The Influence of Prostate Volume on Prostate-Specific Antigen Performance: Implications for the Prostate Cancer Prevention Trial Outcomes
Christopher S. Elliott, 1 Rajesh Shinghal, 2 and Joseph C. Presti, Jr. 1

Abstract
Purpose: Although showing a 25% reduction in the biopsy prevalence of cancer compared with placebo in the Prostate Cancer Prevention Trial, finasteride was associated with a higher prevalence of high-grade disease. This observation was driven by “for-cause” biopsies. We sought to understand how volume-dependent changes in prostate-specific antigen test performance characteristics may have contributed.

Experimental Design: A retrospective review was done on 1,304 men referred for initial biopsy with a prostate-specific antigen between 4 and 10 ng/mL or an abnormal digital rectal examination. Receiver-operator curves and positive predictive values were ascertained for prostate-specific antigen stratified by diagnosis and prostate volume.

Results: The performance of prostate-specific antigen changed for any and high-grade (Gleason, ≥3 + 4) cancer in a volume-specific manner. For any cancer, the area under the curve (AUC) decreased from 0.758 to 0.629 to 0.520 as prostate volume increased (<30, 30-50, >50 cm³, respectively). For high-grade cancer, a similar trend was shown (AUC, 0.712, 0.639, and 0.497, respectively). The positive predictive value of a prostate-specific antigen of ≥4 ng/mL was also affected by prostate volume. Trends for Gleason ≤6 decreased as prostate volume increased (positive predictive value for <30 cm³, 25.0%; positive predictive value for 30-50 cm³, 23.8%; and positive predictive value for >50 cm³, 17.3%). A more significant trend was seen for high-grade cancer (positive predictive value for <30 cm³, 39.0%; positive predictive value for 30-50 cm³, 22.3%; and positive predictive value for >50 cm³, 10.7%).

Conclusion: Decreases in prostate volume over time and the resultant change in prostate-specific antigen performance characteristics may have contributed a bias toward the detection of high-grade disease in the finasteride arm of the Prostate Cancer Prevention Trial.

The overall finding in the Prostate Cancer Prevention Trial, that finasteride treatment lead to an overall reduction in prostate cancer prevalence of ~25% over a 7-year period, was quite remarkable. To date, no other chemopreventive agent had been shown to have such an effect in a randomized placebo controlled trial. This finding, however, was tempered by the observation that the incidence of high-grade cancer (Gleason, ≥7 or) was higher in the finasteride arm as compared with the placebo arm (6.4% versus 5.1%; ref. 1). This 25% increase in high-grade cancer has limited the use of finasteride as a chemopreventive agent by the medical community to date.

Interestingly, upon review of these findings, the indication for prostate needle biopsy in the trial may have affected the outcome. During the Prostate Cancer Prevention Trial, a biopsy was obtained for one of two reasons. The first of these was the “for-cause” biopsy that men underwent if on yearly examination an abnormal digital rectal examination or corrected prostate-specific antigen of ≥4 ng/mL was found. At the end of the trial, all men not previously diagnosed with cancer during the trial were asked to submit to an “end-of-study” biopsy. These men did not have abnormal digital rectal examinations or elevated prostate-specific antigens.

If one compares the incidence of high-grade cancer between these two groups, there is a stark difference. In the end-of-study biopsy cohort, virtually no difference was seen in the diagnosis of high-grade cancers (2.5% in the finasteride arm and 2.3% in the placebo arm). In the for-cause biopsy cohort, however, a large difference in high-grade cancer diagnosis was seen. In this group, the rate of high-grade cancer in the finasteride arm was 11.5%, whereas that of the placebo arm was only 7.7%. Clearly, the for-cause biopsy group drove the observation of an increased prevalence of high-grade cancer in the finasteride arm.

One proposed mechanism for this large difference seen only in the for-cause biopsy groups was an introduction of detection bias. This could have potentially been brought about by an unknown effect of finasteride on prostate cancer screening. Evidence for this type of effect was indeed shown by Thompson et al. (2) In their work, the performance of prostate-specific
antigen as a screening tool was shown to be enhanced in men taking finasteride as opposed to those taking placebo. Questions however still remain. Among these is why finasteride seems to improve prostate-specific antigen performance? One of the mechanisms that were thought to explain this effect was the ability of finasteride to decrease prostate volume and, hence, the confounding effects of benign prostatic hyperplasia (BPH) on prostate-specific antigen testing. It has been shown that prostate volume decreases ~25% in men on finasteride (3). This was also seen in the Prostate Cancer Prevention Trial with men on finasteride having a median prostate size of 25.5 cm³ at the time of prostate biopsy, whereas men on placebo had a median prostate size of 33.6 cm³. However, it is known that finasteride, a 5α reductase inhibitor has effects on local prostate androgen levels, specifically dihydrotestosterone. Thus, the question of how finasteride increases prostate-specific antigen test performance (size effect versus size-independent hormonal effect) has not been directly addressed.

Several other questions also remain because of the nature of the Prostate Cancer Prevention Trial. First, does the observation that finasteride improves prostate-specific antigen performance in a study population, entered into the trial with a prostate-specific antigen of ≤3 ng/mL, correlate to a referral population seen more commonly by a urologist? Second, do these findings apply in men undergoing the more contemporary extended prostate needle biopsy schemes as compared with the sextant biopsies used for most men (>80%) in the Prostate Cancer Prevention Trial? It is well established that sextant schemes underestimate the presence of cancer (4). When the Prostate Cancer Prevention Trial was designed, sextant biopsies represented the standard of care. Over the course of the trial, extended biopsy schemes were introduced and validated, but could not be introduced into the study. In addition, sextant biopsies also increase the risk for undergrading prostate cancer compared with extended biopsy schemes (5).

We sought to better understand the effect of prostate size on prostate-specific antigen test performance, without the possible confounding effect of a hormonal altering agent, in a referral-based population undergoing extended prostate biopsy schemes.

In an attempt to better model the Prostate Cancer Prevention Trial participants, all men had either an abnormal digital rectal examination or a prostate-specific antigen of ≥4 ng/mL but a prostate-specific antigen value of <10 ng/mL.

Materials and Methods

After gaining institutional review board approval, a retrospective review of prospectively collected data was done for men undergoing transrectal ultrasound guided extended prostate biopsy schemes during the years 1996 to 2006 at our institution. These men had been referred for elevations in prostate-specific antigen of ≥4 ng/mL and/or abnormal findings on digital rectal examination. Study participants had not undergone previous prostate biopsy or surgical therapy for BPH. In addition, no participant used either testosterone or 5α reductase inhibitors. All study participants had a prostate-specific antigen level of ≤10 ng/mL as a means of best approximating the Prostate Cancer Prevention Trial study cohort.

All demographic and examination data was collected at the time of biopsy. Ethnicity was self-reported by patients. All digital rectal examination findings were confirmed by an attending physician and were classified as abnormal if either induction or a palpable nodule was noted. Before prostate biopsy, all patients underwent prostate volume measurements. Transrectal ultrasound was done with a biplanar variable-frequency (5-7.5 MHz) probe. Transverse and longitudinal images were obtained continuously. Total prostate volumes were calculated with the prostate ellipsoid formula (volume = 0.52 × length × width × height). Prostate biopsies were taken using the standard 18-gauge needle loaded in a spring-driven biopsy device. All men underwent extended biopsy schemes (8-16 cores). The number of cores taken was a product of the year that the patient underwent biopsy. At our institutions, eight cores were standard practice beginning in 1996. This increased to 10 cores in 1997 and ≥12 cores in 2001. Histopathologic status was classified as either negative (BPH, atrophy, atypia, prostatic intraepithelial neoplasia, or inflammation) or positive (cancer). A Gleason grade was reported for all positive biopsies. A definition of high-grade was used for Gleason sum of ≥7.

Med-Calc version 9 was used for all statistical calculations. The χ² test was used to compare proportions, and a Mann-Whitney test was used to test continuous variables. When multiple strata were used and compared, an appropriate test for trend was used. In assessing test performance, two clinical endpoints were assessed: (a) the presence or absence of cancer and (b) the presence or absence of high-grade cancer. Receiver operator characteristic curves were generated for prostate-specific antigen stratified by prostate volume. The AUC was determined for each and compared using the univariate Z-score test and independent group sampling (6). The positive predictive value was calculated by dividing those with a positive biopsy by all those who underwent a biopsy. Prostate-specific antigen density was calculated by dividing the prostate-specific antigen value by the total prostate volume.

Results

The demographic data for our study population with a prostate-specific antigen level of ≤10 ng/mL can be seen in Table 1. The median age of our population was 66 years of age. The median prostate-specific antigen level was 5.5 ng/mL, the rate of abnormal digital rectal examination was 38.9%, and the median prostate volume was 42.9 cm³. By race, our population was predominantly Caucasian (68%), with the rest being made up of men of African-American (15%), Asian/Pacific-Islander (9%), and Hispanic origin (5%). The ethnicity in 3% of our population was unknown. More than 90% of men had ≥10 cores taken as part of their extended biopsy scheme.

Of the 1,304 men in the primary study group, 497 (38.1%) were diagnosed with prostate cancer. Of the cancer diagnoses,
247 (19%) were high grade (Gleason score, ≥7) and 84 (6.4%) were Gleason ≥8 or above. As seen in Table 2, as prostate volume increased, the rates of any cancer diagnosis, Gleason ≥7 disease and Gleason ≥8 disease all decreased in a statistically significant fashion (P < 0.001 for each).

The receiver operator characteristic curves for the study subjects based on prostate size can be seen for any cancer and high-grade cancer diagnosis in Fig. 1. The performance for the diagnosis of any prostate cancer improved as prostate volume decreased (AUC for <30 cm³, 0.758; AUC for 30-50 cm³, 0.629; and AUC for >50 cm³, 0.520). This trend was statistically significant in nature (P < 0.001 for 30-50 cm³ versus >50 cm³ < 0.001; P for 30-50 cm³ versus >50 cm³ = 0.005). A similar trend was observed for the performance of prostate-specific antigen in the diagnosis of high-grade cancer (AUC for <30 cm³, 0.712; AUC for 30-50 cm³, 0.639; and AUC for >50 cm³, 0.497). This trend, when compared statistically, did not quite reach statistical significance for the comparison of the <30-cm³ group to the 30- to 50-cm³ group (P = 0.123) but did reach significance when comparing the 30- to 50-cm³ group to the >50-cm³ group (P = 0.008).

The positive predictive value of a prostate-specific antigen of ≥4 ng/mL based on prostate size can be seen in Fig. 2. As seen, the positive predictive value for low-grade prostate cancer detection (Gleason, ≤6) significantly decreased as prostate size increased (positive predictive value for <30 cm³, 25.0%; positive predictive value for 30-50 cm³, 23.8%; and positive predictive value for >50 cm³, 17.3%; χ² test for trend P = 0.036). These positive predictive values increased for high-grade cancer detection in prostates of <30 cm³ relative to low-grade cancer detection whereas either staying the same or decreasing for larger prostates (positive predictive value for <30 cm³, 39.0%; positive predictive value for 30-50 cm³, 22.3%; and positive predictive value for >50 cm³, 10.7%; χ² test for trend P < 0.001). Although little difference was seen in the positive predictive value between low-grade and high-grade cancers in the 30- to 50-cm³ size comparison (P = 0.176), large differences were seen in the <30- and >50-cm³ subgroups. In the <30-cm³ subgroup, a diagnosis of high-grade cancer predominated (P = 0.004), whereas in the >50-cm³ subgroup, a diagnosis of low-grade cancer predominated (P = 0.004).

A logistic regression model was also created to test the interaction term of prostate volume (milliliter) × serum prostate-specific antigen (nanogram per milliliter) in regards to any cancer diagnosis and high-grade cancer diagnosis. In both instances, this variable was negative (-0.0012 and -0.0015, respectively) and statistically significant (P < 0.001 in both instances), suggesting that the risk for any cancer and high-grade cancer diagnosis associated with a 1 ng/mL difference in prostate-specific antigen decreases with increasing prostate volume.

The median prostate-specific antigen levels and prostate-specific antigen density for men with a diagnosis of no cancer, low-grade cancer, or high-grade cancer are presented in Table 3. The median prostate-specific antigen and prostate-specific antigen density increased greatly as one compares the diagnosis of no cancer to low-grade cancer and to high-grade cancer diagnosis in the <30-cm³ and 30- to 50-cm³ size cohorts. There was little, if any, difference in prostate-specific antigen and prostate-specific antigen density levels across the three groups in the >50-cm³ cohort. In addition, a significant drop in median prostate-specific antigen density was seen for low-grade and high-grade cancer diagnoses as volume increased from <30 cm³ to 30 to 50 cm³ and to >50 cm³ (P < 0.001 in all cases). It should be noted that there was no associated prostate-specific antigen increase in high-grade cancers across the various volume strata (P = 0.202 and 0.848, respectively).

Table 1. Study subject characteristics

<table>
<thead>
<tr>
<th>Variable</th>
<th>Our study</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>1,304</td>
</tr>
<tr>
<td>Median age (y)</td>
<td>66 (IQR, 59-72)</td>
</tr>
<tr>
<td>Median prostate volume (cm³)</td>
<td>42.9 (IQR, 30.4-60.9)</td>
</tr>
<tr>
<td>Abnormal DRE</td>
<td>507 (38.9%)</td>
</tr>
<tr>
<td>Median PSA level (ng/mL)</td>
<td>5.5 (IQR, 4.4-7.1)</td>
</tr>
</tbody>
</table>

Abbreviations: IQR, interquartile range; DRE, digital rectal examination; PSA, prostate-specific antigen.

Discussion

There currently exist many attempts to explain the findings of the Prostate Cancer Prevention Trial in regards to the outcome of increased high-grade cancers (Gleason, ≥7) in the finasteride arm as compared with the placebo arm. One such study

Table 2. Rates of cancer diagnosis by prostate volume

<table>
<thead>
<tr>
<th>Volume (cm³)</th>
<th>No. in group</th>
<th>Any cancer*</th>
<th>GI ≤ 6 †</th>
<th>GI ≥ 7 †</th>
<th>GI ≥ 8 ‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;20</td>
<td>58</td>
<td>27 (46.6%)</td>
<td>12 (20.7%)</td>
<td>15 (25.9%)</td>
<td>6 (10.3%)</td>
</tr>
<tr>
<td>20-29.9</td>
<td>256</td>
<td>124 (48.4%)</td>
<td>48 (18.8%)</td>
<td>76 (29.7%)</td>
<td>29 (11.3%)</td>
</tr>
<tr>
<td>30-39.9</td>
<td>262</td>
<td>120 (45.8%)</td>
<td>65 (24.8%)</td>
<td>55 (21.0%)</td>
<td>19 (7.3%)</td>
</tr>
<tr>
<td>40-49.9</td>
<td>219</td>
<td>83 (37.9%)</td>
<td>39 (17.8%)</td>
<td>44 (20.1%)</td>
<td>16 (7.3%)</td>
</tr>
<tr>
<td>50-59.9</td>
<td>167</td>
<td>63 (37.7%)</td>
<td>38 (22.8%)</td>
<td>25 (15.0%)</td>
<td>9 (5.4%)</td>
</tr>
<tr>
<td>60-69.9</td>
<td>119</td>
<td>32 (26.9%)</td>
<td>14 (11.7%)</td>
<td>18 (15.1%)</td>
<td>2 (1.7%)</td>
</tr>
<tr>
<td>70-79.9</td>
<td>84</td>
<td>22 (26.2%)</td>
<td>17 (20.2%)</td>
<td>5 (6.0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>&gt;80</td>
<td>139</td>
<td>26 (18.7%)</td>
<td>17 (12.2%)</td>
<td>9 (6.5%)</td>
<td>3 (2.2%)</td>
</tr>
</tbody>
</table>

NOTE: The rates of any cancer, Gleason ≥7 disease, and Gleason ≥8 disease all decrease with increasing prostate volume.

Abbreviation: GI, Gleason.
* χ² Test for trend P < 0.001.
† χ² Test for trend P = 0.07.
‡ χ² Test for trend P < 0.001.
evaluated whether histopathologic changes due to androgen modification brought about by finasteride may have played such a role in differing biopsy readings. Their findings indicate that this was likely not the case because features of hormonal degenerative changes were no different in high-grade disease between the finasteride and placebo arms (7).

The hypothesis with the most support argues that the effect of finasteride on prostate size may have resulted in a sampling bias. In other words, with decreasing prostate size, an increase in biopsy accuracy would occur given that cancer was present. Serfling et al. (8), using a mathematical modeling system, suggested that given a baseline prostate size of 40 cm³ and assuming a tumor volume of 1 cm³, a 25% decrease in prostate size would lead to an increase in tumor diagnosis of 21% using sextant biopsy. However, this study was unable to take into account low-grade versus high-grade tumors. This hypothesis was also evaluated by Cohen et al. (9) in a posthoc analysis of the Prostate Cancer Prevention Trial. Using a logistic regression analysis taking into account prostate size as well as number of biopsy cores, they concluded that, by adjusting for sampling density, the difference in high-grade cancer between the finasteride and placebo arm was eliminated.

More recently, several updated looks at the Prostate Cancer Prevention Trial by the principal authors, and others have lead to speculation that biases in selection and biopsy accuracy may have lead to faulty conclusions. In the first of these analyses, after assuming that all men in the trial underwent biopsy (using a covariate-based approach to model for missing data), the difference in high-grade cancer between the placebo and finasteride-treated groups was shown to be nonsignificant. This was further augmented when modeled using data from men undergoing radical prostatectomy and applying it to the trial as a whole. Using this information, the rate of high-grade disease was estimated to be decreased by 27% in those using finasteride (10). This was similarly shown in the work by Pinsky et al. (11), who showed, using alternative methods in men from the Prostate Cancer Prevention Trial undergoing radical prostatectomy, that misclassification rates differed between the placebo and finasteride-treated men. In their analysis, again, it was argued that the true rate of high-grade disease may have actually been lower in the men on finasteride as compared with the men on placebo (estimated relative risk, 0.84).

Fig. 1. Receiver-operator characteristic curves for any cancer and high-grade cancer diagnosis across three volume stratifications. Significant differences exist between the curves for any cancer diagnosis between the different prostate volume groups (P for 30 cm³ versus 30–50 cm³ = 0.001; P for 50 cm³ versus >50 cm³ = 0.005). A trend for significance was also seen in high-grade cancer diagnosis between the different prostate volumes (P for 30 cm³ versus 30–50 cm³ = 0.123; P for 30–50 cm³ versus >50 cm³ group = 0.008).

I t has previously been shown that the performance of prostate-specific antigen is better in smaller prostates compared with larger prostates (12). In addition, it has been shown in the Prostate Cancer Prevention Trial and in our own referral cohort that prostate-specific antigen and prostate-specific antigen density show improved performance in the detection of high-grade cancer (Gleason ≥7) as compared to any prostate cancer detection (1, 12, 13). To date, however, an analysis of the performance of prostate-specific antigen as it relates to grade of disease and prostate size has not been evaluated. Our study attempts to minimize the sampling error, which is common in patients undergoing sextant biopsy. More than 90% of our patients had ≥10 needle cores taken. In addition, extended biopsy schemes decrease the chance of grading errors.
Our data suggests that the prostate-specific antigen performance is significantly better in men with smaller prostates. This holds true for the detection of low-grade and high-grade disease. To extrapolate our results to the Prostate Cancer Prevention Trial, we present the following example. Supposing two participants on trial start with a prostate size of 40 cm³, if one is randomized to finasteride, over time, his prostate size would be expected to shrink to <30 cm³ (a 25% reduction). At study entry, his prostate-specific antigen level would follow the middle receiver operator characteristic curve of Fig. 1 (30- to 50-cm³ group). However, after finasteride treatment, he would shift curves and follow the upper curve (<30-cm³ group). If the second participant with an initial prostate size of 40 cm³ is randomized to placebo, prostate-specific antigen would again perform in the middle receiver operator characteristic curve of Fig. 1 at study entry and would either stay on that curve throughout the study or possibly shift to the lower receiver operator characteristic curve (>50-cm³ group) if the prostate size increased in size on placebo. In an analogous fashion, if the participant on finasteride were to develop an “abnormal prostate-specific antigen value on study,” the positive predictive value for high-grade cancer would be seen to increase from 22% to 39% only because his prostate decreased in size (see Fig. 2). Conversely, the participant on placebo would have the positive predictive value for high-grade cancer either stay the same (22%) or decline to 10% should his prostate size increase. Thus, changes in prostate-specific antigen performance characteristics as a function of changes in prostate size contribute to a detection bias in the for-cause biopsy group. However, when no prostate-specific antigen prompt was present for the biopsy, that is, the end-of-study biopsy, there was no difference in high-grade cancer diagnosis in the Prostate Cancer Prevention Trial. These findings suggest that the increase in performance of prostate-specific antigen in the finasteride arm of the trial was, in part, related to decreases in prostate size from the drug.

However, prostate volume changes due to finasteride are not an isolated effect. Changes in the volume of cancerous tissue in addition to BPH may arise with finasteride use. In addition, finasteride has known effects on serum prostate-specific antigen, likely from effects on cancerous and BPH tissue. These factors likely also played a role in the biopsy detection rates in the Prostate Cancer Prevention Trial.

As seen in Table 3, prostate-specific antigen levels between various diagnoses of cancer and size strata had minimal variation. Of note, in patients with prostate volumes of >50 cm³, prostate-specific antigen density levels had minimal variation between any histologic diagnosis, benign or malignant. We feel this is a result of preselection bias for BPH in this patient population with large prostates. The median prostate-specific antigen density levels in men without cancer in small or intermediate prostates (<30 cm³ and 30-50 cm³, respectively) were similar. However, the prostate-specific antigen density in patients with cancer (low or high grade) was significantly higher in smaller prostate compared with intermediate-sized prostates. Furthermore, as shown in Fig. 2, the positive predictive value for an abnormal prostate-specific antigen in predicting high-grade cancer on biopsy is higher in men with small prostates compared with intermediate prostates. We feel this is because of a decrease in the false-positive fraction of abnormal prostate-specific antigen levels in men with small prostates, thus, less BPH, the likely confounder in prostate-specific antigen elevation.

The relative strengths of our study include the fact that our study cohort underwent extended scheme prostate needle biopsy, with >90% of men having ≥10 biopsies. This strengthens the study in several ways. First, this theoretically increases the chance of finding cancer and decreases the incidence of missed cancer. Secondly, extended biopsy schemes also reduce cancer undergrading, thus limiting a potential source of detection bias. Third, our referral cohort is more representative of the population seen in urologic practice. Finally, our cohort was free of men either on testosterone replacement or finasteride treatment, thus eliminating any obvious hormonal component.

Several limitations are present in this study that deserve mention. There was a substantial rate of men with abnormal digital rectal examinations within our data set at 38.9%, which is slightly higher than many contemporary series of referral populations (generally 25-30%). This potentially could have lead to an oversampling of higher-grade, higher-volume tumors in our study population that could limit the applicability of our results.

On the other hand, digital rectal examination status was assessed.

### Table 3. Comparison of prostate-specific antigen and prostate-specific antigen density among volume strata by disease status

<table>
<thead>
<tr>
<th>Group (prostate volume)</th>
<th>No. of men</th>
<th>No. with Gl ≤ 6</th>
<th>No. with Gl ≥ 7</th>
<th>Median PSA of men w/o CaP (prostate cancer)</th>
<th>Median PSA with Gl ≤ 6</th>
<th>Median PSA with Gl ≥ 7</th>
<th>Median PSAD w/o CaP (prostate cancer)</th>
<th>Median PSAD with Gl ≤ 6</th>
<th>Median PSAD with Gl ≥ 7</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;30 cm³</td>
<td>314</td>
<td>60</td>
<td>91</td>
<td>3.4 (1.2-5.1)</td>
<td>5.2 (4.2-7.3)</td>
<td>5.9 (4.5-7.6)</td>
<td>0.135 (0.046-0.207)</td>
<td>0.219 (0.166-0.291)</td>
<td>0.24 (0.178-0.306)</td>
</tr>
<tr>
<td>30-50 cm³</td>
<td>481</td>
<td>104</td>
<td>99</td>
<td>5 (4.1-6.3)</td>
<td>5.5 (4.6-7.0)</td>
<td>6.2 (4.7-8.2)</td>
<td>0.095 (0.095-0.163)</td>
<td>0.118 (0.118-0.191)</td>
<td>0.161 (0.121-0.208)</td>
</tr>
<tr>
<td>&gt;50 cm³</td>
<td>509</td>
<td>86</td>
<td>57</td>
<td>6.1 (5.1-7.8)</td>
<td>6.2 (5.2-7.7)</td>
<td>6.3 (4.9-8.2)</td>
<td>0.086 (0.068-0.112)</td>
<td>0.099 (0.073-0.126)</td>
<td>0.099 (0.080-0.124)</td>
</tr>
</tbody>
</table>

**Note:** No significant differences were seen in the prostate-specific antigen levels of those with high-grade cancer among the three strata. Significant differences were only seen in the median prostate-specific antigen of those without cancer between the three groups (P < 0.001 in all cases) and between the <30-cm³ and 30- to 50-cm³ groups as compared with the >50-cm³ group for low-grade cancer (P = 0.002, respectively). When comparing prostate-specific antigen density among the three groups, significant differences were seen between all three groups for low-grade and high-grade cancer (P < 0.001 in all cases). A difference was also seen between the <30-cm³ and 30- to 50-cm³ groups as compared with the >50-cm³ group for men without cancer (P < 0.001 in both cases).

**Abbreviations:** PSAD, prostate-specific antigen density; w/o, without.
at the time of biopsy and may have been biased toward a trend in the positive based on the fact that patients were assumed to be at high risk for having prostate cancer. Thus, a digital rectal examination abnormality may have been overstated in this particular environment. It should also be noted that, in the Prostate Cancer Prevention Trial cohort, >50% of the for-cause biopsies were done for abnormal digital rectal examination.

Conclusion

In our referral-based cohort of men undergoing extended scheme prostate needle biopsy, the performance of prostate-specific antigen for the detection of any cancer and high-grade cancer is affected by prostate size. Prostate-specific antigen performance is significantly better in prostates <30 cm³ in size as compared with those >30 cm³ in size. This finding could explain the differing high-grade prostate cancer diagnosis rates in the for-cause biopsy cohort of the Prostate Cancer Prevention Trial and supports the possibility of detection bias within the trial.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

Clinical Cancer Research

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