African-American Men with Gleason Score 3+3=6 Prostate Cancer Produce Less Prostate Specific Antigen than Caucasian Men: A Potential Impact on Active Surveillance

Oleksandr N. Kryvenko,* Raymond Balise, Nachiketh Soodana Prakash and Jonathan I. Epstein

From the Departments of Pathology (ONK), Urology (ONK, RB, NSP) and Biostatistics (RB), University of Miami Miller School of Medicine, Miami, Florida, and the Departments of Pathology, Urology and Oncology (JIE), The Johns Hopkins Medical Institutions, Baltimore, Maryland

Purpose: We assess the difference in prostate specific antigen production between African-American and Caucasian men with Gleason score 3+3=6 prostate cancer.

Materials and Methods: We measured tumor volume in 414 consecutive radical prostatectomies from men with National Comprehensive Cancer Network® low risk prostate cancer (348 Caucasian, 66 African-American) who had Gleason score 3+3=6 disease at radical prostatectomy. We then compared clinical presentation, pathological findings, prostate specific antigen, prostate specific antigen density and prostate specific antigen mass (an absolute amount of prostate specific antigen in patient's circulation) between African-American and Caucasian men. The t-test and Wilcoxon rank sum were used for comparison of means.

Results: African-American and Caucasian men had similar clinical findings based on age, body mass index and prostate specific antigen. There were no statistically significant differences between the dominant tumor nodule volume and total tumor volume (mean 0.712 vs 0.665 cm^3, p=0.695) between African-American and Caucasian men. Prostates were heavier in African-American men (mean 55.4 vs 46.3 gm, p <0.03). Despite the significantly greater weight of benign prostate tissue contributing to prostate specific antigen in African-American men, prostate specific antigen mass was not different from that of Caucasian men (mean 0.55 vs 0.558 μg, p=0.95). Prostate specific antigen density was significantly less in African-American men due to larger prostates (mean 0.09 vs 0.105, p <0.02).

Conclusions: African-American men with Gleason score 3+3=6 prostate cancer produce less prostate specific antigen than Caucasian men. African-American and Caucasian men had equal serum prostate specific antigen and prostate specific antigen mass despite significantly larger prostates in African-American men with all other parameters, particularly total tumor volume, being the same. This finding has practical implications in T1c cases diagnosed with prostate cancer due to prostate specific antigen screening. Lowering the prostate specific antigen density threshold in African-American men may account for this disparity, particularly in selecting patients for active surveillance programs.

Key Words: prostate-specific antigen, prostatic neoplasms, African Americans, European continental ancestry group, neoplasm grading

Abbreviations and Acronyms

AA = African-American
BMI = body mass index
ISUP = International Society of Urological Pathology
NCCN® = National Comprehensive Cancer Network®
PCa = prostate cancer
PSA = prostate specific antigen
PSAD = PSA density
PSAM = PSA mass
RP = radical prostatectomy
SV = seminal vesicles

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* Correspondence: Department of Pathology, University of Miami Miller School of Medicine, 1400 NW 12th Ave., Room 4076, Miami, Florida 33136 (e-mail: o.kryvenko@med.miami.edu).

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ACCORDING to the latest recommendations by the American Urological Association, PSA remains the only screening test to select men with unremarkable digital rectal examination in whom prostate biopsy should be considered.[1] Four tiers are outlined, mainly based on patient age, comorbidities, race (African-American ethnicity is considered as a risk factor) and family history of prostate cancer. In men with biopsy proven Gleason score 3+3=6 PCa, PSA (less than 10 ng/ml) and PSA density (less than 0.15) are 2 of 4 factors in the original surveillance criteria adopted by the NCCN as very low risk PCa and the recently modified Epstein surveillance criteria.[2–4] Whereas the original Epstein criteria were developed based on a cohort of more than 95% Caucasian men, the modified criteria were separately evaluated for Caucasian and African-American men, with 20% of the cohort being AA.[2,3] The more recent study used contemporary PCa grading following the ISUP 2005 consensus conference.[5] We demonstrated that PCa in AA men had a different cancer distribution within the gland and that active surveillance criteria that were predictive in Caucasian men were not accurate in AA men.[3,6] Despite this finding, active surveillance criteria do not include race as a variable.[7] Active surveillance criteria also do not account for BMI. Controversial reports exist with opposite conclusions comparing PSA secretion by benign prostate tissue and PCa between AA and Caucasian men.[8–10] The current study is a detailed clinicopathological analysis of a large cohort of Caucasian and AA men who underwent radical prostatectomy at a single institution with Gleason score 3+3=6 cancer at RP to evaluate and compare PSA production, controlling for all variables affecting its serum level.

MATERIALS AND METHODS

We studied 414 consecutive RP specimens from men (348 Caucasian and 66 AA) with clinically NCCN low risk PCa who were treated at The Johns Hopkins Hospital from 2008 to 2012 and had Gleason score 3+3=6 disease at final pathology. In contrast to very low risk PCa, NCCN defines low risk PCa as nonpalpable disease (stage T1c), with PSA less than 10 ng/ml and biopsy Gleason score 3+3=6 without including the percentage/laterality of involvement or number of cores with cancer.[4] All men had cancer diagnosed by at least a 10-core prostate needle biopsy and biopsies performed elsewhere were reviewed at The Johns Hopkins Hospital before RP. Fresh RP specimens were measured, weighed, inked for microscopic margin assessment and fixed in ambient formalin with injection. The glands were serially sectioned at 3 mm intervals and submitted entirely as quadrants in usual size cassettes for histological evaluation. All specimens were submitted according to the standard protocol so the location of each section could be correlated to where it was taken from the gland.

The authors rereviewed all specimens to confirm the final grade according to the most contemporary ISUP recommendations.[5] While the 2005 ISUP recommendations retained small cribriform glands as Gleason pattern 3, we considered such glands as pattern 4. This modification was recently adopted in a 2014 grading consensus conference and by the WHO based on data that all cribriform glands are associated with more aggressive behavior.[11–13] The rationale for selecting only patients with Gleason score 3+3=6 disease at final pathology was to study a homogeneous cohort of PCa in which uneven PSA contribution by different Gleason patterns was not introduced.[14] Moreover we evaluated the relation of tumor volume, prostate size and PSA (including its measures not affected by higher BMI and related hemodilution) in the NCCN PCa categories most related to active surveillance evaluating Gleason score 3+3=6.[2,3,7] For the determination of tumor volume we mapped each separate tumor nodule on histology slides. Slides with tumor were photocopied with 1.5 times magnification (for ease of counting) on a background of 1 mm^2 grid and the amount of mm^2 in each tumor nodule was manually counted. The total number of mm^2 was multiplied by 3 (thickness of prostate tissue sections) and 1.12 (fixation shrinkage factor).[3,15] Final tumor volume was recorded in cm^3.

PSA density was calculated by dividing preoperative serum PSA by prostate weight without seminal vesicles.[2,3,6] At The Johns Hopkins Hospital the grossing protocol was modified on August 11, 2010 in accordance with the ISUP 2010 recommendation to weigh the prostate gland separately from SV.[16] Specimens processed before this date uniformly included SV in gross pathology weight. For these specimens we subtracted 6.4 gm, the average weight of bilateral SV, to correct for the extra weight added to the specimens by SV not included in PSAD calculation.[17] PSA mass (μg), the absolute amount of PSA in circulation, was calculated by multiplying plasma volume (liters) by serum PSA (ng/ml).[18] Plasma volume was calculated by multiplying estimated body surface area (m^2) by 1.67 adjustment factor. Estimated body surface area was calculated using the formula, body weight, $kg^{0.425}$ * height, $m^{0.72}$ * 0.007184.[18] BMI was calculated as preoperative patient weight in kilograms divided by the square of height in meters (kg/m^2).

We assessed patient PSA, PSAD and PSAM with respect to prostate weight and dominant and total tumor volumes in AA and Caucasian men. The analysis was performed in patients with a dominant tumor nodule volume of 0.5 cm^3 or less, that is, men with insignificant PCa at RP. In the second step of our analysis we compared the same correlations in all patients enrolled in the study regardless of total or dominant tumor volume.

Graphical and numeric exploratory data analysis methods were used to examine the distributions of variables. Means, medians and standard deviations are reported for each group as well as mean differences between racial groups with the corresponding 95% confidence intervals on the differences. Differences in means between race groups were assessed using unpaired t-tests where appropriate. For variables for which the assumptions for