Published Scientific Evidences of the Clinical Utility of [-2]proPSA and the Prostate Health Index *(phi)** for the Detection of PCa

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Clinical Chemistry 2004;50:1017-25.

Serum pro-prostate-specific antigen preferentially detects aggressive prostate cancers in men with 2 to 4 ng/mL prostate-specific antigen

The Journal of Urology 2004;171:2239-44.

[-2]proenzyme prostate-specific antigen for prostate cancer detection: a National Cancer Institute Early Detection Research Network validation study

The Journal of Urology 2008;180:539-43.

Pro-prostate-specific antigen measurements in serum and tissue are associated with treatment necessity among men enrolled in expectant management for prostate cancer

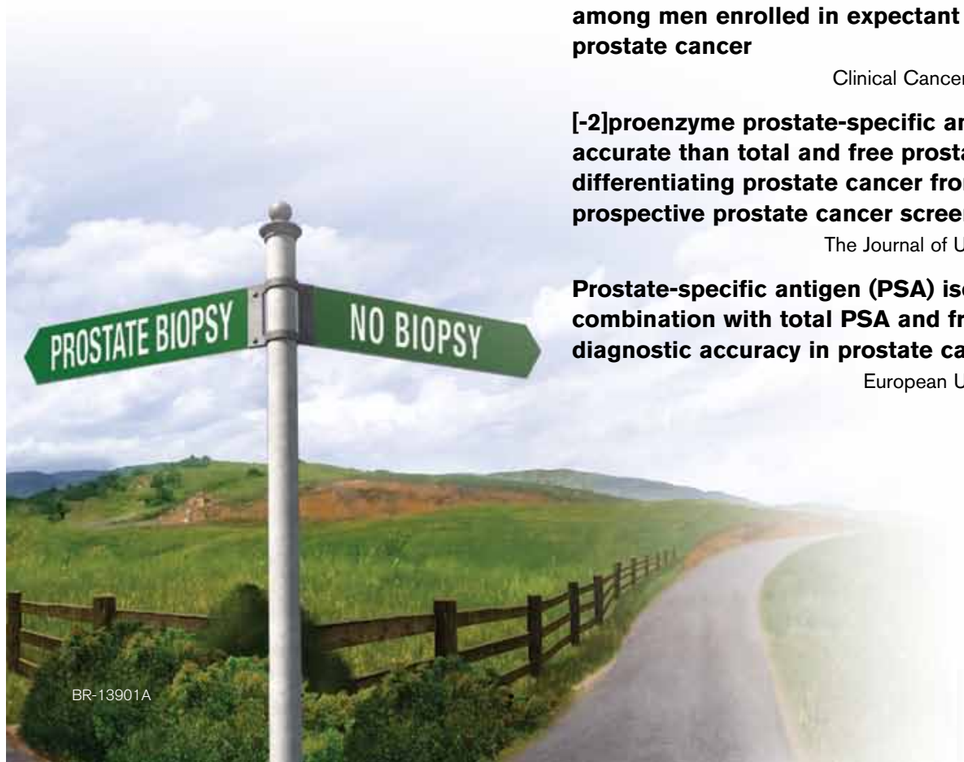
Clinical Cancer Research 2009;15:7316-21.

[-2]proenzyme prostate-specific antigen is more accurate than total and free prostate-specific antigen in differentiating prostate cancer from benign disease in a prospective prostate cancer screening study

The Journal of Urology 2010;183:1355-1359.

Prostate-specific antigen (PSA) isoform p2PSA in combination with total PSA and free PSA improves diagnostic accuracy in prostate cancer detection

European Urology, 2010;57 (6):921-927.



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Clinical Chemistry, 2004 March;50:1017–1025

Proenzyme forms of prostate-specific antigen in serum improve detection of prostate cancer

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Introduction:
Pro or precursor forms of prostate-specific antigen (PSA) have emerged as potentially important diagnostic serum markers for prostate cancer detection. Immunoassays were developed to measure specific proPSA forms containing propeptides of 2, 4 and 7 amino acids ([-2]proPSA, [-4]proPSA and [-7]proPSA respectively).

Materials and Methods:
Research-use dual monoclonal antibody immunoassays using europium-labeled detection monoclonal antibodies were developed for each form of proPSA. Sera from patients with prostate cancer or benign prostate disease containing 4–10 µg/L PSA were assayed and analyzed by area under the ROC curve (AUC) for specificity and sensitivity.

Results:
The proPSA forms had quantification limits of 0.015– 0.025 µg/L in serum, with crossreactivities <1% with PSA.

The sum of the proPSA forms divided by free PSA (percentage proPSA) had a higher AUC than did percentage of [-2]proPSA, free PSA, and complexed PSA with AUC (95% confidence intervals) of 0.69 (0.64–0.74), 0.64 (0.58–0.68), 0.63 (0.58–0.68) and 0.57 (0.51– 0.62), respectively. The proPSA comprised a median of 33% of the free PSA in cancer and 25% in noncancer sera (P <0.0001). One-third (33%) of cancer samples had >40% proPSA, whereas only 8% of noncancer samples did (P <0.0001). In men with cancer and >25% free PSA, the [-2]proPSA had an AUC of 0.77 (0.66–0.86), with 90% sensitivity and 36% specificity at 0.04 µg/L.

Conclusions:
The percentage of proPSA gave better cancer detection in the 4–10 µg/L range than did percentage of free PSA and complexed PSA. [-2]proPSA significantly discriminated cancer in men whose serum had >25% free PSA, for whom there is currently no good marker for cancer detection.

The Journal of Urology, 2004 June;171:2239-2244

Serum pro-prostate-specific antigen preferentially detects aggressive prostate cancer in men with 2 to 4 ng/ml prostate-specific antigen

AUTHORS: Catalona WJ, Bartsch G, Rittenhouse HG, Evans CL, Linton HJ, Horninger W, Klocker H, and Mikolajczyk SD

CENTER: Washington University, St Louis, Missouri, USA, University of Innsbruck, Innsbruck, Austria, Beckman Coulter, Inc., San Diego, California, USA.

Purpose:
Pro forms of prostate-specific antigen (PSA) have been reported to be more cancer-specific markers of prostate cancer than total PSA and they also may preferentially detect the more aggressive forms of the disease.

Materials and Methods:
Research immunoassays with high specificity for pro-PSA forms were used to study 1091 retrospective serum specimens, including 555 with 2 to 4 ng/mL and 536 with 4 to 10 ng/ml PSA, from men enrolled in prostate cancer screening studies who underwent prostate biopsy.

Results:
In the 2 to 4 ng/ml PSA range the ratio of pro- to free-PSA (percent pro-PSA) using a cutoff of 1.8% for recommending prostate biopsy detected 90% of cancers, including 16 of 16 extracapsular tumors and 28 of 29 tumors with a pathology Gleason score of 7 or greater, while avoiding 19% of unnecessary biopsies. Serum percent pro- PSA was significantly increased for Gleason score 7 or greater vs. less than 7 (p = 0.0018).

In the PSA range of 4 to 10 ng/ml percent pro-PSA had the highest cancer specificity, avoiding 31% of unnecessary biopsies, while detecting 34 of 35 cancers with a pathology Gleason score of 7 or greater and 29 of 31 extracapsular tumors. Neither percent free PSA nor complexed PSA enhanced the detection of aggressive cancers in the 4 to 10 ng/ml PSA range.

Conclusions:
Percent pro-PSA was superior to percent free and calculated complexed PSA for the detection of prostate cancer in the PSA range of 2 to 10 ng/ml and it had selectivity for detecting more aggressive cancers, as indicated by Gleason score 7 or greater and/or extracapsular tumor extension.

The Journal of Urology, 2008 August;180:539-543

[-2]proenzyme prostate-specific antigen for prostate cancer detection: A National Cancer Institute Early Dectection Research Network validation study

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CENTER: Departments of Pathology and Urology, Johns Hopkins Medical Institutions, Baltimore, Maryland, USA.

Purpose:
This study evaluated the [-2]proenzyme prostate-specific antigen serum marker using a blinded reference specimen sent from three National Cancer Institute Early Detection Research Network centers from men with an indication for prostate biopsy.

Materials and Methods:
Serum was collected before biopsy from 123 men with no prior biopsy or prostate cancer history. Specimens (cancer cases 51%, noncancer controls 49%) were selected equally from the three sites, and analyzed for prostate-specific antigen, free prostate-specific antigen, [-2]proenzyme prostate-specific antigen, benign prostatespecific-antigen and testosterone (Beckman Coulter Access analyzer).

Results:
There was no difference in total prostate-specific antigen concentrations (noncancer 6.80 +/- 5.20 ng/ml, cancer 6.94 +/- 5.12 ng/ml) among the groups. Overall %[-2]proenzyme prostate-specific antigen had the greatest area under the curve (AUC 0.69) followed by percent free prostate-specific antigen (AUC 0.61). For %[-2]proenzyme prostate-specific antigen maximal sensitivity was 60% and specificity was 70%. A logistic regression model combining prostate-specific antigen, benign prostate-specific antigen, percent free prostate-specific antigen, %[-2]proenzyme prostate-specific antigen, [-2]proenzyme prostate-specific antigen/benign prostate-specific antigen and testosterone had an AUC of 0.73.

The AUC for percent free prostate-specific antigen was 0.53. Specificities for %[-2]proenzyme prostate-specific antigen, the logistic regression model and percent free prostate-specific antigen at 90% sensitivity were 41%, 32% and 18%, and at 95% sensitivity were 31%, 26% and 16%, respectively.

Conclusions:
%[-2]proenzyme prostate-specific antigen was the best predictor of prostate cancer detection compared to percent free prostate-specific antigen, particularly in the 2 to 10 ng/ml total prostate-specific antigen range. These findings provide a rationale for broader validation studies to determine whether %[-2]proenzyme prostate-specific antigen alone can replace other molecular prostate-specific antigen assays (such as percent free prostate-specific antigen) for improving the accuracy of prostate cancer early detection. These findings also support the usefulness of well characterized, carefully collected reference sets to evaluate new biomarkers.

Clinical Cancer Research, 2009 November;15:7316–21

Pro-prostate-specific antigen measurements in serum and tissue are associated with treatment necessity among men enrolled in expectant management for prostate cancer

AUTHORS: Makarov DV[1,2,3], Isharwal S[4], Sokoll LJ[4], Landis P[4], Marlow C[5], Epstein JI[4], Partin AW[4], Ballentine-Carter H[4], and Veltri RW[4]

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[3]Science Applications International Corporation-Frederick, National Cancer Institute, Frederick, Maryland, USA.

Purpose:
We assessed the association of quantitative clinical and pathologic information, including serum and tissue pro–prostate-specific antigen (proPSA) measurements, with outcomes among men with prostate cancer in an expectant management (active surveillance) program.

Experimental Design:
We identified 71 men enrolled in expectant management with frozen serum and tissue available from diagnosis: 39 subsequently developed unfavorable biopsies (Gleason score ≥7, ≥3 cores positive for cancer, >50% of any core involved with cancer), whereas 32 maintained favorable biopsies (median follow-up, 3.93 years). Serum total PSA, free PSA (fPSA), and [-2]proPSA were measured by the Beckman Coulter immunoassay. [-5/-7] proPSA was evaluated in cancer and benign-adjacent areas (BAA) by quantitative immuno-histochemistry. Cox proportional hazards and Kaplan-Meier analyses were used to identify significant associations with unfavorable biopsy conversion.

Results:
The ratio [-2]proPSA/% fPSA in serum was significantly higher at diagnosis (0.87 ± 0.44 versus 0.65 ± 0.36 pg/mL; P = 0.02) in men developing unfavorable biopsies. [-5/-7]proPSA tissue staining was more intense (4104.09 ± 3033.50 versus 2418.06 ± 1606.04; P = 0.03) and comprised a greater fractional area (11.58 ± 7.08% versus 6.88 ± 5.20%; P = 0.01) in BAA of these men. Serum [-2]proPSA/% fPSA [hazard ratio, 2.53 (1.18-5.41); P = 0.02], BAA [-5/- 7]proPSA % area [hazard ratio, 1.06 (1.01-1.12); P = 0.02] and BAA [-5/-7] proPSA stain intensity [hazard ratio, 1.000213 (1.000071-1.000354); P = 0.003] were significantly associated with unfavorable biopsy in Kaplan-Meier and Cox analyses. Serum [-2]proPSA/% fPSA significantly correlated with BAA [-5/-7]proPSA % area (= 0.40; P = 0.002) and BAA [-5/-7]proPSA stain intensity (P = 0.33; P = 0.016).

Conclusions:
In a prospective cohort of men enrolled into expectant management for prostate cancer, serum and tissue levels of proPSA at diagnosis are associated with need for subsequent treatment. The increase in serum proPSA/% fPSA might be driven by increased proPSA production from “premalignant” cells in the prostate BAA.

The Journal of Urology, 2010 April;183, 1355-1359

[-2]proenzyme prostate-specific antigen is more accurate than total and free prostate-specific antigen in differentiating prostate cancer from benign disease in a prospective prostate cancer screening study

AUTHORS: Le BV, Griffin CR, Loeb S, Carvalhal GF, Kan D, Baumann NA and Catalona WJ

CENTER: Department of Urology, Northwestern University, Chicago, Illinois, USA, Department of Pathology, University of Illinois at Chicago, Chicago, Illinois, USA, Department of Urology, Johns Hopkins, Baltimore, Maryland, USA.

Purpose:
Due to the limited specificity of prostate-specific antigen for prostate cancer screening, there is an ongoing search for adjunctive biomarkers. Retrospective studies have suggested that an isoform of proenzyme prostate-specific antigen called [-2]proenzyme prostate-specific antigen may enhance the specificity of prostate-specific antigen based screening. We examined the usefulness of this isoform in a prospective prostate cancer screening study.

Materials and Methods:
From a population of 2,034 men undergoing prostate cancer screening we examined the relationship between the measurement of the [-2]-isoform of proenzyme prostate-specific antigen (p2PSA) and prostate cancer detection. Specifically we compared the usefulness of total prostate-specific antigen, the ratio of free-to-total prostate-specific antigen, the ratio of p2PSA-to-free prostate-specific antigen, and a formula combining prostate-specific antigen, free prostate-specific antigen and p2PSA (the Beckman Coulter Prostate Health Index or *phi*) to predict prostate cancer in men from the study undergoing prostate biopsy with a prostate-specific antigen of 2.5 to 10 ng/ml and nonsuspicious digital rectal examination.

Results:
Despite similar total prostate-specific antigen (p = 0.88), percent free prostate-specific antigen (p = 0.02) and %p2PSA p = 0.0006) distinguished between positive and negative biopsy results. On ROC analysis %p2PSA (AUC 0.76) outperformed prostate-specific antigen (AUC 0.50) and percent free prostate-specific antigen (AUC 0.68) for differentiating between prostate cancer and benign disease. Setting the sensitivity at 88.5%, p2PSA led to a substantial improvement in specificity as well as positive and negative predictive values. The Beckman Coulter Prostate Health Index (AUC 0.77) had the best overall performance characteristics.

Conclusions:
This is the first prospective study to our knowledge to demonstrate that p2PSA provides improved discrimination between prostate cancer and benign disease in screened men with a prostate-specific antigen of 2.5 to 10 ng/ml and a negative digital rectal examination.

European Urology, 2010;57 (6):921-927

Prostate-specific antigen (PSA) isoform p2PSA in combination with total PSA and free PSA improves diagnostic accuracy in prostate cancer detection

AUTHORS: Jansen FH, van Schaik RHN, Kurstjens J, Horninger W, Klocker H, Bektic J, Wildhagen MF, Roobol MJ, Bangma CH, Bartsch G

CENTER: Department of Urology, Erasmus MC, Rotterdam, The Netherlands. Bruck Medical University, Innsbruck, Austria.

Background:
Novel markers for prostate cancer (PCa) detection are needed. Total prostate-specific antigen (tPSA) and percent free prostate-specific antigen (%fPSA = tPSA/fPSA) lack diagnostic specificity.

Objective:
To evaluate the use of prostate-specific antigen (PSA) isoforms p2PSA and benign prostatic hyperplasia–associated PSA (BPHA).

Design, Settings and Participants:
Our study included 405 serum samples from the Rotterdam arm of the European Randomised Study of Screening for Prostate Cancer and 351 samples from the Urology Department of Innsbruck Medical University.

Measurement:
BPHA, tPSA, fPSA, and p2PSA levels were measured by Beckman Coulter Access Immunoassay. In addition, the Beckman Coulter Prostate Health Index was calculated: phi = (p2PSA/fPSA) x √(tPSA).

Results and Limitations:
The p2PSA and phi levels differed significantly between men with and without PCa. No difference in BPHA levels was observed. The highest PCa predictive value in both cohorts was achieved by phi with areas under the curve (AUCs) of 0.750 and 0.709, a significant increase compared to tPSA (AUC: 0.585 and 0.534) and %fPSA (AUC: 0.675 and 0.576). Also, %p2PSA (p2PSA/fPSA) showed significantly higher AUCs compared to tPSA and %fPSA (AUC: 0.716 and 0.695, respectively). At 95% and 90% sensitivity, the specificities of phi were 23% and 31% compared to 10% and 8% for tPSA, respectively. In both cohorts, multivariate analysis showed a significant increase in PCa predictive value after addition of p2PSA to a model consisting of tPSA and fPSA (increase in AUC from 0.675 to 0.755 and from 0.581 to 0.697, respectively). Additionally, the specificity at 95% sensitivity increased from 8% to 24% and 7% to 23%, respectively. Furthermore, %p2PSA, phi, and the model consisting of tPSA and fPSA with or without the addition of p2PSA missed the least of the tumours with a biopsy or pathologic Gleason score ≥7 at 95% and 90% sensitivity.

Conclusions:
This study shows significant increases in PCa predictive value and specificity of phi and %p2PSA compared to tPSA and %fPSA. p2PSA has limited additional value in identifying aggressive PCa (Gleason score ≥ 7).