnose PCa. Currently, the primary indication for prostate biopsy is elevated tPSA levels. However, because tPSA is not PCa specific, moderately elevated PSA levels have limited specificity. As shown in this study, the overall PCa detection rate from this biopsy cohort was only 38.98%, typical for tertiary hospitals in

major cities of China. In other words, more than 50% of patients that currently undergo prostate biopsy for the purpose of diagnosing PCa may be having an unnecessary invasive procedure. However, if we add genetic score information to the information available to make decisions for prostate biopsy, this may reduce the number of unnecessary biopsies while increasing the likelihood of detecting PCa among biopsied patients. For example, the PCa detection rates are below 18% for patients with tPSA <10 ng/ml if they have low or intermediate genetic score and for patients with tPSA at 10–20 ng/ml if they have low genetic score. This rate of <18% for PCa may be accepted by most patients and their treating urologists because it is equivalent to the detection rate of tPSA <2 ng/ml [47]. About 33% of patients in this biopsy cohort belong to these groups based on their tPSA levels and genetic score. On the other hand, the expected PCa detection rate was 47.62% among patients with tPSA of 10–20 ng/ml if they have a high genetic score, considerably higher than the average PCa detection rate of 35.10% in this tPSA subgroup. It is also noted that the added value of genetic score to PSA is most prominent in patients with tPSA <20 ng/ml. For patients with tPSA >20 ng/ml, although higher genetic score was significantly associated with higher PCa detection, the PCa detection rates in all genetic score groups were high enough (>55%) to warrant a biopsy.

Genetic score may have another important clinical application, in determining the need for PSA screening for PCa. The goal of PSA screening is the identification of PCa at an earlier and more treatable stage in order to reduce mortality. However, conflicting results regarding its impact on mortality were reported from two large randomized trials; the European Randomized Study for the Screening of Prostate Cancer (ERSPC) and The Prostate, Lung, Colorectal and Ovarian (PLCO) [48,49]. A updated analysis of the ERSPC in 2012 suggested that PSA screening results in modest reductions in PCa-specific mortality [50]. By weighing the benefit versus potential harms downstream of PSA screening such as prostate biopsy and treatment, the U.S. Preventive Services Task Force (USPSTF) issued new draft recommendations against PSA screening for PCa in all men [51]. In responding to the USPSTF's recommendation, the American Urology Association (AUA) issued a new recommendation for PSA screening in 2013, emphasizing targeted PSA screening based on an individual's risk for PCa. Specifically, the AUA does not recommend a routine screening among men between 40 and 54 years old at "average" risk, and strongly recommends shared decision making for men aging 55–69 years old who need to consider PSA screening [52]. A central question of the new guideline is to understand an individual's risk for PCa prior to a PSA test. Unfortunately, currently approach to define risk, which primarily relies on family history, is limited. Considering that genetic score is a more objective and accurate measurement of inherited risk than family history [43], it is rational to suggest that genetic score should be included to supplement family history in defining PCa risk. This approach is particularly useful for ~80% men in the general population who do not have a positive family history because a subset of these men are also at a higher risk. The clinical utility and cost-effectiveness of this genomic-targeted PSA screening approach, however, needs to be directly assessed in evidence-based studies.

Genetic score is particularly important in countries such as China where family history is uninformative due to historically low incidence of PCa. The percentage of men with a positive family history of PCa is extremely low in China because the disease was rarely diagnosed in this country in prior decades. The historically low incidence is likely attributable to the low adoption of PSA screening and low life expectancy in China, rather than low genetic susceptibility in Chinese. This assumption is supported by the fact that 29 PCa risk-associated SNPs have been implicated in Chinese and that genetic score derived from these SNPs is associated with PCa detection rate. This difference between genetic score and family history in China highlights key distinctions between these two measurements of inherited risk. The former is a direct measurement of genetic material of

individuals self while the latter is an indirect measurement through relatives. Therefore, unlike family history that is influenced by historical disease incidence, family size, age and survival status of male relatives, genetic score is an objective measurement and does not change during a lifetime. As such, genetic score has great potential to be widely used in China to measure inherited risk of PCa for targeted PSA screening, prevention, and early diagnosis.

There are several limitations in this study. First, the sample size of this study was relatively small and all patients were from two tertiary hospitals in Shanghai, China. Although a highly significant association between genetic score and PCa detection rate was observed even with this small study, these limitations may affect the estimate of its association and the ability to generalize the results. Larger and multi-center studies are needed to establish more reliable estimates of PCa detection rates at different cutoffs of genetic score. Second, many important clinical variables and novel biomarkers such as prostate volume, serum p2PSA, and urine PCA3 and fusion genes were not collected in this study. It is expected that a combination of these variables may further improve prediction of PCa detection rates and help to determine the need for biopsy. Finally, although we found that increasing genetic score was significantly associated with a diagnosis of high-grade PCa (Gleason score ≥8), the genetic score did not significantly distinguish risk between high-grade and low-grade PCa. It is noted that none of these 29 PCa risk associated SNPs was significantly associated with Gleason score of PCa in Chinese [41], a similar finding to that of Caucasians [53]. 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, genetic score based on PCa risk-associated SNPs implicated to date is a significant predictor of biopsy outcome. Additional small-effect PCa risk-associated SNPs to be discovered in the future are unlikely to further improve predictive performance.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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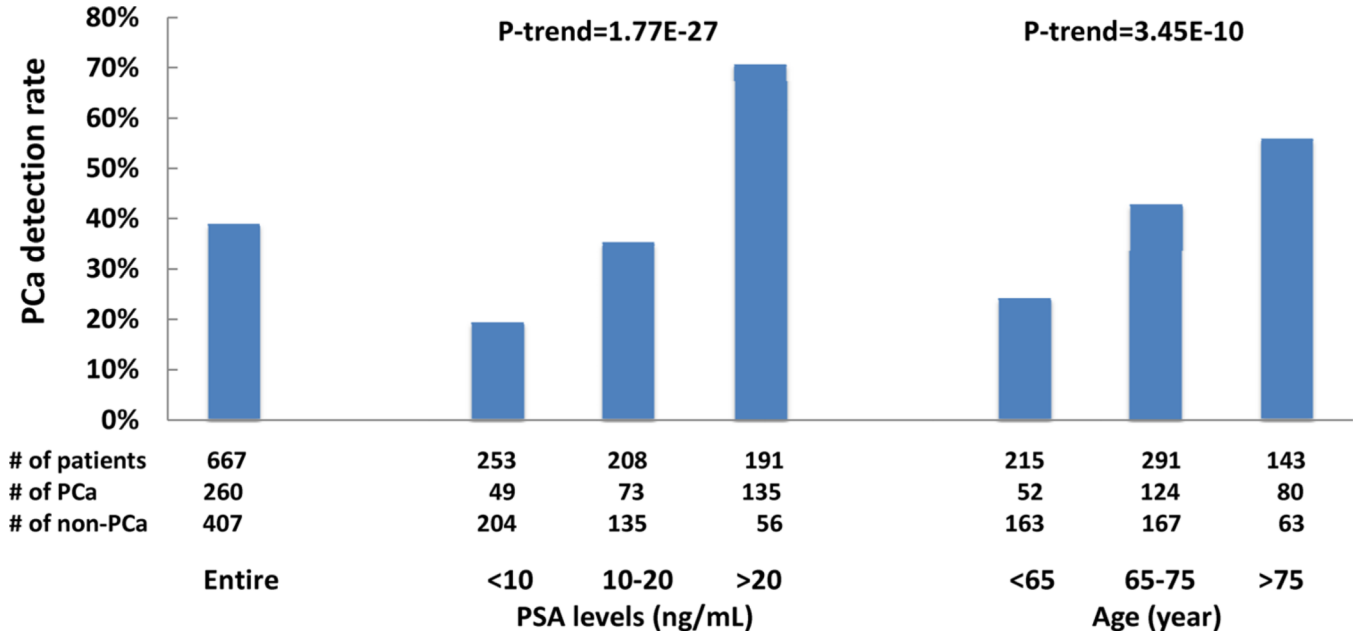

Fig. 1.

Prostate cancer detection rate in the entire biopsy cohort as we as in subgroups based on PSA levels and age.

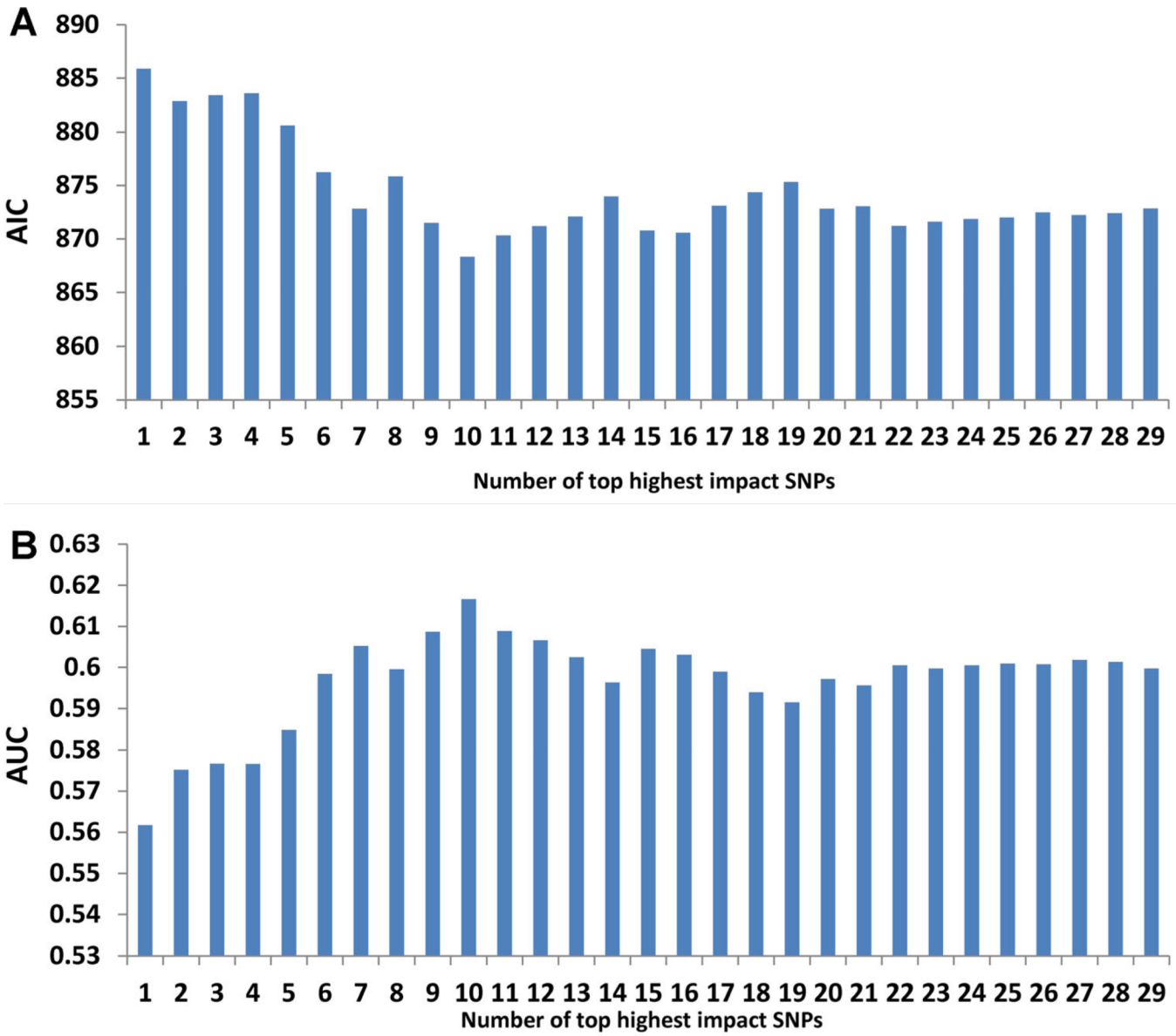

Fig. 2.

Model fitting (**A**) and discriminative performance (**B**) for models derived from the top n highest impact PCa risk-associated SNPs based on contribution of SNPs to the total genetic variance, where n is from1to 29 SNPs. AIC, Akaike information criterion; AUC, area under the curve for the receiver operating characteristic.

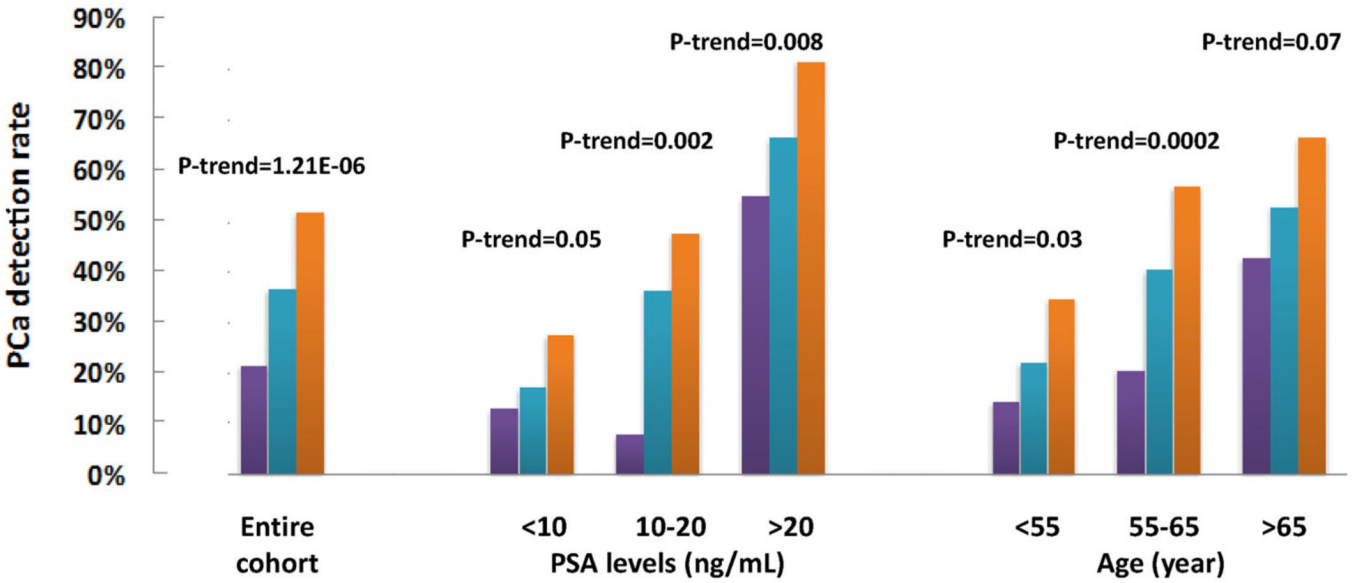

Fig. 3.

Prostate cancer detection rate in subjects with low (purple), intermediate (blue), and high (orange)genetic score in the entire biopsy cohort as we as in subgroups based on PSA levels and age.

TABLE I

Key Demographic and Clinical Variables in Subjects of the Biopsy Cohort

	Biopsy outcomes			
Variables	**All**	**PCa**	**Non-PCa**	**Univariate *P*-value**
No. (%) of subjects	667 (100%)	260 (38.98%)	407 (61.02%)	
Age (n = 649)				
Mean (SD), year	68.24 (9.06)	71.40 (7.92)	66.19 (9.17)	6.28E–14
Total PSA level (n = 652)				
Median (Q1–Q3), ng/ml	11.99 (7.56–23.53)	22.3 (11.88–73.4)	9.73 (6.43–13.99)	7.90E–31
Mean (SD), ng/ml	46.47 (165.08)	98.22 (254.26)	12.80 (11.70)	1.66E–07
Free/total ratio (n = 565)				
Median (Q1–Q3)	0.14 (0.09–0.19)	0.11 (0.07–0.16)	0.16 (0.11–0.21)	3.16E–11
Mean (SD)	0.22 (0.80)	0.14 (0.17)	0.26 (1.00)	2.26E–02
Gleason score (n = 251)				
≤6		70 (27.9%)		
7		104 (41.4%)		
8		35 (13.9%)		
9		32 (12.7%)		
10		10 (4.0%)		

TABLE II

Association of Genetic Score and Prostate Biopsy Outcomes

	29 SNPs	**24 SNPs**
Genetic score (median)		
PCa	1.09	1.19
Non-PCa	0.88	0.88
P-Value	6.05×10^{-6}	5.61×10^{-7}
Association with PCa, OR (95% CI)		
Genetic score ≤1.0	1	1
Genetic score >1.0	1.76 (1.39–0.23)	1.92 (1.49–0.45)
P-Value	2.75×10^{-6}	3.20×10^{-7}
Discrimination of PCa		
AUC (95% CI)	0.60	0.61
Detection rate of PCa (%)		
Genetic score <0.5	29.52	30.95
Genetic score =0.5–1.49	36.10	34.96
Genetic score ≥1.5	50.85	52.30
P-Value	0.0001	9.14×10^{-5}

TABLE III

Discriminative Performance of Genetic Score Derived From the Top 13 Highest Impact SNPs

	Entire cohort			No. of PCa/No. of biopsed patients (PCa detection rate) at genetic score			
	No. of patients	**No. (%) of PCa**	**AUC**	**<0.50**	**0.50–1.50**	**≥1.50**	***P***
All subjects	667	260 (38.98)	0.62	17/79 (21.52%)	151/411 (36.74%)	92/177 (51.98%)	1.21E–06
Stratified by PSA levels							
<10 ng/ml	253	49 (19.37)	0.57	4/31 (12.90%)	27/157 (17.20%)	18/65 (27.69%)	4.97E–02
10–20 ng/ml	208	73(35.10)	0.63	2/26 (7.69%)	51/140 (36.43%)	20/42 (47.62%)	1.50E–03
>20 ng/ml	191	135(70.68)	0.63	11/20 (55.00%)	70/105 (66.67%)	54/66 (81.82%)	7.80E–03
Stratified by age							
<65 years	215	52 (24.19)	0.59	4/28 (14.29%)	30/135 (22.22%)	18/52 (34.62%)	2.95E–02
65–75 years	291	124(42.61)	0.64	7/34 (20.59%)	72/178 (40.45%)	45/79 (56.96%)	2.00E–04
>75 years	143	80(55.94)	0.58	6/14 (42.86%)	46/87 (52.87%)	28/42 (66.67%)	7.26E–02