Benign Prostate Specific Antigen Distribution and Associations With Urological Outcomes in Community Dwelling Black and White Men

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Purpose: We describe cross-sectional associations of benign prostate specific antigen with clinical urological measures and examined the risk of future urological outcomes in 2 population based cohorts of black and white men, respectively.

Materials and Methods: Two population based cohort studies were established to characterize the natural history of and risk factors for prostate disease progression in white and black male residents of Olmsted County, Minnesota, and Genesee County, Michigan, respectively.

Results: The benign prostate specific antigen distribution was similar in black men at a median of 32.9 pg/ml (25th, 75th percentiles 17.3, 68.0) and white men at a median of 32.2 pg/ml (25th, 75th percentiles 16.6, 68.9, respectively). However, it was much lower than in previous reports. For Olmsted County men in the upper quartile of benign prostate specific antigen there was a fifteenfold increased risk of prostate cancer (HR 14.6, 95% CI 3.1–68.6) and a twofold higher risk of treatment for benign prostatic hyperplasia (HR 2.2, 95% CI 1.2–4.2) after adjusting for age. After additional adjustment for baseline prostate specific antigen the association between benign prostate specific antigen and prostate cancer risk was attenuated but remained almost ninefold higher for men in the upper quartile of benign prostate specific antigen (HR 8.7, 95% CI 1.8–42.4). The twofold higher risk of treatment for benign prostatic hyperplasia also remained after adjusting for baseline prostate specific antigen for men in the upper benign prostate specific antigen quartile (HR 1.9, 95% CI 0.9–4.0).

Conclusions: Results suggest that increased benign prostate specific antigen may help identify men with prostate cancer and those at risk for benign prostatic hyperplasia treatment.

Key Words: prostate, prostatic hyperplasia, prostate-specific antigen, prostatic neoplasms, continental population groups

PROSTATE specific antigen is a widely used serum marker for CaP early detection. PSA measurement is recommended in men older than 50 years and those at high risk for CaP by National Cancer Institute[1] and AUA[2] guidelines. However, elevated PSA is not specific to CaP since PSA can also

Abbreviations and Acronyms

AUA = American Urological Association
AUASI = AUA symptom index
AUR = acute urinary retention
BPH = benign prostatic hyperplasia
BPSA = benign PSA
CaP = prostate cancer
FMHS = Flint Men's Health Study
LUTS = lower urinary tract symptoms
OCS = Olmsted County Study of Urinary Symptoms and Health Status among Men
PSA = prostate specific antigen
TRUS = transrectal ultrasound

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be increased in men with benign conditions such as BPH or prostatitis.

BPSA is an inactive form of PSA that has been cleaved at lysine residues 145 and 182.[3,4] This form of free PSA is increased in nodular BPH tissue and also correlates with transition zone volume and prostatic enlargement.[3,5] BPSA was significantly higher in men with increased PSA and percent free PSA less than 15% who were also biopsy negative for CaP.[6] Together these results suggest that BPSA may be associated with benign disease.

BPSA characteristics were described in clinical and convenience samples.[3,5–7] These studies provide initial support for the usefulness of BPSA as a marker for benign prostate disease but they may not reflect the full spectrum of men with and without benign prostate disease. We provide normative data on a population based, biracial sample of men and describe the cross-sectional associations between baseline BPSA and common clinical urological measures. We also examined associations between baseline BPSA and the risk of clinically relevant urological outcomes such as AUR, CaP and BPH treatment.

METHODS

Details on subject selection for OCS and FMHS were published previously.[8,9] Briefly, OCS and FMHS are population based, cohort studies established to characterize the natural history of and risk factors for prostate disease progression in white and black male residents of Olmsted County, Minnesota, and Genesee County, Michigan, respectively. In OCS 2,115 of 3,874 eligible white men (55%) who were 40 to 79 years old in 1990 and had no history of CaP, surgery or other conditions known to interfere with voiding completed the self-administered AUASI.[10] A detailed urological examination, including uroflowmetry, digital rectal examination, TRUS and serum PSA measurement, was done in a 25% random subsample comprising 476 of the 537 participants sampled (89%).[8,11] The cohort was actively followed biennially for 17 years using a protocol similar to that of the initial examination.

By applying criteria and procedures similar to those of OCS 730 of 943 eligible black men (77%) were recruited in 1996 to FMHS to complete an interview administered questionnaire.[9,12] Of the men 369 (51%) who were free of CaP completed a comprehensive urological examination, including uroflowmetry, TRUS, serum PSA measurement and the self-administered AUASI,[9] as in OCS. Selective participation in clinical examination and the potential resulting selection bias were addressed previously.[13,14]

Since FMHS urological measurements were collected in 1996, BPSA measures were obtained from serum samples collected in 1996 for each study and the corresponding 1996 OCS measurements served as initial/baseline values. BPSA was measured in 420 men in OCS and in 329 in FMHS. This study received approval from the Mayo Clinic, Olmsted Medical Center and University of Michigan Medical School institutional review boards.

Urinary Flow Rate

The urinary flow rate was measured using a Model 1000 uroflowmeter (Dantec, Royal Portbury, United Kingdom) calibrated by trained study assistants.[15] Maximum and average urinary flow rates, and voided volume were measured electronically. Measurements were repeated if voided volume was less than 150 ml. The highest rate with a voided volume of 150 ml or greater was used for analysis when multiple measurements existed.

Prostate Volume

Total prostate volume for OCS and FMHS participants was measured by TRUS.[9,16] In addition to assessing the echogenic pattern of the prostate gland, 3 measurements were made to calculate total prostate volume, assuming a prolate ellipsoid shape.[17]

CaP and AUR

Information on medical and surgical LUTS/BPH treatments was obtained by self-report and passive followup of the community medical records of men in OCS. Dates of biopsy confirmed CaP and AUR were abstracted from community medical records. AUR was defined as medical record documentation of the inability to urinate and of catheterization to empty the bladder. Catheterizations done perioperatively were excluded from study but episodes were included in which a catheter was needed after surgery secondary to AUR. Data on CaP, AUR and treatment were not available on men in FMHS. Thus, analysis of associations between BPSA and these outcomes was confined to the OCS cohort.

Assays

For each study serum samples were obtained before prostatic manipulations, including digital rectal examination and TRUS. Samples were frozen at −70C for latter assays. Stored blood samples from the 1996 OCS fourth biennial followup in 420 men and from the 1996 FMHS baseline visit in 329 were used to measure BPSA. Serum PSA for men in OCS was assayed using the Tandem-E PSA assay (Hybritech®). Serum PSA for men in FMHS was assayed using the AxSYM® polyclonal-monoclonal immunoassay with a lower limit of detection of 0.1 ng/ml.[18] We previously reported that PSA determinations were consistent across different assays and laboratories.[19,20] For each study BPSA was assessed using an automated, sequential, 2-step immunoenzymatic sandwich assay developed for the Access® instrument. BPSA measurements were run on an Access 2 Immunoassay analyzer using research use only, 2-site immunoenzymatic reagents. In our hands the intra-assay variation range was 4.3% to 8.1% and the inter-assay variation range was 5.1% to 5.2%.

Statistical Analysis

Descriptive statistics and cumulative distribution function plots were used to describe the BPSA distribution. The Spearman correlation (r_S) and logistic regression were used to investigate relationships between BPSA and other baseline urological measures. Multivariate logistic regression was used to describe the association of BPSA with clinically meaningful diagnostic measures, which are shown as the OR and 95% CI. Moderate to severe LUTS was defined as an AUASI score of greater than 7 while a