Urinary 6-sulfatoxymelatonin Levels and Prostate Cancer Risk among Men in the Multiethnic Cohort

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ABSTRACT

Background: The circadian hormone melatonin has anticancer properties, and prior studies suggest a positive association between low melatonin and prostate cancer risk. The purpose of this study was to examine urinary melatonin levels and prostate cancer in a racially/ethnically diverse cohort.

Methods: We conducted a nested case–control study, including 1,263 prostate cancer cases and 2,346 controls, sampled from participants in the Multiethnic Cohort Study with prediagnostic urine samples assayed for 6-sulfatoxymelatonin, the primary melatonin metabolite. Conditional logistic regression was used to examine the association between melatonin levels and the development of prostate cancer outcomes (all incident cases, advanced, lethal, high-grade, and aggressive), overall and by race/ethnicity.

Results: Among 1,263 cases, 135 were advanced stage, 101 were lethal cases, and 282 were high-grade disease. Median melatonin levels were similar in controls [17.12 ng/mL; interquartile range (IQR), 19.78] and cases (17.93 ng/mL; IQR, 19.76), and we found no significant association between urinary melatonin levels and prostate cancer risk overall or in any clinical or racial subgroup.

Conclusions: In this diverse cohort, there was no significant association between melatonin and any prostate cancer outcome, nor were there any differences by racial/ethnic group.

Impact: These results do not support a strong association between melatonin levels and risk of prostate cancer.

Introduction

Melatonin is a key hormonal output of the circadian system and has anticancer properties, including inhibition of cell proliferation and stimulation of apoptosis (1). In our prior work within an Icelandic cohort, low melatonin levels were associated with an increased risk of advanced prostate cancer (2). To our knowledge, the Icelandic study has been the only study to utilize melatonin measured from prediagnostic urine samples in its analysis of future prostate cancer risk; however, previous cross-sectional studies have demonstrated that men with prostate cancer have lower melatonin levels compared with men with benign prostatic hyperplasia (3). There is emerging evidence that pathways of circadian disruption, including melatonin suppression, vary by race/ethnicity. This study aimed to evaluate the association between overnight/first morning void urinary 6-sulfatoxymelatonin levels and prostate cancer risk in a racially/ethnically diverse cohort.

Materials and Methods

Study population

We conducted a nested case–control study within the Multiethnic Cohort Study (4), selected among men who contributed a prediagnostic urine sample between 1996 and 2005. Incident prostate cancer cases along with respective tumor characteristics were identified through the NCI's Surveillance, Epidemiology and End Results Program in Hawaii and California. Each case was age-matched using risk-set sampling with two randomly selected controls. We additionally matched for geographic location (Hawaii/California), urine collection type (overnight or first morning void), race/ethnicity, birth year, date and time of specimen collection. Men were excluded if they were missing melatonin levels ($n = 48$), had melatonin measurements >120 ng/mL ($n = 29$), used melatonin supplements ($n = 3$), or had another cancer diagnosis at baseline ($n = 261$). To maintain the matched sets, if a case was excluded, so were the corresponding controls ($n = 235$). The final analytic study population included 1,263 cases and 2,346 controls, with 570 total participants excluded from the initial study population. The protocol was approved by the Institutional Review Boards at Harvard T.H. Chan School of Public Health (Boston, HA), the University of Southern California (Los Angeles, CA), and the University of Hawaii (Honolulu, HI), and informed written consent was obtained from the study participants. The studies were conducted in accordance with the ethical guidelines of the Declaration of Helsinki.

Outcome ascertainment

The primary outcome was incident prostate cancer. Secondary analyses considered advanced (T3b/T4, N1 or M1), lethal

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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(M1, development of metastases or death from prostate cancer), high-grade (Gleason 8–10), and aggressive (advanced or high-grade) disease. Deaths were identified through linkage to death-certificate files or the National Death Index.

6-sulfatoxymelatonin measurement

Urine samples were assayed for 6-sulfatoxymelatonin (the primary metabolite of urinary melatonin) using the melatonin sulfate enzyme-linked immunosorbent assay (IBL International) at the Icelandic Heart

Table 1. ORs and 95% CIs from conditional logistic regression analysis of the association between melatonin[a] and prostate cancer risk in the Multiethnic Cohort.

	Total *N*	Matched analysis[b]	Matched analysis, adjusted[c]	P_{trend}[d]
Overall prostate cancer				
Cases/controls	3,609	1,263/2,346	1,263/2,346	
OR (95% CI)				
Melatonin (continuous)[a]		1.02 (0.95–1.10)	1.01 (0.93–1.09)	
Melatonin quartiles[e]				0.42
Q1 (ref)	302/592	1.00	1.00	
Q2	319/582	1.07 (0.86–1.30)	0.99 (0.80–1.22)	
Q3	312/583	1.05 (0.86–1.29)	0.95 (0.76–1.18)	
Q4	330/589	1.11 (0.91–1.36)	1.06 (0.85–1.32)	
Advanced prostate cancer[f]				
Cases/controls	389	135/254	135/254	
OR (95% CI)				
Melatonin (continuous)[a]		0.93 (0.75–1.15)	0.94 (0.75–1.19)	
Melatonin quartiles				0.26
Q1 (ref)	44/73	1.00	1.00	
Q2	32/52	0.98 (0.55–1.75)	0.96 (0.50–1.85)	
Q3	31/69	0.71 (0.39–1.32)	0.65 (0.32–1.32)	
Q4	28/60	0.73 (0.39–1.38)	0.87 (0.43–1.76)	
Lethal prostate cancer				
Cases/controls	291	101/190	101/190	
OR (95% CI)				
Melatonin (continuous)[a]		1.14 (0.89–1.46)	1.18 (0.90–1.55)	
Melatonin quartiles				0.75
Q1 (ref)	29/61	1.00	1.00	
Q2	27/44	1.28 (0.65–2.50)	1.34 (0.61–2.95)	
Q3	19/40	1.03 (0.47–2.22)	0.89 (0.36–2.21)	
Q4	26/45	1.20 (0.59–2.44)	1.63 (0.72–3.68)	
High-grade prostate cancer[g]				
Cases/controls	812	282/530	282/530	
OR (95% CI)				
Melatonin (continuous)[a]		0.99 (0.85–1.15)	0.96 (0.81–1.13)	
Melatonin quartiles				0.62
Q1 (ref)	70/126	1.00	1.00	
Q2	76/138	1.01 (0.67–1.51)	0.96 (0.61–1.51)	
Q3	69/133	0.93 (0.60–1.42)	0.83 (0.52–1.33)	
Q4	67/133	0.91 (0.60–1.40)	0.89 (0.56–1.43)	
Aggressive prostate cancer[h]				
Cases/controls	1,024	356/668	356/668	
OR (95% CI)				
Melatonin (continuous)[a]		1.00 (0.87–1.14)	1.00 (0.87–1.16)	
Melatonin quartiles				0.54
Q1 (ref)	98/173	1.00	1.00	
Q2	91/169	0.96 (0.67–1.38)	0.97 (0.66–1.43)	
Q3	86/166	0.92 (0.63–1.33)	0.90 (0.60–1.36)	
Q4	81/160	0.90 (0.61–1.32)	0.95 (0.63–1.44)	

[a]Melatonin is modeled as the Jackknife residual of melatonin adjusted for creatinine. Because urine samples were not collected over 24 hours and total urinary volume was unknown, we used this method to normalize raw melatonin values using creatinine concentration.
[b]Conditional logistic regression model accounts for matching factors: race/ethnicity, birth year, year of urine collection, study site, and urine collection type.
[c]Adjusted for marital status, body mass index categories, smoking status, and PSA screening.
[d]Cochran–Armitage trend test, exact test, two-sided *P* value.
[e]Quartile cut-off points are −0.56, −0.16, and 0.34.
[f]T3b, T4, N1, M1.
[g]Gleason grade 8–10.
[h]Advanced or high-grade disease.

Table 2. ORs and 95% CIs from conditional logistic regression[a] for the association between melatonin[b] and overall prostate cancer risk, stratified by race/ethnicity.

	Japanese American	White	Black	Latino	Native Hawaiian
Median (IQR) melatonin values					
Jackknife residuals	−0.16 (0.79)	−0.08 (0.94)	−0.28 (1.17)	−0.13 (1.23)	−0.22 (0.88)
Melatonin/creatinine ratio (ng/mL)	23.62 (19.50)	24.95 (20.72)	22.40 (19.67)	25.35 (21.14)	21.41 (20.06)
Melatonin (ng/mL)	14.97 (16.54)	17.95 (19.90)	22.53 (25.17)	23.11 (26.82)	16.14 (18.19)
Overnight void urine	14.67 (16.31)	17.71 (19.69)	—	—	16.04 (17.88)
First morning void urine	19.39 (17.23)	31.17 (24.67)	22.53 (25.17)	23.11 (26.82)	19.23 (16.01)
Overall prostate cancer					
No. of prostate cancer cases/no. of control participants	555/1,059	316/545	163/304	119/226	110/212
Q1	104/249	71/127	68/99	31/58	28/59
Q2	162/296	69/117	25/64	29/48	34/57
Q3	150/292	88/145	28/56	22/43	24/47
Q4	139/222	88/156	42/85	37/77	24/49
OR (95% CI)					
Melatonin (continuous)[b]	1.13 (1.01–1.28)	0.96 (0.84–1.11)	0.94 (0.80–1.11)	1.00 (0.80–1.25)	0.99 (0.77–1.28)
Melatonin quartiles					
Q1 (ref)	1.00	1.00	1.00	1.00	1.00
Q2	1.30 (0.96–1.75)	1.05 (0.69–1.60)	0.54 (0.30–0.96)	1.09 (0.58–2.06)	1.25 (0.68–2.27)
Q3	1.27 (0.93–1.72)	1.07 (0.71–1.62)	0.68 (0.37–1.23)	0.92 (0.47–1.81)	1.03 (0.50–2.14)
Q4	1.55 (1.12–2.15)	1.01 (0.67–1.51)	0.68 (0.41–1.13)	0.91 (0.48–1.71)	0.99 (0.49–2.01)
P_{trend}[c]	0.03	0.95	0.22	0.64	1.00

[a]Conditional logistic regression model accounts for matching factors: birth year, year of urine collection, study site, and urine collection type.
[b]Melatonin is modeled as the Jackknife residual of melatonin adjusted for creatinine.
[c]Cochran–Armitage trend test, exact test, two-sided *P* value.

Association as described previously (2), with a coefficient of variation of 6.69. Because of differing urine collection methods, we calculated jackknife residuals of melatonin adjusted for creatinine. Cut-off points for quartile analyses were established using the distribution of melatonin jackknife residuals in controls.

Statistical analysis

Conditional logistic regression was used to estimate ORs and 95% confidence intervals (CI) for overall, advanced, lethal, high-grade, and aggressive prostate cancer, controlling for set-matching variables. A fully adjusted model incorporated smoking status (never, current, past), body mass index (four categories) marital status (married, separated, divorced, widowed, never married), and PSA screening (ever/never), covariates selected because of differences between exposure groups (Supplementary Table S1). Melatonin jackknife residuals and the derived quartiles were used as a continuous and categorical exposure, respectively. A Cochran–Armitage exact test for trend was used to calculate a two-sided *P* value, setting $P < 0.05$ for statistical significance. Analyses were also stratified by race/ethnicity, family history of prostate cancer, time between urine collection and diagnosis, and urine collection year.

Data availability

The data generated in this study are available upon request from the corresponding author.

Results

Among 1,263 prostate cancer cases, 135 were advanced, 101 were lethal, 282 were high grade, and 356 were aggressive (**Table 1**). Neither unadjusted nor adjusted models showed an association between urinary melatonin and overall prostate cancer ($OR_{continuous}$: 1.01, 0.93–1.09; OR_{Q4vsQ1}: 1.06, 0.85–1.32). Null results were also found for advanced, lethal, high grade, and aggressive prostate cancer.

There was no association between melatonin levels and prostate cancer in Black, Latino, Native Hawaiian, or White men (**Table 2**). However, there was an association between melatonin and overall prostate cancer among Japanese Americans (OR_{Q4vsQ1}: 1.55, 1.12–2.15).

Results remained null for prostate cancer risk after stratification by year of urine collection, time between urine collection and diagnosis (median time of 4 years), and family history of prostate cancer. There was no association when raw melatonin was used as the exposure, nor when the cohort was limited to perfectly matched sets. In race-stratified regression models using all 2,569 controls, there was no association between melatonin and any prostate cancer outcome (Supplementary Tables S2–S5).

Discussion

In this prospective study within the Multiethnic Cohort Study, we found no association between urinary melatonin levels and risk of prostate cancer, overall or advanced disease. Similarly, there were no statistically significant associations among White, Black, Native Hawaiian, or Latino men; the positive finding in Japanese American men may be due to chance or residual confounding. These findings contrast with those from our prior study in Icelandic men showing an increased risk of prostate cancer comparing men with low melatonin levels to high melatonin levels (2). Potential explanations for the contrasting results include differing characteristics of the study populations, specifically age, race, and geographic location; small sample sizes in both populations, leading to low power and chance; and different median time between urine collection and diagnosis for cases, or match date for controls (2.3 years in the Icelandic study and 4.0 years in this current study).

Prior literature has demonstrated that 6-sulfatoxymelatoin measured from first morning void urine has been accurately shown to reflect peak and total overall nocturnal melatonin production and is a feasible biomarker in the context of large epidemiologic studies (5, 6). However, the current study was limited by a single measure of urinary melatonin, which may not represent long-term levels. While the sample size for lethal and advanced analyses was small, the minimum detectable OR was 0.77 for overall and 0.43 for advanced prostate cancer. Given potential differences in circadian rhythm in racially/ethnically diverse populations (7, 8), and higher rates of prostate cancer in Black men, future studies should investigate the role of circadian disruption and prostate cancer in larger, diverse study populations.

Authors' Disclosures

L. Le Marchand reports grants from NCI during the conduct of the study. L.A. Mucci reports grants from NCI during the conduct of the study; personal fees from Bayer; grants from Janssen and AstraZeneca outside the submitted work; and spouse of L.A. Mucci is the CEO of Convergent Therapeutics. S.C. Markt reports grants from NCI during the conduct of the study. No disclosures were reported by the other authors.

Authors' Contributions

J.B. Vaselkiv: Formal analysis, writing–original draft, writing–review and editing. **I. Cheng:** Data curation, writing–review and editing. **I.M. Chowdhury-Paulino:** Writing–review and editing. **A.G. Gonzalez-Feliciano:** Formal analysis, writing–review and editing. **L.R. Wilkens:** Data curation, writing–review and editing. **A.M. Hauksdottir:** Methodology. **G. Eiriksdottir:** Methodology. **L. Le Marchand:** Writing–review and editing. **C.A. Haiman:** Writing–review and editing. **U. Valdimarsdóttir:** Writing–review and editing. **L.A. Mucci:** Conceptualization, supervision, writing–review and editing. **S.C. Markt:** Conceptualization, supervision, writing–original draft, writing–review and editing.

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