Update on PSA Testing

Mark L. Gonzalgo, MD, PhD, and H. Ballentine Carter, MD, Baltimore, Maryland

Abstract

The use of prostate-specific antigen (PSA) testing for prostate cancer screening has increased dramatically over the past decade. Determining the most efficient way to use PSA testing and how to interpret total PSA levels and changes in PSA values over time remain challenging. Guidelines for early detection of prostate cancer have a direct impact on the number of unnecessary tests performed and are critical for developing a successful screening approach for prostate cancer. The age at which PSA screening should begin, PSA testing intervals, and the importance of understanding fluctuations in PSA values over time are discussed in the framework of recent discoveries in the field. Results from ongoing randomized trials will confirm whether prostate cancer screening is an effective method for reducing deaths from prostate cancer and what approaches will provide the most cost-effective screening strategies. (UNCCN 2007;5:737–742)

The goal of any prostate cancer screening program is to identify patients with clinically significant prostate cancers at an early stage when treatment is most likely to be effective. The use of prostate-specific antigen (PSA) testing for prostate cancer screening remains controversial and the proportion of clinically significant tumors detected with PSA testing is unknown. Clinical use of PSA testing has led to the increased detection of prostate cancer that is more likely to be organ-confined. Prostate cancers detected with PSA testing are typically more favorable than those detected without the use of PSA.1

PSA has been shown to improve the positive predictive value of digital rectal examination (DRE) for cancer detection and, when used in combination, yields higher prostate cancer detection rates compared with either test alone.2 Currently, no consensus exists regarding the optimum age at which to begin prostate cancer screening. However, most current guidelines recommend a baseline evaluation consisting of a history and physical examination, including family history, medication history, and history of prostate disease and screening.

Total and Percent Free PSA

A total PSA level of 4.0 ng/mL has been the historically accepted threshold for recommending prostate biopsy. This threshold value was considered reasonable to balance the possibility of missing biologically important cancers against performing unnecessary biopsies and detecting biologically unimportant cancers. More recent evidence suggests that PSA thresholds less than 4.0 ng/mL may be valid for recommending prostate biopsy to increase the detection of curable disease.3 Furthermore, changes in PSA levels over time (PSA velocity [PSAV]) and determination of relative PSAV thresholds may be particularly important for identifying men with total PSA levels less than 4.0 ng/mL who have clinically significant prostate cancer. Despite growing evidence supporting the use of lower PSA thresholds for detecting prostate cancer, applying these recommendations to clinical practice may lead to increased overdiagnosis and overtreatment of prostate cancer.4,5 Further studies are required to help identify men with life-threatening prostate cancer for whom curative intervention will improve outcomes.

Men with prostate cancer have a greater amount of serum PSA complexed to protease inhibitors and typically have a lower percentage of free PSA compared with men without prostate cancer.6,7 Percent free PSA may be most useful in determining the presence of prostate cancer when total PSA is between 4.0 and 10.0 ng/mL. In a prospective multi-institutional study of men between 50 and 75 years of age, a percent free PSA threshold of
25% was shown to detect 95% of cancers while avoiding approximately 20% of unnecessary biopsies. Using percent free PSA to diagnose prostate cancer has been shown to have limited value in preventing unnecessary biopsies among men with total PSA values less than 4.0 ng/mL.9,10

Percent free PSA is not typically used to decide whether to perform an initial biopsy. However, certain screening guidelines have used free PSA when considering an initial biopsy with the following cutoffs: when more than 25%, consider deferring biopsy; when more than 10% but 25% or less, consider biopsy; when 10% or less, perform biopsy.11

**PSA Density**

PSA density (PSAD) was initially introduced by Benson et al.12 to improve the sensitivity and specificity for prostate cancer detection compared with total serum PSA.13 PSAD is calculated by dividing the total PSA level by prostate gland volume and has been suggested to improve the accuracy of PSA testing in detecting prostate cancer through correcting for higher PSA levels associated with larger prostates.

Several studies have reported that PSAD has a higher sensitivity and specificity than conventional serum PSA testing for prostate cancer.14,15 A PSAD cutoff of 0.15 ng/mL/cm³ yielded a 30% higher sensitivity in predicting regional lymph node involvement compared with total PSA with a cutoff of 10 ng/mL.15 Furthermore, Epstein et al.16 reported that a PSAD of less than 0.15 ng/mL/cm³ in patients with fewer than 3 positive biopsy cores, less than 50% involvement of any biopsy core, and no areas of Gleason score 4 or greater was strongly associated with clinically insignificant cancer.16

The usefulness of PSAD for prostate cancer detection, however, has not been confirmed by all studies.17,18 The major limitations of PSAD for prostate cancer detection are probably caused by the profound variability in the amount of epithelium among prostates of similar size and the variability in prostate shape among men, which limit the use of a common equation for accurately calculating prostate volume.19

**Screening Guidelines**

The American Cancer Society (ACS) and the American Urological Association (AUA) recommend annual PSA screening beginning at age 50 years for men at normal risk with a greater than 10-year life expectancy.20,21 The National Comprehensive Cancer Network (NCCN) recommends that men be counselled on the risks and benefits of PSA testing and offered a baseline PSA test at age 40 years (Table 1). Subsequent PSA testing and follow-up depends on the initial PSA result. Men who are at higher risk on screening evaluation (i.e., PSA ≥ 0.6 ng/mL, African-American race, or family history of prostate cancer) should undergo annual DRE and PSA testing. For men 40 years of age and with PSA less than 0.6 ng/mL, repeat testing is recommended at 45 years of age with the interval for further testing determined by the PSA level on follow-up examination.

Long-term data regarding the efficacy of different screening guidelines for prostate cancer detection remains limited. Computer simulations have been used to evaluate competing strategies for PSA screening and cost-effectiveness of alternative screening approaches.22,23 Biennial screening with a PSA threshold of more than 4.0 ng/mL was projected to decrease the number of screening events and false-positive tests by nearly 50% compared with annual screening, while retaining approximately 93% of years of life saved.23 A screening strategy consisting of a PSA test at 40 and 45 years of age, and biennial testing after 50 years of age with a PSA threshold of 4.0 ng/mL also has been

| Table 1 Summary of Key Points from Guidelines for Prostate Cancer Screening |
|-----------------------------|-------------------------------------------------|
| ACS                         | Annual PSA test beginning at age 50 years for men at normal risk with > 10-year life expectancy; may begin testing earlier if risk factors present (e.g., family history of prostate cancer, African-American race). |
| AUA                         | Annual PSA test beginning at age 50 years for men at normal risk with > 10-year life expectancy; may begin testing earlier if risk factors present (e.g., family history of prostate cancer, African-American race). |
| NCCN                        | Baseline PSA test beginning at age 40 years. Men at higher risk on initial evaluation (i.e., PSA ≥ 0.6 ng/mL, African-American race, or family history of prostate cancer) should undergo annual PSA testing. If PSA < 0.6 ng/mL on initial evaluation, repeat testing recommended at age 45 years with interval for further testing determined by PSA level on follow-up evaluation. |

**Abbreviations:** ACS, American Cancer Society; AUA, American Urological Association; NCCN, National Comprehensive Cancer Network; PSA, prostate-specific antigen.
shown to use fewer resources and resulted in more lives saved compared with annual PSA testing beginning at age 50.\textsuperscript{23}

**Screening Intervals**

The ACS, AUA, and NCCN recommend annual PSA screening for all men older than 50 years.\textsuperscript{11,22,24} Results from longitudinal studies suggest that a screening interval of 2 years for men with PSA levels 2.0 ng/mL or less was unlikely to miss curable prostate cancer.\textsuperscript{25} Furthermore, a PSA range from 4.0 to 5.0 ng/mL was acceptable for maintaining the detection of curable prostate cancer in men with a normal DRE. A cost-effective screening strategy based on these data would be for biennial PSA testing of men with PSA levels less than 2.0 ng/mL and annual screening of men with PSA levels 2.0 ng/mL or more.\textsuperscript{23,25}

Results from biennial PSA screening from the Swedish section of the European Randomized Study of Screening for Prostate Cancer (ERSPC) have shown that PSA testing 2 years after a baseline evaluation was sufficient to detect prostate cancers at a curable stage for men with PSA levels less than 2.0 ng/mL at the initial screen.\textsuperscript{26} More frequent screening was recommended for men with a baseline PSA level 2.0 ng/mL or more. Pathologic evaluation of prostate tissue from the ERSPC suggests that most cancers detected between 2 to 4 years after an initial PSA screening remain curable.\textsuperscript{27,28}

**Age Limits for PSA Screening**

PSA screening has been generally recommended for men with a life expectancy of at least 10 or more years. The health benefits and cost-effectiveness of screening decline rapidly with advanced age. In fact, many men with a life expectancy greater than 10 years may not even benefit from screening. Most prostate cancers have an indolent course during the first 10 to 15 years, and men diagnosed with non-screen-detected cancers have been shown to rarely die of disease before 15 years without treatment.\textsuperscript{29} Results from a prospective cohort of men who had serial PSA measurements from age 60 or 65 years until they were diagnosed with prostate cancer or reached age 75 indicated that if PSA testing were discontinued at age 65 with PSA levels less than 0.5 to 1.0 ng/mL, prostate cancer would probably have not been missed.\textsuperscript{30}

Discontinuing PSA screening by 70 years of age may be appropriate for most men who have undergone regular screening up to that point and who have maintained PSA levels considered to be low-risk. However, an accurate clinical history and examination including concerning signs or symptoms (i.e., abnormal DRE, hematuria) should be taken into consideration. The age at which to discontinue PSA testing remains controversial.

Most guidelines do not recommend PSA screening in elderly men who have limited life expectancies because the risks of screening are believed to outweigh potential benefits. However, a recent study that examined PSA screening in a large cohort from the U.S. Department of Veterans Affairs facilities showed that 56% of men older than 70 years underwent PSA testing.\textsuperscript{31} PSA screening rates in this population were not found to decrease as much as estimated 10-year survival decreased with advancing age. Furthermore, a large percentage of men classified as having poor health continued to undergo routine PSA testing.\textsuperscript{32} This study underscores the need for a critical evaluation of individual health status when making PSA testing and prostate biopsy recommendations.

**PSA Thresholds**

An age-dependent log-linear relationship has been recognized between prostate volume and serum PSA with an estimated average annual increase of serum PSA ranging from 0.1 to 0.5 ng/mL in men with benign prostate hyperplasia.\textsuperscript{12,30} African-American men may have higher overall PSA levels than Caucasian men, and race-specific threshold levels have been previously established. The use of age- and race-specific PSA ranges was an early attempt to increase the accuracy of PSA testing for cancer detection (Table 2).\textsuperscript{4,35}

Using a PSA threshold of 4.0 ng/mL regardless of age or race may lead to earlier disease diagnosis and increase the chance for curative intervention, particularly for African-American men because they often have more aggressive disease at presentation. However, a more contemporary understanding of changes in PSA levels over time (PSAV) relative to a baseline value has led to the modification of PSA threshold recommendations in some screening strategies, particularly for men with PSA levels less than 4.0 ng/mL. PSA threshold values as low as 0.6 ng/mL have been
White Men
Prostate biopsy also may be considered
Black Men
Furthermore, the availability of at least 3
PSA levels of men who
Black Men
A PSA V equal to 0.75
Volume 5 Number 7 August 2007
Average prostate-specific antigen (PSA) levels in ng/mL
Based on 95% Sensitivity
740 Original Article
Gonzalgo and Carter
 established for men between 40 and 45 years of age to
determine ... with prostate cancer who
were alive or died of another cause
JN057_Jrnl_50710Cartr.qxd  8/2/07  7:59 PM  Page 740
From Carter HB, Ferrucci L, Kettermann A, et al. Detection of

Table 2 PSA Thresholds Based on Age and Race

<table>
<thead>
<tr>
<th>Age by Decade, y</th>
<th>White Men†</th>
<th>Black Men§</th>
<th>White Men¶</th>
<th>Black Men®</th>
</tr>
</thead>
<tbody>
<tr>
<td>40s</td>
<td>0–2.5</td>
<td>0–2.4</td>
<td>0–2.5</td>
<td>0–2.0</td>
</tr>
<tr>
<td>50s</td>
<td>0–3.5</td>
<td>0–6.5</td>
<td>0–3.5</td>
<td>0–4.0</td>
</tr>
<tr>
<td>60s</td>
<td>0–4.5</td>
<td>0–11.3</td>
<td>0–3.5</td>
<td>0–4.5</td>
</tr>
<tr>
<td>70s</td>
<td>0–6.5</td>
<td>0–12.5</td>
<td>0–3.5</td>
<td>0–5.5</td>
</tr>
</tbody>
</table>

© Journal of the National Comprehensive Cancer Network | Volume 5 Number 7 | August 2007

PSAV

PSAV was introduced to improve the diagnostic accuracy of serial PSA measurements for prostate cancer screening and is equivalent to the rate of change in PSA values with repeated measurements over time.37 PSAV has been reported to be most useful for detecting cancer when calculated over a minimum of 18 months.38-40 Furthermore, the availability of at least 3 serial PSA measurements to calculate PSAV has been shown to optimize the accuracy of PSAV for cancer detection.31,39

Initial studies examining the relationship between PSAV and prostate cancer risk showed that a PSAV of 0.75 ng/mL/y or more was specific for the presence of prostate cancer, and men with cancer were observed to have significantly more rapid rates of PSA increase compared with men without cancer when PSA levels were not elevated.37 A PSAV equal to 0.75 ng/mL/y or more in men with PSA between 4.0 and 10.0 ng/mL suggests that cancer may be present. For men with total PSA less than 4.0 ng/mL, data suggest that a PSAV more than 0.35 ng/mL/y indicates the presence of lethal cancer.41 PSA levels of men who died of prostate cancer were found to increase at an exponential rate 10 to 15 years before diagnosis and were greater than those of both men with prostate cancer who were alive or died of another cause

and men without prostate cancer (Figure 1). Prostate cancer-specific survival was 92% among men with a PSAV equal to or less than 0.35 ng/mL/y and 54% among men with a PSAV more than 0.35 ng/mL/y. Men with a PSAV more than 0.35 ng/mL/y were also found to have a higher relative risk for prostate cancer death than those with a PSAV equal to or less than 0.35 ng/mL/y.41

In a recent large screening study involving 346 men aged 60 years or younger, the PSAV threshold of 0.75 ng/mL/y or more was found to miss approximately

Figure 1 Average prostate-specific antigen (PSA) levels in ng/mL as a function of years before diagnosis (prostate cancer) or last visit (no prostate cancer) showing men who died of prostate cancer (top cross-hatched area); men with prostate cancer who were alive or died of another cause (middle cross-hatched area); and men without prostate cancer (bottom lined area). Areas represent 95% confidence intervals for PSA levels based on mixed-effects models.

48% of prostate cancers. A lower PSAV threshold of more than 0.4 ng/mL/y was found to be more predictive of prostate cancer than age, total PSA, family history, or race. These findings were applicable also to men with total PSA less than 2.5 ng/mL. A PSAV threshold of more than 0.4 ng/mL/y had a 67% sensitivity and an 81% specificity for detecting prostate cancer in young men.

**Risk Count Assessment**

PSAV is determined using multiple PSA measurements that may increase or decrease over a given period. Annualized PSAV calculations based on multiple PSA measurements do not account for fluctuations in PSA that also may be informative. PSA histories of men from the Baltimore Longitudinal Study of Aging were examined to determine if the number of times the PSAV exceeded a given cut point could predict the future development of high-risk prostate cancer. An individual’s risk count is determined by establishing a PSAV threshold and counting the number of times the cut point is exceeded over a given period. After adjusting for age, PSA level, PSAV, and date of diagnosis, higher risk counts using PSAV thresholds of 0.2 or 0.4 ng/mL/y were significantly associated with the development of high-risk prostate cancer. Risk count assessment may prove to be another useful method for interpreting a PSA history to help identify men who would benefit from prostate cancer diagnosed at PSA levels associated with curable disease.

**Conclusions**

The widespread use of PSA testing for prostate cancer screening has resulted in significantly increased numbers of cancer diagnoses. However, the impact of these measures on prolonging survival remains controversial. Contemporary guidelines for prostate cancer screening recommend that serial PSA testing after an initial evaluation be based on risk-stratification to determine how closely each patient should be followed up. Recognition of the importance of changes in serial PSA values over time (PSAV) also has increased. Further validation of appropriate total PSA and PSAV thresholds is needed to accurately identify men at risk for having prostate cancer, particularly those with total PSA levels less than 4.0 ng/mL. The challenge remains to determine optimal criteria for prostate cancer screening to identify patients who should undergo a prostate biopsy because of their high probability of having life-threatening disease.

**References**


