

Percent genome alteration predicts adverse oncologic outcomes after radical prostatectomy in African American men: A profile of cancer genomics by racial ancestry

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Faisal F. ¹, Tomlins S. ², Lotan T. ³, Schaeffer E. ⁴

¹Johns Hopkins University School of Medicine, Dept. of Urology, Baltimore, United States of America, ²University of Michigan, Dept. of Urology and Pathology, Ann Arbor, United States of America, ³Johns Hopkins University School of Medicine, Dept. of Urology and Pathology, Baltimore, United States of America, ⁴Northwestern University Feinberg School of Medicine, Dept. of Urology, Chicago, United States of America

Introduction & Objectives: African American (AA) men have a higher incidence of and mortality from prostate cancer (PCa) than European American (EA) men. The potential biological determinants of these racial disparities are still unknown. Cancer genome evaluations with available clinical outcome data have been limited to EA populations. Here we characterize PCa genomes from a large cohort of AA men and identify the associations between genomic alterations and clinical outcomes.

Materials & Methods: Cancer genomes from 205 AA men treated with radical prostatectomy (RP) were profiled using next-generation sequencing for somatic mutations and percent genome alteration (PGA; defined as percentage of tumor genome with copy number variation). Logistic regression and Cox proportional hazard analyses assessed the association of genomic alterations with pathologic and oncologic outcomes in multivariate models (adjusted for age, PSA, and pathologic grade and/or stage, when applicable). PGA was dichotomized by quartiles in analytical models ($\leq 75^{\text{th}}$ percentile vs $> 75^{\text{th}}$ percentile).

Results: The median PGA was 3.7% (IQR 0.9-9.4) and increased with pathologic grade ($p < 0.001$) and stage ($p = 0.02$). Median follow-up was 5 years. AA men with the highest quartile of PGA had significantly worse biochemical recurrence (BCR)-free survival (10 year: 33.5% vs 50.2%; $p = 0.006$) and metastasis-free survival (10 year: 47.9% vs 89.0%; $p < 0.001$) than men with lower quartiles of PGA. PGA was associated with increased risks of higher grade (OR 2.0, 95% CI 1.1-3.7, $p = 0.03$), higher stage (OR 2.0, 95% CI 1.1-3.8, $p = 0.03$), BCR (univariate: HR 1.9, 95% CI 1.2-3.2, $p = 0.01$), and metastasis (HR 9.6, 95% CI 2.9-31.3, $p < 0.001$). The most common somatic mutations were SPOP (12.5%, 123/184), FOXA1 (9.2%, 17/184), and TP53 (4.4%, 8/184). Only TP53 was associated with increased risks of adverse outcomes, including higher stage (OR 5.3, 95% CI 1.5-19.4, $p = 0.01$), BCR (non-significant univariate: HR 2.4, 95% CI 1.0-5.9, $p = 0.06$), and metastasis (HR 9.5, 95% CI 2.2-40.6, $p = 0.002$).

Conclusions: In AA men, PCa genome profiles reveal unique genomic alterations. Notably, PGA in AA men predicts adverse pathologic and oncologic outcomes after RP and can potentially be considered a prognostic biomarker in this racial group. This research highlights the increasing importance of racial ancestry in cancer genomics studies and in the development of precision medicine strategies.