Adding Genetic Risk Score to Family History Identifies Twice as Many High-risk Men for Prostate Cancer: Results from The Prostate Cancer Prevention Trial

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Abstract

Background—While family history (FH) has been widely used to provide risk information, it captures only a small proportion of subjects with higher genetic susceptibility. Our objective is to assess whether a genetic risk score (GRS) calculated from prostate cancer (PCa) risk-associated single nucleotide polymorphisms (SNPs) can supplement FH for more effective risk stratification for PCa screening decision-making.

Methods—A GRS was calculated based on 29 PCa risk-associated SNPs for 4,528 men of European descent in the placebo arm of the Prostate Cancer Prevention Trial (PCPT). At study

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entry, participants were free of a PCa diagnosis. Performance of FH and GRS were measured by observed detection rate of PCa and high-grade PCa (Gleason score 7) during the 7-year study.

Results—GRS was a significant predictor of PCa in men with or without a positive FH (P=1.18×10^{-4} and P=4.50×10^{-16}, respectively). Using FH alone, as expected, the 17% of men who were FH+ had a PCa detection rate that was significantly higher (29.02%) than FH− men (23.43%, P=0.001). When both FH+ or GRS>1.4 are considered, more than twice as many men (36%) can be classified as higher risk, as evidenced by a significantly higher PCa detection rate (30.98%) than in the remaining men (20.61%, P=5.30×10^{-15}). If targeting only FH+ men, four of five PCa cases would go undetected, as would a similarly large fraction (~80%) of high-grade PCa cases. In comparison, if targeting FH+ or GRS>1.4 men, almost half of all PCa cases would be detected, including 45% of high-grade PCa cases.

Conclusions—GRS can supplement family history to better identify higher risk men for targeted intervention.

Introduction

Screening for prostate cancer (PCa) and prostate biopsies have become controversial. Central among these concerns is that the use of prostate-specific antigen (PSA) for PCa screening may lead to over-detection and overtreatment of indolent cases. While the European Randomized study of Screening for Prostate Cancer (ERSPC) found a 21% reduction in PCa death for men who underwent PSA screening, no difference in PCa mortality was found the U.S. Prostate, Lung, Colorectal and Ovarian (PLCO) trial.[1,2] Considering that risks of PSA screening may outweigh the benefits, the United States Preventive Services Task Force (USPSTF) recommended against PSA screening in 2012. [3,4] The American Urological Association (AUA), on the other hand, recommends risk-based targeted PSA screening.[5] More precisely defining risk of developing PCa is essential for targeted PSA screening.

Family history (FH) of PCa is a commonly used risk stratification tool for PCa, which generally captures both genetic and shared environmental risk factors. Approximately 7–17% of men in the general population have a FH of PCa.[2,6,7] The increased PCa risk among men with a positive FH (FH+) has been consistently documented, with a relative risk estimated to be 1.3–1.5 from prospective studies.[6,7] However, for the majority of men in the general population for which there are no known affected relatives, FH is less informative, as lack of known FH at the time of examination may not necessarily indicate that men are at lower risk for PCa. Thus, additional methods of risk assessment are needed to identify men at higher risk of PCa, particularly among those without a FH of PCa.

Approximately 100 independent PCa risk-associated single nucleotide polymorphisms (SNPs) that have been identified from genome-wide association studies (GWAS) may represent an objective and novel measurement for PCa risk.[8,9] A genetic risk score (GRS)

derived from a combination of these risk-associated SNPs has been consistently demonstrated in various study populations as an objective and significant predictor for PCa that is independent from other clinical and demographic predictors such as FH.[9–11] Importantly, GRS has consistently been shown to have a better predictive performance of PCa risk than FH.[12] Nevertheless, whether GRS can supplement FH to better stratify PCa risk has not previously been explicitly tested in prospective studies.

The primary objective of this study is to assess the predictive performance of FH supplemented by GRS in stratifying PCa risk in men enrolled in the placebo arm of the Prostate Cancer Prevention Trial (PCPT). Because all men in the study were free of PCa diagnosis at study entry and were followed for seven years for detection of PCa through for-cause or end-of-study prostate biopsies, regardless of the status of FH, the PCPT offered a unique study population and design for an objective assessment of GRS and FH as risk stratification tools. An important clinical implication of developing a more predictive risk assessment tool is for targeted PSA screening.

Materials and Methods

Patients

The demographics of the PCPT study have been described elsewhere.[13] Briefly, men 55 years of age or older with a normal digital rectal examination (DRE), no clinically significant coexisting conditions, an AUA symptom score of less than 20, and a PSA level of 3.0 ng/mL or lower were randomly assigned to receive either finasteride or a placebo. Since finasteride was found to significantly reduce PCa prevalence, the current study was limited to men in the placebo arm. Furthermore, since the vast majority of the PCa risk-associated SNPs were discovered and confirmed in men of European descent, the study was limited to Caucasian men with DNA previously available from the PCPT. The analytic cohort consisted of 4,258 men who were screened annually using a PSA and a DRE over a seven-year follow up period. Men not diagnosed with PCa during study follow up were recommended to undergo an end-of-study prostate biopsy. The typical number of biopsy cores taken was 6–10.

Laboratory methods

PCa risk-associated SNPs discovered from GWAS reported prior to December 2009 were included; each exceeded genome-wide significance levels in their initial reports ($P<10^{-7}$) and has been replicated in independent populations. Genomic DNA was isolated from white blood cells or serum of peripheral blood. Genotyping was performed using either the Illumina GoldenGate 384-plex platform at the University of Texas Health Science Center at San Antonio or the Sequenom MassARRAY platform at Wake Forest School of Medicine. Twenty-nine SNPs were approved for genotyping by the PCPT committee (Supplementary Table 1). The average genotype call rate was 98%. None of the SNPs deviated from Hardy-Weinberg Equilibrium after being adjusted for multiple tests ($P>0.05$).

Measured outcomes

FH in this analysis was based on PCa information among first-degree relatives of the participants at study entry, since more distant FH is less associated with one's risk and often unknown. Diagnoses of PCa were made at the participating PCPT sites and were confirmed by a Gleason sum that was made centrally at the Prostate Diagnostic Laboratory at the University of Colorado. High-grade PCa was defined as a Gleason score of 7 or higher.

Statistical methods

A GRS was calculated for each man based on his SNP genotype, which was weighted by the odds ratio (OR) and the allele frequency of each SNP.[14] Briefly, 1) the allelic OR of 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 HapMap CEU population, and 4) a GRS was obtained by multiplying the risks relative to the population of all SNPs. Therefore, a GRS of 1.0 indicates an average risk in the general population.

A univariate logistic regression model was used to test the association of PCa risk with each demographic and clinical variable.

Performance of FH and GRS for stratifying PCa risk were assessed by the detection rate of PCa and high-grade PCa during the seven years of follow up. Men with GRSs between 0.6 and 1.4 were classified as intermediate risk because they represent the middle ~50% of the analytical cohort, and various cutoff points were used to classify men at higher risk (>1.4, >1.6, >1.8, and >2.0) or men at lower risk (<0.6 and < 0.4). Performance of several potential risk stratification strategies based on FH and/or GRS for detection of PCa were assessed using positive predictive values (PPV), negative predictive values (NPV), proportion of cases detected, and proportion of cases missed.

Ethics

The Institutional Review Boards at the participating trial sites approved the PCPT. The Institutional Review Boards at the Wake Forest School of Medicine and the Johns Hopkins Bloomberg School of Public Health approved this study of genetics. All men enrolled in this study provided informed consent for participation.

Results

All PCa

During the seven years of follow-up, 1,104 of 4,528 men in the study (24.38%) were diagnosed with PCa. In the entire analytical cohort, the odds ratio (OR) of FH and GRS (as a continuous variable) for PCa risk was 1.34 (95% CI: 1.12–1.59, P=0.001) and 1.49 (95% CI: 1.37–1.62, P=1.46×10^{-19}), respectively. In FH+ men, GRS was significantly associated with PCa risk, with an OR of 1.57 (95% CI: 1.25–1.97-, P=1.18×10^{-4}). In men with a negative FH (FH-), GRS was also significantly associated with PCa risk, with an OR of 1.47 (95% CI: 1.34–1.61-, P=4.50×10^{-16}) (Table 1).

The performance of risk stratification using FH and GRS was assessed by the detection rate of PCa during the follow-up period. When FH was used to stratify risk, 17% of men were classified as higher risk based on positive FH. The observed PCa detection rates were significantly higher in men classified as higher risk (29.02%) than those classified as lower risk (23.43%), P=0.001 (Figure 1a). In comparison, when various GRS cutoff values were used to identify men at higher risk, considerably more men were implicated, and their higher estimated risks were confirmed by higher observed detection rates of PCa (see below). For example, when GRS >1.4 was used as a cutoff, 24% of men were classified as higher risk. The observed PCa detection rates were significantly higher in men classified as higher risk (33.18%) than those classified as lower risk (21.57%), P=6.30×10^{-15} (Figure 1b). When combining FH and GRS, 36% of men can be classified as higher risk (FH+ or GRS >1.4). The observed PCa detection rates were significantly higher in men classified as higher risk (30.98%) than those classified as lower risk (20.61%), P=5.30×10^{-15} (Figure 1c).

The quantitative nature of GRS makes it feasible to further refine one's risk for PCa (Figure 2a). Starting at GRS >1.4, the observed PCa detection rate became higher than that of FH (red dotted line), and highest at GRS >2.0. Conversely, men with GRS <0.6 had PCa detections rate lower than that of FH– men (blue dotted line). GRS was especially informative in men without FH, who represent the majority of men in the study and in general populations (Figure 2b). Although these men would typically be considered lower risk, many of them could be re-classified to higher risk based on their GRS, which confers a notably high potential PCa detection rate, even higher than that of men with a positive FH. For example, at a cutoff of GRS >1.4, 23% of FH– men were re-classified as higher risk and their observed detection rate of PCa was 32.72%, which is 13% higher than the rate of detection in FH+ men, P=0.10. GRS was also informative for further refining risk among FH + men (Figure 2c). Approximately 22% of FH+ men could be reclassified to lower risk due to having a GRS <0.6, and their PCa detection rate was lower at 20%, which was 28% lower than the PCa detection rate of men with a FH-, P=0.06.

High-grade PCa

A total of 217 (4.79%) men were diagnosed with high-grade PCa. In univariate analysis, positive FH was not significantly associated with the detection of high-grade PCa (OR=1.21, 95% CI: 0.86–1.72, P=0.28). In contrast, GRS was significantly associated with high-grade PCa (OR=1.34, 95% CI: 1.16–1.54, P=5.86×10^{-5}).

Men with a positive FH had a non-significantly (P=0.20) higher detection rate of high-grade PCa (5.70%) than those with a negative FH (4.61%) (Figure 1a and Figure 2d–f). In comparison, men with GRS >1.4 had a significantly higher detection rate of high-grade PCa (6.29%) than those men with lower risk (4.31%), P=0.008 (Figure 1b and Figure 2d). When combining FH and GRS, the observed high-grade PCa detection rate was significantly higher in men with positive FH or GRS >1.4 (5.89%) than the remaining (4.16%), P=0.009 (Figure 1c). GRS also performed better in predicting high-grade PCa among men with a negative FH (Figure 2e) or positive FH (Figure 2f).

Potential risk stratification strategies based on FH and/or GRS

The performances of several potential risk stratification strategies were compared for targeting men at higher risk of developing PCa (Table 2). The 'FH+' strategy, targeting FH+ men for detecting of PCa, would miss most PCa cases in the study. This method targeted only 17% of men and would detect only 20.29% of all PCa cases and 20.28% of all high-grade PCa cases in the study population. The 'GRS' strategy of selecting those with a higher GRS (>1.4) had a slightly better performance; it would target only 24% of men in the study and would detect 32.97% of all PCa cases and 31.80% of all high-grade PCa cases in the study. Finally, the 'FH+ or GRS>1.4' strategy performed best; it would target 36% of men in the study and detect 46.20% of all men who would develop PCa and 44.70% of all men who would develop high-grade PCa in the study population.

Conversely, we also compared the performance of several hypothetical strategies to define men at lower PCa risk in whom targeted PCa screening may be unnecessary (Table 3). Again, the strategy of 'FH− only' performed poorly. With this strategy, the vast majority of men in the study (83%) would not be targeted for PCa detection and, together with its lower NPV, it would miss 79.71% of men with PCa and 79.72% of men with high-grade PCa in the study population. The other two strategies, 'GRS<0.6 only' and 'FH− and GRS<0.6' performed better than that of 'FH-'. For example, if men with negative FH and GRS<0.6 were considered low risk, 20% men in the study would not be targeted for PCa screening, and use of this strategy would miss only 14.13% of PCa and 16.13% of high-grade PCa.

Discussion

Although FH is widely used for PCa risk stratification, its performance is modest, especially for the vast majority of men in the general population who do not have a FH of PCa. Thus, the primary goal of this study was to assess whether GRS can supplement FH to improve PCa risk stratification.

The association of GRS with PCa risk has been demonstrated consistently, including a large case-control study with 43,303 PCa cases and 43,737 controls [9], prospective biopsy cohorts [16–17], existing clinical trial populations [11,18], and others [10,19–24]. However, its association with PCa risk among men with a negative FH has not been previously evaluated. Utilizing the PCPT, we found that GRS was significantly associated with detection of both PCa and high-grade PCa during seven follow-up among men with and without a FH of PCa. More importantly, we found that GRS can identify a substantial proportion of men at higher risk for PCa among FH− men, and the observed risks for PCa and high-grade PCa in these men were even higher than FH+ men. When combining GRS with FH, we can identify twice as many higher risk men in the study than FH+ alone (36% vs 17%, respectively) and their estimated higher risk was supported by their higher observed detection rate of PCa and high-grade PCa during the seven-year study.

The validity of these findings is supported by the PCPT design. First, PCPT was a prospective study in which all men were free of a PCa diagnosis at study entry and were followed for seven years for the diagnosis of PCa. Second, because all men underwent prostate biopsies, either for-cause or end-of-study, the results are less likely to be influenced

by detection bias related to PSA levels or FH. In contrast, the association of PCa risk with PSA and FH may be overestimated in many observational studies in which men with a higher PSA and/or FH+ may receive closer monitoring for PCa. Third, the PCa risk-associated SNPs selected in the study and ORs of these SNPs used in the calculation of GRS were all predetermined based on prior studies [15]. Therefore, the GRS results were not subjected to over-fitting.

The performances of FH, GRS, and even their combination in stratifying PCa risk are modest, which is not unexpected considering that PCa etiology is complex. While their performances are insufficient to justify their use as diagnostic markers, they can likely be useful for identifying men at higher risk for targeted PSA screening in primary care. This is especially relevant given the recent AUA recommendation of a risk-based PSA screening strategy [5]. The benefit of an FH-based targeted PSA screening strategy has already been demonstrated by a re-analysis of the PLCO study. In contrast to a lack of benefit in reducing PCa-specific mortality by non-targeted PSA screening [2], targeted PSA screening in the ~7% of men with a positive FH would reduce PCa-specific mortality by ~50% [25]. From a comparative effectiveness perspective and based on the current study, it is rational to suggest that GRS should be included in risk stratification methods. With better risk stratification by combining FH and GRS, it is expected that targeted PSA screening may further reduce PCa-specific mortality.

Several features and limitations of this study should be noted. First, because the PCPT was limited to men with PSA 3.0 ng/mL, caution should be exercised when attempting to apply our conclusions to men in the general population. Second, because many PCa cases were detected on an end-of-study biopsy, the detection rate of PCa during the seven-year follow-up (~24%) is higher than that in contemporary clinical settings. This is also a strength of the study as it minimizes the false negative PCa rate. Third, because this genetic study was approved in 2010, only 29 SNPs discovered by 2009 were analyzed. It is expected that adding additional risk-associated SNPs in the analysis would strengthen the current findings. Fourth, due to the PCPT design and inclusion criteria, most cases were less aggressive and few men died of PCa, and research is ongoing to link PCPT participants with the National Death Index [26]. As a result, we expect that risk stratification for lethal PCa will be possible in future analyses. Fifth, although we compared the performance of several hypothetical targeted strategies, the PCPT was not designed for PSA screening. Randomized trials for PSA screening such as PLCO and ERSPC would be more appropriate studies for such analyses. Lastly, because less than 8% of men enrolled in the PCPT were of other races and ethnicities, our current study was limited to Caucasian men. It would seem, however, reasonable to expect that the major findings from this study can be generalized to other ethnicities. Indeed, a significant association of PCa risk with race-specific GRS has been consistently reported in African American [23], Japanese [24], and Chinese populations [17], as well as multiethnic groups [27].

In summary, the current study demonstrates the novel finding that a GRS based on multiple PCa risk-associated SNPs can identify men at heightened risk for PCa, particularly among men with a negative FH. Combining FH with GRS may provide a better risk stratification tool for individualized decision making regarding PSA screening.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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a

Family History (FH)

b

Genetic Risk Score (GRS)

c

Combining GRS & FH
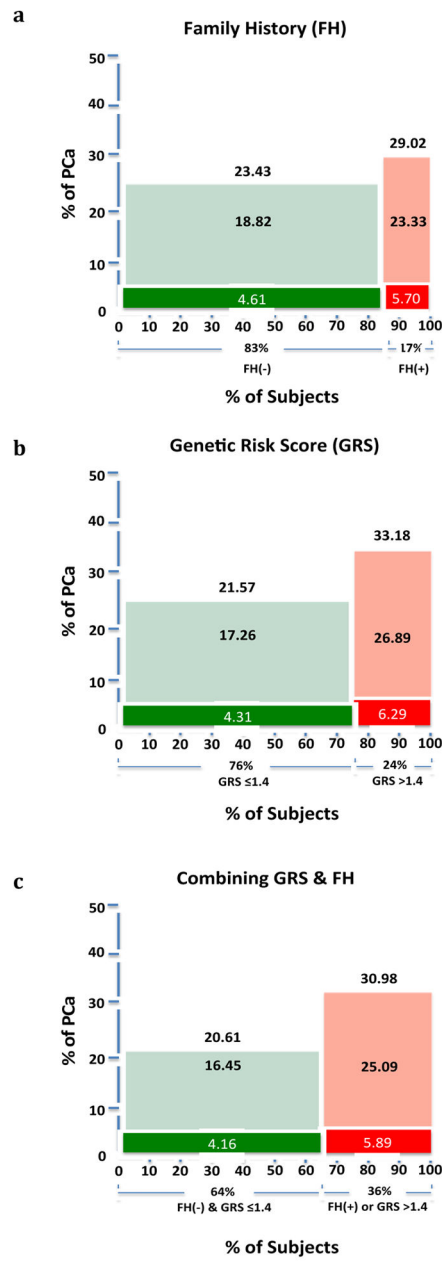
Figure 1.

The detection rate of PCa and high-grade PCa among men defined as higher or lower risk based on family history alone (a), genetic risk score alone (b), and a combination of family history and genetic risk score. Green and red color represents men at lower or higher risk, respectively. Darker colors represent high-grade PCa.
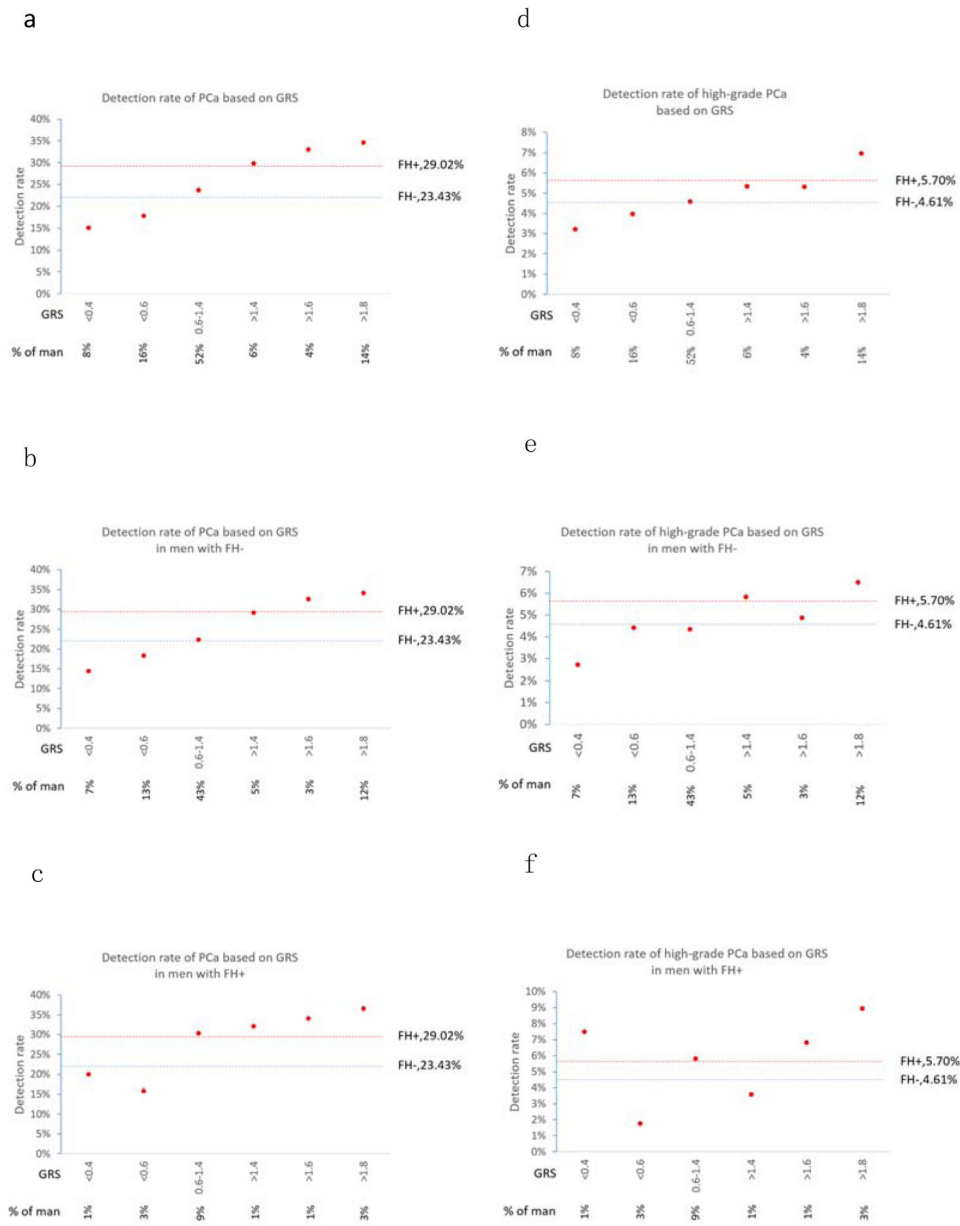
Figure 2.
Detection rate of prostate cancer (PCa) (a–c) and high-grade PCa (d–f) based on family history (FH) and/or genetic risk score (GRS). As a benchmark, detection rate of PCa for men with a positive FH (FH+) and a negative FH (FH-) is indicated in red dotted line and blue dotted line, respectively. Figures a and d were based on GRS for all participants in the study; Figures b and e were based on GRS in men with a negative FH; and Figures c and f were based on GRS in men with a FH+.

Table 1

Characterisics of study participants in the placebo arm of PCPT and results from univariate analyses

Variables	Entire cohort				Men with a positive FH				Men with a negative FH			
	PCa (N=1104)	Non-PCa (N=3424)	OR (95% CI)	P	PCa (N=224)	Non-PCa (N=548)	OR (95% CI)	P	PCa (N=880)	Non-PCa (N=2876)	OR (95% CI)	P
Age, mean, year	63.74	62.82	1.03(1.02–1.04)	1.25E-06	62.9	62.32	1.02(0.99–1.05)	1.89E-01	63.96	62.91	1.04(1.02–1.05)	8.27E-07
tPSA, median, ng/mL	1.40	1.00	2.11(1.88–2.37)	8.96E-36	1.40	1.10	1.85(1.41–2.42)	8.86E-06	1.40	1.00	2.16(1.90–2.46)	3.75E-31
DRE, # (%) positive	15.86	4.49	4.01(3.17–5.06)	2.41E-31	15.98	4.44	4.10(2.34–7.17)	7.86E-07	15.83	4.50	3.99(3.08–5.16)	6.69E-26
FH, # (%) positive	20.29	16.00	1.34(1.12–1.59)	1.02E-03								
GRS, median	1.08	0.87	1.49(1.37–1.62)	1.46E-19	1.15	0.92	1.57(1.25–1.97)	1.18E-04	1.05	0.85	1.47(1.34–1.61)	4.50E-16

PCPT: Prostate Cancer Prevention Trial

PCa: Prostate cancer

tPSA: Total prostate-specific antigen

DRE: Digital rectal examination

FH: Family history

GRS: Genetic risk score

Table 2

Performance of strategies for defining higher PCa risk based on FH and GRS for targeted PCa detection in the placebo arm of PCPT

Criteria for higher risk	#(%) of subjects	Any PCa				High-grade PCa			
		# of cases detected	Positive predictive value (PPV)	Proportion of all cases detected	Detect-to-targeted ratio	# of cases detected	Positive predictive value (PPV)	Proportion of all cases detected	Detect-to-targeted ratio
FH+	772(17%)	224	29.02%	20.29%	1.19	44	5.70%	20.28%	1.19
GRS>1.4	1,097(24%)	364	33.18%	32.97%	1.37	69	6.29%	31.80%	1.31
FH+ and GRS>1.4	223(5%)	78	34.98%	7.07%	1.43	16	7.17%	7.37%	1.5
FH+ or GRS>1.4	1,646(36%)	510	30.98%	46.20%	1.27	97	5.89%	44.70%	1.23

PCPT: Prostate Cancer Prevention Trial

PCa: Prostate cancer

FH: Family history

GRS: Genetic risk score

High-grade PCa is defined as PCa with Gleason score ≥ 7

Table 3

Performance of strategies for defining lower PCa risk based on FH and GRS for targeted PCa detection in the placebo arm of PCPT

Criteria for lower risk	# (%) of subjects	PCa				High-grade PCa			
		# of men negative	Negative predictive value (NPV)	False negative rate	# (%) of cases missed	# of men negative	Negative predictive value (NPV)	False negative rate	# (%) of cases missed
FH−	3,756(83%)	2876	76.57%	23.43%	880(79.71%)	3583	95.39%	4.61%	173(79.72%)
GRS<0.6	1,076(24%)	894	83.09%	16.91%	182(16.49%)	1036	96.28%	3.72%	40(18.43%)
FH− and GRS<0.6	922(20%)	766	83.08%	16.92%	156(14.13%)	887	96.20%	3.80%	35(16.13%)

PCPT: Prostate Cancer Prevention Trial

PCa: Prostate cancer

FH: Family history

GRS: Genetic risk score

High-grade PCa is defined as PCa with Gleason score ≥ 7