Aneuploidy drives lethal progression in prostate cancer

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Background: Aneuploidy, defined as chromosome gains and losses, has long been hypothesized to drive cancer progression. However, aneuploidy is relatively rare in prostate cancer, and its role has been incompletely understood. We tested the hypothesis that extent of aneuploidy is associated with the risk of metastases and prostate cancer-specific death (lethal disease) among patients with primary prostate cancer.

Methods: To leverage biorepositories of archival tumor specimens with RNA profiling data for our study, we developed a computational algorithm based to infer DNA-level chromosome arm gains and losses from whole-transcriptome profiling. We based our approach on normalized gene expression sums from whole-transcriptome profiling in primary prostate tumors from The Cancer Genome Atlas (TCGA). We then studied patients diagnosed with primary prostate cancer during prospective follow-up of the Health Professionals Follow-up Study (HPFS) and the Physicians' Health Study (PHS). We applied our method to infer extent of aneuploidy in their tumor tissue from cancer diagnosis. We compared extent of aneuploidy to Gleason grading from centralized histopathologic review and immunohistochemistry-based proliferation indices (Ki-67), apoptosis (TUNEL), PTEN loss, and MYC amplification. Lethal disease was captured on prospective follow-up.

Results: In primary prostate cancer, 23% of 333 primary prostate cancers from TCGA had extensive aneuploidy (>=5 gained or lost chromosome arms). Even two thirds of tumors considered low risk based on a Gleason grade of 3+4 or less had at least one altered chromosome arm. Tumors with greater extent of aneuploidy had higher Gleason scores. Among tumors without aneuploidy, 15% had Gleason scores >=8, while among tumors with >=5 altered chromosome arms, 45% had Gleason scores >=8. However, there was little to no increase in proliferation (Ki-67) and apoptosis (TUNEL) with higher extent of aneuploidy. We were able to detect aneuploidy in transcriptome profiling using our algorithm with good discrimination (area under the curve [AUC], 0.83 for any aneuploidy; 0.87 for >=5 altered chromosome arms, compared to DNA sequencing). Among the 404 patients from HPFS and PHS, 92% of whom were treated with primary prostatectomy, 113 lethal events occurred over a median follow-up of 15 years. Higher extent of aneuploidy was strongly associated with a higher risk of lethal disease. Compared to patients whose tumors had no aneuploidy, those with >=5 predicted altered chromosome arms had 5.3 times higher odds of lethal disease (95% confidence interval, 2.2 to 13.1) even after adjusting for differences in Gleason grade. We observed a particularly strong association between extent of aneuploidy and lethal disease among men with tumors of Gleason score >=8. As expected, deletions of chromosome arm 10q and gains of chromosome arm 8q were among the most common alterations. Notably, the risk of lethal disease associated with chromosome arm 10q deletion and with 8q gain remained strong even when adjusting for PTEN loss and MYC overexpression on these chromosome arms.

Conclusions: Transcriptome profiling of archival, formalin-fixed paraffin-embedded tumors allows estimating the extent of aneuploidy. Aneuploidy indices capture some of the complex interactions between genes colocalized on a chromosome arm and may provide a more comprehensive assessment of tumor aggressiveness beyond single well-described tumor suppressors or oncogenes. Our results point to a key role of aneuploidy in driving aggressive disease in primary prostate cancer.

Conflict of Interest: As of September 2019, P.W. Kantoff reports the following disclosures for the last 24-month period: he has investment interest in Context Therapeutics LLC, DRGT, Placon, Seer Biosciences, and Tarveda Therapeutics, he is a company board member for Context Therapeutics LLC, and is a consultant/scientific advisory board member for Bavarian Nordic Immunotherapeutics, DRGT, GE Healthcare, Janssen, New England Research Institutes, Inc., OncoCellMDX, Progenity, Sanofi, Seer Biosciences, Tarveda Therapeutics, and Thermo Fisher, and serves on data safety monitoring boards for Genentech/Roche and Merck.

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