REVIEW ARTICLE

Prostate health index vs percent free prostate-specific antigen for prostate cancer detection in men with ``gray'' prostate-specific antigen levels at first biopsy: systematic review and meta-analysis

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The most promising approach to improve the specificity of prostate-specific antigen (PSA) test relies on the measurement of different molecular isoforms of PSA in serum. Currently, in men with a total PSA (tPSA) level between 2 and 10 ng/mL, measurement of %fPSA (free to total PSA ratio ×100) is used as reflex testing to better distinguish between malignant and benign prostate disease. Recently, Beckman Coulter developed the prostate health index (PHI) and several studies suggested that this test may improve the diagnostic ability of %fPSA.We performed a meta-analysis to evaluate the usefulness of PHI compared with %fPSA in the detection of prostate cancer (PCa) at first biopsy in men with tPSA "gray" levels of 2–10 ng/mL. Data on sensitivity and specificity were extracted from 8 eligible studies. Only observational studies comparing the diagnostic ability of PHI and %fPSA in tPSA range of 2–10 ng/mL were included. A total of 8 studies involving 2969 patients with a tPSA range of 2–10 ng/mL undergoing first biopsy were included in this meta-analysis. Biopsy-confirmed PCa was detected in 1287 (43.3%) men. Selected studies determined both PHI and %fPSA as a reflex test. The areas under curve (AUCs) of PHI and %fPSA were 0.74 (95% confidence interval (CI), 0.70–0.77) and 0.63 (95% CI, 0.58–0.67), respectively. Meta-regression analysis confirmed the superiority of PHI which showed, compared with %fPSA, a relative diagnostic odds ratio of 2.81 (95% CI, 2.19–3.6; $P < 0.0001$). In conclusion, PHI instead of %fPSA as a reflex test in men with tPSA "gray" levels is a better predictor of positive first biopsy and can offer a reduction in unnecessary biopsies. (Translational Research 2014;164:444–451)

Abbreviations: AUC = area under curve; CIs = confidence intervals; DOR = diagnostic odds ratio; DRE = digital rectal examination; FDA = food and drug administration; fPSA = freePSA; HSROC = hierarchical summary receiver-operator curves; PCa = prostate cancer; PHI = prostate health index; PSA = prostate specific antigen; pPSA = p roPSA; p2PSA = (-2)proPSA; USPSTF = US preventive services task force

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INTRODUCTION

Prostate-specific antigen (PSA) has been widely used in the management of patients with prostate cancer (PCa). However, serum PSA levels showed limited specificity particularly in a PSA range of 2–10 ng/mL.[1] Several approaches have been proposed to address these limitations, including the measurement of PSA molecular forms especially %fPSA. Anyway, the ability to detect PCa at initial biopsy remains limited.[2] Free PSA (fPSA) comprises proPSAs (pPSAs), benign PSA (BPSA), and intact PSA. Mikolajczyk et al[3] reported that pPSA is associated with cancer and BPSA with benign diseases, whereas the association of intact PSA is currently unknown. pPSA includes several truncated forms that can be measured in serum by immunoassays.[4] The [-2]proPSA (p2PSA) is the most cancer-specific form of all, being preferentially expressed in cancerous prostatic epithelium and significantly increased in serum of men with PCa.[2] During the past 2 years, 2 biomarkers have been approved by the US Food and Drug Administration. These include p2PSA as part of the prostate health index (PHI) by Beckman Coulter, Inc, calculated by a mathematical formula ([-2][pPSA/fPSA) × sqrt (PSA)] combining PSA molecular forms.[5] Currently, several studies suggested that increased PHI levels seem to preferentially detect patients with PCa.[5-9]

The hypothesis regarding the improvement in predicting biopsy outcome of PHI compared with %fPSA is inspiring, but till now, no consensus has been reached on which is the best test recommended in clinical practice. At present, only one meta-analysis has been performed[10] to assess the usefulness of %[-2]proPSA and PHI in PCa detection in the overall PSA range and in the initial and subsequent biopsies. Our meta-analysis is undertaken to evaluate the diagnostic value of PHI compared with %fPSA in the "gray" PSA range of 2–10 ng/mL in patients undergoing first biopsy.

METHODS

Meta-analysis was performed in accordance with the preferred reporting items from systematic reviews and meta-analysis (PRISMA) adapted to the study of diagnostic test.[11]

Relevant published articles were identified by searching computerized bibliographic systems (Pubmed, Web of Science, Scopus, Cochrane Library, and Cancerlit) from January 2009 to December 2013. A search strategy was used that contained the following text words and medical subject headings in their titles, abstracts, or keyword lists: PSA testing (prostate health index, PHI, tumor markers, p2PSA, sensitivity, specificity and performance) and PCa detection (PCa diagnosis or biopsy outcome). This literature search was complemented with the review of 5 specialized journals in Urology (European Urology, Journal of Urology, British Journal of Urology, International Journal of Urology and Prostate). The summary of literature search and selection of studies included is shown in Fig 1.

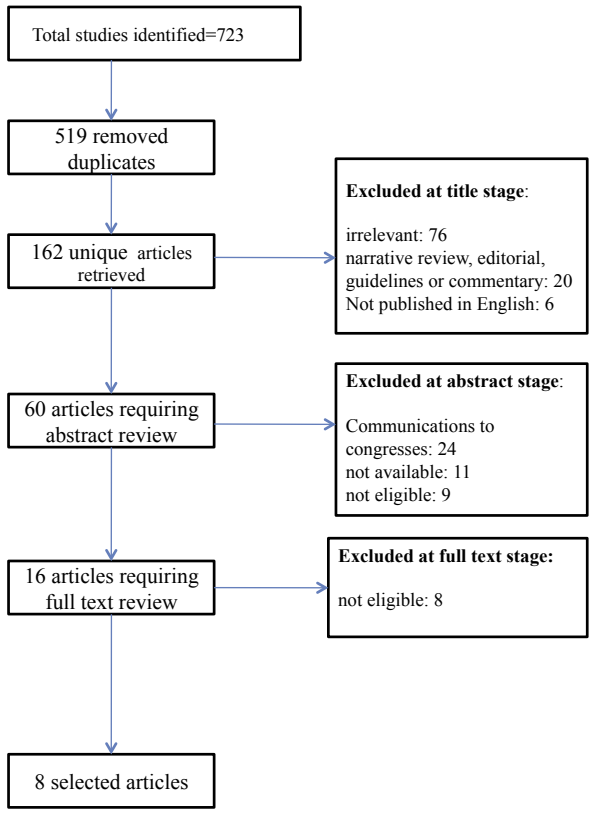

Fig 1. Summary of literature search and selection of studies included.

All the studies were considered eligible for inclusion if they met the following criteria:

1. original data;
2. study including at least 20 patients with PCa;
3. confirmation of PCa on transrectal ultrasound-guided needle biopsy (minimum ≥6 cores)
4. serum levels of fPSA, tPSA, and p2PSA evaluated by commercially available kits of Beckman Coulter using Hybritech calibration;
5. tPSA included between 2 and 10 ng/mL;
6. sufficient data to allow us to calculate true positive (TP), false negative (FN), false positive (FP) and true negative (TN) values for PCa diagnosis;
7. blood was sampled before prostate manipulation or biopsy and antiandrogen therapy;
8. the indication for biopsy was independent of the PHI test result;
9. results were based on first biopsy;