The Prostate Health Index Selectively Identifies Clinically Significant Prostate Cancer

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Purpose: The Prostate Health Index (phi) is a new test combining total, free and [-2]proPSA into a single score. It was recently approved by the FDA and is now commercially available in the U.S., Europe and Australia. We investigate whether phi improves specificity for detecting clinically significant prostate cancer and can help reduce prostate cancer over diagnosis.

Materials and Methods: From a multicenter prospective trial we identified 658 men age 50 years or older with prostate specific antigen 4 to 10 ng/ml and normal digital rectal examination who underwent prostate biopsy. In this population we compared the performance of prostate specific antigen, % free prostate specific antigen, [-2]proPSA and phi to predict biopsy results and, specifically, the presence of clinically significant prostate cancer using multiple criteria.

Abbreviations and Acronyms

FDA = U.S. Food and Drug Administration

fPSA = free prostate specific antigen

%fPSA = percent free prostate specific antigen

PCA3 = prostate cancer antigen 3

phi = Prostate Health Index

PSA = prostate specific antigen

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Study received institutional review board approval.

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Editor's Note: This article is the third of 5 published in this issue for which category 1 CME credits can be earned. Instructions for obtaining credits are given with the questions on pages 1448 and 1449.

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Results: The Prostate Health Index was significantly higher in men with Gleason 7 or greater and "Epstein significant" cancer. On receiver operating characteristic analysis phi had the highest AUC for overall prostate cancer (AUCs phi 0.708, percent free prostate specific antigen 0.648, [-2]proPSA 0.550 and prostate specific antigen 0.516), Gleason 7 or greater (AUCs phi 0.707, percent free prostate specific antigen 0.661, [-2]proPSA 0.558, prostate specific antigen 0.551) and significant prostate cancer (AUCs phi 0.698, percent free prostate specific antigen 0.654, [-2]proPSA 0.550, prostate specific antigen 0.549). At the 90% sensitivity cut point for phi (a score less than 28.6) 30.1% of patients could have been spared an unnecessary biopsy for benign disease or insignificant prostate cancer compared to 21.7% using percent free prostate specific antigen.

Conclusions: The new phi test outperforms its individual components of total, free and [-2]proPSA for the identification of clinically significant prostate cancer. Phi may be useful as part of a multivariable approach to reduce prostate biopsies and over diagnosis.

Key Words: biological markers, prostatic neoplasms, early detection of cancer

SCREENING with serum total PSA measurements has led to a reduction in advanced disease and a decrease in prostate cancer mortality rates. However, due to the limited specificity of the total PSA test, these benefits have come at a cost of unnecessary biopsies and over diagnosis of insignificant disease. In 2012 the USPSTF (U.S. Preventive Services Task Force) recommended against prostate cancer screening[1] and the time has arrived for a major paradigm shift in prostate cancer detection.

Large randomized trials of PSA screening have yielded conflicting results. The ERSPC (European Randomized Study of Prostate Cancer Screening) reported a 21% reduction in prostate cancer mortality with PSA screening.[2] However, the U.S. Prostate, Lung, Colorectal and Ovarian screening trial found no significant difference in prostate cancer mortality between organized PSA and digital rectal examination compared to usual care.[3] Both of these trials were designed in the early 1990s and used total PSA thresholds to determine the need for prostate biopsy.

Since these trials were designed and initiated, various PSA derivatives have been suggested to improve specificity. One is the percentage of PSA circulating in the unbound form (free PSA) that helps distinguish benign conditions from prostate cancer.[4] Free PSA is, in fact, comprised of several different isoforms including [-2]proPSA, which is more specific for prostate cancer than total PSA or free PSA.[5,6]

The Beckman Coulter Prostate Health Index combines total, free and [-2]proPSA into a single score. Large prospective multicenter studies in the U.S. and Europe have demonstrated that phi improves prostate cancer detection,[7] leading to its recent FDA approval as an aid to early prostate cancer detection for men with a PSA of 4 to 10 ng/ml. Several recent international studies have also suggested a role for phi in monitoring patients on active surveillance.[8–10]

In its 2012 recommendation statement the USPSTF emphasized the urgent need for new screening methods that can better identify indolent vs aggressive disease.[1] To address this research gap and the critical issues of over diagnosis and overtreatment, our objective was to determine whether phi improves the detection of clinically significant prostate cancer.

MATERIALS AND METHODS

From 2004 to 2009, 892 men 50 years old or older with PSA 2 to 10 ng/ml and benign findings on digital rectal examination were enrolled in a prospective multicenter U.S. trial of phi.[7] All men underwent prostate biopsy (97.8% had 10 or more cores, 79.3% initial) and, therefore, had a histologically confirmed diagnosis. The study sought to enroll equal numbers of men diagnosed with prostate cancer and men diagnosed with benign disease to maximize statistical efficiency. The study was approved by the institutional review board and all men provided written informed consent. Of these men 658 had a PSA of 4 to 10 ng/ml (FDA approved range) and constitute the current study population.

Serum samples were collected before biopsy using standard techniques and were processed and frozen within 8 hours. Samples were thawed and tested for total PSA, free PSA and [-2]proPSA concurrently using the Beckman Coulter Access® 2 immunoassay analyzer and the respective Access Hybritech® assays. Phi was then calculated according to the formula, [-2]proPSA/fPSA $\times$ $\sqrt{}$PSA, which was developed to maximize specificity at high sensitivity.[11] (Our results apply to the Hybritech p2PSA, PSA and fPSA assays on the Beckman Coulter Access Immunoassay Systems.)

Statistical Analysis

Descriptive statistics were used to characterize patients based on biopsy outcome. The Wilcoxon rank sum test and chi-square test were used to compare clinical characteristics between men with positive biopsy vs those with negative biopsy, clinically significant vs insignificant histopathology based on the Epstein definition of clinically significant prostate cancer (Gleason 7 or greater, 3 or