Prostate-Specific Antigen Levels in the United States: Implications of Various Definitions for Abnormal

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Background: The finding that some men with a normal prostate-specific antigen (PSA) level (i.e., less than 4 ng/mL) nonetheless have microscopic evidence of prostate cancer has led to some suggestions that the threshold defining abnormal should be lowered to 2.5 ng/mL. We examined the effect of this lower threshold on the number of American men who would be labeled abnormal by a single PSA test.

Methods: We obtained PSA data on a nationally representative sample of American men 40 years of age and older with no history of prostate cancer and no current inflammation or infection of the prostate gland (n = 1308) from the 2001–2002 National Health and Nutrition Examination Survey. We obtained data on the 10-year risk of prostate cancer death in the pre-PSA era from DevCan, the National Cancer Institute’s software to calculate the probability of dying of cancer.

Results: Based on NHANES data, approximately 1.5 million American men aged 40 to 69 years have a PSA level over 4.0 ng/mL. Lowering the threshold to 2.5 ng/mL would label an additional 1.8 million men as abnormal, if all men were screened. For men aged 70 years or older, the corresponding numbers are 1.5 and 1.2 million. The proportion of the population affected by different thresholds would vary with age. Among men in their 60s, for example, 17% have a PSA level over 2.5 ng/mL, 5.7% have a PSA level over 4.0 ng/mL, and 1.7% have a PSA level over 10.0 ng/mL. For context, only 0.9% of men in their 60s are expected to die from prostate cancer in the next 10 years. Conclusion: Lowering the PSA threshold to 2.5 ng/mL would double the number of men defined as abnormal, up to 6 million. Until there is evidence that screening is effective, increasing the number of men recommended for prostate biopsy—and the number potentially diagnosed and treated unnecessarily—would be a mistake. [J Natl Cancer Inst 2005;97:1132–7]

Several studies have demonstrated that a substantial number of men have microscopic evidence of prostate cancer despite having a prostate-specific antigen (PSA) level below the standard threshold used to define abnormal, i.e., 4.0 ng/mL (1–3). These findings have led some physicians to advocate a lower PSA threshold of 2.5 ng/mL (4,5). A lower threshold inevitably means that more men would be labeled as abnormal, have a prostate biopsy, and be treated for prostate cancer. However, because clinically insignificant disease (also known as pseudodisease) is a well-known problem in prostate cancer (6), others are concerned that a lower PSA threshold will lead to more overdiagnosis and have urged caution in pursuing a diagnosis of prostate cancer in men who have a PSA level of 4.0 ng/mL or lower (7).

Although some data on the number of men who would be identified as abnormal with various PSA thresholds are available from invitational studies of prostate cancer screening (8,9), population-based data on the distribution of PSA levels among men in the United States have not been previously available.
We use newly released data from the 2001–2002 National Health and Nutrition Examination Survey (NHANES) on the distribution of PSA levels in American men to investigate how many men would be labeled as having abnormal PSA levels if the threshold were to change.

We first determined the distribution of PSA levels for screen-eligible American men and the number of these men who would be labeled abnormal using various PSA thresholds (assuming that all such men were screened). To put these numbers in perspective, we attempted to estimate the true burden of clinically important disease using the risk of prostate cancer death.

METHODS

Distribution of PSA Levels

Data on the distribution of PSA levels for American men were obtained from the National Center for Health Statistics’ most recent NHANES (2001–2002 data release). These surveys, which have been conducted periodically since the 1970s, involve household interviews and standardized medical examinations that include a variety of blood tests (10). The sampling design, data collection methods, and weighting approach of NHANES have been described elsewhere (11,12). The 2001–2002 NHANES data are based on a randomly selected, nationally representative sample of approximately 11,000 people of all ages. This survey was the first NHANES to include a PSA test for men aged 40 years or older as part of the medical examination.

Figure 1 shows the selection process recommended by NHANES that we used to identify a representative PSA screen-eligible population of men aged 40 years or older (23). Men who had a history of prostate cancer were excluded, as were those who had an examination or condition that might spuriously elevate PSA level (i.e., prostate biopsy or cystoscopy during the previous month, rectal examination during the previous week, or current inflammation or infection of the prostate). We also excluded men who had missing data for any of these eligibility criteria or for their PSA level. Our final sample included 1308 men.

10-year Risk of Prostate Cancer Death

Data on the risk of prostate cancer death for American men were obtained by using DevCan 5.2 software from the National Cancer Institute (13). DevCan allows users to calculate the age-specific chance of developing or dying from specific cancers for a given time frame. These probabilities are based on cancer incidence data from the Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute, mortality data from the National Center for Health Statistics, and population estimates from the U.S. Bureau of the Census. We chose a 10-year time frame to examine the risk of dying from prostate cancer because it is an intermediate interval (i.e., somewhere between an annual and a lifetime risk) during which annual screening could plausibly affect clinical diagnosis and mortality.

We obtained the 10-year risk of death due to prostate cancer for men at each year of age and then averaged these 10-year risks within each decade of life. For example, to obtain the 10-year risk of death due to prostate cancer for men in their 40s, we first determined the 10-year risk of death for men at each year of age (e.g., 10-year risk for a 40 year old, 10-year risk for a 41 year old, and so on) and then averaged the 10-year risks for men aged 40 years, men aged 41 years, and so on through men aged 49 years.

Because prostate cancer mortality has declined somewhat since the introduction of PSA screening, it is possible that some of the decline is due to PSA screening itself. If so, 10-year risks based on current mortality data would underestimate the 10-year risks expected in the absence of screening. To avoid this problem, we used prostate cancer mortality data from 1984 through 1986 (i.e., before the advent of PSA screening). In addition, because the risk data are based on the entire U.S. population (a small fraction of which already has clinically evident prostate cancer), they may actually overstate the risk of death in the screen-eligible population reported here.

Statistical Analysis

We examined results for five age groups: 40–49 years, 50–59 years, 60–69 years, 70–79 years, and 80 years or older. For each age group, we first calculated the number and proportion of men whose PSA level exceeded the following threshold values: 2.5 ng/mL, 4.0 ng/mL, 6.0 ng/mL, 8.0 ng/mL, and 10.0 ng/mL. We then compared the number of men whose PSA level exceeded each of those threshold values with the number of men who were expected to die of prostate cancer in the next 10 years without undergoing PSA testing.

To make national estimates from the NHANES sample, all analyses incorporated the sampling variable (WTMEC2YR) which weights the sample up to the 2000 census as well as accounting for differential probability of selection across subjects and nonresponse. The analyses also incorporated design effects variables (variable names: SDMVPUS and SDMVSTRA) to account for the survey’s complex multistage sampling strategy when calculating 95% confidence intervals. All analyses used the SVY series of commands in STATA statistical software (version 8.0; College Station, TX).
RESULTS

Figure 2 illustrates the estimated distribution of PSA levels among American men in each of five age groups, and Table 1 shows the estimated number of men in the general screen-eligible population in each age group who would be labeled abnormal using various PSA thresholds if all men were screened. Among men typically thought of as being of screening age (i.e., 40–69 years old), approximately 1.5 million would have a PSA level greater than 4.0 ng/mL. Lowering the threshold to 2.5 ng/mL would label an additional 1.8 million men as abnormal. For men aged 70 years or older, the corresponding numbers are approximately 1.5 million and 1.2 million.

Table 1 also shows the number of men who are expected to die from prostate cancer. Among men aged 50–59 years, for example, approximately 35,000 are expected to die from prostate cancer in the next 10 years. This number of men contrasts sharply with the 1.5 million men aged 50–59 years who would be labeled abnormal using a PSA threshold of 2.5 ng/mL. For each age group, even at the highest PSA threshold (i.e., 10 ng/mL), considerably more men are labeled abnormal than are expected to die from the disease in the next 10 years.

Figure 3 and Table 2 illustrate the effect of PSA threshold on the proportion of screen-eligible men who, if screened, would be labeled as abnormal. For example, among men aged 50–59 years, 10.7% have a PSA level greater than 2.5 ng/mL, 5.3% have a PSA level greater than 4.0 ng/mL, and 1.6% have a PSA level greater than 10.0 ng/mL. To put these proportions in context, only 0.3% of men aged 50–59 years are expected to die from prostate cancer in the next 10 years. Among men aged 60–69 years, 17% have a PSA level greater than 2.5 ng/mL, 5.7% have a PSA level greater than 4.0 ng/mL, and 1.7% have a PSA level greater than 10.0 ng/mL, but only 0.9% of men in this age group are expected to die from prostate cancer in the next 10 years. Almost half of men age 70 years or older have a PSA level greater than 2.5 ng/mL, yet even in this age group, the 10-year risk of death from prostate cancer is less than 3%.

DISCUSSION

The PSA test was developed as an assay for an immunologic marker that corresponded well with clinical stage in patients known to have prostate cancer (14) and was subsequently found to be able to identify prostate cancer in men not known to have the disease (15). However, PSA screening was widely adopted in the United States before there was any evidence of its effectiveness in reducing prostate cancer mortality. Although many adjustments have been suggested to define abnormal (e.g., PSA density, PSA velocity, age-specific PSA norms, free PSA) (16), the PSA threshold used in the seminal article that advocated PSA screening (15)—4.0 ng/mL—remains, for practical reasons, the standard to define abnormal. This threshold value was selected not on the basis of a randomized trial but arbitrarily (2). Although there is still no evidence that screening reduces prostate cancer mortality, there are now calls (4,5) to lower the PSA threshold to 2.5 ng/mL simply because more prostate cancer would be found.

Just because a lower PSA threshold allows more prostate cancer to be detected does not mean it is a better threshold than the current one. The logic behind the call for a PSA threshold

Fig. 2. Distribution of prostate-specific antigen (PSA) levels among screen-eligible American men by age group.
of 2.5 ng/mL is that there are men who have PSA levels between 2.5 and 4.0 ng/mL who have prostate cancer. But the same logic could be extended to argue that any PSA level is abnormal and that all men should have a prostate biopsy, given the finding that more than 10% of those with PSA levels less than 2.5 ng/mL nonetheless have prostate cancer (1).

There are several limitations to our analysis. Our data are only as good as our data sources. NHANES and DEVCAN are among the most credible nationally representative sources for information on the distribution of laboratory tests and cancer mortality. Nevertheless, both have missing data and may not be perfect estimates. In addition, the PSA data from NHANES is limited by the small number of younger men with elevated PSA levels. To deal with this uncertainty, we provided confidence intervals in Table 2. Nevertheless, these data make it possible to examine the likely effect of lowering the PSA threshold.

If all men were screened using the current threshold of 4.0 ng/mL, 1.5 million American men aged 40 to 69 years would be labeled abnormal. Lowering the PSA threshold to 2.5 ng/mL would more than double this number, such that approximately 1.8 million additional men aged 40 to 69 years would be labeled abnormal and face negative consequences of the test result (i.e., biopsy or a cycle of repeated testing and anxiety as long as the uncertainty about whether or not they have prostate cancer persists). If all 1.8 million men had a biopsy, about 1.35 million men would undergo the procedure unnecessarily (i.e., their PSA test results would be considered false positives). The remaining men, approximately 450,000, would be diagnosed with prostate cancer (1). Whether the lower PSA threshold would have any benefit on morbidity or mortality is not known, but its burden is clear. If all of these men underwent radical prostatectomy, approximately 180,000 men would be expected to be made impotent, approximately 40,000 men would be expected to have at least moderate incontinence (17), and approximately 1000 men would be expected to die from the procedure alone (18). The problem is that although it is easy to diagnose more prostate cancer, it is not easy to know who has clinically important disease.

The overdiagnosis of prostate cancer reflects the fact that the cellular abnormality that pathologists call prostate cancer is far

### Table 1. Number of American men who would be labeled abnormal using three PSA thresholds*

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>PSA&gt;2.5 ng/mL</th>
<th>PSA&gt;4 ng/mL</th>
<th>PSA&gt;6 ng/mL</th>
<th>PSA&gt;8 ng/mL</th>
<th>PSA&gt;10 ng/mL</th>
<th>No. of prostate cancer deaths in next 10 years†</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–49</td>
<td>506,900</td>
<td>323,200</td>
<td>Insufficient sample</td>
<td>Insufficient sample</td>
<td>7000</td>
<td></td>
</tr>
<tr>
<td>50–59</td>
<td>1,523,700</td>
<td>747,000</td>
<td>232,900</td>
<td>34,400</td>
<td></td>
<td></td>
</tr>
<tr>
<td>60–69</td>
<td>1,213,800</td>
<td>407,300</td>
<td>118,600</td>
<td>67,200</td>
<td></td>
<td></td>
</tr>
<tr>
<td>70–79</td>
<td>2,019,600</td>
<td>1,056,000</td>
<td>162,000</td>
<td>109,500</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥80</td>
<td>713,800</td>
<td>461,700</td>
<td>129,500</td>
<td>49,200</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Total screen-eligible population is 49 million. All values rounded to the nearest 100. PSA = prostate-specific antigen.

†Calculated using age-specific death rates from 1984 through 1986 (i.e., before the introduction of PSA testing).

### Table 2. Proportions and 95% confidence intervals for the proportion of screen-eligible American men labeled abnormal using various PSA thresholds (from 2001–2002 NHANES)*

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>PSA&gt;2.5 ng/mL</th>
<th>PSA&gt;4 ng/mL</th>
<th>PSA&gt;6 ng/mL</th>
<th>PSA&gt;8 ng/mL</th>
<th>PSA&gt;10 ng/mL</th>
</tr>
</thead>
<tbody>
<tr>
<td>40–49</td>
<td>2.4% (1.0% to 5.5%)</td>
<td>1.5% (0.5% to 4.6%)</td>
<td>0.1% (0.01% to 0.8%)</td>
<td>0.1% (0.01% to 0.8%)</td>
<td>Insufficient sample</td>
</tr>
<tr>
<td>50–59</td>
<td>10.7% (6.7% to 16.7%)</td>
<td>5.3% (3.1% to 8.9%)</td>
<td>2.4% (0.9% to 6.2%)</td>
<td>2.4% (0.9% to 6.2%)</td>
<td>1.6% (0.5% to 5.1%)</td>
</tr>
<tr>
<td>60–69</td>
<td>17.0% (12.1% to 23.5%)</td>
<td>5.7% (3.8% to 8.5%)</td>
<td>2.7% (1.2% to 5.8%)</td>
<td>1.7% (0.6% to 4.8%)</td>
<td>1.7% (0.6% to 4.8%)</td>
</tr>
<tr>
<td>70–79</td>
<td>40.0% (35.1% to 45.2%)</td>
<td>20.9% (16.0% to 26.8%)</td>
<td>9.2% (5.3% to 15.3%)</td>
<td>6.6% (3.9% to 11.1%)</td>
<td>3.2% (1.1% to 8.7%)</td>
</tr>
<tr>
<td>≥80</td>
<td>43.1% (31.4% to 55.6%)</td>
<td>27.9% (18.4% to 39.8%)</td>
<td>18.3% (13.0% to 25.1%)</td>
<td>10.3% (5.9% to 17.4%)</td>
<td>7.8% (4.4% to 13.4%)</td>
</tr>
</tbody>
</table>

*PSA = prostate-specific antigen; NHANES = National Health and Nutrition Examination Survey.

Fig. 3. Proportion of screen-eligible American men of different age groups who would be labeled abnormal by prostate-specific antigen (PSA) threshold.
too prevalent to be consistently clinically important. How much prostate cancer is found seems to be directly related to how hard it is looked for. Consider the prostate biopsy process: because generally there is no obvious lump to remove, urologists sample cells from different portions of the organ. Historically, six needle biopsy samples were taken; now, many urologists are advocating taking 12 or more biopsy samples—noting that the more samples that are taken, the more cancer is found (19). Some researchers have even advocated the use of “saturation biopsy” (a procedure involving from 32 to 38 needle biopsy samples) because this procedure has demonstrated that microscopic cancers can still be found in men who have had cancer free on three or more prior biopsy procedures (20). Furthermore, when pathologists systematically searched the prostate glands removed from older men who were not known to have the disease, they found that at least half had microscopic evidence of prostate cancer (21).

In the absence of data on the effectiveness of screening, we believe that it would be inappropriate to select the PSA threshold simply to maximize how much prostate cancer is found. The choice of a threshold should be equally informed by how many men would be drawn unnecessarily into the process of prostate cancer diagnosis and treatment. That is, the PSA threshold should be selected to target the number of men who are expected to develop clinically important disease. In other words, given that the effectiveness of the PSA screening test is not known, the threshold selected should not result in many more men labeled abnormal than could conceivably benefit from early detection.

To apply this principle, we considered the risk of prostate cancer death over 10 years—a time period during which annual PSA screening could plausibly affect mortality. Because more than two-thirds of men diagnosed with metastatic prostate cancer in the SEER data ultimately die of the disease (22), the risk of death also captures most men who develop symptomatic metastatic disease—a group of men who certainly warrant the label of having “clinically important” disease. Using the 10-year risk of death as the standard for clinically important disease, we found that roughly 10 times more men had an abnormal PSA level using the current PSA threshold of 4.0 ng/mL than would be expected to die from the disease in the next 10 years. Our results, from a population of screen-eligible men (i.e. those without symptoms of prostate cancer), suggest that raising the threshold—perhaps to 10 ng/mL—would identify a number of men that more closely approximates the number at risk for prostate cancer death. Furthermore, because screening always has benefits and harms, it is possible that raising the PSA threshold would enhance the net effect of PSA screening by identifying the people at highest risk of clinically significant disease and thereby limiting the number of healthy people harmed. Although it is possible that a higher PSA threshold could cause some cases of clinically important disease to be missed (some of which may benefit from earlier therapy), it is incumbent on those who would argue for keeping the current PSA threshold of 4 ng/mL to demonstrate that finding such cases outweighs the inevitable harms of involving millions of men in the screening process.

We recognize that many clinicians will find the suggestion of higher PSA thresholds both radical and difficult to accept. Ideally, randomized trials that test a variety of thresholds should be performed to inform the choice of threshold. However, no such trials are in progress. In the meantime, it does not make sense to adopt a PSA threshold that causes the number of men identified as abnormal to move yet further away from the number of men who are destined to develop clinically important disease. We believe that lowering the PSA threshold to 2.5 ng/mL would be a mistake.

References

(3) 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.

NOTES

The views expressed herein do not necessarily represent the views of the Department of Veterans Affairs or the United States Government.

This study was supported in part by a Research Enhancement Award from the Department of Veterans Affairs (03-098). L. M. Schwartz is supported by Veterans Affairs Career Development Awards in Health Services Research and Development. L. M. Schwartz and S. Woloshin are supported by the Generalist Physician Faculty Scholars Program of The Robert Wood Johnson Foundation.

Manuscript received February 4, 2005; revised May 26, 2005; accepted June 1, 2005.