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Platinum Priority – Brief Correspondence

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Urinary Melatonin Levels, Sleep Disruption, and Risk of Prostate Cancer in Elderly Men

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Abstract

Melatonin has anticarcinogenic properties in experimental models. We undertook a case–cohort study of 928 Icelandic men without prostate cancer (PCa) nested within the Age, Gene/Environment Susceptibility (AGES)-Reykjavik cohort to investigate the prospective association between first morning-void urinary 6-sulfatoxymelatonin (aMT6s) levels and the subsequent risk for PCa, under the hypothesis that men with lower aMT6s levels have an increased risk for advanced PCa. We used weighted Cox proportional hazards models to assess the association between first morning-void aMT6s levels and PCa risk, adjusting for potential confounders. A total of 111 men were diagnosed with incident PCa, including 24 with advanced disease. Men who reported sleep problems at baseline had lower morning aMT6s levels compared with those who reported no sleep problems. Men with morning aMT6s levels below the median had a fourfold statistically significant increased risk for advanced disease compared with men with levels above the median (hazard ratio: 4.04; 95% confidence interval, 1.26–12.98). These results require replication in larger prospective studies with longer follow-up.

Patient summary: In this report, we evaluated the prospective association between urinary aMT6s levels and risk of PCa in an Icelandic population. We found that lower levels of aMT6s were associated with an increased risk for advanced PCa.

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The circadian rhythm regulates diverse physiologic and metabolic activities [1]. Melatonin is a hormone secreted by the pineal gland in a 24-h circadian rhythm; under normal conditions, production peaks at night. Melatonin secretion can be inhibited by many factors, including light exposure at night. Most epidemiologic studies support a positive association between measures of circadian disruption or sleep loss and prostate cancer (PCa) risk [2]. In experimental studies, melatonin exhibits chemopreventive properties [3]. Cross-sectionally, men with PCa had lower melatonin levels compared with men with benign prostatic hyperplasia [4]. No prior study has evaluated the prospective association between prediagnostic 6-sulfatoxymelatonin (aMT6s) levels, the primary melatonin metabolite in urine, and PCa [5].

We undertook a case–cohort study (Supplemental Fig. 1) within the Age, Gene/Environment Susceptibililty-Reykjavik (AGES-Reykjavik) study to investigate the association between morning urinary aMT6s levels and PCa risk. We leveraged questionnaire data on sleep disruption, previously linked with PCa risk [6], to investigate cross-sectional associations with aMT6s levels.

Full study methods are provided in the online Supplement. Briefly, AGES-Reykjavik collected information via physical examination, questionnaire, and biologic specimens during a 2-day assessment between 2002 and 2006. Subjects collected a first morning-void urine sample. Urine samples were assayed for aMT6s using the melatonin-sulfate enzyme-linked immunosorbent assay (IBL International, Toronto, ON, Canada).

PCa diagnosis and cause of death were identified by linkage with the nationwide Icelandic Cancer Registry and Statistics Iceland using unique identification numbers. We studied risk for total PCa, advanced cancer (extraprostatic stage T3a or higher, N1/M1, cancer death), and lethal cancer (N1/M1 or cancer death).

Participant characteristics were summarized by aMT6s levels dichotomized at the subcohort median. We used Cox proportional hazards regression, modified for the case–cohort design using the Prentice method to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between aMT6s levels and incident PCa. Models were adjusted for age and creatinine levels, and additionally for family history of PCa, beta-blocker use, depression, sleep problems, and diabetes. Results were similar when additionally adjusted for cortisol.

Men with lower aMT6s levels tended to drink less alcohol and had slightly lower creatinine levels, but were more likely to have diabetes and to be taking beta-blockers or psychotropic drugs (Supplemental Table 1). There were no material differences in season of urine collection.

aMT6s levels were lower among men who reported sleep problems compared to men without problems (Supplemental Table 1). We determined the 25th percentile of aMT6s in men without sleep problems and defined values less than the 25th percentile as low. Twenty-five percent of men without sleep problems had low aMT6s levels (Fig. 1). In contrast, 35% of men taking medications for sleep and 34% of men with severe sleep problems had low aMT6s levels.

Men with aMT6s levels below the median had a 47% higher, although not statistically significant, PCa risk overall compared to men with higher levels (Table 1). Men with lower aMT6s levels had a fourfold increased risk for advanced disease (HR: 4.04; 95% CI, 1.26–12.98); results were similar for lethal PCa (Table 1). In subanalyses to consider potential biases (Supplemental Table 3), including limiting analyses to men who returned their urine samples

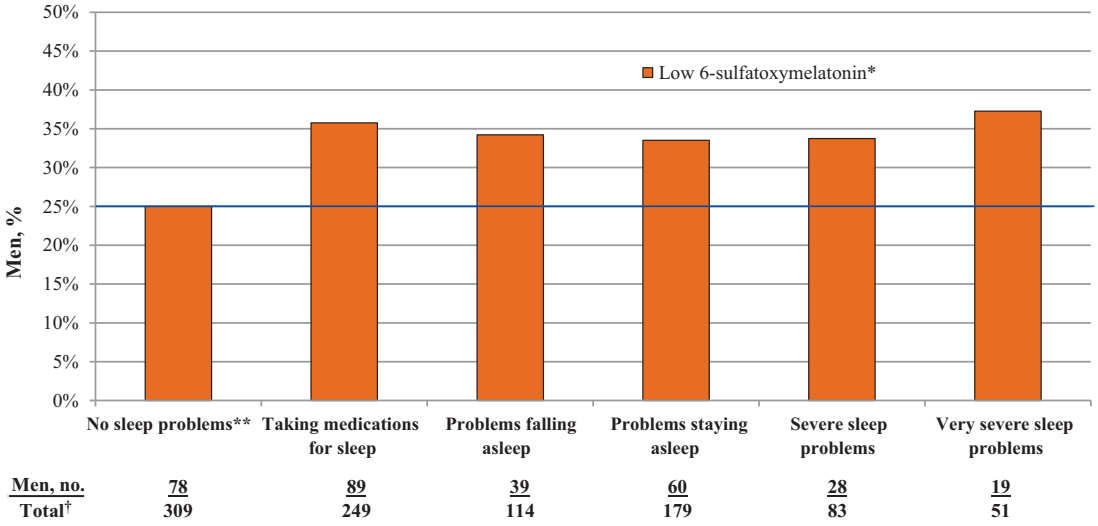

Fig. 1 – Percent of people in each sleep disruption category with low 6-sulfatoxymelatonin (aMT6s) levels in the Age, Gene/Environment Susceptibility (AGES)-Reykjavik case–cohort study.
***In men without sleep problems (*n* = 309), the distribution of aMT6s was as follows: mean = 22.0 ng/ml, median = 18.8 ng/ml, 25th percentile = 11.1 ng/ml, and 10th percentile = 6.5 ng/ml.**
****Low aMT6s: aMT6s levels below the 25th percentile in men without sleep problems (11.1 ng/ml).**
† Number of men with low aMT6s levels (ie, <11.1 ng/ml).