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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 Susceptibility-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

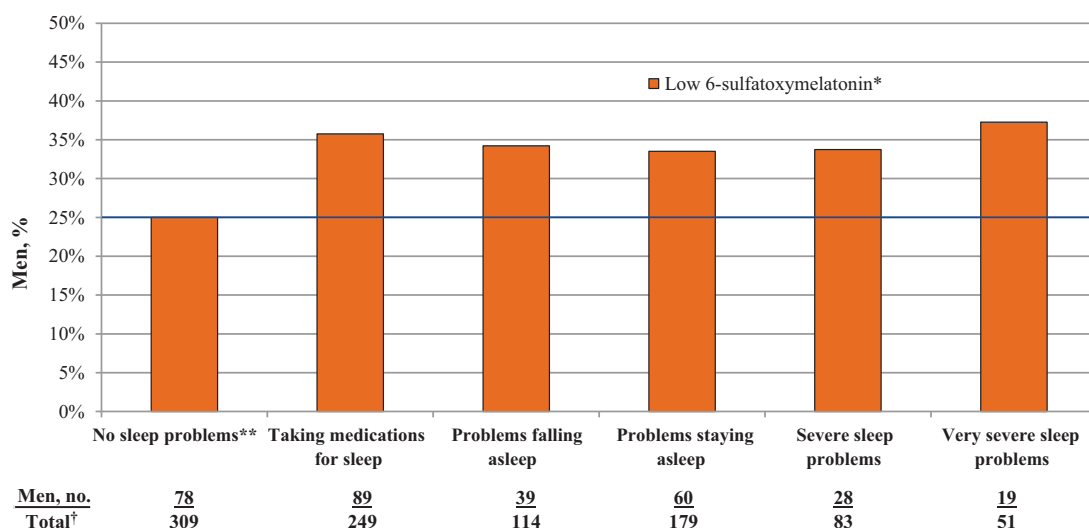


Fig. 1 – Percent of people in each sleep disruption category with low 6-sulfatoxymelatonin (aMT6s) levels in the Age, Gene/Environment Susceptibility (AGES)-Reykjavik case-cohort study.

\*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).

**Table 1 – Association between 6-sulfatoxymelatonin levels and risk of prostate cancer: Age, Gene/Environment Susceptibility (AGES)-Reykjavik case-cohort study 2002–2009**

	High	Low <sup>*</sup>	p value
Overall PCa, no.			
PCa cases/subcohort control participants	52/432	59/432	–
HR (95% CI)			
Age and creatinine level adjusted	Ref.	1.31 (0.85–2.04)	0.22
Fully adjusted <sup>**</sup>	Ref.	1.47 (0.94–2.30)	0.09
Nonadvanced PCa <sup>†</sup> , no.			
PCa cases/subcohort control participants	45/432	42/432	–
HR (95% CI)			
Age and creatinine level adjusted	Ref.	1.07 (0.66–1.72)	0.79
Fully adjusted <sup>**</sup>	Ref.	1.11 (0.67–1.82)	0.69
Advanced PCa <sup>‡</sup> , no.			
PCa cases/subcohort control participants	7/432	17/432	–
HR (95% CI)			
Age and creatinine level adjusted	Ref.	2.92 (1.00–8.56)	0.05
Fully adjusted <sup>**</sup>	Ref.	4.04 (1.26–12.99)	0.02
Lethal PCa <sup>^</sup> , no.			
PCa cases/subcohort control participants	4/432	14/432	–
HR (95% CI)			
Age and creatinine level adjusted	Ref.	4.39 (1.18–16.31)	0.03
Fully adjusted <sup>**</sup>	Ref.	4.83 (1.26–18.45)	0.02

PCa = prostate cancer; HR = hazard ratio; CI = confidence interval.  
<sup>\*</sup> 6-sulfatoxymelatonin (aMT6s) levels were dichotomized at the median in subcohort (17.14 ng/ml); HR compares low aMT6s levels (below the median) to high levels (above the median).  
<sup>\*\*</sup> Fully adjusted model adjusted for age (as time scale), creatinine level, family history of PCa, history of depression, history of diabetes, severe sleep problems, and current beta-blocker use.  
<sup>†</sup> Nonadvanced PCa defined as less than stage T3a at diagnosis without distant metastases or death due to PCa.  
<sup>‡</sup> Advanced PCa defined as stage T3a or T3b at diagnosis, distant metastases at diagnosis or death from PCa over follow-up.  
<sup>^</sup> Lethal PCa defined as distant metastases at diagnosis or death from PCa over follow-up.

in the morning or to men reporting no sleep problems, or starting follow-up 2 yr after urine collection, point estimates remained similar but were not statistically significant.

In this prospective study of older men, we found an inverse association between urinary aMT6s levels and advanced or lethal PCa. We are unaware of any prior prospective evaluation of melatonin, as measured by its urinary metabolite, and PCa, although the findings are broadly in line with prior epidemiologic and experimental studies. A study showed serum melatonin levels measured over 24 h were lower in PCa patients than in controls [4]. Experimental studies suggest that melatonin has anticarcinogenic properties, as melatonin inhibits prostate tumor growth in vitro and in vivo [3,7].

This study adds to accumulating epidemiologic data investigating associations between circadian disruption or sleep loss and PCa [2], and provides a potential mechanism and framework for understanding prior results. Night-shift work, which disrupts circadian rhythms and suppresses melatonin secretion through nocturnal exposure to artificial light, was categorized as a probable human carcinogen by the International Agency for Research on Cancer, based primarily on data in breast cancer. Night-shift work has been associated with increased risk of PCa [8] as well as elevated prostate-specific antigen (PSA) levels among men without PCa [9]. Moreover, blind men, some of whom may have uninhibited melatonin secretion, have lower PCa incidence compared to the general population [10].

Our results rest on a single morning urinary aMT6s measurement, which may not represent long-term levels.

We were also limited by a small number of events. Follow-up is short and men may have had underlying disease at the time of exposure assessment. We attempted to address the possibility of reverse association, although power was limited given the median follow-up time from urine collection to diagnosis of 2.3 yr. Although we had broad information on various covariates and were able to control for possible confounders, we lacked information on factors such as vitamin D levels. We also lacked information on Gleason grade, screening history, or PSA levels, and stage information was missing for 35% of cases. Finally, this study was restricted to elderly men in Iceland; levels of melatonin in this population may vary from those of other populations, such as those with less extreme variation in daylight during the year or younger men, although it is noteworthy that levels did not vary by season of collection. While this limits generalizability of our findings, it is unlikely that underlying biologic impact on PCa pathogenesis would differ.

In summary, men with lower morning aMT6s levels were at increased risk for advanced or lethal PCa. These results require replication in larger prospective cohort studies with longer follow-up and more detailed clinical information. Given that disruption of melatonin levels is potentially avoidable, further studies of melatonin and PCa risk should be a priority.

**Author contributions:** Sarah C. Markt and Lara G Sigurdardottir had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

*Study concept and design:* Sigurdardottir, Markt, Rider, Fall, Batista, Launer, Harris, Aspelund, Stampfer, Gudnason, Czeisler, Lockley, Valdimarsdottir, Mucci.

*Acquisition of data:* Sigurdardottir, Markt, Valdimarsdottir, Harris, Gudnason.

*Analysis and interpretation of data:* Sigurdardottir, Markt, Rider, Haneuse, Fall, Schernhammer, Tamimi, Flynn-Evans, Batista, Launer, Harris, Aspelund, Stampfer, Gudnason, Czeisler, Lockley, Valdimarsdottir, Mucci.

*Drafting of the manuscript:* Sigurdardottir, Markt.

*Critical revision of the manuscript for important intellectual content:* Sigurdardottir, Markt, Rider, Haneuse, Fall, Schernhammer, Tamimi, Flynn-Evans, Batista, Launer, Harris, Aspelund, Stampfer, Gudnason, Czeisler, Lockley, Valdimarsdottir, Mucci.

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*Obtaining funding:* Valdimarsdottir, Mucci.

*Administrative, technical, or material support:* Sigurdardottir, Harris, Aspelund, Gudnason.

*Supervision:* Valdimarsdottir, Mucci.

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## Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.eururo.2014.07.008>.

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