A Multicenter Study of [-2]Pro-Prostate Specific Antigen Combined With Prostate Specific Antigen and Free Prostate Specific Antigen for Prostate Cancer Detection in the 2.0 to 10.0 ng/ml Prostate Specific Antigen Range

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Abbreviations and Acronyms

DRE = digital rectal examination
fPSA = free PSA
NIH/NCI = National Institutes of Health/National Cancer Institute
p2PSA = [-2]proPSA
PCa = prostate cancer
PHI = prostate health index
PSA = prostate specific antigen

Purpose: Prostate specific antigen and free prostate specific antigen have limited specificity to detect clinically significant, curable prostate cancer, leading to unnecessary biopsy, and detection and treatment of some indolent tumors. Specificity to detect clinically significant prostate cancer may be improved by [-2]pro-prostate specific antigen. We evaluated [-2]pro-prostate specific antigen, free prostate specific antigen and prostate specific antigen using the formula, ([-2]pro-prostate specific antigen/free prostate specific antigen $\times$ prostate specific antigen$^{1/2}$) to enhance specificity to detect overall and high grade prostate cancer.

Materials and Methods: We enrolled 892 men with no history of prostate cancer, normal rectal examination, prostate specific antigen 2 to 10 ng/ml and 6-core or greater prostate biopsy in a prospective multi-institutional trial. We examined the relationship of serum prostate specific antigen, free-to-total prostate specific antigen and the prostate health index with biopsy results. Primary end points were specificity and AUC using the prostate health index to detect overall and Gleason 7 or greater prostate cancer on biopsy compared with those of free-to-total prostate specific antigen.

Results: In the 2 to 10 ng/ml prostate specific antigen range at 80% to 95% sensitivity the specificity and AUC (0.703) of the prostate health index exceeded those of prostate specific antigen and free-to-total prostate specific antigen. An increasing prostate health index was associated with a 4.7-fold increased risk of prostate cancer and a 1.61-fold increased risk of Gleason score greater than or equal to 4 + 3 = 7 disease on biopsy. The AUC of the index exceeded that of free-to-total prostate specific antigen (0.724 vs 0.670) to discriminate prostate cancer with Gleason 4 or greater + 3 from lower grade disease or negative biopsy. Prostate health index results were not associated with age and prostate volume.

Conclusions: The prostate health index may be useful in prostate cancer screening to decrease unnecessary biopsy in men 50 years old or older with prostate specific antigen 2 to 10 ng/ml and negative digital rectal examination with minimal loss in sensitivity.

Key Words: prostate, prostatic neoplasms, prostate specific antigen, diagnosis, mass screening

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PROSTATE specific antigen testing was Food and Drug Administration approved using a 4.0 ng/ml cutoff to recommend prostate biopsy. Lower cutoffs further enhance early PCa detection[1] since PSA correlates with the risk of overall and high grade PCa at PSA less than 4 ng/ml.[2] However, PSA testing may be confounded by benign conditions.

The low specificity at PSA less than 10 ng/ml has created a diagnostic gray zone in which PCa is found on biopsy in about 25% of patients. This is important since most PCa is curable at PSA less than 10 ng/ml while PSA greater than 10 ng/ml often portends advanced disease.[3]

Serum PSA is complexed with proteins or circulates in an unbound form called fPSA.[4] At PSA 4.0 to 10.0 ng/ml the free-to-total PSA ratio significantly improves discrimination between PCa and benign conditions.[5]

Different prostate regions contain varying proportions of fPSA isoforms, including proPSA, which is associated with PCa. The primary form in PCa tissue is p2PSA.[6–8] At PSA 2.0 to 10.0 ng/ml p2PSA further improves specificity for PCa detection relative to the free-to-total PSA ratio.[9–13]

The usefulness of p2PSA at PSA less than 4.0 ng/ml and its relationship to PCa aggressiveness are relevant to the PCa screening debate, including concerns about over diagnosis and overtreatment.[13–18] Preliminary evidence suggests that higher percent p2PSA may be associated with more aggressive PCa.[10,12,13,18]

Selecting thresholds for clinical use of p2PSA has received limited study. We evaluated the relationship of p2PSA (the assay for which is not available in the United States), combined with fPSA and PSA in a mathematical formula called PHI, with PCa detection and tumor features.

METHODS

Study

Design. We performed a multicenter, double-blind, case-control clinical trial to validate PHI in the 2.0 to 10.0 ng/ml PSA range. The formula was developed from an independent data set,[19] that is p2PSA is measured in pg/ml and fPSA and PSA are measured in ng/ml. The study protocol was approved by the institutional review board at each participating institution and all participants provided informed consent.

Population. We evaluated 1,372 men from a total of 8 medical centers from October 2003 to June 2009. The study cohort included men 50 years old or older who met certain criteria, including 1) no PCa history, 2) nonsuspicious DRE, 3) pre-study PSA 1.5 to 11.0 ng/ml, 4) 6-core or greater biopsy and 5) a histological diagnosis from prostate biopsy. Study exclusion criteria were 1) medications or surgical interventions that alter PSA before blood draw, 2) urinary infection at blood draw, 3) a final Access® Hybritech® PSA value outside the 2.0 to 10.0 ng/ml range, 4) no blood draw or biopsy at the appropriate time or 5) prior androgen replacement therapy.

A total of 326 participants did not meet study eligibility requirements, such as no appropriate informed consent in 107, no PSA within 2 to 10 ng/ml in 92 and other study specific exclusions in 120. Seven men were excluded from analysis due to unevaluable tests from hemolyzed or hyperlipidemic samples, or p2PSA duplicate results with a high coefficient of variation that could not be retested. Finally, at 1 site only 154 men 62 to 74 years old were enrolled. They were not included in final analyses since the age distribution at this site may not have been representative of the target population.

The final study population of 892 men included 121 (13.6%) who were prospectively enrolled and 743 (83.3%) who were prospectively enrolled under separate protocols as well as 28 retrospective samples (3.1%). The study population included 706 initial (79.2%) and 159 repeat (17.8%) biopsies, and 27 men (3%) with an unknown biopsy history. At each institution an approximately equal number of men with (430 or 48.2%) and without (462 or 51.8%) PCa was enrolled. Participants and investigators were blinded to p2PSA results and personnel at testing sites were blinded to individual clinical information.

Testing

Access Hybritech p2PSA, PSA and fPSA assays were measured on the Access 2 Immunoassay Analyzer. Thus, our results apply to Access Hybritech p2PSA, PSA and fPSA assays on the Access Immunoassay System. Serum samples were collected, processed within 8 hours and stored frozen at −70C or less before testing, which allowed accurate PHI measurement.[20] The p2PSA assay was run in duplicate. Evaluation of the first replicate compared to the mean of duplicates using Passing-Bablock regression