Assessing the Clinical Role of Genetic Markers of Early-Onset Prostate Cancer among High-Risk Men Enrolled in Prostate Cancer Early Detection

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Abstract

Background: Men with familial prostate cancer and African American men are at risk for developing prostate cancer at younger ages. Genetic markers predicting early-onset prostate cancer may provide clinically useful information to guide screening strategies for high-risk men. We evaluated clinical information from six polymorphisms associated with early-onset prostate cancer in a longitudinal cohort of high-risk men enrolled in prostate cancer early detection with significant African American participation.

Methods: Eligibility criteria include ages 35 to 69 with a family history of prostate cancer or African American race. Participants undergo screening and biopsy per study criteria. Six markers associated with early-onset prostate cancer [rs2171492 (7q32), rs6983561 (8q24), rs10993994 (10q11), rs4430796 (17q12), rs1799950 (17q21), and rs266849 (19q13)] were genotyped. Cox models were used to evaluate time to prostate cancer diagnosis and prostate-specific antigen (PSA) prediction for prostate cancer by genotype. Harrell’s concordance index was used to evaluate predictive accuracy for prostate cancer by PSA and genetic markers.

Results: Four hundred and sixty participants with complete data and follow-up visit were included. Fifty-six percent were African American. Among African American men, rs6983561 genotype was significantly associated with earlier time to prostate cancer diagnosis (P = 0.005) and influenced prediction for prostate cancer by the PSA (P < 0.001). When combined with PSA, rs6983561 improved predictive accuracy for prostate cancer compared with PSA alone among African American men (PSA = 0.57 vs. PSA + rs6983561 = 0.75, P = 0.03).

Conclusions: Early-onset marker rs6983561 adds potentially useful clinical information for African American men undergoing prostate cancer risk assessment. Further study is warranted to validate these findings.

Impact: Genetic markers of early-onset prostate cancer have potential to refine and personalize prostate cancer early detection for high-risk men. Cancer Epidemiol Biomarkers Prev; 21(1); 53–60. ©2011 AACR.

Background

Prostate cancer is the second leading cause of cancer-related deaths in men in the United States (1). Men with a family history of prostate cancer and African American men are at significantly increased risk for the disease (1, 2) and of onset at younger ages (3, 4). A report from 2009 found that the diagnosis of prostate cancer among men ≤55 years has increased from 2.3% between 1988–1991 to 9% between 2000–2003 (5), and these men with young-onset prostate cancer have more threat of morbidity and mortality from prostate cancer, especially if they are diagnosed with high-grade or advanced disease (5). The challenge, however, is predicting which high-risk men are at risk of developing prostate cancer at younger ages and appropriately recommending screening to those men, while sparing other men unnecessary tests and procedures.

Prostate-specific antigen (PSA)-based methods have been the traditional tests used to screen men for prostate cancer and make risk-management decisions. Among high-risk men undergoing prostate biopsies based on PSA criteria, prostate cancer detection rates range between 10% to 17% (3, 4). Therefore, a subset of high-risk men undergo unnecessary prostate biopsies, whereas others have aggressive prostate cancer detected. Genetic markers have the potential to personalize and refine prostate

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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cancer screening and interpretation of PSA if their clinical role is better understood.

Several genetic single nucleotide-polymorphisms (SNP) have been identified from genome-wide association studies (GWAS) to be associated with prostate cancer risk (6), and several GWAS markers have been evaluated for association to early-onset prostate cancer in substudies (7–10). A chromosomal region of great interest in prostate cancer genetics research is 8q24 (8, 11–14). One study found that carrying the minor allele of one polymorphism (rs6983561) at chromosomal locus 8q24 was associated with an increased risk for prostate cancer in men <50 years (7). Another chromosomal region of interest for potentially harboring prostate cancer susceptibility variants is 17q12 (15). One study found that the A-allele of a polymorphism (rs4430796) at 17q12 increased the risk for prostate cancer in men <50 years (16). New genomic regions of interest for prostate cancer risk have continued to be identified. Some of these regions are on chromosomes 3, 6, 7, 10, 11, 19, and X (9). One polymorphism (rs266849) on chromosome 19 was found to be associated with an increased risk for prostate cancer in men <60 years (9). Another study examining genetic variants at 10q11 and Xp11 found that polymorphism rs10993994 was associated with a 2-fold increased risk for prostate cancer in men ≤65 years (10).

A subset of men in families with potential hereditary prostate cancer may be at increased risk for early-onset disease, and one study found a common variant in BRCA1 (rs1799950) was overtransmitted to younger men (age <50 years) affected with prostate cancer from hereditary and early-onset prostate cancer families (17).

Other polymorphisms that reside in known genes have been characterized for association to early-onset prostate cancer (18, 19). One study found a polymorphism (rs2171492) in Carboxypeptidase 4 to be associated with risk for aggressive prostate cancer in men <66 years (18). Therefore, although markers associated with early-onset prostate cancer from various studies are promising for identifying risk for disease diagnosis at younger ages, further study of the clinical information gained from these and other genetic markers is needed to help guide patients and physicians in making individualized screening recommendations.

Here, we evaluate the potential clinical information gained from 6 genetic markers associated with early-onset prostate cancer among high-risk men undergoing prostate cancer screening (7–10, 17, 18). These markers were chosen for study in high-risk men (men with familial prostate cancer and African American men) as subsets of these men undergoing screening have been diagnosed with prostate cancer at ages <55 years (3, 4). Genetic markers of early-onset prostate cancer may add clinical information beyond predicting early-onset disease among high-risk men useful in refining screening decisions. We carried out this study in an ethnically diverse longitudinal cohort of high-risk men enrolled in a prostate cancer early detection program with significant African American participation. We took a broad approach to evaluating the clinical role of early-onset genetic markers to formulate hypotheses about the potential role of genetic markers in clinical prostate cancer risk assessment.

Methods

Prostate cancer risk assessment program cohort

The prostate cancer risk assessment program (PRAP) at Fox Chase Cancer Center (FCCC) was established in 1996 to provide screening and carry out research for men at high risk for prostate cancer (4). Eligibility criteria and cancer detection rates have been described previously (4). Briefly, eligibility for PRAP include any man between ages 35 to 69 years without a previous diagnosis of prostate cancer, with 1 first-degree relative with prostate cancer, 2 second-degree relatives with prostate cancer on the same side of the family, any African American man regardless of family history, or men with known mutations in BRCA1 or BRCA2. Men with BRCA mutations (n = 13) were excluded from the clinical analysis. Accrual to PRAP is ongoing and participants are followed longitudinally for prostate cancer screening and early detection. The PRAP study is approved by the Institutional Review Board at FCCC and at all previous and currently active community hospital sites that enrolled participants to PRAP.

Prostate cancer screening in PRAP

Prostate cancer screening procedures, biopsy criteria, prostate cancer incidence, and prostate cancer features have been described previously (4). Briefly, screening tests include the total PSA, percent free PSA (fPSA), digital rectal examination (DRE) by a PRAP physician, and the PSA velocity (PSAv).

Criteria for biopsy

Until November 2005, the criteria for prostate biopsy were (i) PSA >4 ng/mL, (ii) PSA 2.0–4.0 ng/mL with fPSA less than 27%, (iii) any abnormality on DRE, or (iv) PSAv of 0.75 ng/mL/year. After November 2005, the criteria for biopsy were changed to (i) PSA >2.0 ng/mL, (ii) PSA 1.5–2.0 ng/mL with fPSA ≤25%, (iii) any abnormality on DRE, or (iv) PSAv of 0.75 ng/mL/year to investigate the detection of prostate cancer at lower PSA values (3). All biopsies are transrectal ultrasound-guided 5-region patterned prostate biopsies (20, 21). If all screening parameters are within normal limits based on these biopsy criteria, no biopsy is done and the participant is recommended to return to clinic in 1 year for repeat screening. Men diagnosed with prostate cancer within 6 months after their first visit to PRAP were excluded (n = 42) to eliminate preexisting prostate cancer from this analysis.

Genotyping of six early-onset genetic polymorphisms

Six genetic markers reported to be associated with early-onset prostate cancer were chosen for this study: rs6983561 (8q24; ref. 7), rs4430796 (17q12; ref. 8), rs266849

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addition, Hardy–Weinberg equilibrium was tested for by self-reported race and compared using the Statistical methods. 100% concordance. In addition, genotypes were confirmed on a random selection of 2% of the samples by standard sequencing with 100% concordance.

Statistical methods

Distribution of early-onset markers was summarized by self-reported race and compared using the χ2 test. In addition, Hardy–Weinberg equilibrium was tested for each allele using the χ2 test (22).

Time to prostate cancer diagnosis

For inferences on the relationship between time to prostate cancer and the markers, individual genotype-specific Kaplan–Meier curves were constructed. Each SNP was examined as 3 genotypes and then collapsed into the heterozygous or homozygous genotypes. Time from enrollment to prostate cancer was analyzed. Participants were censored at the last follow-up if they were not diagnosed with prostate cancer at the time of the analysis. Cox proportional hazards regressions were used with each marker tested separately among African American and Caucasian men and adjusted for age and PSA at baseline. Continuous variables were entered as linear terms in models. The risk genotypes were determined as those that created the most separation in the Kaplan–Meier curve, had larger HRs, and greater level of statistical significance.

PSA prediction for prostate cancer by genotype

To evaluate the effect of early-onset marker genotype on longitudinal prediction for prostate cancer by PSA at baseline, the interaction terms between PSA at baseline and risk genotype were entered into each Cox model. To account for multiple hypotheses testing, we set the false discovery rate to 5% using Benjamini and Hochberg’s method (23). Any significant interactions were considered as evidence of differential prediction ability of PSA for prostate cancer by genotype. The HR of one point increase on PSA by genotype was also presented to show the differential prediction ability by genotype. To display the relationship of PSA with time to diagnosis in the models, age and PSA were entered into the Cox model as restricted cubic splines. The 3-year probabilities of being diagnosed with prostate cancer were estimated for each participant. The estimated probabilities were plotted against the baseline PSA. Due to multiple age values, restricted cubic splines were fit to all estimated probabilities to represent the trend of the PSA prediction in each subpopulation.

Predictive accuracy of genetic markers

Harrell’s C index was used to evaluate the accuracy of longitudinal prediction for prostate cancer by early-onset markers and PSA. We created a training dataset and validation dataset by randomly assigning each observation to either dataset and used the program somerD in STATA to compare Harrell’s C from different models (24). Considering our outcome was longitudinal prediction for prostate cancer and traditional area under the receiver operating characteristic curve analyses do not take into account the varied follow-up time, we used the C index which is a member of the “Kendall family” of rank parameters and is used to estimate the concordance probability with censored data. Like area under the curve, a value of 0.5 implies complete discordance. Higher values suggest higher concordance between the data and the predicted values from the model. All analyses were done using STATA 10.1.

Results

Genotype distribution

At the time of this analysis, 778 participants were accrued to PRAP. Genotype distributions in the overall cohort for all 6 early-onset genetic markers differed significantly by race (Supplementary Table S1). Genotype distribution differences were also evaluated comparing those included in this analysis (n = 460) and those excluded (n = 310) for African American and Caucasian PRAP participants (Supplementary Table S2). Only rs4430796 was found have a statistically significant difference in distribution among African American men between those included versus excluded from the analysis (P = 0.001). No differences in genotype frequency were observed for African American or Caucasian men for the other 5 early-onset markers by inclusion in the analysis.

Demographic and clinical features

The sample size for the clinical analysis of the 6 early-onset genetic markers included 460 of the 778 participants accrued. Exclusions from the overall cohort of 778 were as follows: race other than African American or Caucasian (n = 8), BRCA1 or BRCA2 positive (n = 13), missing clinical data (n = 4), diagnosed with prostate cancer within 6 months of first PRAP visit (n = 42) and no follow-up (either lost to follow-up after first visit or first visit was within 12 months of this analysis and participant was not due for follow-up; n = 251). Men diagnosed with prostate cancer within 6 months were removed to exclude preexisting prostate cancer. The demographics of this sample set of 460 participants included in the analysis by self-reported race are shown in Table 1. Approximately 56% of...
participants in the analysis were African American. The mean age at diagnosis for Caucasian participants was 57.5 years (range 46.3–67.4 years) and for African American participants was 57.5 years (range 40.8–73.7 years). The mean time to prostate cancer diagnosis for African American men was 37.9 months (range 6.4–92.0 months) and for Caucasian men was 54.7 months (range 9.4–131.7 months).

### Analysis of clinical role of genetic markers of early-onset prostate cancer

Of the 460 participants included in this analysis, genotypes were able to be determined by marker as follows: rs6983561 (n = 441), rs4430796 (n = 430), rs266849 (n = 436), rs10993994 (n = 447), rs1799950 (n = 444), and rs2171492 (n = 432).

#### Time to prostate cancer diagnosis

Among African American participants, rs6983561 genotype significantly predicted earlier time to prostate cancer diagnosis for men carrying the CC versus AA/AC genotype (HR = 3.34, 95% CI: 1.45–7.70, P = 0.005; Table 2). Rs6983561 genotype was not predictive of time to prostate cancer diagnosis among Caucasian PRAP participants, although no CC genotype was observed among this group. No difference was observed in mean Gleason score by rs6983561 genotype among African American men. None of the other 5 early-onset markers were predictive of time to prostate cancer diagnosis in either race groups. Figure 1 displays the Kaplan–Meier curves for time to prostate cancer diagnosis for rs6983561 by race.

#### Prediction for prostate cancer by PSA

Among African American participants, rs6983561 genotype influenced the 3-year prediction for prostate cancer by the PSA (interaction P < 0.001). The HR for prostate cancer for African American participants carrying CC and AA/AC were 4.29 (95% CI: 2.33–7.91) and 1.33 (95% CI: 1.05–1.69), respectively. Among Caucasian participants, although there was no CC genotype observed, there was a trend toward AC genotype influencing PSA prediction for prostate cancer (P = 0.04; Table 3). The predicted probability of developing prostate cancer at 3 years by rs6983561 genotype is represented in Fig. 2. None of the other 5 early-onset genetic markers influenced PSA prediction for prostate cancer in this analysis.

#### Assessing predictive accuracy for prostate cancer

Analysis of the predictive accuracy for prostate cancer was done only for rs6983561 as this marker was associated with earlier time to prostate cancer diagnosis and with

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### Table 1. Demographics and prostate cancer characteristics of 460 PRAP participants included in the clinical analysis by self-reported race

<table>
<thead>
<tr>
<th></th>
<th>African American (n = 257)</th>
<th>Caucasian (n = 203)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at entry (y)</td>
<td>257 50.9 35–69</td>
<td>203 50.2 35–69</td>
</tr>
<tr>
<td>Duration of follow-up (mo)</td>
<td>257 51.6 0.6–152.0</td>
<td>203 58.4 0.3–163.4</td>
</tr>
<tr>
<td>PSA at baseline (ng/mL)</td>
<td>257 1.6 0.1–27.2</td>
<td>203 1.5 0.2–9.8</td>
</tr>
<tr>
<td>Percent-free PSA at baselinea</td>
<td>257 19.0 7.8–39.4</td>
<td>42 17.7 4.6–30.0</td>
</tr>
<tr>
<td>DRE at baseline (28 missing)</td>
<td>Normal/BPH 235 (96.3)</td>
<td>182 (96.8)</td>
</tr>
<tr>
<td>Biopsy history (reported at baseline)</td>
<td>Abnormal 9 (3.7)</td>
<td>6 (3.2)</td>
</tr>
<tr>
<td>Number of biopsy sessions while in PRAP</td>
<td>257 0.46 0–6</td>
<td>203 0.51 0–7</td>
</tr>
<tr>
<td>prostate cancer diagnosisb</td>
<td>25 (9.7)</td>
<td>24 (11.8)</td>
</tr>
<tr>
<td>Age at diagnosis (y)</td>
<td>25 57.5 40.8–73.7</td>
<td>24 57.5 46.3–67.4</td>
</tr>
<tr>
<td>Mean time to prostate cancer diagnosis (mo)</td>
<td>25 37.9 6.4–92.0</td>
<td>24 54.7 9.4–131.7</td>
</tr>
<tr>
<td>Last PSA prior to prostate cancer diagnosis (ng/mL)</td>
<td>25 4.3 0.9–31.6</td>
<td>24 3.3 1.5–9.8</td>
</tr>
<tr>
<td>Gleason score</td>
<td>25 6.2 5–8</td>
<td>24 6.2 6–7</td>
</tr>
</tbody>
</table>

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*aPercent-free PSA is only done for men with a PSA 2.0 to 4.0 ng/mL by the previous criteria or a PSA 1.5 to 2.0 ng/mL by the current criteria in PRAP. Therefore, not all men have a percent-free PSA done at baseline.

*bPercent of the race group.
higher prediction for prostate cancer by the baseline PSA. Table 4 shows the Harrell's C estimates as a measure of accuracy of prediction for prostate cancer. Among African American men, there was improvement in predictive accuracy for prostate cancer when rs6983561 genotype was added to PSA, particularly when the interaction term was included (Harrell's C: PSA alone = 0.57 vs. PSA + rs6983561 (CC) genotype + interaction term = 0.75, P = 0.03).

Discussion

Over the past 4 years, many genetic markers have been identified through GWAS for association to prostate cancer (6). Although many of these markers have a strong statistical association to prostate cancer risk with P values less than 10^{-7}, the magnitude of risk for prostate cancer is typically modest with ORs less than 2.0 (6). Therefore, the clinical role of these markers and assessing individual risk for prostate cancer is unclear. A particular subgroup of men to benefit from efforts to understand individual risk and clinical role of genetic markers are men with familial prostate cancer and African American men, as these men are susceptible to early-onset disease, which has greater potential impact for prostate cancer–related morbidity and mortality.

Our study was done to evaluate genetic markers associated with early-onset prostate cancer and gain an understanding of the potential clinical information these markers may provide that can be useful to the individual patient for risk assessment. We assessed the clinical information gained from 6 genetic markers previously associated with early-onset prostate cancer and evaluated these markers for their prediction of time to prostate cancer diagnosis, influence on PSA prediction for prostate cancer, and accuracy of these markers over the PSA in predicting prostate cancer in an ethnically diverse, longitudinal cohort of high-risk men enrolled in prostate cancer early detection. Of the 6 early-onset markers analyzed, our results show that rs6983561 is informative in predicting time to prostate cancer diagnosis among African American men. In addition, this marker influences PSA prediction for prostate cancer and adds predictive accuracy to PSA for longitudinal prediction for prostate cancer. Our findings suggest
that markers associated with early-onset prostate cancer deserve further clinical study as they may add useful clinical information that can help guide clinicians and patients in making prostate cancer screening recommendations to diagnose life-ending prostate cancer at a curable point and decrease unnecessary biopsies in high-risk men.

Our study found that rs6983561 genotype has potential clinical use in prostate cancer risk assessment. This polymorphism is located at chromosomal locus 8q24 (6), which is a gene-poor region. The actual function of rs6983561 is unknown; however, the c-myc proto-oncogene is located downstream of this region. Studies to date have not found

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**Table 3.** Cox model results for PSA prediction for prostate cancer by rs6983561 genotype among PRAP participants with ≥1 follow-up visit

<table>
<thead>
<tr>
<th>Genetic marker</th>
<th>n</th>
<th>Genotype</th>
<th>HR^b (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American^a</td>
<td>168</td>
<td>AC/CC</td>
<td>1.42 (1.19–1.71)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>179</td>
<td>AA</td>
<td>1.32 (0.92–1.90)</td>
<td>0.13</td>
</tr>
<tr>
<td></td>
<td>247^c</td>
<td>AC/CC vs. AA</td>
<td>4.29 (2.33–7.91)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>53</td>
<td>CC</td>
<td>1.33 (1.05–1.69)</td>
<td>0.018</td>
</tr>
<tr>
<td></td>
<td>194</td>
<td>AC/AA</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>247^c</td>
<td>CC vs. AC/AA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian^a</td>
<td>20</td>
<td>AC</td>
<td>4.74 (1.35–16.63)</td>
<td>0.015</td>
</tr>
<tr>
<td></td>
<td>174</td>
<td>AA</td>
<td>1.23 (1.02–1.49)</td>
<td>0.033</td>
</tr>
<tr>
<td></td>
<td>194^d</td>
<td>AC vs. AA</td>
<td></td>
<td>0.04</td>
</tr>
</tbody>
</table>

^aAnalysis by race adjusted for age at entry.
^bHRs are the genotype-specific HRs for one point increase on PSA.
^cTwo group comparison P value is based on comparing the 2 genotype-specific HRs.
^dSignificant interaction between PSA and marker genotype is bold after controlling for FDR at 5%.

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**Figure 2.** Race-specific 3-year prediction for prostate cancer by PSA at entry into PRAP by rs6983561 genotype. PCA, prostate cancer. Three-year prediction for prostate cancer was computed from Cox models where the covariates-included the cubic spline of age and PSA at baseline. Probabilities were computed using STATA 10.0. Participant specific predictions were computed on the basis of their individual characteristics (age and baseline PSA) and fitted model coefficient. Each participant who was used in the analysis received a unique prediction. Prostate cancer cases diagnosed within 6 months of enrollment into PRAP were excluded (n = 42 cases excluded).
Overall, our study finds early-onset genetic marker rs6983561 to provide potentially important clinical information about time to prostate cancer diagnosis and influences PSA prediction for prostate cancer among African American men. Validation of these findings about rs6983561 is needed prior to drawing definitive conclusions with regard to the incorporation of this marker in prostate cancer risk assessment. In an era in which genomic information is becoming rapidly available due to advances in technology, it is imperative to study the clinical information gained from genomic markers to develop optimal early detection approaches. Efforts to elucidate the clinical utility of genetic markers associated with early-onset prostate cancer or clinically meaningful prostate cancer should inform future personalized risk assessment.

**Disclosure of Potential Conflicts of Interest**

Timothy R. Rebbeck is the editor-in-chief of *Cancer, Epidemiology, Biomarkers & Prevention*. In keeping with the AACR’s editorial policy, the paper was peer reviewed and a member of the AACR’s publications committee rendered the decision with regard to acceptability.

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Table 4: Accuracy of longitudinal prediction for prostate cancer by PSA and rs6983561 genotype among African American PRAP participants with ≥1 follow-up visit

<table>
<thead>
<tr>
<th></th>
<th>PSA</th>
<th>PSA + rs6983561 (CC)</th>
<th>PSA + rs6983561 (CC with interactiona)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>Harrell’s C</td>
<td>Harrell’s C (Pb)</td>
</tr>
<tr>
<td>African American men</td>
<td>247</td>
<td>0.5713</td>
<td>0.6679 (0.15)</td>
</tr>
</tbody>
</table>

**NOTE:** Caucasian participants not shown as no CC genotype for rs6983561 was observed.

aInteraction is the interaction term for rs6983561 (CC) genotype with PSA.

bP values reflect pairwise comparisons of Harrell’s C in each column to the Harrell’s C for PSA.

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an effect on c-myc expression based on carrier status of markers at 8q24 (25), but research is ongoing to determine potential alternate mechanisms leading to prostate cancer risk (26).

There are some limitations to consider when interpreting the findings of this study. It is noted that there may be clinical utility from the other markers in this study which were not detected due to our sample size. Our results need further confirmation and validation in larger sample sets. Our study did not identify prostate cancer of higher Gleason score. Further research will need to be done to determine whether identifying intermediate risk prostate cancer will have clinical impact with reducing morbidity and mortality from prostate cancer, particularly in younger men. The overall follow-up rate in the PRAP cohort is 66.8%, which may have limited the ability to detect the clinical impact of the other early-onset genetic markers. However, we did not find any difference in genotype distribution between those included versus excluded from the analysis except for rs4430796, which was not associated with significant findings in the clinical analysis. Furthermore, our follow-up rate is close to follow-up rates of other screening cohorts (3). In addition, prostate biopsies are not done in all PRAP participants, only for those who meet biopsy criteria. Therefore, there may be undetected prostate cancer among some participants which may have influenced our results. Confirmation of our findings is required in larger longitudinal screening studies. Finally, more genetic markers associated with early-onset prostate cancer are being identified and will need study with regard to their clinical role in prostate cancer risk assessment (27).

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**References**


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