Evaluation of a Multiethnic Polygenic Risk Score Model for Prostate Cancer

Anna Plym, PhD, a,b,c Kathryn L. Penney, ScD, b,d Sarah Kalia, ScM, b Peter Kraft, PhD, b,e,f David V. Conti, PhD, g Christopher Haiman, ScD, g Lorelei A. Mucci, ScD, b Adam S. Kibel, MD a

a Urology Division, Department of Surgery, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts

b Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, Massachusetts.

c Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden

d Channing Division of Network Medicine, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, Massachusetts.

e Program in Genetic Epidemiology and Statistical Genetics, Harvard T.H. Chan School of Public Health, Boston, Massachusetts.

f Department of Biostatistics, Harvard T. H. Chan School of Public Health, Boston, Massachusetts.

g Center for Genetic Epidemiology, Department of Preventive Medicine, Keck School of Medicine, University of Southern California/Norris Comprehensive Cancer Center, Los Angeles, California.

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Corresponding author: Anna Plym, Urology Division, Department of Surgery, Brigham and Women's Hospital, Harvard Medical School, 45 Francis Street, Boston, Massachusetts 02115. (E-mail: aplym@bwh.harvard.edu)
Abstract

Polygenic risk scores (PRS) of common genetic variants have shown promise in prostate cancer risk stratification, but their validity across populations has yet to be confirmed. We evaluated a multiethnic PRS model based on 269 germline genetic risk variants (261 were available for analysis) using an independent population of 13,628 U.S. men. The PRS was strongly associated with prostate cancer, but not with any other disease. Comparing men in the top PRS decile to those at average risk (40%-60%), the odds ratio of prostate cancer was 3.89 (95% confidence interval = 3.24 to 4.68) for men of European ancestry and 3.81 (95% confidence interval = 1.48 to 10.19) for men of African ancestry. By age 85, the cumulative incidence of prostate cancer for European American men was 7.1% in the bottom and 54.1% in the top decile. This suggests that the PRS can be used to identify a substantial proportion of men at high risk for prostate cancer.
Genome-wide association studies (GWAS) have identified over 260 germline genetic variants independently associated with prostate cancer risk (1-3). While individual variants contribute to risk only modestly, combining information from multiple variants into a polygenic risk score (PRS) has shown promise to aid in stratification of future prostate cancer risk (1, 3-5). In a multiethnic GWAS of 107,247 prostate cancer cases and 127,006 controls, a PRS including 269 genetic variants effectively stratified prostate cancer risk across ethnic groups (3). In the replication sample, the odds ratio (OR) comparing men in the top decile to men at average genetic risk in the 40–60th percentile of the PRS ranged between 3.53 (95% confidence interval [CI] = 2.66 to 4.69) for men of African ancestry to 4.17 (95% CI = 3.85 to 4.51) for men of European ancestry. The estimated lifetime risk of prostate cancer in the top decile of the PRS was just below 40% for men in the European and African ancestry groups.

Before widespread integration of a PRS into clinical practice, the external validity of findings across populations and settings should be assessed. While the association between the PRS from the multiethnic GWAS and prostate cancer was confirmed in the replication samples, it is unrealistic to assume that genetic variants influence the risk of prostate cancer equally in all populations (6). Furthermore, a PRS model should be validated in populations and settings in which it is intended to be used. To address this, we evaluated this multiethnic PRS in an independent study population of men included in the Mass General Brigham Biobank (7). Individuals in the biobank were patients seen at affiliated hospitals in the greater Boston area and were not recruited for any specific disease.

We first designed a case-control study of men age 40 or above, recruited between 2010 and 2018. Cases were defined as having a biopsy-confirmed prostate cancer documented by a pathology report (82.5%) or at least two prostate cancer-related billing codes. The case-control
population consisted of 13,628 men (1,643 cases and 11,985 controls), of whom 12,473 (91.5%) were of European, 524 (3.8%) of African, 402 (2.9%) of Admixed American, and 229 (1.7%) of Asian ancestry (based on genetically-defined ancestry). We also designed a cohort study of men initially free from prostate cancer, restricted to men of European ancestry due to the small number of men with non-European ancestries. Of the 11,908 men included in the cohort analysis, 847 presented with prostate cancer during a median of 7 (interquartile range = 5-9) years of follow-up. To evaluate if the PRS was specific to prostate cancer, we also conducted a phenome-wide association study (PheWAS) (8) of 1,093 ICD-9 and ICD-10 disease categories in men of European ancestry. Detailed information on material and methods can be found in the Supplementary Materials. All participants provided written informed consent and the study was approved by the Partners Human Research IRB (2019P002655). All statistical tests were two-sided.

In the case-control analysis, the PRS was strongly associated with prostate cancer in the European and African ancestry groups, with an 11-fold gradient in odds of disease. Compared with men at average risk (40-60th percentile), the OR of prostate cancer for men of European ancestry was 0.34 (95% CI = 0.25 to 0.46) in the bottom decile and 3.89 (95% CI = 3.24 to 4.68) in the top decile (Table 1). In men of African ancestry, the OR was 0.15 (95% CI = 0.01 to 0.92) in the bottom decile and 3.81 (95% CI = 1.48 to 10.19) in the top decile. The analysis was underpowered for the other ancestry groups due to few cases (Supplementary Table 1).

The PRS was highly specific for prostate cancer in men of European ancestry. In the PheWAS of over 1,000 disease categories, only two yielded statistically significant associations with the PRS after correction for multiple testing: 1) prostate cancer and 2) presence of elevated prostate-specific antigen (PSA) (Figure 1A and Supplementary Table 2).
In the cohort analysis, the cumulative incidence of prostate cancer in men of European ancestry by age 85 was 42.9% for men in the top quartile of the PRS compared to 10.3% in the bottom quartile (by deciles: 54.1% in the top decile compared to 7.1% in the bottom decile) (Figure 1B and Supplementary Table 3). The PRS did not demonstrate a difference for high, intermediate, and low grade prostate cancer. However, since the PRS was strongly associated with an increased risk of overall prostate cancer, the absolute risk of a Gleason score 7 or higher tumor was highest in the highest PRS quartile. By age 85, it was 19.9% in the top quartile compared to 7.0% in the bottom quartile.

Our results were largely in agreement with the prior multiethnic GWAS. We observed a slightly weaker association between the PRS and prostate cancer in men of European ancestry—but not in men of African ancestry—compared to both the main analysis and the replication sample, which may be related to differences in population structures, prostate cancer screening, or the hospital-based design. The studied population may be enriched with men seeking healthcare for prostate cancer and may not represent the general population in terms of PRS distribution. Although the trend was similar, we observed higher lifetime absolute risk estimates for men of European ancestry across all PRS categories compared to those estimated in the multiethnic GWAS.

Our findings support the use of a PRS as part of risk stratification for prostate cancer in men of European or African ancestry. An advantage of a multiethnic PRS is a single tool that can be used in all individuals. While the PRS on its own is not specific to risk of aggressive disease (3, 9), it provides an opportunity to integrate markers with other serum, urine, or imaging diagnostic tests (10-12) that are specific for aggressive disease. The PRS can narrow the number of men at high risk of prostate cancer, and enable a more focused assessment for aggressive...
disease. This PRS could potentially be used to identify men at increased risk of prostate cancer who would then undergo targeted screening and prophylaxis. Meanwhile, men in the lowest risk of the PRS could safely avoid future screenings. The evaluated PRS may provide a more refined risk estimation than current clinical tools allow.

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Prior presentations: Preliminary result from this study has been presented at the Thirteenth Annual Prostate Cancer Program Retreat, Fort Lauderdale, Florida March 3, 2020.

Data Availability

Variants and weights used to generate the PRS can be found under:

https://www.pgscatalog.org/publication/PGP000122/. Individual-level genotype and clinical data can be obtained from the Mass General Brigham Biobank (https://personalizedmedicine.partners.org/biobank/), but restrictions apply to the availability of these data and data are not publicly available. Data are available for all Mass General Brigham investigators and their external affiliates, including academic and commercial affiliates, provided a protocol from the Institutional Review Board (IRB) and a data use agreement. Samples and data shared with an external entity must be de-identified. Investigators can contact the corresponding author or biobank@partners.org for more information.

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Table 1. Odds ratio (OR) with 95% confidence interval (CI) for the association between polygenic risk score (PRS) and prostate cancer from the case-control analysis

| PRS category | European | | African | |
|--------------|----------|--------------------------|----------|--------------------------|
|              | Cases/Controls | OR\textsuperscript{a} (95% CI) | Cases/Controls | OR\textsuperscript{b} (95% CI) |
| By quartiles | (1,554/10,918) | | (67/457) | |
| 0-25%        | 177/2943 | 0.45 (0.38-0.54) | 8/123 | 0.59 (0.24-1.35) |
| 25-75%       | 700/5536 | 1.00 (Ref.) | 28/234 | 1.00 (Ref.) |
| 75-100%      | 677/2440 | 2.46 (2.18-2.78) | 31/100 | 2.66 (1.44-4.98) |
| By deciles  | | | | |
| 0-10%        | 55/1193 | 0.34 (0.25-0.46) | 1/52 | 0.15 (0.01-0.92) |
| 10-20%       | 79/1168 | 0.51 (0.39-0.67) | 6/46 | 1.21 (0.37-3.70) |
| 20-30%       | 98/1149 | 0.66 (0.52-0.85) | 5/48 | 0.73 (0.21-2.32) |
| 30-40%       | 100/1148 | 0.68 (0.53-0.87) | 5/47 | 0.59 (0.16-1.93) |
| 40-60%       | 285/2210 | 1.00 (Ref.) | 10/94 | 1.00 (Ref.) |
| 60-70%       | 166/1080 | 1.21 (0.98-1.50) | 5/48 | 0.77 (0.21-2.49) |
| 70-80%       | 183/1064 | 1.42 (1.15-1.74) | 7/45 | 1.31 (0.42-3.90) |
| 80-90%       | 223/1024 | 1.87 (1.54-2.29) | 13/39 | 2.27 (0.85-6.16) |
| 90-100%      | 365/883 | 3.89 (3.24-4.68) | 15/38 | 3.81 (1.48-10.19) |

\textsuperscript{a}Adjusted for age at blood collection, genotyping platform/batch and the first 10 principal components.  
\textsuperscript{b}Adjusted for age at blood collection, genotyping platform/batch and the first 2 principal components.
Figure 1. Polygenic risk score (PRS) phenome-wide association results and absolute lifetime risk of prostate cancer in men of European ancestry.

A) Manhattan plot for phenome-wide association study (PheWAS) of 1,093 disease categories (based on billing codes) with the prostate cancer PRS in men of European ancestry. The horizontal pink line indicates phenome-wide-level significance (2-sided $P=4.6\times10^{-5}$) using Bonferroni correction. Adjustments were made for age at blood collection, genotyping platform/batch and the first 10 principal components. Odds ratios (ORs) reported as per one standard deviation increase in the PRS. B) Cumulative incidence of prostate cancer (overall and by Gleason score) for men of European ancestry included in the cohort analysis, stratified by PRS quartile.
Prostate cancer OR = 2.04

Elevated prostate specific antigen (PSA) OR = 1.54

B. Absolute prostate cancer risk

PRS 0–25%

PRS 25–75%

PRS 75–100%

Cumulative incidence

Age

Gleason score

8+
4+3=7
3+4=7
<7
Missing
Prostate cancer
OR = 2.04

Elevated prostate specific antigen (PSA)
OR = 1.54

A. PheWAS of PRS

B. Absolute prostate cancer risk

PRS 0–25%
PRS 25–75%
PRS 75–100%