Verification bias can influence the interpretation of the most important screening test for prostate cancer, measurement of prostate-specific antigen (PSA). Such bias arises when the presence or absence of prostate cancer has not been verified by prostate biopsy in all subjects in the screened population. In this issue of the Journal, Punglia et al. report on how verification bias alters the sensitivity and specificity of the PSA test, and how this bias can influence the clinical decision about whether to perform a biopsy of the prostate. The problem has been recognized previously, but Punglia et al. address it with the use of advanced statistical techniques.

Calculations of the sensitivity and specificity of the PSA test require knowledge of the total number of cancers revealed by autopsy studies of the tested population. The true sensitivity and specificity of the PSA test cannot be established by prostate biopsy, which rarely detects small tumors. Nevertheless, the overall diagnostic performance of the PSA test can be measured against the gold standard of prostate-cancer screening, the prostate biopsy. Punglia et al. did this in a sample of men who underwent biopsy because of an elevated PSA level, an abnormal digital rectal examination, or both. They found that the characteristics of the PSA test can be misleading if correction for verification bias is not performed.

To estimate the true test characteristics of the PSA measurement (i.e., after correction for verification bias), the best approach is to perform a prostate biopsy in all men (or, if this is not possible, in a random sample of the population under study). If this cannot be done, an alternative approach is to carry out a multivariate analysis in which known predictors of the outcome of the biopsy are studied in relation to the true state of disease as revealed by the biopsy, which is what Punglia et al. did. They used a logistic-regression model that included all available variables that can affect the diagnosis of prostate cancer. The information obtained by this analysis of the 705 men who underwent a prostate biopsy was used to assess the probability of detecting prostate cancer by means of a biopsy in all 6691 men in the cohort. These probabilities were then used to calculate the sensitivity and specificity of specific threshold PSA values.

The differences between the uncorrected and corrected PSA results were considerable, especially for younger men. Punglia et al. found that if biopsies were performed only when the PSA value was higher than 4.0 ng per milliliter, 82 percent of cancers would be missed in men who were younger than 60 years of age, and 65 percent would be missed in those who were 60 or older. Should we further decrease the PSA threshold and the age at which a prostate biopsy is recommended, as Punglia et al. suggest?

These findings are difficult to apply clinically. Clinicians want absolute numbers that show the effect of lower PSA cutoff points with respect to the detection rate, number of cancers missed, and number of cases requiring a biopsy if all cancers that could be detected by biopsy were diagnosed. Such data have been obtained in a study of a consecutive sample of 8621 men between the ages of 55 and 74 years who participated in the European Randomized Study of Screening for Prostate Cancer and who were screened by means of a digital rectal examination, transrectal ultrasonography, and a PSA test, with a threshold value of 4.0 ng per milliliter for biopsy.
A priori prevalence assessment (the estimated probability of detecting prostate cancer on the basis of the outcome of the PSA test, prostate volume, digital rectal examination, and transrectal ultrasonography before biopsy) showed that in this sample, in which 93 percent of all indicated biopsies were carried out, 31.9 percent of prostate cancers were missed (Table 1).8

It is evident that below the threshold value of 4.0 ng per milliliter on the PSA test, most cancers were missed by digital rectal examination and transrectal ultrasonography. The proportion of missed cancers was 69.2 percent at a PSA value between 0 and 2.9 ng per milliliter and 46.8 percent at a value between 3.0 and 3.9 ng per milliliter, but cancer-detection rates were exceedingly low when the PSA value was below 2.0 ng per milliliter. With a PSA value between 1.0 and 1.9 ng per milliliter, 2663 biopsies would have to be performed to detect 96 cancers, and 58 cancers (60.4 percent) were missed by digital rectal examination and transrectal ultrasonography (the positive predictive value and detection rate would be 3.6 percent; 96.4 percent of biopsies would be “unnecessary”). These data are not dissimilar to those reported by Punglia et al. The very large number of biopsies that would be necessary to detect prostate cancer at a PSA value of 1.0 to 1.9 ng per milliliter is unacceptable and ethically difficult to defend.

At first glance, the recommendation to lower the age limit for prostate-cancer screening to less than 50 years seems sensible. The deaths from prostate cancer that occur in men 60 to 70 years of age could be prevented by screening at an earlier age, and the number of life-years saved is greater in these younger men. However, the number of tests that would need to be done would be excessive because of the low incidence and the resulting low detection rates.

A mechanism that identifies young men with a high likelihood of having clinically evident prostate cancer later in life would be helpful. A study of 1634 men showed that a positive family history (a father or brother with prostate cancer) doubled the risk of clinically evident prostate cancer.9 Another study, however, showed that among men who were 40 to 49 years old, the frequency of PSA values above 2.5 ng per milliliter did not differ according to the presence or absence of a family history of prostate cancer; only 3 of the 343 men in the study were found to have prostate cancer (0.9 percent).10 A third study suggests that a more powerful way of identifying men who should be screened at a younger age may be to perform a PSA test at approximately 40 years of age, regardless of the family history: a PSA value of greater than 0.60 ng per milliliter (found in 177 of 351 men between the ages of 40 and 49) was associated with a relative risk of 3.6 with respect to the development of prostate cancer within 25 years.11

Important questions that remain to be answered are whether the detection of missed cancers will reduce mortality and improve the quality of life among treated patients. Predictions based on prognostic indicators have limited value. A large, randomized study of men with locally confined prostate cancer that was detected clinically (not by screening) showed a significantly lower rate of death from prostate cancer in the group of men who underwent radical prostatectomy than in the watchful-waiting group.12 After eight years of follow-up, however, the death rate from prostate cancer in the watchful-waiting group was only 13.6 percent, and it was necessary to treat 17 men to prevent 1 death from prostate cancer eight years after the diagnosis.

The recommendation to lower the PSA threshold for performing a prostate biopsy to a value below 3.0 or below 2.5 ng per milliliter must be considered on the basis of the characteristics of the PSA test and its overall diagnostic performance. Lower-

---

### Table 1. Prostate Cancers Found, Expected, and Missed in 8621 Men, According to the Prostate-Specific Antigen (PSA) Range.9

<table>
<thead>
<tr>
<th>PSA Range</th>
<th>No. of Men Screened</th>
<th>No. Who Underwent Biopsy</th>
<th>Prostate Cancer Found</th>
<th>Prostate Cancer Expected</th>
<th>Prostate Cancer Missed</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–2.9 ng/ml</td>
<td>6801</td>
<td>853</td>
<td>65</td>
<td>211 (3.1)</td>
<td>146 (69.2)</td>
</tr>
<tr>
<td>0–0.9 ng/ml</td>
<td>3045</td>
<td>183</td>
<td>4</td>
<td>34 (1.1)</td>
<td>30 (88.2)</td>
</tr>
<tr>
<td>1.0–1.9 ng/ml</td>
<td>2663</td>
<td>468</td>
<td>38</td>
<td>96 (3.6)</td>
<td>58 (60.4)</td>
</tr>
<tr>
<td>2.0–2.9 ng/ml</td>
<td>1093</td>
<td>202</td>
<td>23</td>
<td>81 (7.4)</td>
<td>58 (71.6)</td>
</tr>
<tr>
<td>3.0–3.9 ng/ml</td>
<td>642</td>
<td>159</td>
<td>41</td>
<td>77 (12.0)</td>
<td>36 (46.8)</td>
</tr>
<tr>
<td>≥4.0 ng/ml</td>
<td>1178</td>
<td>1094</td>
<td>319</td>
<td>336 (28.5)</td>
<td>17 (5.1)</td>
</tr>
<tr>
<td>4.0–9.9 ng/ml</td>
<td>980</td>
<td>908</td>
<td>213</td>
<td>222 (22.7)</td>
<td>9 (4.1)</td>
</tr>
<tr>
<td>≥10 ng/ml</td>
<td>198</td>
<td>186</td>
<td>106</td>
<td>114 (57.6)</td>
<td>8 (7.0)</td>
</tr>
<tr>
<td>Total</td>
<td>8621</td>
<td>2106</td>
<td>425</td>
<td>624 (7.2)</td>
<td>199 (31.9)</td>
</tr>
</tbody>
</table>

8 In addition to PSA testing, the men, who ranged in age from 55 to 74 years, underwent digital rectal examination and transrectal ultrasonography. Data are from Kranse et al.8

---
Epidermal Growth Factor for Ulcerative Colitis

Richard J. Farrell, M.D.

The treatment of active ulcerative colitis largely relies on the nonspecific antiinflammatory effects of aminosalicylates (mesalamine and sulfasalazine) and the broad immunosuppressive actions of corticosteroids and other potent immunomodulators. Data from animal models and patients with ulcerative colitis have highlighted the importance of the enteric microflora in the pathogenesis of the disease, yet in clinical trials, antibiotics and probiotics have had only limited efficacy against active disease. In ulcerative colitis, in contrast to Crohn’s disease, there are few clinical data on the value of infliximab and other biologic agents.

The pathogenesis of ulcerative colitis remains unknown, but the disease may result from an overwhelming exposure to normal enteric flora because of a defective mucosal barrier, ineffective mucosal repair after intestinal injury, or both. Attempts to enhance the mucosal barrier in active ulcerative colitis with the use of mucosal protectants such as bis-muth and ecabet sodium enemas have had moderate success. The realization that several key growth factors, including epidermal growth factor (EGF), transforming growth factor (TGF) α and β, and trefoil factors, regulate the preservation of barrier function and the integrity of healthy colonic mucosa has stimulated interest in the therapeutic role of growth factors in inflammatory bowel disease. By far the most highly characterized growth factor is EGF, which was first isolated in 1962 from mouse salivary glands. Studies in animals and humans suggest that EGF has a fundamental role in topical, oral, and enteral wound healing, and its high concentration in saliva provides scientific rationale for why animals lick their wounds.

In this issue of the Journal, Sinha et al. describe a novel approach based on the use of EGF enemas in active distal ulcerative colitis. In this single-center, double-blind, controlled trial, 24 patients with active mild-to-moderate distal ulcerative colitis were randomly assigned to receive daily 100-ml enemas containing EGF or inert carrier alone for two weeks. Both study groups had similar numbers of patients with established colitis and proctitis. Clinical, sigmoidoscopy, and histologic assessments were performed at 0, 2, and 4 weeks, and a final clinical as-

From the Erasmus Medical Center, Rotterdam, the Netherlands.

7. Catalona WJ, Smith DS, Ornstein DK. Prostate cancer detection in men with serum PSA concentrations of 2.6 to 4.0 ng/mL and benign prostate examination: enhancement of specificity with free PSA measurements. JAMA 1997;277:1452-5.