

ORIGINAL ARTICLE

Effect of Verification Bias on Screening for Prostate Cancer by Measurement of Prostate-Specific Antigen

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ABSTRACT

BACKGROUND

The sensitivity and specificity of a screening test are biased when disease status is not verified in all subjects and when the likelihood of confirmation depends on the test result itself. We assessed the screening characteristics of the prostate-specific antigen (PSA) measurement after correction for verification bias.

METHODS

Between 1995 and 2001, 6691 men underwent PSA-based screening for prostate cancer. Of these men, 705 (11 percent) subsequently underwent biopsy of the prostate. Under the assumption that the chance of undergoing a biopsy depends only on the PSA-test result and other observed clinical variables, we used a mathematical model to estimate adjusted receiver-operating-characteristic (ROC) curves.

RESULTS

Adjusting for verification bias significantly increased the area under the ROC curve (i.e., the overall diagnostic performance) of the PSA test, as compared with an unadjusted analysis (0.86 vs. 0.69, $P < 0.001$, for men less than 60 years of age; 0.72 vs. 0.62, $P = 0.008$, for men 60 years of age or older). If the threshold PSA value for undergoing biopsy were set at 4.1 ng per milliliter, 82 percent of cancers in younger men and 65 percent of cancers in older men would be missed. A digital rectal examination that is abnormal but not suspicious for cancer does not affect the overall performance characteristics of the test.

CONCLUSIONS

A lower threshold level of PSA for recommending prostate biopsy, particularly in younger men, may improve the clinical value of the PSA test.

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ABOUT 75 PERCENT OF MEN IN THE United States who are 50 years of age or older have undergone screening for prostate cancer by measurement of prostate-specific antigen (PSA).¹ Controversy exists as to whether the traditional threshold for recommending prostate biopsy, a PSA level of 4.1 ng per milliliter, should be lowered to improve the sensitivity of the test.^{2,3} An improvement in sensitivity would, however, reduce the specificity of the test and thereby lead to an increase in the number of unnecessary biopsies. Correction for verification bias improves the estimated sensitivity and specificity of the test and permits better-informed decisions to be made about recommendations for prostate biopsy.

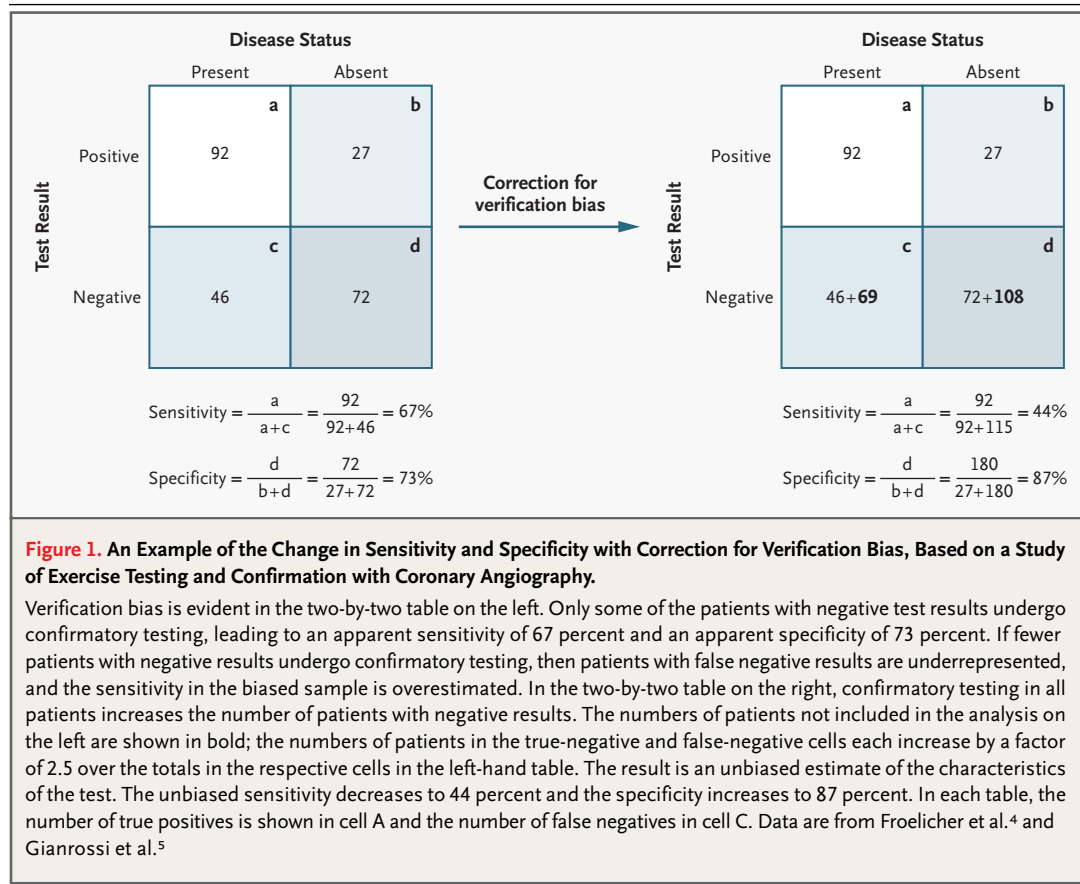
Verification bias occurs when disease status (e.g., the presence or absence of biopsy-confirmed prostate cancer) is not determined in all subjects who are tested and when the probability of verification depends on the test result, other clinical variables, or both. When verification of disease status is more likely among men with positive tests, a bias is

introduced that can markedly increase the apparent sensitivity of the test and reduce its apparent specificity (Fig. 1). For the PSA test, the probability that disease status will be determined by biopsy depends on the results of the PSA test and the digital rectal examination and on age, race, and the presence or absence of a family history of prostate cancer.⁶⁻⁹ In an ideal situation, unbiased estimates of the sensitivity and specificity of the PSA test could be obtained by requiring each man in a randomly selected screening population to undergo both PSA testing and biopsy. There is, however, a mathematical method to correct for verification bias.¹⁰ We used this method to obtain more accurate estimates of the diagnostic characteristics of the test for total PSA.

METHODS

SELECTION AND EVALUATION OF PATIENTS

Between May 1995 and November 2001, 6691 consecutive eligible men were enrolled in a screening study at the Washington University School of Med-



icine, in St. Louis, and underwent both measurement of total PSA and a digital rectal examination. Before May 2000, the PSA tests were performed with an enzyme immunoassay (Tandem-E PSA, Hybritech). Beginning in May 2000, the chemiluminescence method on the Access Analyzer (Beckman Coulter) with PSA antibody (Hybritech) was used. To be enrolled, men had to be 50 years of age or older; the exceptions were men who had a family history of prostate cancer or who were black, in which case the minimal age was 40. A previous prostate biopsy or diagnosis of prostate cancer, the use of finasteride, active urinary tract infection, and prostatitis were exclusion criteria. We selected a study period during which the criterion for a recommendation for biopsy was consistent; specifically, biopsy was recommended if PSA values were greater than 2.5 ng per milliliter or the findings on digital rectal examination were suspicious for prostate cancer. Neither the patient nor the physician recommending biopsy was provided the free PSA value if it was measured.

All biopsies were ultrasound-guided, and in 89 percent of biopsies, five to eight cores were removed. Although prospective studies have indicated that increasing the number of cores improves the detection of cancer,¹¹⁻¹³ a randomized trial showed that increasing the number of cores from 6 to 12 did not improve cancer detection.¹⁴ We therefore did not expect the variation in the number of cores to affect our analyses significantly. Moreover, to compensate for any missed cancers, a diagnosis of prostate cancer up to 18 months after the first PSA test was considered evidence that prostate cancer was present at the time of the initial biopsy. Of the 705 men who underwent prostate biopsy (11 percent of the total), 182 received a diagnosis of prostate cancer. We used the PSA value from the initial enrollment visit to determine the sensitivity and specificity of the test at various cutoff values. Comparison of the characteristics of the men who underwent biopsy with the characteristics of the men who did not was performed with the use of t-tests for normal continuous variables, Wilcoxon tests for non-normal variables, and chi-square tests for categorical covariates; two-sided P values are reported.

ESTIMATION OF RECEIVER-OPERATING-CHARACTERISTIC CURVES

Receiver-operating-characteristic (ROC) curves are plots of the sensitivity versus 1 minus the specificity; each point along the curve is specific for a particular

threshold value for biopsy. We estimated unadjusted ROC curves calculated for the sample of 705 men who underwent biopsy. PSA levels were categorized into ranges that resulted in adequate separation between the points on the ROC curve (for men less than 60 years of age, the categories were 0.8 ng per milliliter or less, 0.9 to 1.3 ng per milliliter, 1.4 to 2.5 ng per milliliter, 2.6 to 4.0 ng per milliliter, 4.1 to 6.0 ng per milliliter, and 6.1 ng per milliliter or greater; for men aged 60 years of age or older, they were 1.0 ng per milliliter or less, 1.1 to 2.0 ng per milliliter, 2.1 to 4.0 ng per milliliter, 4.1 to 6.0 ng per milliliter, 6.1 to 10.0 ng per milliliter, and 10.1 ng per milliliter or greater).

ROC-curve analyses were performed with ROC Analyzer software (developed by Centor and Keightley, University of Alabama, Birmingham). Areas under the curve were calculated by the trapezoidal (nonparametric) method and compared by methods proposed by Hanley and McNeil,¹⁵ with two-sided P values. An area under the curve of 1.0 indicates a test with perfect discrimination between subjects with disease and those without disease, whereas an area under the curve of 0.5 indicates a test with no discriminatory power.

Table 1. Characteristics of Men According to Whether the Results of the PSA Test Were Verified by Biopsy.

Characteristic	No Biopsy (N=5986)	Biopsy (N=705)	P Value
Mean age (yr)*	56.0±8.5	61.4±8.7	<0.001
Median PSA (ng/ml)	0.9	3.3	<0.001
PSA >2.5 ng/ml (%)	9.0	65.2	<0.001
Abnormal digital rectal examination (%)†	10.2	16.7	<0.001
Suspicious findings on digital rectal examination (%)‡	1.4	9.4	<0.001
Black race (%)‡	17.2	14.5	0.06
Family history of prostate cancer (%)§	23.0	23.2	0.88
PSA >2.5 ng/ml or suspicious findings on digital rectal examination (%)¶	10.0	70.2	<0.001

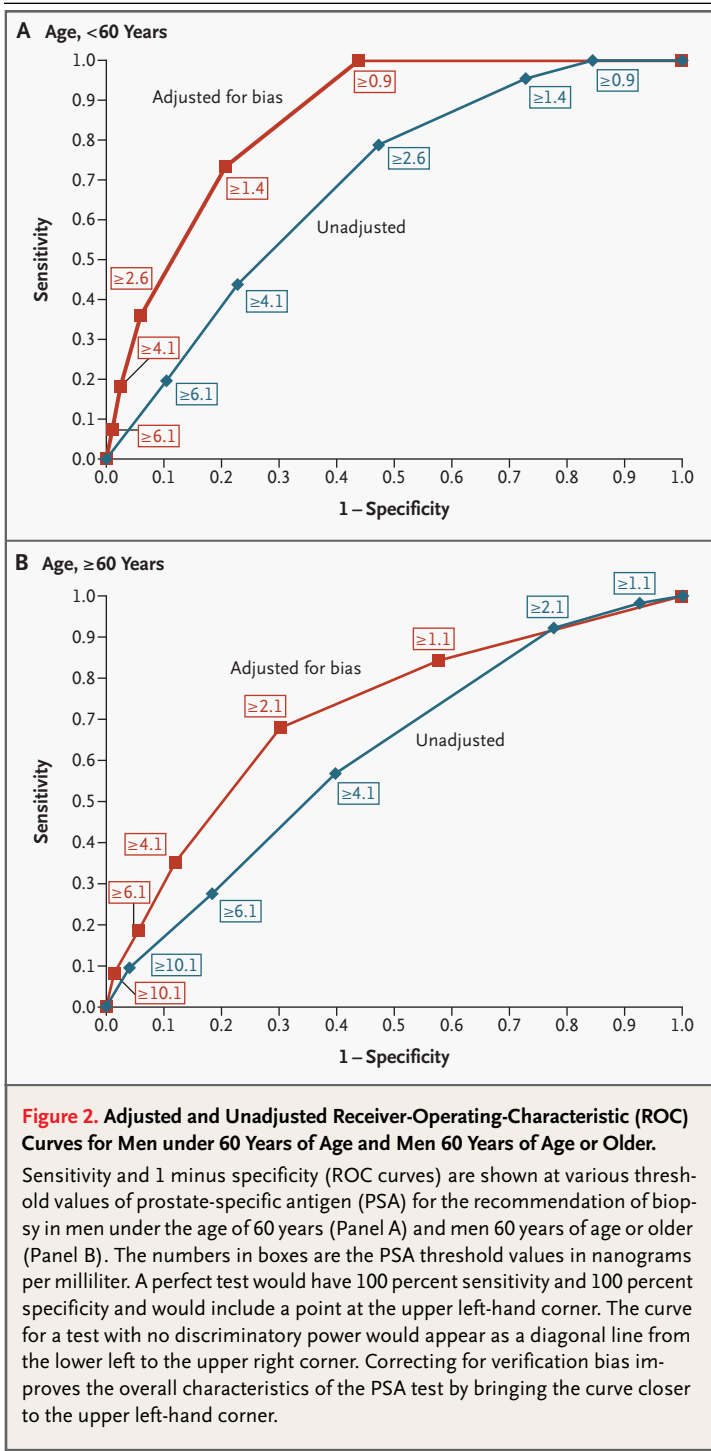
* Plus-minus values are means ±SD. Data were available for 5960 men in the no-biopsy group and 704 in the biopsy group.

† Data were available for 5871 men in the no-biopsy group and 694 in the biopsy group.

‡ Data were available for 5731 men in the no-biopsy group and 689 in the biopsy group.

§ Data were available for 5784 men in the no-biopsy group and 663 in the biopsy group. A family history of prostate cancer was self-reported.

¶ Data were available for 5883 men in the no-biopsy group and 702 in the biopsy group.



CORRECTION FOR VERIFICATION BIAS

We used the method of Begg and Greenes,¹⁰ which corrects for verification bias by adjusting for the verification process, to estimate the sensitivity and specificity of the PSA test in the entire population

undergoing the test and not just in the subgroup in which disease status was verified by prostate biopsy. The key assumption of this method is that the chance that a man will undergo prostate biopsy depends only on observed variables (e.g., the PSA level or the results of digital rectal examination) and not on the presence or absence of cancer, which cannot be directly observed.

To apply this method, we first estimated the probability of cancer as a function of clinical variables, using a logistic-regression model, in the sample in which disease status was verified by biopsy. The variables included in the model were the results of digital rectal examination (prostate abnormal or enlarged, suspicious for cancer, or normal), race (black vs. other), family history with respect to prostate cancer (present vs. absent), and category of PSA-test result. Separate models were constructed for men under the age of 60 years (4556 men, with disease status verified in 316) and those 60 years of age or older (2108 men, with disease status verified in 388), because the higher incidence of benign prostatic hyperplasia in older men is hypothesized to reduce the specificity of the test in this group.¹⁶⁻¹⁸ (Data on age were not available for 27 men.) We then used the fitted logistic-regression model obtained from the subgroup undergoing biopsy to predict the probability of prostate cancer in the entire group, according to the specified covariates. From this analysis, we derived an adjusted ROC curve by calculating the probability of being in a particular PSA test-result category for men in the entire sample with and without prostate cancer. We then compared the adjusted ROC curves with the unadjusted curves, using the methods proposed by Hanley and McNeil,¹⁵ with two-sided P values and standard errors based on the number of men undergoing biopsy (316 younger men and 388 older men).

RESULTS

As compared with the men who did not undergo biopsy, those who did were on average 5.4 years older and had a median PSA value that was 2.4 ng per milliliter higher, and were 1.6 and 6.7 times as likely to have an abnormal or suspicious digital-examination result, respectively (Table 1).

After adjustment for the results of the PSA test and digital rectal examination, we found that within the subgroup of men who had a biopsy, black race was significantly associated with prostate cancer for those under the age of 60 years (odds ratio, 2.75;

$P=0.004$) but not for those 60 years of age or older (odds ratio, 1.56; $P=0.19$). Having a family history of prostate cancer was not significantly associated with prostate cancer among either the younger men (odds ratio, 0.79; $P=0.49$) or the older men (odds ratio, 1.17; $P=0.62$).

Figure 2 shows the estimates of the ROC curves, both adjusted and unadjusted for verification bias. For a particular PSA value used as the threshold for the recommendation of prostate biopsy, the points on the adjusted ROC curve were to the lower left of the corresponding points on the unadjusted curve (indicating lower sensitivity and higher specificity). In addition, the areas under the ROC curves were significantly greater (indicating better diagnostic accuracy) for the adjusted curves. In men under the age of 60 years, the adjustment increased the area under the curve from 0.69 to 0.86 ($P<0.001$). For men 60 years of age or older, the area under the curve increased from 0.62 without adjustment to 0.72 after adjustment ($P=0.008$). The PSA test performed significantly better in men under the age of 60 years than in older men ($P<0.001$).

The sensitivity and specificity of the PSA test at selected threshold PSA levels, after adjustment for verification bias, are shown in Table 2. The sensitivity and specificity for threshold values not used in the analysis can be approximated by linear interpolation from the reported values. For men under 60 years of age, if a PSA value of 4.1 ng per milliliter were used as the threshold for a recommendation of biopsy, the test would have a sensitivity of 0.18, so that 82 percent of prostate cancers would be missed, but it would have a specificity of 0.98, so that only 2 percent of men without prostate cancer would undergo biopsy. The unadjusted estimates of sensitivity and specificity were 0.43 and 0.77, respectively, at this threshold value in the younger age group. In men 60 years of age or older, a test with the same threshold of 4.1 ng per milliliter used for a recommendation of biopsy would have a sensitivity of 0.35, so that 65 percent of prostate cancers would be missed, but it would have a specificity of 0.88, so that 12 percent of men without prostate cancer would undergo biopsy. The unadjusted estimates for this threshold in older men were 0.57 for sensitivity and 0.60 for specificity.

Figure 3 shows the adjusted ROC curves for men with a normal digital rectal examination and men with a digital rectal examination indicating benign hyperplasia (suspicious results were excluded from this analysis). Among men under the age of 60

Table 2. Characteristics of the PSA Test after Adjustment for Verification Bias, According to Age.*

<60 Yr			≥60 Yr		
Threshold for Biopsy Recommendation (ng/ml)	Sensitivity	Specificity	Threshold for Biopsy Recommendation (ng/ml)	Sensitivity	Specificity
0.9	1.00	0.56	1.1	0.84	0.43
1.4	0.74	0.79	2.1	0.68	0.70
2.6	0.36	0.94	4.1	0.35	0.88
4.1	0.18	0.98	6.1	0.19	0.94
6.1	0.08	0.99	10.1	0.08	0.99

* Values reflect the distribution of race, family history of prostate cancer, and results of digital rectal examination in the entire study population.

years, the ROC areas under the curve were 0.86 for those with a normal digital rectal examination and 0.84 for those with an abnormal digital rectal examination ($P=0.82$). Likewise, for men 60 years of age or older, the areas under the curve did not differ significantly when the data were stratified according to the results of the digital rectal examination, with a value of 0.71 for men with normal results and 0.72 for men with abnormal results ($P=0.94$).

Although the curves did not change significantly after data from men with abnormal results of the digital rectal examination and data from those with normal results were separated, the cutoff points differed between these groups, with increased sensitivity and decreased specificity for each PSA threshold in the group of men who had abnormal examination results as compared with the group of men who had normal results. This difference can be explained by a shift toward higher PSA levels in all men with abnormal results on digital rectal examination.

DISCUSSION

We found that correction for verification bias improved the estimated sensitivity and specificity of the PSA test for a screened population. Unadjusted estimates of areas under the ROC curve for the PSA test have been reported to be as low as 0.52.¹⁹ Our analysis showed that, after adjustment for verification bias, the area under the ROC curve increased, providing evidence of an increase in the discriminatory power of the PSA test. The estimated geometric mean of PSA levels derived from the adjusted ROC curves for men with prostate cancer ranged from

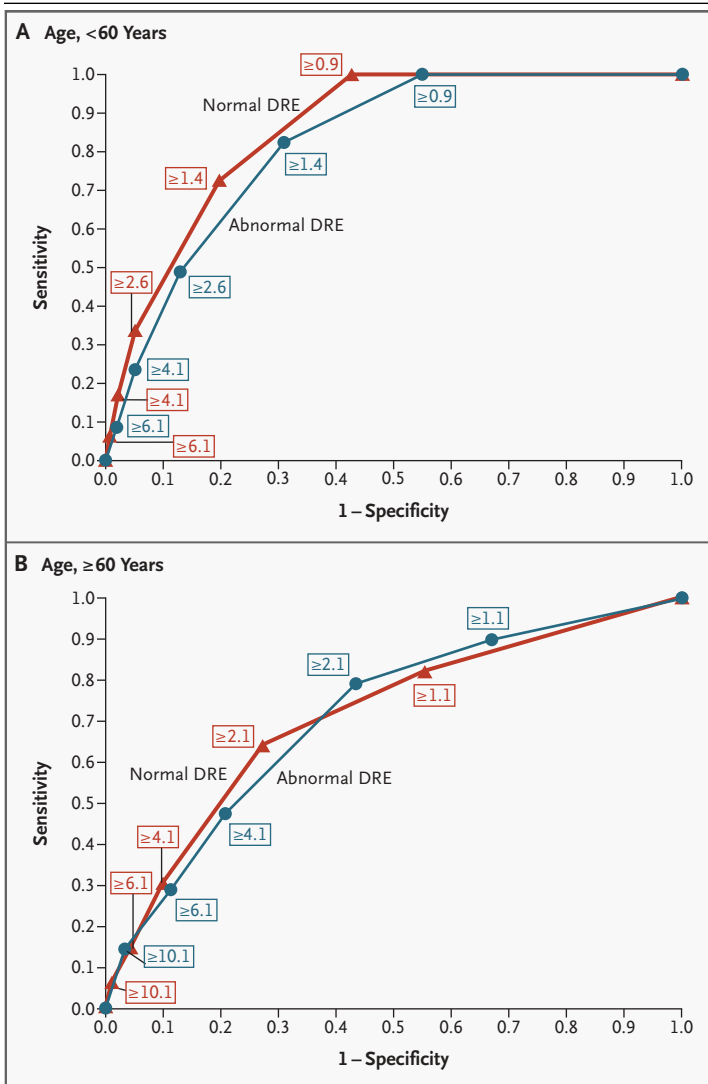


Figure 3. Adjusted Receiver-Operating-Characteristic (ROC) Curves for Men under 60 Years of Age and Men 60 Years of Age or Older, According to the Results of Digital Rectal Examination.

The ROC curves are shown for men with abnormal results on digital rectal examination (DRE) (enlarged prostate, but not suspicious for cancer) and those with normal results, after correction for verification bias. Panel A shows the results for men under 60 years of age, and Panel B shows the results for older men. The numbers in boxes are the threshold values of prostate-specific antigen (PSA) in nanograms per milliliter for the recommendation of biopsy. In each age group, the overall shape of the ROC curve did not differ significantly according to the results of the digital rectal examination. However, the sensitivity and 1 minus specificity of the PSA test at a given threshold value did change. At each threshold value, the test had a lower sensitivity and a higher specificity in the group with a normal digital rectal examination than in the group with an abnormal examination.

2.1 to 3.9 ng per milliliter, depending on age and the results of the digital rectal examination. These values are significantly lower than the levels of 6.3 and 7.5 ng per milliliter reported in a previous study.²⁰ The discrepancy between these values suggests a strong selection bias in the latter study, the results of which were unadjusted, and in which men with higher PSA values were more likely to receive a diagnosis of prostate cancer, resulting in inflation of the sensitivity of the test. This bias led to the incorrect assumption that the PSA test has nearly perfect discriminatory power, with the area under the curve in that study ranging from 0.91 to 0.94.²⁰ The adjusted estimates of specificity from our analysis are similar to the ranges reported by Oesterling et al.²¹ However, in that study, men without disease were randomly selected to undergo biopsy, thereby avoiding verification bias.

Analyses according to the results of the digital rectal examination (an abnormal or enlarged prostate vs. a normal prostate, excluding suspicious results) revealed that the ROC curves have the same overall diagnostic performance, but with altered cutoff points. This result is consistent with a constant shift to higher PSA levels in all men with abnormal results on the digital rectal examination, regardless of disease status, and suggests that the threshold value for recommending biopsy should be higher among men with abnormal findings on digital rectal examination. The use of PSA density, in which increased values of PSA are adjusted for prostate size, follows the same principle.

Our study was limited by the use of prostate biopsy as the gold standard; this choice may have resulted in underestimation of the adjusted sensitivity of the test because the small amount of tissue removed may have introduced sampling error. To reduce this possibility, we used all diagnoses of cancer made within 18 months after PSA screening in calculating outcomes. This method may have introduced bias, however, because patients with rising PSA levels may be more likely to have additional biopsies. We therefore removed such men from the analysis (78 men, 44 of whom had cancer) and re-estimated the adjusted ROC curves. A rising PSA level did not alter the ROC curves (results not shown), but the shift in the adjusted cutoff points to the lower left of the unadjusted points was less for younger men. Moreover, there may be variables besides age, PSA level, results on digital rectal examination, race, and family history that both predict the chance of undergoing prostate biopsy and are related to un-

derlying disease status. This is a problem with retrospective studies. In addition, although our analysis was based on 705 men with verified disease status from a subgroup of 6691 men, the results may be applicable only to a volunteer population.

The prospective Prostate Cancer Prevention Trial conducted by the Southwest Oncology Group may provide unbiased estimates of the sensitivity and specificity of the PSA test that are not limited by verification bias, since all men in the trial underwent biopsy at the completion of the study.²² We studied only total PSA measurements, which are commonly used in the primary care setting for screening.²³ Measurements other than total PSA, such as PSA velocity, PSA density, and free PSA, may provide more discriminatory power and further improve the test. Nevertheless, an analysis of data from the Physicians' Health Study showed that a single measurement of total PSA had relatively high sensitivity and specificity for the detection of prostate cancer diagnosed within four years after the test.²⁴ That study sought to minimize verification bias by assessing the relation between PSA levels in base-line serum samples and the subsequent diagnosis of prostate cancer. For a population with a mean age of 63 years at the time of PSA testing, the sensitivity and specificity of a threshold value of 4.1 ng per milliliter were 0.46 and 0.91, respectively.²⁴ The latter value is close to the 88 percent specificity found for the adjusted estimates with a threshold value of 4.1 ng per milliliter in our analysis for men who were at least 60 years old. The sensitivity of 0.35 for the threshold value of 4.1 ng per milliliter in our study may be lower than 0.46, since the Physicians' Health Study used a case-control design and included only clinically evident cancers, whereas we sought to account for all prostate cancers.

The ideal threshold value for a recommendation of prostate biopsy depends on the tradeoff between

false positive and false negative results. Our analysis therefore did not address which PSA threshold is optimal, but it does show the implications of following current screening recommendations. We found that lowering the threshold for biopsy from 4.1 to 2.6 ng per milliliter in men younger than 60 years would double the cancer-detection rate from 18 percent to 36 percent, whereas the specificity would fall only from 0.98 to 0.94. Other studies of men who underwent biopsy showed that the use of PSA cutoff values between 2.6 and 4.1 ng per milliliter yielded a positive predictive value of 22 to 25 percent, findings that are similar to the positive predictive value for higher PSA levels and consistent with the doubling in sensitivity in our analysis resulting from lowering the threshold for biopsy to 2.6 ng per milliliter.^{2,21,25}

In conclusion, we found that prior estimates of unadjusted sensitivity are significantly higher than adjusted estimates. Moreover, unadjusted values for specificity underestimate the true specificity of the PSA test. Both of these findings support the use of a lower threshold PSA value for a recommendation of biopsy. Early detection may increase the probability that the disease is confined to the prostate,^{3,26} and patients with such confined disease may be more likely to be free from PSA failure after treatment.²⁷ These findings, as well as recent data from a randomized trial showing that prostate-cancer treatment improves disease-free survival,²⁸ indicate that reduction of the threshold PSA level at which biopsy is recommended to 2.6 ng per milliliter, at least in men under 60 years of age, may be reasonable.

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