Among men with higher-grade prostate cancer, Black men are significantly more likely to have greater cancer cell-to-cell variability in telomere length than White men: a clue to racial disparity in prostate cancer outcomes

Christopher M. Heaphy[1,2,5], Corinne E. Joshu[4,5], John R. Barber[4], Christine Davis[1], Reza Zarinshenas[1], Angelo M. De Marzo[1,2,4,5], Karen S. Sfanos[1,2,4,5], Alan K. Meeker[1,2,4,5], Elizabeth A. Platz[2,3,4,5]

Departments of Pathology[1], Oncology[2] and Urology[3], Johns Hopkins University School of Medicine
Department of Epidemiology[4], Johns Hopkins Bloomberg School of Public Health
[5]Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins

Background: Black men diagnosed with prostate cancer have worse outcomes following primary treatment of their disease than White men even after taking into account differences in prognostic factors. Biological explanations for this racial disparity have not been identified. We previously showed that more variation in telomere lengths among cancer cells and shorter telomere lengths in cancer-associated stromal cells individually and together ("telomere biomarker") are associated with prostate cancer death in men surgically treated for clinically localized prostate cancer. These associations were independent of currently used prognostic indicators. We now hypothesize that Black-White differences in the prevalence of the telomere biomarker and/or in its components may help explain the racial disparity in prostate cancer outcomes. Thus, in this study we evaluated whether the prevalence of these telomere length measurements differ in prostatectomy tissues between age, stage- and grade-matched Black and White men.

Methods: We used two tissue microarray sets (TMA) designed to investigate tissue-based biomarkers that may differ by race. Black (higher-grade=34, lower-grade=93) and White (higher-grade=34, lower-grade=89) men treated by prostatectomy at Johns Hopkins were sampled to be matched on age, pathologic stage, and grade. We measured telomere lengths on a per cell basis in cancer and cancer-associated stromal cells using a robust telomere-specific fluorescence *in situ* hybridization assay. Using the telomere measurements that comprise the telomere biomarker – cancer cell-to-cell variability in telomere length and stromal cell telomere length, we identified TMA and grade-specific distributional cutpoints without regard to race as follows: more variable (top tertile of variability) in telomere length among cancer cells versus less variable (bottom and middle tertiles), and shorter (shortest and middle tertiles) median telomere length in cancer-associated stromal cells versus longer (longest tertile).

Results: Among men with higher-grade disease (Gleason $\geq$4+3), the proportion of Black men (47.1%) with more variable telomere lengths in cancer cells was 2.3-times higher ($p=0.02$) than that in White men (20.6%). In contrast, among men with lower-grade tumors, variability in telomere length did not differ by race ($p=0.3$). The proportion of men with shorter telomeres in cancer-associated stromal cells did not differ by race either in men with higher- ($p=0.44$) or lower-grade ($p=0.99$) disease.

Conclusions: Since Black men with prostate cancer are more likely to have worse outcomes than White men, and given our prior observations linking more variability in telomere lengths in cancer cells at the time of prostatectomy with worse outcome, our finding that Black men with higher-grade disease have a greater proportion of this adverse telomere phenotype than White men with higher-grade disease suggests a possible explanation for the racial disparity in prostate cancer outcomes.

Conflicts of Interest: None.

Funding Acknowledgments: This work is supported by PCF Young Investigator Awards (C. Heaphy & C. Joshu), DOD grant W81XWH-12-1-0545, DOD grant W81XWH-14-1-0364, Prostate Cancer Biorepository Network (PCBN) W81XWH-14-2-0182, P50 CA58236, and P30 CA006973.