Race and the Linkage Between Serum Prostate-Specific Antigen and Prostate Cancer

A Study of American Veterans

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Key Words: Prostate cancer; Serum PSA; Prostate-specific antigen; Tumor mass; Race; Risk factors; Nomograms

Abstract

Many aspects of prostate cancer differ between black men and white men, including incidence, stage, grade, sensitivities and specificities of serum prostate-specific antigen (PSA) levels, and survival. In general, the level of serum PSA reflects the mass of the prostate and the amount of tumor present, but the question to consider is whether this relationship is the same for blacks as for whites. If it is the same, then the ways we use serum PSA to screen, stage, and follow up white men with cancer should work equally for black men. If it is not, then we need alternative strategies for using serum PSA levels in blacks. I used regression analysis to study how the serum PSA level depends on prostate mass and the amount of tumor in 194 American veterans, including 87 black men. I found that black men produced higher levels of serum PSA for any given amount of tumor compared with whites, and I demonstrated that this difference can significantly affect the assessment of risk for outcomes in blacks.

During the past 10 to 20 years, many have observed that prostate cancer expresses itself differently in black men compared with white men. For example, whereas the incidence of prostate cancer in whites peaked in 1992 at 179 per 100,000, the incidence in blacks peaked in 1993 at 250 per 100,000.1 Although mortality due to prostate cancer has declined recently in the United States, the mortality rate in blacks remains more than twice that in whites.2 In general, blacks have been found to have significantly higher tumor stage than whites,3 and survival adjusted for stage often has been shorter for blacks than for whites.2 At least 2 studies have found that after controlling for other important prognostic factors, disease-free survival was shorter in blacks than whites.4,5 However, other studies have reported multivariable analyses demonstrating that survival times for blacks and whites is similar after radical prostatectomy.6,9 Such improvements in survival after surgery combined with the general adverse circumstances for blacks have led to recommendations for early screening for prostate cancer in black men.7,10

Early screening for prostate cancer, of course, implies early testing for serum prostate-specific antigen (PSA), and a complicating factor is that blacks, with or without cancer, have higher levels of PSA than whites. For example, Figure 1 summarizes the experience of 21 studies representing altogether 3,371 black men and 9,950 white men with prostate cancer.4-8,10-25 The plot shows mean PSA values for black groups on the vertical axis and mean PSA values for their comparable white groups on the horizontal axis, and more than half of these studies controlled the values for stage. The line on the graph shows where the points would fall if PSA levels in blacks equaled those of whites. Because nearly all points fall above the line, the plot demonstrates that black
men with cancer have higher PSA levels, a result that was significant by paired *t* test performed on the logarithm of these mean values (*t* = 9.2; *P* = 0). Because the serum PSA level is correlated roughly with tumor volume, several have proposed that higher PSA levels in black men with cancer are due to larger tumor volumes. In fact, all 4 groups that measured tumor volume in blacks and whites found that blacks had slightly higher tumor volumes than whites. The weighted mean of tumor volume across the 4 studies was 5.9 cc in blacks vs 3.6 cc in whites. In addition, Iselin et al found that a topological measure of tumor volume—the percentage of prostate with tumor—was 29.5% in blacks and 22.1% in whites. Finally, another group reported that after controlling for the volumes of tumor and benign tissues in the prostate, there remained a small residual racial effect on PSA level.

A significant confounder for the linkage between serum PSA level and tumor volume is the amount of benign tissue in the prostate. Clearly, the PSA level reflects the mass of benign and malignant tissues. Although the flux of PSA from benign tissue is likely to be less than that from tumor, in most cancer patients, benign tissues comprise a greater part of total prostate mass than do tumor tissues. Thus as Stamey et al recently put it, benign tissues, including benign prostatic hyperplasia, comprise a strong contender for the cause of elevated PSA. Magnifying this complication for black men is the observation that even without tumor, blacks have higher levels of PSA than do whites, and the difference increases with age. For example, analysis of the results of paired reporting of PSA in blacks and whites from 4 studies representing altogether 4,975 black men and 5,706 white men without prostate cancer demonstrated that at higher levels of PSA, there was a significant discrepancy between blacks and whites. In the upper ranges of PSA, which in these studies corresponded to older age groups, black men had higher values of PSA (*t* = 10.9; *P* = 0 on the logarithm of PSA). Although higher levels of PSA in black men without cancer decreases the specificity of PSA for a diagnosis of cancer and lowers the odds for tumor at any given value of PSA, this issue has been largely put aside for concerns about the incidence of prostate cancer in black men and the associated survival and mortality. For example, no one has suggested significantly raising the screening thresholds of PSA for blacks.

Because decisions about screening men for prostate cancer depend on our understanding of how the serum PSA level links to the amounts of benign and malignant tissues and because this linkage might be different in blacks and whites, my objective in the present study was to examine this issue using data collected from 194 American veterans, including 87 black men, who underwent total prostatectomy for prostate cancer. My study hypothesis was that linkage between serum PSA levels and amounts of benign and malignant tissues of the prostate is different in blacks vs whites. Herein I report a regression analysis that demonstrated that higher levels of serum PSA in black men with cancer are due neither to increased tumor mass nor to increased benign tissue mass, but rather to a different linkage between the amount of tumor and the serum PSA level.

### Materials and Methods

This study comprised 194 men, including 87 black men and 107 non-Hispanic white men, who underwent radical prostatectomy for prostate cancer at the Durham Veterans Administration Medical Center (DVAMC), and it was approved by the DVAMC Institutional Review Board. Their ages ranged from 47 to 76 years (median, 64 years), and clinically, all had localized stage (T1-T2). The prostates were submitted for total histologic examination, and I evaluated these specimens and determined the Gleason score and the extent of tumor. I also estimated the percentage of prostate involved by tumor in 5% increments during microscopic examination. I did this by evaluating the percentage of tumor in each slide and then obtaining an average for the entire prostate. Tumor mass was estimated as the product of this percentage times prostate mass divided by 100, and benign tissue mass was taken as the difference between this estimate and the overall mass of the prostate. Serum PSA levels were determined by the DVAMC Centralized Laboratory using the Beckman version of the Hybritech methodology (Beckman Coulter, Fullerton, CA).
Statistical Methods

Linear regression was used to relate serum PSA levels to the total mass of prostate, the percentage of tumor present, and to race. Based on previous studies, the starting assumption was that serum PSA levels directly reflected the total mass of the prostate and the amount of tumor present. Two interaction terms were used to test whether the multiplicative coefficients linking PSA to total mass and to amount of tumor differed between blacks and whites. Although I did not transform PSA by analyzing its logarithm, I examined the residuals from the regression model to ensure that they were symmetric and approximately normally distributed. Analyses were done using S-PLUS statistical software (MathSoft, Seattle, WA), and all reported P values were for 2-sided tests.

Results

Table 1 gives observations between black and white patients. The results demonstrate that although black patients had higher levels of PSA (P = .0009; Wilcoxon test), their composite values for all other key variables, including age, size of prostate, extent of tumor, mass of benign tissue, and mass of tumor were similar to those of whites. The question then to consider is how serum PSA levels could differ between blacks and whites when the masses of benign and malignant tissues did not. The explanation comes from the regression analysis given in Table 2.

Table 2 demonstrates that total mass of prostate contributed significantly to the serum PSA level, and the F statistic from analysis of variance for this variable was 284, the largest for any of the variables. Percentage of tumor also contributed significantly to the serum PSA level, and its F statistic was 105. The Black × Prostate Mass interaction variable was not associated significantly with PSA. With all 4 variables in the model, its coefficient was 0.002, so that this variable was not related significantly to the serum PSA level.

Table 1
Comparison of Black and White Patients*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Blacks (n = 87)</th>
<th>Whites (n = 107)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (y)</td>
<td>62.9</td>
<td>64.6</td>
<td>&gt;.1</td>
</tr>
<tr>
<td>Mean PSA (ng/mL)</td>
<td>14.8</td>
<td>9.0</td>
<td>&lt;.0009</td>
</tr>
<tr>
<td>Mean prostate mass (g)</td>
<td>43.6</td>
<td>39.0</td>
<td>&gt;.1</td>
</tr>
<tr>
<td>Mean percentage of tumor</td>
<td>19.5</td>
<td>18.5</td>
<td>&gt;.8</td>
</tr>
<tr>
<td>Margins positive (%)</td>
<td>75.9</td>
<td>67.9</td>
<td>&gt;.2</td>
</tr>
<tr>
<td>Extracapsular tumor (%)</td>
<td>32.2</td>
<td>32.7</td>
<td>&gt;.9</td>
</tr>
<tr>
<td>Seminal vesicle positive (%)</td>
<td>23.0</td>
<td>17.0</td>
<td>&gt;.3</td>
</tr>
<tr>
<td>Mean nontumor mass (g)</td>
<td>35.5</td>
<td>31.9</td>
<td>&gt;.5</td>
</tr>
<tr>
<td>Mean tumor mass (g)</td>
<td>8.1</td>
<td>7.1</td>
<td>&gt;.5</td>
</tr>
</tbody>
</table>

PSA, prostate-specific antigen. *Continuous variables (age, PSA, mass, and percentage of tumor) were compared by using the Wilcoxon test, and binary variables (margins, extracapsular tumor, and seminal vesicle tumor) were compared by using the χ² test.

Table 2
Linear Dependence of Serum PSA on Tissue Masses*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>SE</th>
<th>t</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate mass</td>
<td>0.131</td>
<td>0.018</td>
<td>7.1</td>
<td>&lt; 0</td>
</tr>
<tr>
<td>Percentage of tumor</td>
<td>0.186</td>
<td>0.041</td>
<td>4.5</td>
<td>&lt; 0</td>
</tr>
<tr>
<td>Black × Prostate Mass</td>
<td>—</td>
<td>—</td>
<td>0.05</td>
<td>&gt;.9</td>
</tr>
<tr>
<td>Black × Percentage of Tumor</td>
<td>0.299</td>
<td>0.051</td>
<td>5.8</td>
<td>&lt; 0</td>
</tr>
</tbody>
</table>

PSA, prostate-specific antigen; SE, standard error of the coefficient. *Units of tissue mass are in grams. Black × Prostate Mass and Black × Percentage of Tumor denote interaction variables that take the value of prostate mass and percentage of tumor, respectively, only if the patient was black; otherwise these 2 variables were 0. Coefficients and standard errors are given for just a 3-variable model that excluded Black × Prostate Mass, because this variable was not related significantly to the serum PSA level.

g (median value in the present study) contributed 4.8 ng/mL to the serum PSA level. In the present study, this contribution was the same for blacks and whites. The second coefficient indicates that each percent of tumor contributed an additional 0.186 ng/mL to the serum PSA level, so that, on average, a cancer comprising 12.9% of the prostate (median in the present study) contributed 2.4 ng/mL to the serum PSA level in whites. However, the coefficient for the Black × Percentage of Tumor variable indicated that in blacks, there was an additional contribution of 0.299 ng/mL for each percent of tumor, so that in a black man, a tumor of 12.9% contributed, on average, 6.3 ng/mL to the serum PSA level. Consequently, the contribution of tumor tissues to serum PSA levels in blacks was approximately 2.6 times that of whites. The residuals from the regression analysis seemed symmetric and approximately normally distributed. The 3-variable model explained just 69% of the variance in the data, but examination of the residuals from the model revealed no trends with patient age, Gleason grade, pathologic stage, or status of surgical margins, implying that there probably are other unknown factors that contribute to serum PSA levels.
A second regression analysis was performed using as explanatory variables the estimated masses of benign and malignant tissues (see the “Materials and Methods” section) and race, and the results were nearly identical to those given above. The serum PSA level was associated significantly with mass of benign tissue \((P = 0.0)\), mass of tumor tissue \((P = 0.0)\), and interaction between race and mass of tumor tissue \((P = 2 \times 10^{-9})\). The contribution of benign tissues to serum PSA levels was, once again, the same for blacks and whites. The results indicated that tumor tissues in blacks contributed more to serum PSA than did tumor tissues in whites. This second model explained just 60% of the variance in the data, so that it was slightly inferior to the model in Table 2.

Implications of Regression Model

The preceding linear models provide an understanding of how race should affect the level of serum PSA in average men with cancer. For example, the coefficients of the model in Table 2 suggest that the average difference in the level of serum PSA between blacks and whites with cancer could be estimated as:

**Equation 1**

\[
\text{Difference in PSA} = 0.299 \times \text{Percentage of Tumor}
\]

In other words, the difference in PSA between blacks and whites should depend on the amount of tumor in the prostate but not on total mass of prostate. Consequently, when the tumor mass is small, the average serum PSA in blacks should be close to that for whites with the same amount of tumor. However, the larger the amount of tumor, the larger should be the discrepancy in serum PSA levels between blacks and whites. This effect is illustrated in **Figure 2**, which shows a plot of serum PSA levels predicted by the model of Table 2 vs percentage of tumor present for a constant total mass of prostate of 45 g. The upper line provides the expected PSA for blacks and the lower line the expected PSA for whites. As the percentage of cancer increases to 30% (approximately the first 3 quartiles in the present study population), the discrepancy in serum PSA levels between blacks and whites increases, even though blacks and whites have the same mass of prostate and amount of tumor. The plot also demonstrates that this racial discrepancy in PSA levels is sufficient to place blacks into a higher perceived risk category than whites, using, for example the cut points of 10 and 20 ng/mL (horizontal lines on the plot) and the Partin risk tables. Nevertheless, because racial differences in serum PSA are not likely to be important when the tumors are small, the results suggest that PSA-based algorithms for watchful waiting in men with small tumors (ie, \(< 5\%)\) should work approximately the same in both races.

Another demonstration of how race and the linkage between tumor and serum PSA can affect estimates of risk comes from the preoperative nomogram published by Kattan et al. This nomogram uses preoperative values of serum PSA, clinical stage, and Gleason score to tally prognostic points, which then are used to predict the probability of being free of prostate cancer after radical prostatectomy. Thus, this nomogram could be used to decide who is likely to be cured by prostatectomy. For example, if the predicted probability for disease-free status is low (or equally the probability of recurrence in 5 years is high), then one might consider alternative treatments. Examination of the nomogram demonstrates that the greatest influence on the tally of prognostic points comes from the serum PSA level, so that the racial differences I observed might lead to different predictions of risk for black and white men.

Thus, I used this nomogram to predict the probability of tumor recurrence within 5 years after surgery for 288 simulated black and 288 simulated white men with matched values of clinical stage, Gleason score, mass of prostate, and percentage of tumor present. Clinical stages were T1c or T2c. Gleason scores were 3 + 3, 3 + 4, or 4 + 3. Mass of prostate ranged from 25 to 60 g, and percentage of tumor ranged from 5% to 30%, because these values comprised the middle 50% of our study population. The expected values of serum PSA, however, differed and were estimated from the regression coefficients of Table 2 using prostate mass, percentage of tumor, and race. The results are given in **Figure 3**. The vertical axis gives the nomogram-derived estimate for the probability of 5-year tumor recurrence in blacks, and the horizontal axis gives the comparable estimate in whites. Each point comprises a separate pair of men, and the line shows where the points would fall if blacks and whites had the same estimated probability of failure. Clearly,

![Figure 2](https://example.com/figure2.png)

**Figure 2** Plot of expected values of serum prostate-specific antigen (PSA) for blacks and whites by percentage of tumor present and when the mass of the prostate is held constant at 45 g. The horizontal lines show the commonly used prognostic cut points of 10 and 20 ng/mL.

![Figure 3](https://example.com/figure3.png)

**Figure 3**
higher values of estimated serum PSA in blacks caused a higher estimated risk of tumor recurrence compared with whites, demonstrating that the nomogram of Kattan et al41 could behave differently for blacks and whites with the same amount of tumor.

Discussion

The results of the present study suggest that prostate cancer in blacks accounts for greater amounts of PSA in the serum than observed in whites. In other words, the notion that higher levels of PSA in blacks are always due to greater amounts of tumor probably is incorrect. Instead, the results demonstrate that black men with prostate cancer should be expected to have higher values of serum PSA, even when the amounts of their tumors and sizes of their prostates are identical to those of white men. The increased contribution of tumor to serum PSA levels in blacks implies that the flux of PSA from the tumor into the bloodstream is higher in blacks than in whites, but further details are, for the moment, a matter of speculation.

Possible mechanisms include greater tumor-vascular interface in blacks, which might lead to more efficient transfer of PSA to the bloodstream. Because tumor-vascular interface can be evaluated by counting tumor vessels in tissues stained for CD31 or CD34, clearly, there is a need and a method for studying this issue in blacks and whites. For example, if tumor angiogenesis were found to be greater in blacks than in whites, then the difference would support the notion that blacks have tumors with worse biologic potential, because angiogenesis has been found to be important for progression of many tumors, including prostate cancer.42

A second possible mechanism for the racial effect on PSA-tumor linkage could come from higher cell turnover in the tumors of blacks with subsequent release of PSA. Because tumor cell turnover reflects tumor cell proliferation, a portion of this mechanism can be evaluated by staining for Ki-67. For example, Demark-Wahnefried et al43 recently studied tumor cell proliferation in prostates of men treated briefly with a flaxseed-supplemented diet. The study included 10 black men, and a reanalysis of the data revealed that after controlling for the effect of the flaxseed diet, blacks had no higher tumor cell proliferation than whites (P > .3).

Finally, a third possible mechanism is that there is a greater amount of PSA in tumor cells in blacks than in whites. If true, this mechanism might have the most profound effect on the use of serum PSA levels, because it would require us to change how we use serum PSA levels not only for screening and staging but also for follow-up.

Regardless of the mechanism, my results favor the need for race-specific criteria in the use of PSA levels for screening and staging of men with prostate cancer. Regarding screening, my results suggest that for small tumors—eg, less than 5%—screening strategies using serum PSA levels should work the same for blacks and whites. However, for larger tumors, 2 issues could confound the comparison of screening in blacks vs in whites. The first considers the problem from the point of view of a particular tumor of intermediate size and the second from the point of view of a particular value of serum PSA. In blacks, a given amount of tumor should cause a higher serum PSA level than the same tumor in whites, and the higher serum PSA level then could lead to more frequent biopsy and, therefore, more frequent discovery of the tumor. Thus, the probability of biopsy and discovery of a tumor that displaces 10% of the prostate might be higher in blacks than in whites. Could some of the reported higher incidence of prostate cancer in blacks be due to this issue? From the point of view of serum PSA level, a particular value like 10 ng/mL should imply a larger tumor in a white man than in a black man. Therefore, biopsies might reveal the tumor in the white man but not in the black man, so that the probability of diagnosing a tumor for a given level of PSA could be higher in whites than in blacks. Could this issue explain, in part, how for any cut point of PSA, the tables in the article by Morgan et al35 demonstrate lower specificities in blacks than in whites?
Regarding staging, I demonstrated that when the amount of tumor is typical for that found in a prostatectomy population, racial differences in serum PSA levels can lead to a patient being placed into a higher risk category by the Partin tables. Perhaps this is one reason why blacks have not undergone prostatectomy as often as whites. For all of the aforementioned reasons, I recommend further study of how serum PSA levels are used in blacks compared with whites to predict likely outcomes and to make recommendations about treatments and follow-up. Investigators studying these issues should strive to include a sufficient number of black patients to recognize the influence of race on the results. In this regard, further studies of patients in the US veterans and military health systems should help, because they include many blacks.

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