Population-standardized genetic risk score: the SNP-based method of choice for inherited risk assessment of prostate cancer

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Several different approaches are available to clinicians for determining prostate cancer (PCa) risk. The clinical validity of various PCa risk assessment methods utilizing single nucleotide polymorphisms (SNPs) has been established; however, these SNP-based methods have not been compared. The objective of this study was to compare the three most commonly used SNP-based methods for PCa risk assessment. Participants were men (n = 1654) enrolled in a prospective study of PCa development. Genotypes of 59 PCa risk-associated SNPs were available in this cohort. Three methods of calculating SNP-based genetic risk scores (GRSs) were used for the evaluation of individual disease risk such as risk allele count (GRS-RAC), weighted risk allele count (GRS-wRAC), and population-standardized genetic risk score (GRS-PS). Mean GRSs were calculated, and performances were compared using area under the receiver operating characteristic curve (AUC) and positive predictive value (PPV). All SNP-based methods were found to be independently associated with PCa (all P < 0.05; hence their clinical validity). The mean GRSs in men with or without PCa using GRS-RAC were 55.15 and 53.46, respectively, using GRS-wRAC were 7.42 and 6.97, respectively, and using GRS-PS were 1.12 and 0.84, respectively (all P < 0.05 for differences between patients with or without PCa). All three SNP-based methods performed similarly in discriminating PCa from non-PCa based on AUC and in predicting PCa risk based on PPV (all P > 0.05 for comparisons between the three methods), and all three SNP-based methods had a significantly higher AUC than family history (all P < 0.05). Results from this study suggest that while the three most commonly used SNP-based methods performed similarly in discriminating PCa from non-PCa at the population level, GRS-PS is the method of choice for risk assessment at the individual level because its value (where 1.0 represents average population risk) can be easily interpreted regardless of the number of risk-associated SNPs used in the calculation.

Asian Journal of Andrology (2016) 18, 520–524; doi: 10.4103/1008-682X.179527; published online: 15 April 2016

Keywords: genetic risk score; prostate cancer; single nucleotide polymorphisms

INTRODUCTION
As the second most commonly diagnosed cancer among men worldwide, there has been frequent debate regarding prostate cancer (PCa) screening for men in the general population. However, most clinicians agree that screening high-risk men provides improved benefits to those men at higher risk while reducing overdiagnosis and overtreatment of indolent cases. To determine which men are at higher risk of developing PCa, various risk assessment methods are currently used. In addition to age and race, family history (FH) information is often used. Extensive evidence exists to support that men with FH of PCa are at significantly increased risk of developing PCa themselves.

Although data support the use of FH for assessing one’s risk of developing PCa, its use is often limited in clinical practice. First, FH is effective at identifying only ~10% of men in the population at higher risk. Second, the majority of men do not know their FH, and are even less likely to know accurate information of disease phenotypes. Third, FH is an indirect measure of inherited risk and is not capable of distinguishing risk between individuals with the same degree of relation to an affected family member (e.g., brothers whose father had PCa are estimated to have the same risk as each other despite the fact that they only share 50% of their DNA). Newer genetic-based risk assessment methods have been shown to be clinically valid, be complementary to FH assessments, distinguish between family members, and be capable of providing novel and individualized risk assessment. One such method utilizes genotyping of genetic alterations known as single nucleotide polymorphisms, or “SNPs”. To date, more than 100 of these SNPs have been associated with PCa through genome-wide association studies (GWAS). While SNPs can be easily assessed in patient saliva or blood samples, their use in clinical settings to guide PCa screening is still in its infancy. Three major and different methods can be used to determine genetic risk based on the >100 known PCa SNPs.
risk-associated SNPs: (a) a simple count of risk-associated alleles, in this paper referred to as “GRS-RAC” (AC); (b) weighted risk allele count (GRS-wRAC),13−15 where risk alleles are weighted by their odds ratios (ORs); and (c) a population-standardized genetic risk score (GRS-PS),16 in which alleles are weighted by OR and frequency in the population.

While all three methods of SNP analysis have been validated in various study populations and numerous peer-reviewed publications, few studies have systematically compared their characteristics and predictive performance. In the present analyses, we seek to compare these methods (GRS-RAC, GRS-wRAC, or GRS-PS) in their ability to predict PCa risk both at the population and individual levels by testing each method in a large PCa prevention cohort (Reduction by Dutasteride of Prostate Cancer Events trial; REDUCE).

METHODS

Study population

Subjects in this study were enrolled in the REDUCE clinical trial of dutasteride, which examined the effect of this drug on PCa development. The specific study design is described elsewhere.17 Briefly, eligible men had a serum PSA of 2.5–10.0 ng ml−1 (50–60 years of age) or 3.0–10.0 ng ml−1 (61–75 years of age) and had undergone one negative 6–12 core biopsy within 6 months of enrollment. Participants in this 4-year trial were randomized to receive 0.5 mg of dutasteride daily or to receive a placebo. Here, the placebo arm (n = 1654) is used for the primary analyses reported due to the effects of dutasteride on decreasing PCa incidence; however, the drug arm of this trial (n = 1585) is used as an independent cohort in which the analyses were replicated. The Institutional Review Board at all participating institutions approved these studies, and all patients provided informed consent.

Genotyping

DNA samples were genotyped using the Illumina HumanOmniExpress BeadChip that included 729 755 SNPs in the Center for Cancer Genomics at Wake Forest University. All 3225 samples reached a genome-wide call rate of 99.7%, of which 14 samples were not able to be genotyped due to the sample quality. For SNPs that were not included in the GWAS array, imputation was performed using IMPUTE 2.2.2 based on the combined data of the 1000 Genomes project and HapMap3 data. A posterior probability of >0.9 was applied to call imputed genotypes.

Assessment of genetic risk

SNP selection

A total of 59 SNPs known to be associated with risk of PCa were assessed in this study. The criteria used to ensure that SNPs were truly risk associated and independent from each other include (a) discovered from GWAS studies with at least 1000 cases and 1000 controls, (b) met the gold standard GWAS significance level of P < 5 × 10−8, (c) replicated in at least one independent study, (d) reported in a paper published in a high-impact journal, and (e) independent, linkage disequilibrium measurement (r² < 0.2) between any pair of SNPs.

Genetic risk assessment

The three most frequently used methods of genetic risk assessment were used for the evaluation of individual disease risk. The calculations of the three methods are as follow.

Method 1 (GRS-RAC)

Risk alleles (R) and nonrisk alleles (N) were counted at each locus. Genotype RR was counted as 2, RN as 1, and NN as 0. Then, the number of risk alleles was summed.

Method 2 (GRS-wRAC)

The allelic odds ratio (OR) of each SNP was obtained from external studies. The natural log (In) of each OR for each SNP was multiplied by the number of risk alleles (2, 1, or 0) to generate a genotypic OR; said values for each locus were then summed.

Method 3 (GRS-PS)

As for Method 2, allelic ORs for each SNP were obtained from external studies, and genotypic ORs were calculated. The risk relative to the average risk in the population was then calculated based on genotypic OR and risk allele frequency of each SNP in Caucasians; said values for each locus were then multiplied.

Statistical analysis

Student’s t-tests (for normal variables) and Mann–Whitney U-tests (for nonnormal variables) were used to compare the variables among groups in univariate analyses. In multivariate analyses, logistic regression was used to evaluate the three genetic risk assessment methods after adjusting for clinical variables. The predictive ability of FH and the three methods of genetic risk assessment were evaluated using area under the receiver operating curve (AUC) analyses. The AUCs were compared by Z-tests. Positive predictive values (PPVs) were used to describe the performance of each risk assessment method over a certain cutoff. All statistical analyses were performed using SPSS 22.0 (IBM Corporation, New York, USA). Two-tailed P < 0.05 was considered statistically significant.

RESULTS

Among the 1654 men in the placebo arm of the REDUCE study, 410 men (24.8%) were diagnosed with PCa and 108 men (6.5%) were diagnosed with high-grade PCa (defined as Gleason score ≥ 7) as shown in Table 1. Of all subjects diagnosed with PCa, 16.6% (n = 68) reported a FH of PCa while only 11.7% (n = 146) of non-PCa subjects reported a FH of PCa (P = 0.014). In addition, 19.4% (n = 21) of high-grade PCa subjects reported an FH of PCa. PSA levels and prostate volumes for each group of patients (high-grade PCa, all PCa, and non-PCa subjects) are shown in Table 1. Results from the dutasteride arm are shown in Supplementary Table 1.

Table 1 also compares the three methods of interest among four subsets of patients: all PCa patients, non-PCa patients, high-grade PCa patients, and non-high-grade PCa patients (i.e., low-grade PCa and non-PCa). Scores for Methods 1 and 2 approach normal distribution, and means ± standard deviation (s.d.) are shown in Table 1. Scores from Method 3 are not normally distributed, so logarithm means after a logarithm transformation were calculated. Mean allele counts for Method 1 (GRS-RAC) among PCa and non-PCa subjects were 55.15 and 53.46, respectively (P = 5.61 × 10−18). Mean allele counts among high-grade PCa and all other patients were 54.97 and 53.80, respectively (P = 0.015). For Method 2, mean GRS-wRACs for all PCa patients and non-PCa patients were 7.42 and 6.97, respectively (P = 1.56 × 10−13). Mean GRS-wRACs among high-grade PCa and all other patients were 7.31 and 7.04, respectively (P = 0.002). For Method 3, mean GRS-PSs for all PCa patients and non-PCa patients were 1.12 and 0.84, respectively (P = 8.51 × 10−13). Mean GRS-PSs for high-grade PCa patients were 1.12 and 0.89, respectively (P = 0.001). Similar results were found in the dutasteride arm (Supplementary Table 1).

To assess whether each method was independently associated with PCa and with high-grade PCa, multivariate analyses adjusting for age, FH, PSA, fPSA, and PV were performed when testing the association of each method with disease (Table 2). Method 1, GRS-RAC, had an OR of 1.08 (95% CI: 1.05–1.11) for PCa and an
Table 1: Baseline clinical, demographic and SNP analysis data of subjects in placebo group of REDUCE study

| Variables          | PCA   | Non-PCA | P      | High-grade PCA | Others | P      |
|--------------------|-------|---------|--------|----------------|--------|--------|
| n (%)              | 410   | (24.8)  | 1244   | (75.2)         | -      | 108    | (6.5)  | 1546 | (93.5) | -      |
| Age (years, mean±s.d.) | 63.52±5.99 | 62.22±6.01 | 1.47x10^{-4} | 64.92±5.72 | 62.38±6.02 | 2.27x10^{-5} |
| Family history (%) | 68 (16.6) | 146 (11.7) | 0.014 | 21 (19.4) | 193 (12.48) | 0.037 |
| PSA (ng ml^{-1}, median and IQR) | 5.70 (4.70–7.40) | 5.70 (4.30–7.20) | 0.030 | 5.90 (4.80–7.80) | 5.70 (4.40–7.20) | 0.018 |
| IPSA (ng ml^{-2}, median and IQR) | 0.90 (0.60–1.20) | 0.90 (0.70–1.20) | 0.59 | 0.90 (0.60–1.20) | 0.90 (0.70–1.20) | 0.82 |
| %PSA (median and IQR) | 15.49 (11.54–18.87) | 15.96 (12.50–19.74) | 0.014 | 14.76 (10.65–18.18) | 15.87 (12.36–19.61) | 0.032 |
| PV (ml, median and IQR) | 41.61 (30.90–54.60) | 45.46 (35.04–56.74) | 1.43x10^{-4} | 40.63 (29.58–51.33) | 44.89 (34.00–56.55) | 0.001 |
| PSAD (ng ml^{-1}, median and IQR) | 0.14 (0.10–0.20) | 0.12 (0.09–0.17) | 6.33x10^{-6} | 0.14 (0.11–0.21) | 0.13 (0.09–0.17) | 1.45x10^{-4} |
| GRS-RAC (mean±s.d.) | 55.14±6.44 | 53.46±4.80 | 5.61x10^{-10} | 54.97±4.80 | 53.80±4.81 | 0.015 |
| GRS-wRAC (mean±s.d.) | 7.42±0.69 | 6.97±0.92 | 1.56x10^{-11} | 7.31±0.71 | 7.04±0.89 | 0.002 |
| GRS-PS (mean±s.d.)^a | 1.12±1.99 | 0.84±1.97 | 8.51x10^{-13} | 1.12±2.03 | 0.89±1.99 | 0.001 |

^aThe means and P values were calculated by t-test after taking log_{10} of GRPS. PCA: prostate cancer; PSA: prostate-specific antigen; IPSA: free prostate-specific antigen; %PSA: percentage free prostate-specific antigen; PV: prostate volume; PSAD: prostate-specific antigen density; s.d.: standard deviation; IQR: interquartile range; RAC: risk allele count; wRAC: weighted risk allele count; PS: population-standardized; SNP: single nucleotide polymorphism; REDUCE: Reduction by Dutasteride of Prostate Cancer Events; GRS: genetic risk score.

OR of 1.06 (95% CI: 1.01–1.10) for high-grade PCA (P = 7.32 x 10^{-10} and P = 0.011, respectively). Method 2, GRS-wRAC, had an OR of 1.83 (95% CI: 1.54–2.17) for PCa and an OR of 1.62 (95% CI: 1.23–2.15) for high-grade PCA (P = 7.32 x 10^{-9} and P = 0.001, respectively). Method 3, GRS-PS, had an OR of 1.35 (95% CI: 1.21–1.50) for PCA and an OR of 1.35 (95% CI: 1.07–1.43) for high-grade PCA (P = 8.19 x 10^{-8} and P = 0.004, respectively).

AUC for discriminating PCa and high-grade PCa was also significantly higher (P < 0.05). All three SNP-based methods had significantly higher AUCs than FH (all P < 0.05).

Table 2: Multivariate analyses of three SNP-based GRS methods in placebo group of REDUCE study

| Variables          | OR (95% CI) | P       | OR (95% CI) | P       |
|--------------------|-------------|---------|-------------|---------|
| GRS-RAC            | 1.08 (1.05–1.11) | 7.32x10^{-10} | 1.06 (1.01–1.10) | 0.011 |
| Age                | 1.06 (1.04–1.08) | 1.45x10^{-7} | 1.10 (1.07–1.15) | 1.14x10^{-7} |
| Family history     | 1.68 (1.20–2.33) | 0.002 | 2.18 (1.29–3.67) | 0.004 |
| PSA                | 1.14 (1.06–1.22) | 4.71x10^{-4} | 1.23 (1.10–1.39) | 0.001 |
| IPSA               | 0.59 (0.41–0.86) | 0.006 | 0.55 (0.29–1.04) | 0.067 |
| PV                 | 0.99 (0.98–1.00) | 0.012 | 0.98 (0.97–0.99) | 0.004 |
| GRS-wRAC           | 1.83 (1.54–2.17) | 2.58x10^{-12} | 1.62 (1.23–22.15) | 0.001 |
| Age                | 1.06 (1.04–1.08) | 1.19x10^{-7} | 1.11 (1.07–1.15) | 1.04x10^{-7} |
| Family history     | 1.68 (1.20–2.34) | 0.002 | 2.16 (1.28–3.65) | 0.004 |
| PSA                | 1.13 (1.05–1.02) | 0.001 | 1.23 (1.09–1.38) | 0.001 |
| IPSA               | 0.60 (0.41–0.87) | 0.008 | 0.56 (0.29–1.06) | 0.074 |
| PV                 | 0.99 (0.98–1.00) | 0.012 | 0.98 (0.97–0.99) | 0.001 |
| GRS-PS             | 1.35 (1.21–1.50) | 8.19x10^{-8} | 1.23 (1.07–1.43) | 0.004 |
| Age                | 1.06 (1.04–1.08) | 2.22x10^{-7} | 1.10 (1.06–1.15) | 1.34x10^{-7} |
| Family history     | 1.67 (1.20–2.32) | 0.002 | 2.16 (1.28–3.63) | 0.004 |
| PSA                | 1.13 (1.05–1.02) | 0.001 | 1.23 (1.09–1.39) | 0.001 |
| IPSA               | 0.61 (0.42–0.89) | 0.010 | 0.57 (0.30–0.99) | 0.087 |
| PV                 | 0.99 (0.98–1.00) | 0.011 | 0.98 (0.97–0.99) | 0.004 |

PCa: prostate cancer; PSA: prostate-specific antigen; IPSA: free prostate-specific antigen; PV: prostate volume; RAC: risk allele count; wRAC: weighted risk allele count; PS: population-standardized; SNP: single nucleotide polymorphism; REDUCE: Reduction by Dutasteride of Prostate Cancer Events; GRS: genetic risk score; OR: odds ratio

DISCUSSION

The basis of the United States Preventive Services Task Force's (USPSTF's) recommendation against PSA screening for PCa is that the benefit of reducing PCa mortality by PSA screening is outweighed by its harms of overscreening, over biopsy, and overtreatment of indolent PCa. While recommendation against PSA screening by USPSTF is one way to address these challenges, a more rational approach is to offer PSA screening for a targeted group of high-risk men as recommended by the American Urological Association. Men at heightened risk of developing PCa, such as those with a positive FH, are more likely to be benefited by PSA screening. However, FH captures only a small proportion of men who are at higher risk for PCa. Many studies in the past several years have provided strong support for the use of PCa risk-associated SNPs to identify men who have higher inherited risk for PCa, in addition to those with an FH of the disease.
Table 3: Discriminative performance of risk assessment methods in the placebo group of REDUCE study

| Variables          | Predicting PCa | Predicting high-grade PCa |
|--------------------|----------------|---------------------------|
|                    | AUC (95% CI)   | SE                         | P   | P  | SE             | P   | P  |
| Family history     | 0.53 (0.49–0.56) | 0.017                       | -   | -  | -               | -   | -  |
| GRS-RAC            | 0.60 (0.57–0.63) | 0.016 0.002 All P<0.05<sup>a</sup> | -   | -  | -               | -   | -  |
| GRS-wRAC           | 0.62 (0.59–0.65) | 0.016 0.0001                | -   | -  | -               | -   | -  |
| GRS-PS             | 0.62 (0.59–0.65) | 0.016 0.0001                | -   | -  | -               | -   | -  |

aComparing AUCs of family history with others; bComparing AUCs between GRS-RAC and GRS-wRAC, GRS-wRAC and GRS and GRS-RAC and GRS. RAC: risk allele count; wRAC: weighted risk allele count; PS: population-standardized; AUCs: area under the receiver operating characteristic curves; SE: standard error; PCa: prostate cancer; REDUCE: Reduction by Dutasteride of Prostate Cancer Events; CI: confidence interval; GRS: genetic risk score

Table 4: Positive predictive values of family history and SNP-based methods for predicting PCa and high-grade PCa in placebo group of REDUCE study

| Variables | PPVs % (n) | P       |
|-----------|------------|---------|
|           | Family history | RAC | wRAC | PS |
| PCa       | Family history | 31.8 (n=214) | -   | -   | -   |
|           | GRS-RAC (cutoff=58) | 34.2 (n=363) | 0.58 | -   | -   |
|           | GRS-wRAC (cutoff=7.61) | 36.3 (n=353) | 0.32 | 0.81 | -   |
|           | GRS-PS (cutoff=1.50) | 36.3 (n=353) | 0.32 | 0.81 | 1   |
| High-grade PCa | Family history | 9.8 (n=214) | -   | -   | -   |
|           | GRS-RAC (cutoff=57) | 8.5 (n=363) | 0.65 | -   | -   |
|           | GRS-wRAC (cutoff=7.61) | 9.9 (n=353) | 1   | 0.61 | -   |
|           | GRS-PS (cutoff=1.50) | 9.9 (n=353) | 1   | 0.61 | 1   |

RAC: risk allele count; PS: population-standardized; PPVs: positive predictive values; SNP: single nucleotide polymorphism; PCa: prostate cancer; REDUCE: Reduction by Dutasteride of Prostate Cancer Events; GRS: genetic risk score; wRAC: weighted risk allele count

Although the clinical validity of SNP-based analysis for measuring inherited risk of PCa is consistently demonstrated by comparing means in groups of men with or without PCa (i.e., at a population level), a robust, easy-to-interpret and more discriminative method of SNP analysis at an individual level is needed for implementation in clinic. In this study, we compared three quantitative, commonly used SNP analysis methods to assess inherited risk of developing PCa in a prospective cohort. Several important findings emerged from this study and their implications for risk stratification at both population and individual levels are discussed below.

At the population level, all three SNP analysis methods performed similarly in discriminating PCa from non-PCa and high-grade PCa from others (AUC) and in predicting risk for PCa and high-grade PCa (PPV). This finding was expected since these three methods are all based on the same risk-associated SNPs. In addition, because the ORs of these SNPs are similar (range: 1.06–2.23), the benefit of incorporating ORs into risk assessment calculations of GRS-wRAC and GRS-PS compared the method that does not include the OR information (GRS-RAC), is likely small. Finally, because allele frequency only affects the values of scores for GRS-wRAC and GRS-PS, but does not affect the ranking of risk for subjects relative to each other, the discriminative and predictive performances of these two methods are the same (the exact values of AUC and PPV for these two methods are the same). Therefore, if the intended purpose of SNP analysis is to test whether the cumulative effect of multiple PCa risk-associated SNPs is a predictor of PCa risk, any of the three examined methods can be used.

At the level of the individual patient, however, GRS-PS is the preferred method considering it is the only method that determines risk using a population-standardized method that incorporates both OR and population risk allele frequency of each SNP. As such, a GRS-PS equal to 1 represents the average population risk, a GRS-PS below 1 represents lower risk, and a GRS-PS above 1 represents higher risk of PCa compared to the general population. This unique property of the GRS-PS calculation is not affected by the number of risk-associated SNPs used in determining PCa risk. In comparison, the scores of GRS-RAC and GRS-wRAC will change depending on the number of risk-associated SNPs included in the calculation, which makes it difficult to interpret SNP analysis results for GRS-RAC and GRS-wRAC as they relate to individualized risk.

The mean GRS-PSs were close to 1.0 in this prospective study cohort (0.91 and 0.95 in the placebo and treatment arms, respectively). This is expected based on the formula for calculating GRS-PSs, as long as the OR estimates and risk allele frequencies used in the calculations are representative of the study cohort. This finding is also supported by a comprehensive simulation analysis that mimics real-life situations where OR and risk allele frequencies are often over- or under-estimated (data has not been published). However, the means are slightly lower than 1.0 in both placebo and treatment arms. This is likely due to overestimated risk allele frequencies and ORs of SNPs used in the calculation, which came from the 1000 Genome Project data. Using the risk allele frequencies from this REDUCE population, means were 1.005 and 1.016 for the placebo and drug groups, respectively (data not shown). These data suggest that using the risk allele frequencies for calculating GRS-PS is an important factor in the quality of results. Another possible explanation for the mean GRS-PS being below 1.0 is that patients in the REDUCE cohort have lower inherited risk than the general population. This is plausible because all patients in the population had an initially negative prostate biopsy, indicating decreased likelihood of developing PCa than the general population.

In this prospective cohort, assessing the inherited risk of developing PCa using SNP-based analysis was found to be a better discriminator of biopsy outcomes than FH, as measured by AUC, for PCa versus non-PCa, and high-grade PCa versus others. In contrast, we did not find statistically significant differences in the PPVs between SNP-based methods and FH in predicting risk for PCa and high-grade PCa among men classified as higher risk. AUC is a statistically more powerful measurement than PPV because it does not require a subjective cutoff value, and all subjects are utilized in the calculation. Despite the lower statistical power, however, PPV is a more relevant measurement than AUC for targeted PSA screening among high-risk men because it directly measures the percentage of men with positive biopsies among men defined as high risk using a specific method. When comparing SNP-based methods to FH, it is also important to note that more men were classified as higher risk using SNP analyses (~22%) than FH (13%).

Findings from the primary analyses in this study were replicated in men in the treatment arm of the REDUCE study (i.e., those who received dutasteride). Although PCa incidence was lower in the treatment arm than in the placebo arm, likely due to the effects of dutasteride, the trends seen in the placebo arm were confirmed in this independent population (Supplementary Tables 1–4).
Each of the three SNP analysis methods has advantages and disadvantages. GRS-RAC is easy to calculate and does not require knowledge of OR or risk allele frequency. GRS-wRAC is more powerful than GRS-RAC, but requires estimates of ORs for each SNP. Finally, GRS-PS requires estimates of both OR and population risk allele frequency. GRS-PSs performance is the same as GRS-wRAC, but its score (where 1.0 represents population average risk regardless of the number of risk-associated SNPs used in the calculation) is easier to interpret clinically than either GRS-RAC or GRS-wRAC.

CONCLUSIONS
Results from this study suggest that although the three most commonly used SNP analysis methods performed similarly in discriminating PCa and non-PCa at the population level, GRS-PS is the method of choice at the individual level.

AUTHOR CONTRIBUTIONS
CAC drafted the manuscript. RN and HC calculated individual GRSSs and conducted statistical analyses. CBB provided input to the drafted manuscript. XL and SLZ performed genotyping and other experimental works. JX designed and supervised the study and revised the manuscript. All authors have read and approved the final version of the manuscript and agree with the order and presentation of the authors.

COMPETING INTERESTS
None of the authors declared competing financial interests.

ACKNOWLEDGMENTS
We would like to thank all subjects for their participation in this study and the REDUCE Study Team. This study is partially supported by the Ellrott-Schweighauser Family Chair of Cancer Genomic Research of Northshore University HealthSystem to JX. This work was also in part supported by the grants from the Key Project of the National Science Foundation of China to JX (81130047), the National Key Basic Research Program Grant 973 of China to JX (81402339), and the National Science Foundation of China to RN (81402339).

Supplementary information is linked to the online version of the paper on the Asian Journal of Andrology website.

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### Supplementary Table 1: Baseline clinical, demographic and SNP analysis data of subjects in drug group of REDUCE study

| Variables | PCa | Non-PCa | P  | High-grade PCa | Others | P  |
|-----------|-----|---------|----|----------------|--------|----|
| n (%)     | 304 (19.2) | 1281 (80.8) | -  | 101 (6.4)      | 1484 (93.6) | -  |
| Age (years, mean±s.d.) | 63.88±5.87 | 62.78±5.97 | 0.004 | 64.59±5.51 | 62.88±5.98 | 0.005 |
| Family history (%) | 48 (15.8) | 176 (13.7) | 0.36 | 14 (13.9) | 210 (14.2) | 0.94 |
| PSA (ng ml⁻¹, median and IQR) | 5.80 (4.60–7.50) | 5.60 (4.30–7.20) | 0.049 | 6.00 (5.00–7.98) | 5.60 (4.30–7.20) | 0.010 |
| fPSA (ng ml⁻¹, median and IQR) | 0.80 (0.60–1.20) | 0.90 (0.70–1.20) | 0.013 | 0.80 (0.53–1.10) | 0.90 (0.70–1.20) | 0.002 |
| %fPSA (median and IQR) | 14.95 (11.00–18.80) | 16.36 (12.99–20.37) | 3.22×10⁻⁶ | 12.77 (9.04–16.06) | 16.28 (12.90–20.27) | 1.53×10⁻⁹ |
| PV (ml, median and IQR) | 40.69 (31.00–53.00) | 45.62 (35.53–59.52) | 5.80×10⁻⁶ | 34.64 (28.25–48.09) | 45.20 (35.27–58.86) | 3.31×10⁻⁷ |
| PSAD (ng ml⁻², median and IQR) | 0.14 (0.10–0.20) | 0.12 (0.09–0.16) | 0.17 (0.12–0.24) | 0.12 (0.09–0.16) | 3.30×10⁻¹⁰ |
| GRS-RAC (mean±s.d.) | 55.70±4.70 | 53.69±4.76 | 5.13×10⁻¹¹ | 55.09±4.27 | 54.00±4.84 | 0.029 |
| GRS-wRAC (mean±s.d.) | 7.35±0.81 | 7.06±0.79 | 6.87×10⁻⁹ | 7.23±1.00 | 7.11±0.78 | 0.13 |
| GRS-PS (mean±s.d.) | 1.20±2.00 | 0.89±1.98 | 1.65×10⁻¹¹ | 1.11±2.00 | 0.93±2.00 | 0.012 |

†The means and P values were calculated by t-test after taking log₁₀ of GRS. PCa: prostate cancer; PSA: prostate-specific antigen; fPSA: free prostate-specific antigen; %fPSA: percentage free prostate-specific antigen; PV: prostate volume; PSAD: prostate-specific antigen density; s.d.: standard deviation; IQR: interquartile range; RAC: risk allele count; wRAC: weighted risk allele count; PS: population-standardized; GRS: genetic risk score; SNP: single nucleotide polymorphism; REDUCE: Reduction by Dutasteride of Prostate Cancer Events

### Supplementary Table 2: Multivariate analyses of three SNP-based GRS methods in drug group of REDUCE study

| Variables | PCa | Non-PCa | P  | High-grade PCa | Others | P  |
|-----------|-----|---------|----|----------------|--------|----|
| OR (95% CI) | 1.10 (1.07–1.13) | 6.79×10⁻¹¹ | 1.05 (1.00–1.10) | 0.033 |
| Age | 1.06 (1.03–1.08) | 2.66×10⁻⁸ | 1.09 (1.05–1.13) | 9.12×10⁻⁶ |
| Family history | 1.25 (0.87–1.90) | 2.20×10⁻⁶ | 1.10 (0.60–2.01) | 0.77 |
| PSA | 1.23 (1.13–1.34) | 2.00×10⁻⁶ | 1.53 (1.27–1.65) | 3.30×10⁻⁸ |
| fPSA | 0.38 (0.25–0.59) | 2.00×10⁻⁶ | 0.20 (0.10–0.42) | 1.93×10⁻⁵ |
| PV | 0.99 (0.98–1.00) | 2.00×10⁻⁶ | 0.97 (0.96–0.99) | 4.35×10⁻⁴ |

PCa: prostate cancer; PSA: prostate-specific antigen; fPSA: free prostate-specific antigen; PV: prostate volume; PSAD: prostate-specific antigen density; s.d.: standard deviation; IQR: interquartile range; RAC: risk allele count; wRAC: weighted risk allele count; PS: population-standardized; GRS: genetic risk score; SNP: single nucleotide polymorphism; REDUCE: Reduction by Dutasteride of Prostate Cancer Events
### Supplementary Table 3: Discriminative performance of risk assessment methods in the drug group of REDUCE study

| Variables | Predicting PCa | Predicting high-grade PCa |
|-----------|----------------|--------------------------|
|           | **AUC (95% CI)** | **SE**       | **P**  | **AUC (95% CI)** | **SE** | **P**  | **P**  |
| Family history | 0.51 (0.47–0.55) | 0.019 | - | - | 0.50 (0.44–0.56) | 0.030 | - | - |
| GRS-RAC | 0.61 (0.58–0.65) | 0.018 | 1.14×10^{-4} | All P>0.05 | 0.56 (0.51–0.61) | 0.027 | 0.13 | All P>0.05 |
| GRS-wRAC | 0.61 (0.58–0.65) | 0.018 | 9.73×10^{-5} | 0.56 (0.50–0.61) | 0.028 | 0.16 | 0.16 |
| GRS-PS | 0.61 (0.58–0.65) | 0.018 | 9.73×10^{-5} | 0.56 (0.50–0.61) | 0.028 | 0.16 | 0.16 |

*Comparing AUCs of family history with others; **Comparing AUCs between GRS-RAC and GRS-wRAC, GRS-wRAC and GRS, GRS-RAC and GRS. Cl: confidence interval; REDUCE: Reduction by Dutasteride of Prostate Cancer Events; RAC: risk allele count; wRAC: weighted risk allele count; PS: population-standardized; AUCs: area under the receiver operating characteristic curves; SE: standard error; PCa: prostate cancer; GRS: genetic risk score

### Supplementary Table 4: Positive predictive values of family history and SNP-based methods for predicting PCa and high-grade PCa in placebo group of REDUCE study

| Variables | PPVs % (n) | P | | | | |
|-----------|------------|---|---|---|---|---|
| Family history | 21.4 (n=224) | - | - | - | - | - |
| GRS-RAC (cutoff=57) | 25.9 (n=456) | 0.30 | - | - | - | - |
| GRS-wRAC (cutoff=7.60) | 28.1 (n=381) | 0.08 | 0.48 | - | - | - |
| GRS-PS (cutoff=1.50) | 28.1 (n=381) | 0.08 | 0.48 | 1 | - | - |
| High-grade PCa | 6.3 (n=224) | - | - | - | - | - |
| GRS-RAC (cutoff=57) | 6.8 (n=456) | 0.87 | - | - | - | - |
| GRS-wRAC (cutoff=7.60) | 28.1 (n=381) | 0.62 | 0.69 | - | - | - |
| GRS-PS (cutoff=1.50) | 7.6 (n=381) | 0.62 | 0.69 | 1 | - | - |

RAC: risk allele count; wRAC: weighted risk allele count; PS: population-standardized; PPVs: positive predictive values; SNP: single nucleotide polymorphism; PCa: prostate cancer; REDUCE: Reduction by Dutasteride of Prostate Cancer Events; GRS: genetic risk score