COMMENTARY

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Four no more: The 'PSA cutoff era' is over

PROSTATE-SPECIFIC ANTIGEN (PSA) testing has been mired in controversy throughout the short time it has been a clinical tool for detecting prostate cancer. During the first decade after it was approved for prostate cancer screening, the dogma prevailed that the upper limit of normal was 4.0 μg/L. Healthy patients with values above this cutoff were believed to be at risk of prostate cancer and were usually advised to undergo biopsy. Patients with levels below this threshold were told they had normal readings and were reassured that they did not have prostate cancer.

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PSA is only one of the risk factors for prostate cancer

NO PSA VALUE RULES CANCER IN OR OUT

But more men have prostate cancer than we thought. Initial reports suggested that men with a slightly elevated PSA value (4.0–9.9 μg/L) had a 22% chance of having prostate cancer, and those with a significant elevation (values of 10.0 μg/L or higher) had a 67% risk.[1] However, these numbers were based on "sextant" biopsies (ie, in which only six samples are taken)—a technique fraught with a high false-negative detection rate. If more biopsy samples per patient are taken, approximately twice as many men with PSA levels above 4.0 are found to harbor prostate cancer, in the range of 40% to 50%.[2]

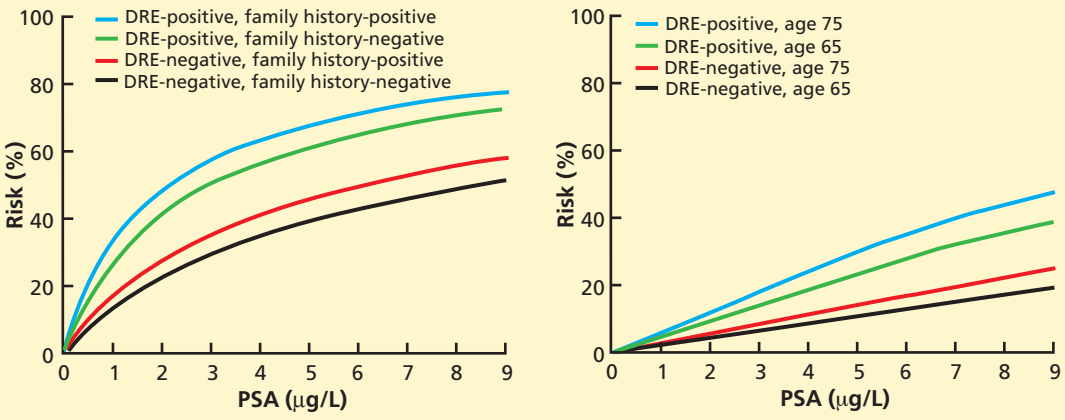
Moreover, many physicians began to recognize that the widely accepted cutoff between normal and abnormal was relatively empiric and based on minimally rigorous scientific analysis. Multiple studies have now shown that many men with "normal" PSA values harbor prostate cancer. The most definitive was the Prostate Cancer Prevention Trial,[3,4] which found no PSA level below which prostate cancer can be ruled out, and no level above which prostate cancer is certain (**FIGURE 1**).

An individual patient's PSA value is only part of the equation. Other risk factors need to be considered, such as his age, race, family history, findings on digital rectal examination, prostate size, results of earlier prostate biopsies, percent free PSA ratio, and whether he takes a 5-alpha reductase inhibitor. Moreover, PSA levels in men who have undergone treatment for prostate cancer are completely independent of the reference ranges in widespread laboratory use, making such references and thresholds even more meaningless in this setting.

Depending on their other risk factors, two men with identical PSA levels can have very different risks of prostate cancer. Conversely, if all their other risk factors are the same and one man has a PSA level of 3.9 μg/L and the other has a level of 4.1, their risk is essentially identical.

Many patients and physicians are perplexed about PSA testing, often framing their concern in terms of "inaccuracy." However, accuracy is not the problem with PSA testing. Rather, the problem is that physicians insist on categorizing patients as either normal or abnormal, when it is abundantly clear that such a dichotomy does not exist. Nevertheless, laboratories around the world continue to foster this false division by printing a PSA reference range of less than 4.0 μg/L on their reports.

PSA level and risk of prostate cancer



*Gleason score of 7 or higher.

Data are from men 55 years and older in the Prostate Cancer Prevention Trial, 3-year follow-up. DRE = digital rectal examination.

ADAPTED FROM THOMPSON IM, ANKERST DP, CHI C, ET AL. ASSESSING PROSTATE CANCER RISK: RESULTS FROM THE PROSTATE CANCER PREVENTION TRIAL. J NATL CANCER INST 2006; 98:529–534. WITH PERMISSION OF OXFORD UNIVERSITY PRESS.

Comment: Published data from the Prostate Cancer Prevention Trial showed that there is no PSA level below which the risk of having prostate cancer is zero. For an individual patient, the significance of a PSA level should be interpreted in a broad clinical context, including age, race, family history, findings on digital rectal examination, prostate size, results of prior prostate biopsy, and use of 5-alpha reductase inhibitors. Considering the high incidence of asymptomatic cancer (which may not pose an ultimate risk to the patient) in the general population, the decision to recommend urologic evaluation or prostate biopsy should be individualized and take into consideration all of these factors.

A useful tool that incorporates many of these variables for calculating the risk of finding any cancer and high-grade cancer for the individual patient by considering the above factors, including PSA, can be found at: **www.compass.fhcrc.org/edrnnci/bin/calculator/main.asp**. This tool provides not only the risk of prostate cancer but the risk of high-grade (aggressive) prostate cancer. The two risks combined help men and their physicians to decide whether prostate biopsy is appropriate.

FIGURE 1.

We will tell patients their actual risk, rather than whether their PSA is above or below 4.0 μg/L

A MORE MEANINGFUL LABORATORY REPORT

In view of the unequivocal data, urologists at Cleveland Clinic Glickman Urological and Kidney Institute, in collaboration with the Department of Laboratory Medicine, have eliminated 4.0 μg/L as the upper limit of normal from our PSA reports. Instead of a normal range, our reports now include risk ranges from large series (as shown in FIGURE 1), which provide a more meaningful clinical picture than the categories normal or abnormal.[3–5] Moreover, the report also carries an explanation, including a reference to a risk calculator, to assist the patient and physician in interpreting the reading.

Interpreting these data will inevitably create new controversy, like any major challenge to the status quo. Nevertheless, it is certainly more appropriate to inform patients of their actual risk of having prostate cancer than it is to tell them that their PSA level is normal or abnormal.

Moreover, because many older men have asymptomatic cancer that may never pose a problem in their lifetime, the decision to recommend urologic evaluation or prostate biopsy should be individualized. Indeed, this will take greater consideration than it did with the old 4.0 cutoff: interpreting PSA levels is more complex than once believed.

This change is long overdue and will require substantial education of both physicians and patients. They need to know that there is no PSA level at which a biopsy is mandated, and that the decision to consider biopsy should be based on solid information: ie, what are the odds that this patient has cancer? And what are the odds that he has high-grade, aggressive cancer, as opposed to a more indolent form that might be appropriately ignored?

We anticipate concern that changing the way we report PSA values may increase patients' anxiety and lead to more prostate biopsies being performed. That is emphatically not the intent of this initiative. Rather, our intent is to accurately report PSA values with a meaningful interpretation of their implications instead of reporting an artificial—and relatively meaningless—cutoff. Interpreting PSA levels in the context of all the above factors will help advance the understanding and management of prostate cancer risk and diagnosis.

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