Disruption of the circadian rhythm and advanced prostate cancer

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Background: The circadian system regulates many physiological and metabolic activities including an array of cancer-related pathways. There is little epidemiological data – although strong biologic rationale – for associations between the circadian system and prostate cancer. Using an integrative molecular epidemiological approach, we evaluated the association between pathways of circadian disruption with risk of advanced prostate cancer.

Methods: We studied three cohorts – the Icelandic AGES-Reykjavik cohort, and the U.S. based Health Professionals Follow-up Study (HPFS) and Physicians' Health Study (PHS). We assessed circadian disruption using complimentary approaches: information on sleep disruption and sleep duration from prediagnostic questionnaires, prediagnostic 6-sulfatoxymelatonin – the main metabolite of melatonin – measured on first morning void urine samples, prediagnostic pineal gland volume and calcifications, and genetic variation across twelve circadian-related genes. We used multivariable regression models to calculate odds ratios (OR) and hazard ratios (HR) and 95% confidence intervals (CI) of the associations between aspects of the circadian rhythm with advanced prostate cancer.

Results: In AGES-Reykjavik, men with problems falling or staying asleep had significantly lower morning 6-sulfatoxymelatonin levels compared to those who reported no sleep problems. Smaller pineal volume was also associated with lower 6-sulfatoxymelatonin levels. Men with low 6-sulfatoxymelatonin levels had a four-fold statistically significant increased risk of advanced disease compared to men with higher levels (HR = 4.01, 95% CI: 1.25-12.90). In HPFS, we did not find an association between self-reported sleep duration and risk of prostate cancer. However, among the 6% of men who reported never feeling rested when they wake up, there was a significantly increased risk of lethal disease compared to those who reported always feeling rested (RR=2.80, 95% CI=1.04-7.53). Finally, pathway analyses showed that variation in the *CRY1* gene was nominally associated with fatal prostate cancer. In AGES-Reykjavik, SNPs in the *TIMELESS, NPAS2, PER3,* and *CSNK1E* genes were differentially associated with 6-sulfatoxymelatonin levels.

Conclusions: These results provide human based evidence that inputs and regulators of the circadian rhythm, including melatonin suppression, sleep problems and circadian disruption may be important in prostate tumorigenesis and progression.
Future Directions: We are currently investigating the hypothesis of circadian disruption and prostate cancer in an ethnically diverse population from the Multiethnic Cohort (MEC). We will investigate genetic variants in circadian genes and known prostate cancer risk loci with 6-sulfatoxymelatonin levels, and the association between 6-sulfatoxymelatonin levels with prostate cancer risk, with a primary goal to formally compare and contrast the associations by race/ethnicity. The results of this study could increase our understanding of modifiable risk

factors for aggressive prostate cancer and identify risk factors that contribute to disparities, and are highly translational (potentially by altering melatonin levels and sleep patterns) and could illuminate opportunities for primary and secondary prevention.

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