Prostate-Specific Antigen (PSA) and PSA Density: Racial Differences in Men Without Prostate Cancer

R. Jonathan Henderson, James A. Eastham, Daniel J. Culkin, Michael W. Kattan, Terence Whatley, John Mata, Dennis Venable, Oliver Sartor*

Background: Many physicians now use serum prostate-specific antigen (PSA) to screen for prostate cancer in asymptomatic men. Whether or not a prostate biopsy should also be performed depends on an accurate definition of what constitutes a normal PSA value. Until recently, studies conducted to establish normal serum PSA values have involved study populations that have included few African-American men. Purpose: We sought to compare serum PSA levels and PSA density (i.e., serum PSA level/prostate volume ratio) in African-American and white men without histologic evidence of prostate cancer. Methods: We reviewed the medical records of 826 consecutive men who underwent one or more prostate biopsies at the Veterans Affairs Medical Center in Shreveport, LA, from January 1993 through December 1995. In this retrospective review, we recorded patient’s age, race, serum PSA level, digital rectal examination result, ultrasound-determined prostate volume, indications for biopsy, and biopsy results. Data from a total of 752 consecutive men who were either white or African-American and whose indication for biopsy included a serum PSA of greater than 4.0 ng/mL and/or an abnormal digital rectal examination were analyzed. To examine possible differences in serum PSA level, PSA density, prostate volume, and patient age, the two-sided Student’s t test was employed. Multivariate linear regression analysis was used to determine if serum PSA levels were associated with the patient’s age, race, or prostate volume in men without prostate cancer. Results: Of the 752 men included in this analysis, 254 had histologic evidence of prostate cancer and 498 did not. Of the 498 men without prostate cancer, 367 (74%) men were white and 131 (26%) were black. There were no racial differences in age or calculated prostate volume. Serum PSA levels and calculated PSA density, however, were significantly (both \( P<.0001 \)) higher in African-American men than in white men. A multivariate linear regression analysis indicated that race and prostate volume were independent variables associated with serum PSA level. For African-American and white men, serum PSA values of greater than 4 ng/mL were associated with prostate cancer with sensitivities of 89.5% and 81.9%, respectively, and specificities of 38.2% and 52.3%, respectively. Conclusion: Among biopsied men without histologic evidence of prostate cancer, African-Americans have a significantly higher PSA level and PSA density than similarly aged white men. Implications: Published criteria for normal PSA level and density have been derived primarily from white men and may not be directly applicable to other populations. Race-specific data are needed to fully optimize PSA as a tumor marker in racial populations that are at high risk for prostate cancer death [J Natl Cancer Inst 1997;89:134-8]

The prostate is the most common site of internal cancer in men and is second only to lung cancer as the leading cause of male cancer death. The American Cancer Society has projected that 317,000 men will be diagnosed with prostate cancer in the United States in 1996 and that 41,400 will die of this disease (1). Because the incidence of prostate cancer increases with age more than any other cancer and because the population of men at risk for this disease is rapidly expanding because of increased longevity, the number of men afflicted by prostate cancer is expected to increase steadily in the coming years.

Prostate cancer is of even greater concern for the African-American (black) community. The incidence of prostate cancer in African-American men has been reported to be 50% higher than that of age-matched U.S. Caucasian (white) men, and African-American men have the highest incidence of prostate cancer of any ethnic group in the world (2). African-American men tend to have a younger age at diagnosis, a more advanced stage at presentation, and a poorer 5-year survival rate compared with white Americans (3,4). The reasons for these racial differences are poorly understood, although genetic, nutritional, and socioeconomic factors have all been implicated (4).

Men with prostate cancer generally exhibit elevated levels (i.e., concentrations) of prostate-specific antigen (PSA) in their serum; this tumor marker is now frequently used for prostate cancer screening, diagnosis, and monitoring response to therapy (5). Critical for determining the clinical indications for biopsy in asymptomatic men is a definition of what constitutes a normal PSA value. Until recently, studies conducted to establish normal serum PSA values have involved study populations that have included few African-American men. However, recent investigations have suggested that serum PSA levels may be higher in African-American men with clinically localized prostate cancer compared with other ethnic groups. Vijayakumar et al. (6) examined a cohort of 161 men undergoing radiation therapy for

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See “Notes” following “References.”
clinically staged local-regional prostate cancer. Among those patients, the mean PSA level was higher in African-American men compared with whites, and this finding remained statistically significant after adjusting for tumor stage and grade in some (but not all) cohorts. Moul et al. (7) evaluated 541 patients with newly diagnosed prostate cancer. African-American men had a higher serum PSA level compared with whites after adjusting for stage, grade, and patient age. After analysis of a subset of patients undergoing radical prostatectomy, these researchers postulated that larger tumor volumes, within disease-stage categories, were responsible for racial disparities in serum PSA levels.

Given these data, which suggest that African-American men with biopsy-proven early stage prostate cancer may have a higher serum PSA level on a stage-for-stage basis, we investigated whether or not African-American men whose biopsy revealed no histologic evidence of cancer might also have higher serum PSA levels and PSA densities (i.e., serum PSA level/prostate volume ratio) than white men in the same situation. We investigated this question in a single hospital serving a racially mixed population and discuss the results herein.

Methods

To examine the relationship between race and PSA, we reviewed the medical records of all patients who underwent one or more prostate biopsies at the Overton Brooks Veterans Affairs Medical Center of Shreveport, LA, from January 1993 through December 1995. This hospital serves a racially mixed group of veterans living in a predominantly rural region of northern Louisiana, southern Arkansas, and east Texas. Information on the patient’s age, race, digital rectal examination (DRE) result, serum PSA level, PSA density, prostatic volume, and biopsy result (cancer or no cancer) was entered in a computerized database for analysis. For the inclusive dates noted above, 943 ultrasound-guided transrectal prostate biopsies were performed on 826 patients. Patients were excluded from this analysis if race was other than African-American or white (n = 4), if prostate biopsy was based on considerations other than a serum PSA level greater than 4 ng/mL or abnormal prostate examination (n = 63), or if the prebiopsy PSA was unknown (n = 7). If a patient had more than one set of biopsies and no cancer was detected, only data pertaining to the first set of biopsies were analyzed. If a patient had more than one set of biopsies and cancer was detected in any set, only data associated with the cancer-containing biopsies were analyzed. By taking these measures, data from each patient were included for analysis on only one occasion. The study population, therefore, consisted of 752 white or African-American men who received a prostate biopsy for a PSA level of greater than 4.0 ng/mL and/or an abnormal prostate examination (n = 63), or if the prebiopsy PSA was unknown (n = 7). If a patient had more than one set of biopsies and no cancer was detected, only data pertaining to the first set of biopsies were analyzed. By taking these measures, data from each patient were included for analysis on only one occasion. The study population, therefore, consisted of 752 white or African-American men who received a prostate biopsy for a PSA level of greater than 4.0 ng/mL and/or an abnormal DRE. We defined an abnormal DRE as being any DRE that was suspicious for cancer in the notes of the examining physician. Glands that were simply enlarged or compatible with prostatitis were not classified as being abnormal for the purposes of this study. All patients underwent at least one set of sextant biopsies under ultrasound guidance after giving written informed consent for the procedure. The volume of the prostate was calculated using the prostate ellipse formula: Volume equals 0.52 (L × W × H), where L is the length (in centimeters) obtained from the longitudinal sonographic view, W is the width obtained from the transaxial view, and H is the height or the transaxial view. To examine possible differences in serum PSA level, PSA density, prostate volume, and patient age, the two-sided Student’s t test was used. A multivariate linear regression analysis was used to determine if serum PSA levels were associated with the patient’s age, race, or prostate volume in men without prostate cancer. Because the variance of the serum PSA values increased as a function of the mean PSA value, PSA values were log-transformed prior to statistical analysis.

Sensitivity was defined as being equal to the number of true positives divided by the sum of the true positives plus false negatives. Specificity was defined as being equal to the number of true negatives divided by the sum of the true negatives plus false positives. We used serum PSA levels of less than or greater than 4 ng/mL as it related to men with and without prostate cancer to calculate the number of true positives (PSA >4 ng/mL and cancer), true negatives (PSA <4 ng/mL and no cancer), false positives (PSA >4 ng/mL and no cancer), and false negatives (PSA <4 ng/mL and cancer).

Results

Many clinicians use two distinct methods for the early detection of prostate cancer. These methods include evaluation of serum PSA levels and a digital rectal examination. We have examined our biracial population of 752 consecutive biopsied patients to determine the presence or absence of a serum PSA greater than 4 ng/mL and/or a DRE suspicious for prostate cancer (abnormal DRE). A descriptive analysis of our entire patient cohort is shown in Table 1. We note that a total of 254 men (105 blacks and 149 whites) were diagnosed with cancer and that 498 men (131 blacks and 367 whites) were not.

A total of 498 African-American or white men were without histologic evidence of prostate cancer after examination of at least one set of sextant biopsies. Forty-five of these men had two negative biopsies, 13 had three negative biopsies, and one had four negative biopsies. Included in this group were 367 (73.7%) white and 131 (26.3%) African-American men (Table 2). The serum PSA levels were significantly higher in African-American men compared with white men (P<.0001 by t test). The mean (± standard error [SE]) PSA level in African-American men without evidence of prostate cancer was 7.97 ± 0.95 ng/mL compared with 4.3 ± 0.24 ng/mL for white men. The median PSA for these African-American men was 4.93 ng/mL (range, 0.16-78 ng/mL) and the median PSA for these white men was 3.5 ng/mL (range, 0.1-50 ng/mL). Because age and prostate volume are known to be associated with levels of serum PSA, we next examined whether or not age and/or prostate volumes varied in a racially defined manner. As shown in Table 2, neither age nor prostate volume was different in our biracial population.

### Table 1. Analysis of 752 men having a prostate biopsy stratified by serum prostate-specific antigen (PSA) level >4 ng/mL and digital rectal examination (DRE)* findings at the time of biopsy†

<table>
<thead>
<tr>
<th></th>
<th>Black men (%)</th>
<th>White men (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Cancer</td>
<td>No cancer</td>
</tr>
<tr>
<td>PSA &gt;4 ng/mL only</td>
<td>39 (37)</td>
<td>46 (35)</td>
</tr>
<tr>
<td>Abnormal DRE only</td>
<td>11 (10)</td>
<td>50 (38)</td>
</tr>
<tr>
<td>Both abnormal</td>
<td>55 (52)</td>
<td>35 (27)</td>
</tr>
<tr>
<td>Total</td>
<td>105</td>
<td>131</td>
</tr>
</tbody>
</table>

*An abnormal DRE was defined as a DRE suspicious for cancer.
†Percentages calculated by column. In some cases (due to rounding), the sum of percentages does not equal 100%.
When comparing the serum PSA level/prostate volume ratio (PSA density), however, a strong racial difference emerged. The mean PSA density (±SE) was 0.19 ± 0.03 for African-American men compared with 0.11 ± 0.01 for white men. Thus, the mean units of PSA density in African-American men without prostate cancer in this series was 1.8 times higher than that of a comparably aged group of white men.

To better examine relationships between serum PSA levels, race, and age, and PSA distributions in men without prostate cancer, patient age was stratified by decade. As seen in Table 3, the mean serum PSA level increased with each decade in both white and African-American men, and African-American men had a higher distribution of serum PSA values.

Because the serum PSA level is known to vary as a function of age and prostate volume in normal men, we next questioned whether or not serum PSA levels would be associated with race in our dataset when using a multivariate linear regression analysis. The logarithm of the serum PSA value was used as the response variable to alleviate problems with heteroskedasticity. The results indicate that African-American race was associated with increased PSA (P = 0.0001) after controlling for prostate volume (also associated with PSA; P = 0.0001) and age. Because the effect of race on PSA may be age dependent, the age–race interaction term was tested but found to be insignificant (P = 0.8937) when added to a model containing age, black race, and volume. Thus, it appears that the effect of race does not depend on age in our dataset. A multivariate linear regression analysis was also performed with the logarithm of PSA density as the response variable and age and black race as the predictors. The results suggest that black race remains associated with an increase in PSA density (P = 0.0001) after controlling for age. Again, an age–race interaction was tested but found to be insignificant (P = 0.9809). Based on these data, we conclude that the effect of race on serum PSA level and PSA density appears to be uniform with age.

Of the 752 men analyzed in this study, 254 had biopsy-proven prostate cancer. As noted in the “Methods” section, some men had more than one set of sextant biopsies. Twenty men had cancer detected on a second set of biopsies after a first set was negative, three had cancer detected after two sets of negative biopsies, and two had cancer detected after three sets of negative biopsies.

Table 2. Analysis of 498 men whose biopsy yielded no evidence of cancer

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Black men</th>
<th>White men</th>
<th>Combined</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–49</td>
<td>2.14 ± 1.16</td>
<td>3.25 ± 1.42</td>
<td>2.84 ± 0.96</td>
</tr>
<tr>
<td>(n = 4)</td>
<td>(n = 7)</td>
<td>(n = 11)</td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>4.56 ± 0.94</td>
<td>3.40 ± 0.50</td>
<td>3.64 ± 0.46</td>
</tr>
<tr>
<td>(n = 13)</td>
<td>(n = 48)</td>
<td>(n = 61)</td>
<td></td>
</tr>
<tr>
<td>60–69</td>
<td>6.70 ± 0.99</td>
<td>4.68 ± 0.39</td>
<td>5.20 ± 0.38</td>
</tr>
<tr>
<td>(n = 68)</td>
<td>(n = 195)</td>
<td>(n = 263)</td>
<td></td>
</tr>
<tr>
<td>70–79</td>
<td>11.22 ± 2.31</td>
<td>4.29 ± 0.36</td>
<td>6.18 ± 0.71</td>
</tr>
<tr>
<td>(n = 43)</td>
<td>(n = 115)</td>
<td>(n = 158)</td>
<td></td>
</tr>
<tr>
<td>≥80</td>
<td>12.90 ± 3.94</td>
<td>4.70 ± 2.91</td>
<td>9.62 ± 3.14</td>
</tr>
<tr>
<td>(n = 3)</td>
<td>(n = 2)</td>
<td>(n = 5)</td>
<td></td>
</tr>
</tbody>
</table>

The availability of PSA measurements and biopsy data derived from men with and without prostate cancer allows determination of sensitivity and specificity in a race-specific fashion (Table 4). In African-Americans, a PSA value of greater than 4 ng/mL was associated with prostate cancer in this particular cohort, with a sensitivity and specificity of 89.5% and 38.2%, respectively. In whites, a PSA value of 4 was associated with an 81.9% sensitivity and 52.3% specificity for prostate cancer in this population. We note that these data are not derived from a population-based cohort but rather from a group of men, all of whom had abnormal PSA values and/or abnormal prostate examinations. Thus, the applicability of these calculations to a more general population is not clear at this time.

Discussion

Catalona et al. (8) have extensively reported on the use of serum PSA measurements in conjunction with DRE as a screening test for prostate cancer. In these studies, the use of both PSA and DRE substantially increased the detection of organ-confined prostate cancer over DRE alone. Similarly, Brawer et al. (9) demonstrated that PSA was able to detect carcinoma in men with normal prostates and concluded that PSA was an important adjunct to DRE for the early detection of prostate cancer. Despite these findings, there is considerable overlap in the measured serum PSA levels between men with benign prostatic hyperplasia and those with prostate cancer, resulting in a lack of optimal sensitivity and specificity of serum PSA in the detection of prostate cancer (10,11). Because of these limitations, investigators have attempted to improve the usefulness of PSA as a screening tool by using various techniques, such as age-related normal serum values and PSA density.

Age-specific reference ranges for serum PSA levels have been suggested as a means to increase the accuracy of PSA as a screening tool by Oesterling et al. (12), who prospectively studied 471 men to determine decade-specific reference ranges for PSA. These investigators concluded that such ranges have the potential to make PSA a more sensitive marker in younger men and a more specific marker in older men. The disadvantage of this study, however, is that the study population was almost exclusively white and the age-specific reference ranges proposed by these investigators may or may not be applicable to other racial populations. Indeed, racial variation in PSA is sup-
ported by Oesterling et al. (13) who reported that Japanese men have lower serum PSA levels than age-matched whites. Our analysis clearly supports the concept of racial differences in PSA between African-American and white men and suggests that if age-normalized PSA values are used, then race-specific normal values should be determined to enhance the accuracy of PSA as a screening tool. Even though our data indicate that African-American men without prostate cancer have a higher serum PSA level than do whites, these data do not indicate that the PSA cutoff for prostate biopsies should simply be increased in African-American men. A recent paper by Morgan et al. (14) has directly addressed this issue in a large cohort of men with no known prostate cancer. These authors concluded, as we have, that African-American men without prostate cancer have higher PSAs than white men. However, they have recommended that the criteria for PSA-driven prostate biopsies be established at a serum PSA level sufficient to maintain the sensitivity for prostate biopsies at 95% in all race and age subgroups. In African-American men aged 40-49 years, this results in recommendations for a lower PSA cutoff in African-American men than white men. Although the conclusions of Morgan et al. (14) will be subject to considerable discussion, these investigators have clearly addressed the issue of age- and race-normalized PSA in a manner that emphasizes sensitivity rather than specificity in the recommended criteria for PSA-driven biopsies.

In additional attempts to enhance the accuracy of serum PSA in prostate cancer screening, Benson et al. (15) described PSA density that is simply calculated by dividing the serum PSA (ng/mL) by the prostate volume in cubic centimeters. Despite initial enthusiasm that PSA density may be useful in distinguishing benign prostatic hyperplasia from prostate cancer, other reports (16,17) question the use of this quotient. Our data clearly show a racial difference in PSA density among men who are biopsy negative for prostate cancer and suggest that, if this quotient were used, race-normalized data would be most appropriate. We note that these studies address the operating characteristics of PSA and PSA density; impact on mortality awaits testing in randomized prospective trials, some of which are ongoing.

As noted in the introduction, several studies (6,7) have indicated that African-American men with prostate cancer have higher PSAs on a stage-for-stage basis as compared with white men. Our study raises the issue as to whether or not these previously reported results are due to production of PSA from benign or malignant tissues. We note that current methods of measuring PSA cannot distinguish the source from which the PSA was derived. We note that in low volume, early stage cancers, the majority of PSA production is actually derived from non-malignant epithelium. Thus, given the results of this study, we hypothesize that racial differences in PSA production arise either prior to and/or independently of cancer. Regardless, we conclude that race-specific data for African-American men are required if PSA is to reach its full potential as a screening tool in this high-risk population.

### References


(17) Lookner DH, Crawford ED, Donohue RE, Miller GJ, Clark JE, Stark GL. Prostate specific antigen and prostate specific antigen density in cases of pathologically proven prostate cancer [abstract]. J Urol 1993;149:414A.

Notes

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