Race, Genetic West African Ancestry, and Prostate Cancer Prediction by Prostate-Specific Antigen in Prospectively Screened High-Risk Men

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Abstract

“Race-specific” prostate-specific antigen (PSA) needs evaluation in men at high risk for prostate cancer for optimizing early detection. Baseline PSA and longitudinal prediction for prostate cancer were examined by self-reported race and genetic West African (WA) ancestry in the Prostate Cancer Risk Assessment Program, a prospective high-risk cohort. Eligibility criteria were age 35 to 69 years, family history of prostate cancer, African American race, or BRCA1/2 mutations. Biopsies were done at low PSA values (<4.0 ng/mL). WA ancestry was discerned by genotyping 100 ancestry informative markers. Cox proportional hazards models evaluated baseline PSA, self-reported race, and genetic WA ancestry. Cox models were used for 3-year predictions for prostate cancer. Six hundred forty-six men (63% African American) were analyzed. Individual WA ancestry estimates varied widely among self-reported African American men. Race-specific differences in baseline PSA were not found by self-reported race or genetic WA ancestry. Among men with ≥1 follow-up visit (405 total, 54% African American), 3-year prediction for prostate cancer with a PSA of 1.5 to 4.0 ng/mL was higher in African American men with age in the model (P = 0.025) compared with European American men. Hazard ratios of PSA for prostate cancer were also higher by self-reported race (1.59 for African American versus 1.32 for European American, P = 0.04). There was a trend for increasing prediction for prostate cancer with increasing genetic WA ancestry. “Race-specific” PSA may need to be redefined as higher prediction for prostate cancer at any given PSA in African American men. Large-scale studies are needed to confirm if genetic WA ancestry explains these findings to make progress in personalizing prostate cancer early detection.

African American men and European American men with a family history of prostate cancer are at substantially increased risk for the disease and may have clinically more aggressive disease (1–3). Early detection of prostate cancer in these high-risk men presents the ideal situation in which to diagnose prostate cancer while at a curable point, with screening likely leading to the detection of intermediate to high-grade prostate cancer (4, 5). However, several issues remain about the optimal prostate-specific antigen (PSA) level at which to recommend prostate biopsies to detect prostate cancer and at which not to subject these men to unnecessary biopsies. High-risk men have been found to have prostate cancer detected at low PSA values, even <2.5 ng/mL (5, 6). Determining which high-risk men should have prostate biopsies at low PSA values is crucial to early detection and avoiding unnecessary biopsies. An important concept about the PSA in African American men is the “race-specific” PSA. This concept is based on several previous reports that found that African American men had higher PSA values stage-for-stage or at baseline (7–10). Many of these studies were done when PSA was being implemented for prostate cancer screening in the late 1980s to mid 1990s. In addition, due to population admixture, self-reported African American men exhibit large variance in individual genetic West African (WA) ancestry (11, 12), which has not been explored in the context of the race-specific PSA. Furthermore, concerns have been raised about missing high-grade prostate cancer if PSA is adjusted for race based on this concept (13). Thus, issues of prostate cancer prediction at lower PSA values and “race-specific” PSA deserve further study in a prospective high-risk cohort with characterization of genetic markers of WA ancestry to...
gain insight on how to use the PSA to make tailored diagnostic decisions in high-risk men. Reports from previous studies about PSA characteristics in the screening setting are challenging to apply to younger, ethnically diverse, high-risk men undergoing aggressive prostate cancer screening. The Prostate Cancer Prevention Trial reported on PSA performance characteristics in the control arm when describing their risk assessment calculator (14). However, this population was predominantly European American (95.6%), were 55 years or older, and had prostate biopsies recommended for a PSA >4.0 ng/mL. PSA characteristics were also reported from the more diverse population enrolled in prostate cancer screening in the San Antonio Center of Biomarkers of Risk for Prostate Cancer (SABOR; ref. 15). This cohort, whereas having 13.5% African American men and 37.2% Hispanics, reported on sensitivity/specificity characteristics of the PSA in relation to the Prostate Cancer Prevention Trial risk calculator and not on point-by-point PSA predictions for prostate cancer by race. African American men were also underrepresented in this cohort. The European Randomized Study of Screening for Prostate Cancer enrolled more than 21,000 men in Europe to be randomized to screening versus no screening (16). Men in this study are >55 years and are predominantly European American. Prostate biopsies are not recommended at PSA values <3.0 ng/mL in the setting of a normal rectal examination, thus making these data difficult to apply to high-risk U.S. men of diverse racial background.

The purpose of this study was to investigate if the baseline PSA and PSA predictive ability for prostate cancer were substantially different in self-reported African American men compared with self-reported European American men with a family history of prostate cancer undergoing aggressive screening in the Prostate Cancer Risk Assessment Program (PRAP) at Fox Chase Cancer Center, a prospective, longitudinal prostate cancer screening and research program for men at high risk. PRAP has ~60% African American participation, a demographic not seen in other screening studies. Another distinguishing feature of the PRAP cohort is that recommendations for prostate biopsy have been made at PSA values as low as 1.5 ng/mL to study aggressive screening measures (6). Therefore, the predictive ability for prostate cancer at low PSA values was able to be investigated. We investigated the concept of “race-specific” PSA by determining if baseline PSA differed by self-reported race or was associated with genetic markers of WA ancestry based on a panel of 100 previously validated ancestry informative markers in African American men (17). We further explored if differences in PSA predictive ability for prostate cancer were due to variation in WA ancestry. By grouping self-reported African American men from lowest to highest genetic WA ancestry, we explored the ability to identify subsets of African American men in whom the PSA has a higher prediction for prostate cancer to move forward with personalized prostate cancer early detection.

Materials and Methods

**PRAP cohort**

The PRAP at Fox Chase Cancer Center was established in 1996 to provide screening and perform research for men at high risk for prostate cancer (18). Eligibility for PRAP include any man between ages 35 and 69 y with one first-degree relative with prostate cancer, two 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. Recruitment is primarily through radio advertisements in the Philadelphia area, as well as through physician referrals, newsletters, and community events. Accrual to PRAP is ongoing and participants are followed longitudinally for prostate cancer screening and early detection. Three community partner hospitals also participate in PRAP.

**Prostate cancer screening in PRAP**

Prostate cancer screening procedures, biopsy criteria, prostate cancer incidence, and prostate cancer features have been described previously (5). Briefly, screening for prostate cancer is done on an annual basis. Screening tests include the total PSA, percent free PSA (6), digital rectal examination by a PRAP physician, and the PSA velocity. If all screening parameters are within normal limits per PRAP criteria (see “Criteria for biopsy”), then the participant returns in 1 y for repeat screening.

**Criteria for biopsy**

Until November 2005, the criteria for prostate biopsy were (a) PSA >4 ng/mL, (b) PSA of 2.0 to 4.0 ng/mL with free PSA <27%, (c) any abnormality on digital rectal examination, or (d) PSA velocity of 0.75 ng/mL/y. After November 2005, the criteria for biopsy were changed to (a) PSA >2.0 ng/mL, (b) PSA of 1.5 to 2.0 ng/mL with free PSA <25%, (c) any abnormality on digital rectal examination, or (d) PSA velocity of 0.75 ng/mL/y to investigate the detection of prostate cancer at lower PSA values based on emerging guidelines recommending discussing aggressive prostate cancer screening in high-risk men (19).

**Biopsy approach**

All biopsies are transrectal ultrasound-guided five-region patterned prostate biopsies (20, 21). The mean number of cores from these five regions was identical for African American and European American men (mean, 9.4 cores; median, 10.0 cores, for both race groups). All pathology is evaluated at Fox Chase Cancer Center by the Department of Pathology or by the pathology departments at three partner hospital sites.

**Ascertainment of self-reported race**

Self-reported race is determined by phone during the eligibility interview. Participants are asked for their race/ethnicity and the majority will volunteer the information. However, if they are unclear, several categories are offered to them to identify their race/ethnicity as follows: White/European American, Black/African American/Caribbean, Hispanic/Latino, Southeast Asian, South Asian, Native American, Other, or Unknown. Participants are classified as African American or White/European American if either of these groups is chosen regardless of other race/ethnic indications. If both African American and White/European American are indicated, the participant is classified as African American. Twenty-five participants indicated more than one race, of whom 22 were classified as African American and 3 were classified as European American. Because these 25 participants represented only 3.9% of the entire cohort, we have included these men in the analysis.

**Genetic markers of ancestry**

One hundred carefully selected ancestry informative markers were genotyped for all samples. These autosomal markers have previously been identified and validated and can be used to extract continental ancestry information in African Americans (17). Genotyping methods are available by request.

**Statistical methods**

Individual genetic ancestry was determined for each person using 100 ancestry informative markers for West African and European
Results

As of June 2007, 657 high-risk men were accrued to PRAP. This analysis includes 646 of these men with complete data for race, baseline PSA, and ancestry informative marker genotypes. The demographics of this cohort by self-reported race are shown in Table 1. No differences exist in mean baseline age, PSA, percent free PSA, digital rectal examination findings, or biopsy history. In addition, the median age at entry was identical for self-reported African American and European American men when testing for race-specific PSA effect (1.60 versus 1.67 ng/mL, respectively; \( P = 0.69 \)).

To further explore the concept of race-specific PSA, we investigated if the baseline PSA was higher for PRAP men with higher genetic WA ancestry. The distribution of WA ancestry by individual ancestry estimates grouped by self-reported race is shown in Fig. 1, and the demographics of this cohort of 646 men is the same as in Table 1.

As can be seen from Fig. 1, genetic WA ancestry was significantly higher in self-reported African American men compared with European American men. The distribution of WA ancestry varied widely in self-reported African American men compared with European American men. We found no significant correlation between individual ancestry estimates of WA ancestry and baseline PSA in self-reported European American men; however, for African American men there

Table 1. Demographics and prostate cancer characteristics by self-reported race of 646 PRAP participants

<table>
<thead>
<tr>
<th></th>
<th>African American (n = 408)</th>
<th>European American (n = 238)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at entry (y)</td>
<td>408</td>
<td>238</td>
</tr>
<tr>
<td>Duration of follow-up (mo)</td>
<td>223</td>
<td>188</td>
</tr>
<tr>
<td>PSA at baseline (ng/mL)</td>
<td>408</td>
<td>238</td>
</tr>
<tr>
<td>Percent free PSA at baseline*</td>
<td>81</td>
<td>50</td>
</tr>
<tr>
<td>DRE at baseline†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal/BPH (%)</td>
<td>371 (95.6)</td>
<td>210 (95.4)</td>
</tr>
<tr>
<td>Abnormal (%)</td>
<td>17 (4.4)</td>
<td>10 (4.6)</td>
</tr>
<tr>
<td>Biopsy history (reported at baseline)‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No prior biopsy/unknown</td>
<td>298 (92.3%)</td>
<td>205 (98.7%)</td>
</tr>
<tr>
<td>Had prior negative biopsy</td>
<td>25 (7.7%)</td>
<td>16 (7.2%)</td>
</tr>
<tr>
<td>Genetic West African ancestry§</td>
<td>408 (98.7%)</td>
<td>238 (98.7%)</td>
</tr>
<tr>
<td>PCA diagnosis¶</td>
<td>37 (9.1%)</td>
<td>29 (12.2%)</td>
</tr>
<tr>
<td>PSA prior PCA dx (ng/mL)</td>
<td>37</td>
<td>29</td>
</tr>
<tr>
<td>Gleason score</td>
<td>37</td>
<td>29</td>
</tr>
</tbody>
</table>

Abbreviations: DRE, digital rectal examination; PCA, prostate cancer; dx, diagnosis.

*Difference in percent free PSA by race at baseline was not statistically significant, \( t \)-test \( P = 0.783 \). (Percent free PSA is done only for men with PSA 2.0-4.0 ng/mL by the previous criteria or PSA 1.5-2.0 ng/mL by the current criteria in PRAP. Therefore, not all men have a percent free PSA done at baseline.)

†Difference in abnormal DRE by race at baseline was not statistically significant, Fisher's exact test \( P = 1.00 \). (DRE information is missing for 18 African American and 20 European American participants.)

‡Difference in biopsy history by race was not statistically significant, Fisher’s exact test \( P = 0.870 \). (Biopsy history is missing for 85 African American men and 17 European American men.)

§Highest possible is 1.00. This is based on genotyping 100 ancestry informative markers.

¶Percent of the group; last diagnosis was April 2008.
 seemed to be a nominal yet nonsignificant correlation (Pearson correlations: 0.071, \(P = 0.30\) (European American men); \(-0.024, P = 0.06\) (African American men)].

We next explored if the PSA prediction for prostate cancer differed between African American and European American men by self-reported race using Cox models. This cohort included 411 of the total 646 men; the remaining 235 men who were excluded were 46 men who were not yet scheduled to return for their follow-up visit and 189 men who did not return for any follow-up visits. Compared with the men included in the analysis, men lost to follow-up tended to be younger (mean age, 46.9 versus 50.9 years; \(P < 0.0001\), \(t\) test) and have lower baseline PSA values (mean PSA, 1.25 versus 1.86 ng/mL; \(P = 0.001\), \(t\) test). African American men were more likely to be lost to follow-up than European American men (40% versus 19%; \(P < 0.0001\), \(\chi^2\) test). Table 2 shows the demographics and prostate cancer characteristics of this group of 411 PRAP participants. For the Cox model analysis, an additional six PRAP men with a baseline PSA >10 ng/mL were removed to reduce the possibility that they would be influential points (PSA levels of excluded men were 13, 15, 15, 22, 23, and 27 ng/mL). Therefore, the final Cox model analyses were done on 405 PRAP men and the results in this article are hence only generalizable to men with PSA ≤10 ng/mL. Figure 2 shows the plots of the Cox models of the PSA prediction for prostate cancer at 3 years with age in the model. This 3-year time frame was chosen for study because the mean duration of follow-up in PRAP has been ∼40 to 48 months. As can be seen from Fig. 2, the PSA had a noticeably higher prediction for prostate cancer in the range of ∼1.5 to 4.0 ng/mL in self-reported African American men compared with self-reported European American men. A statistically significant difference was seen by race in the association of baseline PSA to prostate cancer development based on the Cox model when testing for interactions for race-PSA and race-age (\(P = 0.025\)). When testing the model for the race-PSA interaction only, the interaction was still statistically significant (\(P = 0.04\)).

We next investigated if the higher prediction for prostate cancer in self-reported African American men was due to the influence of genetic WA ancestry. We divided 219 self-reported African American men from Fig. 2 into tertiles of lowest to highest individual ancestry estimates for WA ancestry. Each tertile included 73 African American men, and the mean and range of WA ancestry were as follows: 0.561 (0.045-0.684) for tertile 1, 0.785 (0.686-0.865) for tertile 2, and 0.921 (0.866-0.995) for tertile 3. Figure 3 shows the Cox model plots of 3-year prediction for prostate cancer by baseline PSA in these tertiles of African American men with point estimates included on each figure. There is a trend for higher prediction for prostate cancer at any given PSA in the range of ∼1.5 to 4.0 ng/mL with increasing genetic WA ancestry by individual ancestry estimates, although this was not statistically significant. Hazard ratios of PSA for prostate cancer were significantly higher in self-reported African American men compared with self-reported European American men [1.59 (95% confidence interval, 1.38-1.84) versus 1.30 (95% confidence interval, 1.12-1.51), respectively; \(P = 0.04\)]. By tertiles of WA ancestry, hazard ratios of PSA for prostate cancer were as follows: tertile 1, 2.19 (95% confidence interval, 1.49-3.22); tertile 2, 1.46 (95% confidence interval, 1.19-1.79); and tertile 3, 1.45 (95% confidence interval, 1.04-2.01). The joint

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### Table 2. Demographics and prostate cancer characteristics by self-reported race in 411 PRAP participants with at least one follow-up visit

<table>
<thead>
<tr>
<th></th>
<th>African American (n = 223)</th>
<th>European American (n = 188)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n)</td>
<td>Mean (range)</td>
</tr>
<tr>
<td>Age at entry (y)</td>
<td>223</td>
<td>51.6 (35-69)</td>
</tr>
<tr>
<td>Duration of follow-up (mo)</td>
<td>223</td>
<td>40.4 (0.3-122.5)</td>
</tr>
<tr>
<td>PSA at baseline (ng/mL)</td>
<td>223</td>
<td>2.0 (0.1-27.2)</td>
</tr>
<tr>
<td>Genetic WA ancestry*</td>
<td>223</td>
<td>0.755 (0.045-0.995)</td>
</tr>
<tr>
<td>PCA diagnosis†</td>
<td>37</td>
<td>4.8 (0.3-31.6)</td>
</tr>
<tr>
<td>PSA before PCA dx (ng/mL)</td>
<td>37</td>
<td>6.2 (5-8)</td>
</tr>
</tbody>
</table>

*Highest possible is 1.00. This is based on genotyping 100 ancestry informative markers.
†Last diagnosis was April 2008. PCA, prostate cancer.
test of equality of interaction terms in an interaction model was not statistically significant ($P = 0.150$). The hazards estimated from the interaction models did not substantially differ from those reported above.

**Discussion**

Screening for prostate cancer in high-risk men (African American men and in European American men with a family history of prostate cancer) can be challenging. The potential benefits include early detection of intermediate or high-grade prostate cancer with improved chances for cure with modern approaches. The risks include performing unnecessary prostate biopsies and subjecting these men to physical and psychological morbidities. Previous studies (including from our group) have shown that early detection strategies do detect intermediate to high-grade prostate cancer and at lower PSA values (4, 5). In addition these high-risk men are at risk for developing prostate cancer at a relatively young age, adding to the potential benefits of early detection (5). However, using the PSA for screening for prostate cancer in high-risk men is challenging, with positive predictive values ranging from 38% to 45% in our cohort. Novel strategies are needed to personalize the early detection of prostate cancer in high-risk men. PRAP is an ideal cohort in which to investigate prostate cancer screening issues in high-risk men because there is 60% African American participation, participants are followed longitudinally, and prostate biopsies have been done at lower PSA values for several years.

In this study, we investigated the concept of “race-specific” PSA with the high-risk, prospective, and longitudinal cohort in PRAP. The “race-specific” PSA concept implies that African American men have higher PSA at baseline and at diagnosis, and therefore, these men may need to have prostate biopsies recommended at higher PSA values compared with European American men when performing prostate cancer screening. The concern here is missing high-grade or advanced prostate cancer (13). Indeed, we did not find an association between higher baseline PSA and self-reported race in our cohort. We further explored the concept of “race-specific” PSA by investigating for any association of baseline PSA to genetic markers of WA ancestry and found no association, further showing evidence against a higher baseline PSA in African American men. Of importance is the wide range of genetic ancestry estimates of WA ancestry among self-reported African American men, indicating that each individual African American man seeking screening for prostate cancer does not have the same genetic ancestral proportions and, therefore, may not have the same risk for prostate cancer.

We did find that the PSA has a higher prediction for prostate cancer at any given value between $\sim 1.5$ and 4.0 ng/mL in self-reported African American compared with European American men with a family history of prostate cancer (all a higher-risk group compared with the general population). We have the unique ability to study lower PSA values (<4.0 ng/mL) because of the aggressive screening approaches being studied in the PRAP high-risk cohort in a longitudinal fashion. These results have the opposite implication of the “race-specific” PSA, wherein the same PSA value has a higher risk for prostate cancer at 3 years in African American men. Clinically, our data support aggressive screening measures in self-reported African American men based on higher predictions for prostate cancer.

Given the wide variation in genetic WA ancestry among African American men and the recent studies that reveal higher risk for prostate cancer among African Americans with higher genetic WA ancestry (11, 12), we explored if genetic WA ancestry was the contributing factor for higher prostate cancer risk among our African American subjects. Based on tertiles of increasing genetic WA ancestry, we did find higher...
3-year point estimates for predictions of prostate cancer for PSA between 1.5 and 4.0 ng/mL. The apparent paradox between these increasing point estimates for prostate cancer shown in Fig. 3 and the lower hazard ratios for PSA by tertile of genetic WA ancestry is likely related to the fact that the baseline hazard for prostate cancer at low PSA levels increases for African American men in tertiles 2 and 3 compared with tertile 1, which is shown by Cox modeling as follows: tertile 2 versus tertile 1, hazard ratio of 10.0, \( P = 0.08 \); tertile 3 versus tertile 1, hazard ratio of 2.4, \( P = 0.56 \). If such a higher baseline hazard is indeed found to be significant in a larger sample, it could negate previous beliefs that African American men inherently have a higher PSA than European American men. Furthermore, these hazard ratios of PSA for prostate cancer by tertile of WA ancestry need to be interpreted cautiously because they were estimated from models in which baseline PSA was entered as a linear term rather than the flexible way in which PSA was modeled for Fig. 3. Figure 3 gives a more accurate depiction of the flexible relationship of baseline PSA with tertile of WA ancestry in our sample. Given the trend in increasing prostate cancer prediction at lower PSA values with increasing genetic WA ancestry among African American men, we have identified a potentially higher-risk group of men based on markers of ancestry in which to further investigate aggressive screening approaches in larger studies. These genetic markers of ancestry may have clinical use in individualizing prostate cancer screening among African American men, particularly because our data show a wide range of WA ancestry estimates among self-reported African American men. Other factors to explore on the difference in the PSA predictive ability for prostate cancer between African American and European American men include genetic modifiers, diet, environment, and socioeconomic factors.

There are some limitations in this study. The overall follow-up rate among PRAP participants is 60%, which can hinder the interpretation of prostate cancer development over time. This is a known challenge in prospective screening studies and highlights the need for efforts to enhance adherence to screening protocols. This follow-up rate of 60% is close to rates reported by other high-risk screening cohorts of 60% to 72% (4). We also do not perform prostate biopsies in all PRAP participants as has been done in the control arm of the Prostate Cancer Prevention Trial (24). Therefore, there may be some men who have prostate cancer in PRAP that is undetected at this time. However, our cohort represents a true clinical setting of aggressive prostate cancer screening that would not include prostate biopsies for everyone. Another limitation is that at this time, we were able to evaluate

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Fig. 3. Predicted probability for prostate cancer at 3 y of the baseline PSA with increasing generic WA ancestry in 219 African American men in PRAP with age in the model.
prostate cancer prediction at 3 years. Longer follow-up in PRAP is needed and is planned to determine the prediction for prostate cancer at 5 and 10 years. Finally, the sample size limited the ability to firmly assess the association of estimates of WA genetic ancestry to predictions for prostate cancer based on PSA among African American men. PRAP is continuously accruing participants, and we plan to analyze our findings in a larger cohort in the future. Follow-up on outcomes from prostate cancer treatment (biochemical recurrence after radical prostatectomy versus radiation therapy, distant recurrence, quality of life after treatment, and death from prostate cancer) is also planned in the future with longer follow-up.

Overall, we find no evidence in support of the traditional "race-specific" PSA. We do find that the PSA has a higher prediction for prostate cancer in African American men—a new concept of the "race-specific" effect. This finding may be explained by genetic WA ancestry, which deserves further study. Our findings of the role of genetic WA ancestry in modifying the ability of the PSA to predict for prostate cancer in African American men need to be confirmed on a larger scale to explore for personalizing prostate cancer early detection in high-risk men.

Disclosure of Potential Conflicts of Interest
R.G. Uzzo received honoraria from Pfizer Speakers Bureau. No other potential conflicts of interest were disclosed.

Acknowledgments
We thank all the participants of the Prostate Cancer Risk Assessment Program.

References
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