Operating Characteristics of Prostate-Specific Antigen in Men With an Initial PSA Level of 3.0 ng/mL or Lower

Ian M. Thompson, MD
Donna Pauler Ankerst, PhD
Chen Chi, MS
M. Scott Lucia, MD
Phyllis J. Goodman, MS
John J. Crowley, PhD
Howard L. Parnes, MD
Charles A. Coltman, Jr, MD

One of the most common cancer screening activities in the United States is the measurement of prostate-specific antigen (PSA) levels for the early detection of prostate cancer. In 2001, approximately 75% of men in the United States aged 50 years and older reported that they had previously undergone PSA screening and 54% have reported regular PSA screening. Prostate cancer screening with PSA has been controversial, as no studies have proven that this strategy reduces mortality from prostate cancer. After almost 2 decades of PSA screening in the United States, mortality from prostate cancer has decreased, but it is unknown if the mortality reduction is due to screening or to other factors such as treatment efficacy. Of concern relative to a causal interpretation is that prostate cancer mortality rates have declined in countries where PSA screening is uncommon.

Context Three fourths of US men older than 50 years have been screened with prostate-specific antigen (PSA) for prostate cancer.

Objective To estimate the receiver operating characteristic (ROC) curve for PSA.

Design, Setting, and Participants Calculation of PSA ROC curves in the placebo group of the Prostate Cancer Prevention Trial, a randomized, prospective study conducted from 1993 to 2003 at 221 US centers. Participants were 18,882 healthy men aged 55 years or older without prostate cancer and with PSA levels less than or equal to 3.0 ng/mL and normal digital rectal examination results, followed up for 7 years with annual PSA measurement and digital rectal examination. If PSA level exceeded 4.0 ng/mL or rectal examination result was abnormal, a prostate biopsy was recommended. After 7 years of study participation, an end-of-study prostate biopsy was recommended in all cancer-free men.

Main Outcome Measures Operating characteristics of PSA for prostate cancer detection, including sensitivity, specificity, and ROC curve.

Results Of 8575 men in the placebo group with at least 1 PSA measurement and digital rectal examination in the same year, 5587 (65.2%) had had at least 1 biopsy; of these, 1225 (21.9%) were diagnosed with prostate cancer. Of 1213 cancers with Gleason grade recorded, 250 (20.6%) were Gleason grade 7 or greater and 57 (4.7%) were Gleason grade 8 or greater. The areas under the ROC curve (AUC) for PSA to discriminate any prostate cancer vs no cancer, Gleason grade 7 or greater cancer vs no or lower-grade cancer, and Gleason grade 8 or greater cancer vs no or lower-grade cancer were 0.678 (95% confidence interval [CI], 0.666-0.689), 0.782 (95% CI, 0.748-0.816), and 0.827 (95% CI, 0.761-0.893), respectively (all P values <.001 for AUC vs 50%). For detecting any prostate cancer, PSA cutoff values of 1.1, 2.1, 3.1, and 4.1 ng/mL yielded sensitivities of 83.4%, 52.6%, 32.2%, and 20.5%, and specificities of 38.9%, 72.5%, 86.7%, and 93.8%, respectively. Age-stratified analyses showed slightly better performance of PSA in men younger than 70 years vs those 70 years or older with AUC values of 0.699 (SD, 0.013) vs 0.663 (SD, 0.013) (P=.03).

Conclusion There is no cutpoint of PSA with simultaneous high sensitivity and high specificity for monitoring healthy men for prostate cancer, but rather a continuum of prostate cancer risk at all values of PSA.

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Author Affiliations: Department of Urology, University of Texas Health Science Center at San Antonio (Dr Thompson); Fred Hutchinson Cancer Research Center, Seattle, Wash (Dr Ankerst and Ms Chi and Goodman); University of Colorado, Denver (Dr Lucia); Cancer Research and Biostatistics, Seattle (Dr Crowley); National Cancer Institute, National Institutes of Health, Bethesda, Md (Dr Parnes); and Southwest Oncology Group, San Antonio (Dr Coltman).

Corresponding Author: Ian M. Thompson, MD, Department of Urology, University of Texas Health Science Center at San Antonio, 7703 Floyd Curl Dr, San Antonio, TX 78229 (thompsoni@uthscsa.edu).

Reprint Requests: Southwest Oncology Group Operations Office, 14980 Omicron Dr, San Antonio, TX 78245-3217.
A potential explanation for these observations may be due to the characteristics of PSA measurement as a screening test. In general, prostate biopsy has not been recommended unless PSA levels exceed a threshold value, generally 4.0 ng/mL, with slightly lower values recommended recently by some authors.11,12 We have reported that as many as 15% of men with a PSA value less than 4.0 ng/mL have prostate cancer and that 15% of these cancers are high grade.13 With an understanding that the performance characteristics of a screening test play an important role in determining its efficacy and efficiency, we report the receiver operating characteristic (ROC) curve for PSA.

METHODS

The Prostate Cancer Prevention Trial, conducted from 1993 to 2003 at 221 US centers, randomized 18 882 men aged 55 years or older with a normal digital rectal examination result and PSA level less than or equal to 3.0 ng/mL to receive either finasteride or placebo for 7 years.14 Measurement of PSA levels and digital rectal examination were performed annually. Measurements of PSA levels were performed in a central laboratory using the Tandem E assay (Hybritech; Beckman Coulter Inc, Fullerton, Calif) until 2000, when this was replaced with the Access assay (Beckman Coulter). A prostate biopsy with a minimum of 6 cores was recommended if PSA levels exceeded 4.0 ng/mL or the digital rectal examination result was suspicious for cancer. At the end of 7 years all participants not previously diagnosed with cancer were requested to undergo an end-of-study prostate biopsy within 90 days of the randomization anniversary date. Race was defined because of the greater impact of prostate cancer on African American men; race was self-reported by the participants using categories defined by the National Institutes of Health. All participants provided written informed consent, and the study was approved by the institutional review boards of the participating institutions.

Two groups of participants were analyzed. Verified participants were defined as those who underwent prostate biopsy and had had a PSA measurement and digital rectal examination within 1 year previous to their biopsy. For individuals with multiple biopsies the last biopsy was used; all analyses were repeated using instead the first biopsy and confirmed results. Unverified participants were defined as those without a prostate biopsy over the course of the trial; for this group, the last PSA measurement available with an accompanying digital rectal examination result within the year was used for analysis.

The operating characteristics are summarized in terms of the sensitivity and specificity for cutoff values of PSA and the calculated ROC curve for prostate cancer vs no prostate cancer. To examine the operating characteristics of PSA for detecting more-aggressive, higher-grade disease, the operating characteristics for Gleason grade 7 or greater prostate cancer vs Gleason grade less than 7 or no prostate cancer, and Gleason grade 8 or greater prostate cancer vs Gleason grade less than 8 or no prostate cancer were also calculated. The sensitivity is defined as the proportion of cases with a PSA value exceeding each cutoff value, and the specificity as the proportion of noncases with a PSA value equal to or below each cutoff value. The ROC curve is a plot of 1-specificity vs sensitivity for all cutoff values in the range of PSA levels observed. A test of the null hypothesis that the area under the ROC curve (AUC) is 50% was performed using the Wilcoxon rank sum test.

A confirmatory ROC analysis for prostate cancer vs no prostate cancer was performed by adding unverified participants to biopsy-verified participants and using a verification bias adjustment.15,16 To perform the adjustment, a Markov Chain Monte Carlo algorithm using the covariates age, family history of prostate cancer (0 = no; 1 = yes), current digital rectal examination result (0 = negative or normal; 1 = positive indicating suspicion for cancer), and PSA level was used to estimate the probability of cancer and to impute the missing disease status indicator for each of the unverified participants.17 The algorithm essentially weights the unknown disease statuses for the unverified participants by what was observed for similar verified cases. Similar ROC curves with and without verification bias adjustment indicate a lack of verification bias. The program was executed in the C programming language. P < .05 was used to determine statistical significance.

RESULTS

Of 9459 men randomized to the placebo group of the study, 8573 had a PSA value and digital rectal examination result available for analysis; characteristics of these participants are shown in Table 1. Of these 8575 participants, 5587 (65.2%) had at least 1 biopsy performed during the 7 years of the study, with a respective PSA and digital rectal examination result available. The participants who were verified were more likely to be older, to have a family history of prostate cancer, and to be white than those who did not undergo a biopsy (P < .001). Of the participants who underwent biopsy, 1225 (21.9%) had prostate cancer.

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Table 2. Prostate-Specific Antigen (PSA) Values and DRE Results Used in Calculation of the Receiver Operating Characteristic Curve

<table>
<thead>
<tr>
<th>PSA ≥4.0 ng/mL</th>
<th>Verified (n = 5587)</th>
<th>Unverified (n = 2988)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRE result</td>
<td>No. (%))</td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>60 (1.1)</td>
<td>11 (0.4)</td>
</tr>
<tr>
<td>Normal</td>
<td>577 (10.3)</td>
<td>95 (3.2)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>PSA ≤4.0 ng/mL</th>
<th>Verified (n = 5587)</th>
<th>Unverified (n = 2988)</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRE result</td>
<td>No. (%))</td>
<td></td>
</tr>
<tr>
<td>Abnormal</td>
<td>497 (8.9)</td>
<td>82 (2.7)</td>
</tr>
<tr>
<td>Normal</td>
<td>4453 (79.7)</td>
<td>2800 (93.7)</td>
</tr>
</tbody>
</table>

DRE indicates digital rectal examination.

AUC indicates area under the receiver operating characteristic curve.

The performance characteristics of PSA for detecting prostate cancer of any grade, Gleason grade 7 or greater, and Gleason grade 8 or greater are shown in the FIGURE and Table 3. For detecting any grade of cancer, the ROC curve for verified participants only (AUC, 0.682; 95% CI, 0.664-0.699) is nearly identical to that corrected for verification bias (AUC, 0.678; 95% confidence interval, 0.666-0.689), so results are shown only after verification bias adjustment. Although the AUC is significantly better than 50% (P<.001), a clear-cut decision rule for prostate biopsy based on PSA values would be challenging to derive from these data. On one hand, the commonly used cutoff value of 4.1 ng/mL would have a 6.2% false-positive rate (1-specificity) but would detect only 20.3% of cancer cases (sensitivity). To improve cancer detection, the cutoff could be lowered to 1.1 ng/mL, thus detecting 83.4% of cancer cases, but would subject 61.1% of men without cancer to prostate biopsy. The recently recommended cutoff of 2.6 ng/mL would detect only 40.5% of cancer cases. Scanning the first 3 columns of Table 3 shows that there is no single cutoff that would simultaneously yield both high sensitivity and high specificity.

The operating characteristics of PSA measurement improve for detection of higher-grade disease, as shown in the Figure and Table 3. The AUCs for Gleason grade 7 or greater and Gleason grade 8 or greater cancer are 0.782 (95% confidence interval, 0.748-0.816) and 0.827 (95% confidence interval, 0.761-0.893), respectively. For each PSA cutoff value, the test is more sensitive for higher-grade disease (Table 3). The standard cutoff of 4.1 ng/mL detects 50.9% of highest-grade (Gleason grade ≥8) disease. Lowering the cutoff to 1.6 ng/mL would increase sensitivity for highest-grade disease to 90% at the expense of decreasing the specificity to 53.3%. To examine the impact of age on PSA performance, men younger than 70 years (n=2956) were compared with men aged 70 years and older (n=2631). For the younger than 70 years vs 70 years and older age ranges, PSA measurement performed slightly better for younger men with AUC values of 0.699 (SD, 0.013) and 0.663 (SD, 0.013), respectively (P=.03). Sensitivity and specificity for PSA measurement in these 2 age ranges are provided in Table 3. The AUC for PSA measurement in men with normal digital rectal examination results was 0.684 (SD, 0.010) vs 0.662 (SD, 0.024) for men with abnormal results (P=.38).

COMMENT

The Prostate Cancer Prevention Trial provides the first large-scale opportunity to evaluate the operating characteristics of PSA measurement in a prospective-screening setting. The ability to do so results from a unique aspect of the trial—the protocol recommendation for universal verification by prostate biopsy for all men at the end of the study, regardless of PSA levels and digital rectal examination findings. Previous studies have retrospectively estimated sensitivity and specificity.18 Other
prospective screening studies have generally performed a prostate biopsy only in those men with PSA levels above 4.0 ng/mL and consequently have been subject to verification bias. Punglia et al\textsuperscript{16} attempted to correct for verification bias, but the conditions necessary for verification bias adjustment were not strictly satisfied since the study protocol did not require prostate biopsy in men with negative test results.

It is important to recognize the unique nature of this study population. At enrollment, all participants had PSA values of 3.0 ng/mL or less and were older than 54 years (mean age, 62 years), an age similar to that of participants in previous screening studies.\textsuperscript{19} The participants in the current trial anticipated semiannual visits and annual examinations for 7 years of study. By selecting a healthier, more compliant population, with generally low initial PSA values, these criteria could affect generalizability of the estimates of performance characteristics of PSA measurement to the general population.

The high frequency of cancer in men with PSA levels less than 4.0 ng/mL, previously reported from the Prostate Cancer Prevention Trial, implies that the use of PSA measurement for early detection of prostate cancer may result in delayed detection with the common 4.0 ng/mL cutoff.\textsuperscript{13} However, test performance may differ in men who have not had previous screening or who have clinically important disease.\textsuperscript{20} We found sensitivity to increase within the subset of higher-grade cases. Among men with Gleason grade 8 and higher, the sensitivity of the standard PSA cutoff of 4.1 ng/mL was 50.9%, considerably greater than the 20.5% sensitivity observed among all cases. By comparison, Gann et al\textsuperscript{18} found a 73% sensitivity for PSA measurement among symptomatic cancer cases diagnosed within the 4 years following their serum draw. Cases in the series by Gann et al had never undergone clinical PSA testing, whereas all participants in the current study had PSA levels less than or equal to 3.0 ng/mL and a negative digital rectal examination result at study enrollment. Because of repeated screening, cases in our series were more likely to be diagnosed at an early stage in their disease progression.

This analysis of the operating characteristics of PSA measurement may help explain several observations regarding PSA screening and trends in prostate can-

| Table 3. Sensitivity and Specificity for Prostate Cancer and High-Grade Disease, by Cutpoints of Prostate-Specific Antigen (PSA) and by Age* |
|-----------------|-----------------|-----------------|
| PSA, ng/mL      | Sensitivity     | Specificity     |
|                 | Any Cancer (n = 1225) vs No Cancer (n = 4362) | Glyeason Grade ≥7 (n = 250) vs Glyeason Grade <7 or No Cancer (n = 5325) | Glyeason Grade ≥8 (n = 57) vs Glyeason Grade <8 or No Cancer (n = 5518) |
| 1.1             | 83.4            | 38.9            | 92.8            | 37.0            | 94.7            | 35.9            |
| 1.6             | 67.0            | 58.7            | 84.4            | 54.8            | 86.0            | 65.9            |
| 2.1             | 52.6            | 72.5            | 75.6            | 67.3            | 78.9            | 75.1            |
| 2.6             | 40.5            | 81.1            | 67.2            | 76.5            | 68.4            | 81.0            |
| 3.1             | 32.2            | 86.7            | 57.6            | 82.3            | 50.9            | 89.1            |
| 4.1             | 20.5            | 93.8            | 40.4            | 90.0            | 26.3            | 97.5            |
| 6.1             | 4.6             | 98.5            | 13.2            | 97.8            | 10.5            | 99.0            |
| 8.1             | 1.7             | 99.4            | 4.8             | 99.0            | 5.3             | 99.5            |
| 10.1            | 0.9             | 99.7            | 2.4             | 99.5            | 0.9             | 99.3            |
| 1.1             | 82.6            | 43.2            | 92.7            | 39.1            | 96.3            | 38.0            |
| 1.6             | 66.6            | 62.0            | 84.7            | 57.7            | 96.3            | 56.4            |
| 2.1             | 54.8            | 72.8            | 75.0            | 68.9            | 92.6            | 67.6            |
| 2.6             | 45.1            | 80.8            | 66.1            | 77.1            | 88.9            | 75.9            |
| 3.1             | 37.3            | 85.0            | 54.0            | 81.8            | 74.1            | 80.8            |
| 4.1             | 27.7            | 91.7            | 42.7            | 89.0            | 59.3            | 88.1            |
| 6.1             | 5.7             | 97.5            | 15.3            | 97.3            | 33.3            | 97.1            |
| 8.1             | 2.5             | 99.1            | 5.6             | 99.0            | 14.8            | 98.9            |
| 10.1            | 1.3             | 99.4            | 2.4             | 99.4            | 3.7             | 99.3            |
| 1.1             | 81.4            | 37.6            | 92.9            | 34.6            | 93.3            | 33.6            |
| 1.6             | 68.3            | 55.1            | 84.1            | 51.5            | 83.3            | 50.2            |
| 2.1             | 53.9            | 68.5            | 76.2            | 65.5            | 80              | 64.0            |
| 2.6             | 42.0            | 78.3            | 68.3            | 75.8            | 70              | 74.2            |
| 3.1             | 34.3            | 85.2            | 61.1            | 82.9            | 63.3            | 81.3            |
| 4.1             | 21.1            | 92.9            | 38.1            | 91.2            | 43.3            | 90.1            |
| 6.1             | 5.0             | 98.6            | 11.1            | 98.2            | 20              | 98.0            |
| 8.1             | 1.5             | 99.1            | 4.0             | 99.1            | 6.7             | 99.0            |
| 10.1            | 0.7             | 99.7            | 2.4             | 99.7            | 6.7             | 99.7            |

*Twelve cancer cases did not have Gleason grade recorded and are omitted from the grade-related comparisons. For any cancer vs no cancer, n = 2956 for age <70 years and n = 2631 for age ≥70 years; for the grade-related comparisons, n = 2956 for age <70 years and n = 2625 for age ≥70 years.
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cancer diagnosis and mortality in the United States since 1985. That many prostate
cancers, including high-grade tumors, are missed at low levels of PSA could
explain the discrepancy between the rate of PSA screening and the change in pro-
tate cancer mortality over the past 15 years of intensive PSA screening. The delay in
diagnosis of high-grade tumors until PSA levels exceed current threshold
level “normal” values could also explain why there is a 35% risk of subsequent
treatment after radical prostatectomy, presumably due to disease recur-
rence.21 However, lowering the threshold would have 2 consequences: increased biopsy rates and the possibility
of increased detection and treatment of biologically inconsequential can-
cers. Currently, men in the United States have a 17.3% lifetime risk of prostate
cancer diagnosis, while the lifetime risk of prostate cancer death is 3%.22 An inher-
ent property of all screening tests is that they disproportionately enhance the
detection of slower-growing cancers, because more-aggressive tumors have a greater likelihood of becoming clini-
cally apparent between screenings.23 While lowering the PSA threshold is
likely to increase the detection of such aggressive cancers at an earlier stage, the unavoidable tradeoff is the increased
detection of biologically inconsequential cancers.

The implications of this analysis are substantial. Prior to clinical use of bio-
markers or other tests for cancer screening, properly designed validation stud-
ies are essential. A multistep process for validation is currently used by the Early
Detection Research Network of the Na-
tional Cancer Institute.24 While pros-
tate cancer is not unique, it has a vari-
nable natural history, ranging from markedly aggressive to indolent. Con-
sideration should be given to the develop-
ment of biomarkers that incorporate disease prognosis. Finally, it will be a
challenge to the medical community to change the long-held notion that there is a “normal” PSA level. Patients and
health care professionals must be reedu-
cated that there is a continuum of risk and no clearly defined PSA cutoff at
which to recommend biopsy. It will be the
patient, in concert with his health care
professional, who will ultimately have to weigh the sensitivity-specificity
tradeoffs in combination with the un-
certain natural history of the disease to
determine whether further evaluation
with a prostate biopsy is appropriate.

Author Contributions: Drs Thompson, Ankerst, and
Crowley and Miss Chi and Goodman had full access
to all of the data in the study and takes responsibility
for the integrity of the data and the accuracy of the
data analysis.

Study concept and design: Thompson, Ankerst,
Goodman, Parnes, Colman.

Acquisition of data: Thompson, Lucia, Goodman,
Crowley

Analysis and interpretation of data: Ankerst, Chi, Lucia,
Goodman, Crowley.

Drafting of the manuscript: Thompson, Ankerst,
Colman.

Critical revision of the manuscript for important
intellectual content: Thompson, Ankerst, Chi, Lucia,
Goodman, Crowley, Parnes.

Statistical analysis: Ankerst, Chi, Goodman,

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initial data analysis), but had no role in the data anal-
ysis or the decision to publish.

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ing, properly designed validation stud-

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CORRECTIONS

Data Error: In the Original Contribution entitled “Development and Validation of a Prognostic Index for 4-Year Mortality in Older Adults” published in the February 15, 2006, issue of JAMA (2006;295:801-808), a data error was published. In the Box, the number of points assigned for diabetes should have been 1.

Incorrect Study Listed: In the Review Article entitled “Effects of Omega-3 Fatty Acids on Cancer Risk: A Systematic Review” published in the January 25, 2006, issue of JAMA (2006;295:403-415), a study was incorrectly identified. In Figure 2, in the “Prostate” cancer section, the “Swedish Women,42 2001” entry should read “Swedish Twin Registry,46 2001.”

Incorrect Data: In the Original Contribution entitled “Operating Characteristics of Prostate-Specific Antigen in Men With an Initial PSA Level of 3.0 ng/mL or Lower” published in the July 6, 2005, issue of JAMA (2005;294:66-70), the data in the “Race” section of Table 1 were incorrect. These data should have read as follows:

Table 1. Characteristics of Participant Population

<table>
<thead>
<tr>
<th>Race</th>
<th>No. (%)</th>
<th>Verified (n = 5587)</th>
<th>Unverified (n = 2988)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White</td>
<td>5341 (95.6)</td>
<td>2775 (92.9)</td>
<td></td>
</tr>
<tr>
<td>African American</td>
<td>176 (3.2)</td>
<td>139 (4.7)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>70 (1.3)</td>
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<td>0</td>
<td>3 (0.1)</td>
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</table>

LETTERS

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