

# Prostate Cancer Screening and Determining the Appropriate Prostate-Specific Antigen Cutoff Values

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## Key Words

Prostate cancer, PSA, screening, threshold, kinetics

## Abstract

Prostate-specific antigen (PSA) in combination with digital rectal examination forms the basis for current prostate cancer (CaP) screening programs. Although PSA screening was recently shown to reduce CaP-specific mortality in the European randomized trial, its limitations include the risk for unnecessary prostate biopsy and the diagnosis and treatment of some CaP that might never have caused suffering or death. A potential way to minimize these pitfalls is through the use of derivatives of PSA, particularly PSA kinetics, to increase the specificity for clinically relevant CaP. CaP is the second-leading cause of cancer death in men in the United States and many other westernized countries; accordingly, judicious screening of healthy men allows for diagnosis sufficiently early that all options (i.e., treatment or surveillance) are still available in most cases. (*JNCCN* 2010;8:265–270)

The prostate-specific antigen (PSA) blood test is the foundation for modern prostate cancer (CaP) screening. Initially it was used in forensic medicine. The subsequent discovery that it could be measured in serum,

and that serum levels increase in the setting of prostatic disease, led to its current application as a CaP marker.<sup>1,2</sup> It is now used to screen for CaP and monitor disease course.

Beginning in 1989, the authors' research group performed the initial large-scale study of PSA and digital rectal examination (DRE) as first-line tests for CaP screening.<sup>2</sup> Because abnormalities of PSA alone were not considered sufficient to recommend a prostate biopsy at that time, the first phase of the trial screening was performed in a sequential fashion, whereby a verified PSA greater than 4 ng/mL prompted additional evaluation with DRE and transrectal ultrasonography (TRUS). Findings suspicious for CaP on either DRE or TRUS were then used as a trigger for biopsy. In this first phase of the study, a greater proportion (43%) of cancers would have been missed by TRUS than by PSA or DRE, suggesting PSA and DRE as the best 2-test combination.<sup>2</sup>

Because of the complementary nature of PSA and DRE, the authors changed the study protocol in 1991 to include these simultaneous measurements. Prostate biopsy was recommended for suspicious DRE results or a PSA level greater than 4 ng/mL. This phase of the screening study showed that PSA detected more cancers than DRE and that cancers detected with PSA-based screening were more likely to be organ-confined than those identified with DRE alone.<sup>3</sup> Because serial screening showed that nearly half of men with initially low PSA levels that had risen above 2.5 ng/mL continued to experience an increase to greater than 4 ng/mL within 4 years, in 1995 the authors reduced the PSA threshold for biopsy to 2.5 ng/mL, similar to the threshold of 3 ng/mL used in the European Randomized Study of Screening for Prostate Cancer (ERSPC).<sup>4</sup>

From this study, the authors learned that PSA is

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useful to assess the current and future risk for CaP. In addition, CaPs detected at lower PSA levels generally (but not always) have more favorable tumor features and are more likely to be cured with definitive treatment. Although lower PSA thresholds reduce the specificity of PSA-based screening, the authors believe that these shortcomings may be overcome partly through use of PSA velocity (PSAV), percent free PSA (fPSA), and other adjunctive measures. Controversy is currently ongoing regarding the extent of diagnosing potentially indolent CaP through screening.<sup>5</sup> Nevertheless, more judicious screening practices, together with the uncoupling of diagnosis and treatment decisions, may allow the maximal benefit from screening.

### Advantages Associated with Using a Lower PSA Threshold

The FDA approved the PSA test for monitoring patients with established CaP in 1986, and in 1994 approved PSA as an aid for early detection of CaP, using 4 ng/mL as the upper limit of normal. Nevertheless, even at PSA levels less than 4 ng/mL, a direct relationship exists between PSA with CaP risk and tumor aggressiveness. Among men with PSA levels less than 4 ng/mL and nonsuspicious DRE in the Prostate Cancer Prevention Trial, 15.2% had CaP on biopsy.<sup>6</sup> Furthermore, on multivariate analysis, the odds ratio for high-grade disease was 2.08 per unit increase in PSA (95% CI, 1.64–2.64;  $P < .001$ ).

The PSA level at diagnosis also predicts outcomes after definitive CaP treatment. For example, the authors' research group previously compared radical prostatectomy pathology features among men diagnosed with CaP at PSA levels of 0 to 2.5; 2.6 to 4.0; 4.1 to 10.0; and greater than 10.0 ng/mL.<sup>7</sup> Both tumor volume and the proportion of non-organ-confined disease were significantly higher with increasing PSA ( $P < .0001$ ). Furthermore, 10-year progression-free survival rates were 88%, 80%, 76%, and 61% for patients with clinical stage T1c CaP diagnosed at PSA levels of 2.6 to 4.0; 4.1 to 7.0; 7.1 to 10.0; and greater than 10.0 ng/mL ( $P = .0001$ ), respectively.<sup>8</sup>

Studies have also shown that PSA predicts CaP mortality after treatment. For example, a recent multi-institutional radical prostatectomy series reported 15-year CaP-specific mortality rates of 4%,

9%, 11%, and 22% for patients with pretreatment PSA levels of less than 4; 4 to 10; 10 to 20; and 20.1 to 50 ng/mL, respectively.<sup>9</sup> On multivariable analysis, PSA was significantly associated with CaP-specific mortality after radical prostatectomy ( $P = .021$ ), in addition to the biopsy Gleason score.

Finally, the ERSPC showed that screening using a PSA threshold of 3 ng/mL at most screening sites reduced CaP-specific mortality by 20% (27% in men who were actually screened) and the rate of metastatic disease by 41% at 9 years.<sup>4</sup> Thus, level 1 evidence from a randomized trial in which PSA screening reduced CaP mortality used a relatively low PSA threshold for recommending biopsy. A second randomized trial, the Prostate, Lung, Colorectal, and Ovarian (PLCO) Screening Trial, used a PSA threshold of 4 ng/mL and did not find a difference in CaP mortality between the screening and control arms.<sup>10</sup> Nevertheless, other aspects of the PLCO trial, including high rates of screening in both groups before trial entry, substantial contamination (opportunistic screening in the control arm), and delays in biopsy after abnormal results, likely accounted for differences between its results and those of the ERSPC.

The findings from the ERSPC corroborate data from the Surveillance Epidemiology and End Results national cancer registry showing an annual percent change of  $-4.1\%$  in CaP mortality in the United States from 1994 to 2006,<sup>11</sup> and thus a total decline in CaP mortality of approximately 40% between 1993 and 2006. Simulation studies have estimated that screening accounts for approximately 45% to 70% of this mortality reduction.<sup>12</sup>

### Disadvantages Associated with a Lower PSA Threshold

Although the ideal screening test would have both 100% sensitivity and specificity for detecting a disease, this is virtually never the case in clinical medicine. Accordingly, the selection of a cutoff value for clinical use involves an ever-present trade-off between sensitivity and specificity.

Specificity is important because the confirmatory prostate biopsy for abnormal screening results involves both cost and potential risk. The use of a higher PSA threshold increases the likelihood of a delayed or missed cancer diagnosis, but decreases the proportion of unnecessary prostate biopsies and sub-

sequent possible treatment of cancers that might not have produced symptoms.

An illustration of the sensitivity–specificity trade-off was described by Welch et al.<sup>13</sup> in men aged 40 to 69 years from the 2001–2002 National Health and Nutrition Examination Survey. Based on the PSA distributions in these men, they estimated that approximately 1.5 million men in the United States have PSA levels greater than 4 ng/mL. A reduction in the PSA threshold from 4.0 to 2.5 ng/mL would additionally label approximately 1.8 million men as abnormal. However, these men would appropriately be labeled as being at a substantially greater risk for CaP.

In the authors' screening study, men in their 40s and 50s had median PSA levels of 0.7 and 0.9 ng/mL, respectively.<sup>14</sup> Moreover, the baseline PSA level at a young age is a useful predictor of future CaP risk. For example, a PSA level between 0.7 and 2.5 ng/mL (the threshold for biopsy) in men in their 40s was associated with a greater than 14-fold increased risk for subsequent CaP detection. In men in their 50s, a PSA level between the age-specific median (0.9 ng/mL) and 2.5 ng/mL conferred a 7.6-fold increased risk for CaP. Data from the Baltimore Longitudinal Study of Aging (BLSA) similarly showed that a comparison of the baseline PSA to the age-specific median value is useful for risk-assessment.<sup>15</sup> Whittemore et al.<sup>16</sup> also reported on the association between PSA at a young age with future CaP risk. Accordingly, the NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer Early Detection (in this issue; to view the most recent version of these guidelines, visit the NCCN Web site at [www.NCCN.org](http://www.NCCN.org)) suggest offering an initial PSA test at age 40 to establish a baseline and guide the subsequent screening protocol.<sup>17</sup>

A final disadvantage of using lower PSA thresholds is the diagnosis of tumors that may not cause harm. For example, the ERSPC authors estimated that 1410 men would need to be screened and 48 treated to prevent 1 CaP death at 9 years.<sup>4</sup> Nevertheless, this number-needed-to-treat (NNT) estimate was made just as the survival curves began to separate, and therefore may decrease with additional follow-up.<sup>18</sup> A final consideration is that many published studies emphasize CaP mortality as the primary end point of interest; however, the prevention of local progression and metastatic disease are

also important goals. It is noteworthy that the NNT was approximately 25 to prevent 1 case of metastatic CaP when comparing the screening and control arms of the ERSPC, and 15 when comparing the ERSPC screening arm with the unscreened population of Northern Ireland.<sup>19</sup>

In general, PSA-based screening, particularly using lower thresholds, may lead to diagnosis of some CaP cases that would otherwise remain asymptomatic. However, as stated in a recent editorial by Smith,<sup>20</sup> “treatment or non-treatment decisions can be made once a cancer is found, but not knowing about it in the first place surely burns bridges.”

It is noteworthy that the updated NCCN Prostate Cancer Early Detection Guidelines (in this issue and at [www.NCCN.org](http://www.NCCN.org)) are designed for individuals who have made an informed decision to undergo screening and state that “it is neither the intent nor the suggestion of the panel that all men diagnosed with prostate cancer require treatment.”<sup>17</sup> Diagnosis does not necessitate aggressive treatment. Rather, intelligent screening practices followed by more selective use of effective high-quality treatment can help reduce adverse effects of diagnosing and treating cancers not destined to cause symptoms, while enabling potentially curative therapy for patients who are more likely to benefit.

### Should Age Affect the PSA Threshold for Prostate Biopsy?

Oesterling et al.<sup>21</sup> studied PSA levels among 471 presumed healthy, unscreened men from a Minnesota community. Based on the 95th percentile of PSA distribution in these men, they proposed a series of age-specific PSA thresholds: 2.5 ng/mL in the 40s, 3.5 ng/mL in the 50s, 4.5 ng/mL in the 60s, and 6.5 ng/mL in the 70s. Age-specific reference ranges have also been reported in populations with different ethnicities.<sup>22,23</sup>

Possible reasons to use a higher PSA threshold for biopsy in older men are the increasing prevalence of benign prostatic hyperplasia (BPH) with advancing age, and a greater risk for death from competing causes. Accordingly, rather than recommending the use of age-specific PSA thresholds, some experts now recommend discontinuing PSA screening altogether after a certain age. For example, the newly updated United States Preventive Services Task Force

(USPSTF) Clinical Practice Guidelines recommend against CaP screening in men older than 75 years.<sup>24</sup> These guidelines have generated controversy in both the medical community and general public. For example, Moul et al.<sup>25</sup> surveyed 340 men presenting for a free CaP screening and reported that 78% were “upset” by this recommendation. More significantly, these guidelines were issued in the absence of level 1 evidence on screening in men older than 75 years. The maximum age was 74 years for enrollment in the ERSPC and PLCO randomized trials of CaP screening, and the ERSPC core age group included men aged 55 to 69 years.<sup>4,10</sup> Accordingly, the benefits (or lack thereof) of screening in older men cannot be assessed from these data.

Other professional organizations, such as the American Cancer Society and American Urological Association, instead recommend discontinuing CaP screening for men with a life expectancy less than 10 years. Similarly, the updated NCCN Prostate Cancer Early Detection Guidelines state that “screening in men over 75 years should be considered individually.”<sup>17</sup> The authors believe that this represents a more personalized and rational approach than applying a single age cutoff to all men regardless of comorbidities.

Furthermore, the authors do not use age-specific PSA reference ranges for recommending a biopsy. Once the decision is made to proceed with screening, they believe that all men who are healthy enough to receive PSA testing should be provided the same opportunity for detection at a curable stage. Their research group previously reported similar pathologic tumor features in men younger than 60 years, aged 60 to 70 years, and older than 70 years diagnosed with CaP at PSA levels between 2.6 and 4.0 ng/mL.<sup>26</sup> Furthermore, none of the tumors in men older than 70 years who underwent radical prostatectomy fulfilled published pathologic criteria for potentially insignificant CaP, suggesting that clinically significant CaP may be detected at PSA levels between 2.5 and 4.0 ng/mL among men older than 70 years. Thus, men in this age group with sufficient life expectancy to undergo screening should be provided the same opportunity for early diagnosis, permitting an informed discussion of the appropriate subsequent management.

## Alternatives to a Threshold-Based Approach to PSA Screening

Recently, the authors have moved away from an approach to CaP screening based exclusively upon the absolute PSA value, given increasing evidence showing a potential role for PSA kinetics in predicting CaP risk and aggressiveness. Carter et al.<sup>27</sup> reported that PSA levels had a nonsignificant increase over time in controls compared with a gradual rise in PSA in men with histologically confirmed BPH leading up to simple prostatectomy and an exponential increase in PSA approximately 10 years before diagnosis among participants with CaP. Thus, they suggested that PSAV (i.e., PSA trajectory over time) could help distinguish between BPH and CaP.

In a screening program from Austria, Berger et al.<sup>28</sup> subsequently reported an annualized PSAV of 0.39 ng/mL per year and 0.03 ng/mL per year, respectively, in men who were and were not diagnosed with CaP over the 10 years before biopsy or censorship.<sup>28</sup> In the authors' screening study, the median PSAV in the year before diagnosis was 0.6 to 0.7 ng/mL per year for men in all age groups (40–49, 50–59, 60–69, and ≥ 70 years) with CaP, compared with 0 to 0.1 ng/mL per year in controls ( $P < .005$ ).<sup>29</sup>

As with PSA, PSAV also predicts CaP aggressiveness. Among patients in the authors' radical prostatectomy series with Gleason scores of 6, 7, and 8 to 10, the median preoperative PSAV was 0.84, 0.97, and 1.39 ng/mL per year, respectively ( $P = .05$ ).<sup>30</sup> With respect to long-term outcomes, PSAV is a strong predictor of CaP-specific mortality after radiation therapy and radical prostatectomy.<sup>31,32</sup> A PSAV greater than 0.35 ng/mL per year was also shown to distinguish men at risk for life-threatening CaP more than 10 years before diagnosis, at a time when total PSA levels were low.<sup>33</sup> Accordingly, the NCCN Prostate Cancer Early Detection Guidelines (in this issue and at [www.NCCN.org](http://www.NCCN.org)) recommend considering a prostate biopsy for men with a PSA less than 4 ng/mL who have a suspicious PSAV greater than 0.35 ng/mL per year.<sup>17</sup>

A novel and potentially more reliable way to examine PSA kinetics is the PSAV risk count,<sup>34</sup> which is the number of serial occasions that PSAV exceeds a specific threshold, such as 0.4 ng/mL per year. The BLSA showed that 2 serial PSAVs greater than 0.4 ng/mL per year conferred a greater risk of life-threatening CaP than 1 or no PSAV measure-

ments greater than 0.4 ng/mL per year. Additional study is necessary to test the PSAV risk count concept in screening.

Limitations of PSAV are that a lengthy PSA history is not always available and potential confounding from differences in PSA assay standardization<sup>35</sup> and from prostatitis.<sup>36</sup> Thus, the NCCN Prostate Cancer Early Detection Guidelines (in this issue and at [www.NCCN.org](http://www.NCCN.org)) suggest that “antibiotic therapy and repeated PSA measurements may be considered to minimize these sources of confusion.”<sup>17</sup> This is another reason why PSAV risk count may be particularly useful, because it indicates a persistently rising PSA trajectory over serial PSAV evaluations.

Not all studies have shown that PSAV adds incremental predictive value for CaP diagnosis or prognosis beyond a single PSA measurement.<sup>37</sup> This may relate to the method of PSAV calculation (insufficient PSA measurements over lengthy or variable time intervals)<sup>38</sup> or colinearity between PSA and PSAV.<sup>39</sup>

In addition to PSAV, other PSA derivatives (e.g., percent fPSA, other PSA isoforms, and PSA density) may help increase the specificity of screening. For example, a multi-institutional study previously examined the usefulness of percent fPSA among men with PSA levels of 4 to 10 ng/mL and nonsuspicious DRE.<sup>40</sup> Applying a 25% fPSA cutoff in these men would have detected 95% of cancers, while avoiding 20% of unnecessary biopsies.<sup>40</sup> Moreover, a percent fPSA greater than 25% was significantly associated with low-grade, low-volume disease at radical prostatectomy, suggesting that it may increase specificity of screening for clinically significant CaP. Accordingly, among men with a PSA of 4 to 10 ng/mL and major comorbidities that may impact the cost-to-benefit ratio of biopsy, the NCCN Prostate Cancer Early Detection Guidelines (in this issue and at [www.NCCN.org](http://www.NCCN.org)) suggest using percent fPSA to aid in decision-making. In addition, percent fPSA is used to help assess the need for repeat biopsy.

Other approaches to screening include the use of personal risk calculators that incorporate individual risk factors such as race and family history.<sup>41</sup> Finally, new markers, such as PCA3, are currently being examined for a potential role in CaP screening.<sup>42,43</sup> One particularly promising new marker,  $-2$  proPSA, was recently approved in Europe and may help selectively identify more aggressive CaP.<sup>44</sup>

## Conclusions

The authors recommend PSA screening for healthy men older than 40 years with greater than a 10-year life expectancy. For men who have decided to undergo screening, the authors agree with the NCCN Guidelines recommendation to offer a baseline PSA and DRE at age 40 years, considering the strong relationship between the baseline PSA value and future CaP risk. Subsequent serial PSA measurements can also be used to establish the baseline PSAV. A PSAV greater than 0.35 ng/mL per year predicts life-threatening CaP many years before diagnosis, at a time when PSA is low. Thus, PSAV may be useful to facilitate the diagnosis of potentially life-threatening disease within the window for curability. Other PSA derivatives, such as percent fPSA and  $-2$  proPSA, may also be useful to increase the specificity of PSA-based screening.

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