Research Article

Cancer Epidemiology, Biomarkers & Prevention

Sleep Duration and Disruption and Prostate Cancer Risk: a 23-Year Prospective Study

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Abstract

Background: Sleep deficiency is a major public health problem. There are limited human data on whether sleep duration or disruption are risk factors for prostate cancer.

Methods: We prospectively followed 32,141 men in the Health Professionals Follow-Up Study who reported their typical sleep duration in 1987, 2000, and 2008. We identified 4,261 incident prostate cancer cases, including 563 lethal cases through 2010. Sleep disruption was assessed in 2004 among 19,639 men, with 930 prostate cancer cases (50 lethal) identified from 2004 to 2010. Cox proportional hazards models were used to evaluate the association between sleep insufficiency and risk of overall and lethal prostate cancer.

Results: In 1987, 2% of men reported sleeping ≤5 hours per night. We found no association between habitual sleep duration or change in sleep duration with the risk of advanced or lethal prostate cancer. We also found no association between waking up during the night, difficulty falling asleep, or waking up too early, and risk of prostate cancer. In 2004, 6% of men reported never feeling rested when they woke up; these men had an increased risk of developing lethal prostate cancer compared with those who reported always feeling rested when they woke up (RR, 3.05; 95% CI, 1.15–8.10).

Conclusions: We found no consistent association between self-reported sleep duration or sleep disruption and any of our prostate cancer outcomes.

Impact: We did not find support for a consistent association between self-reported sleep and risk of advanced or lethal prostate cancer in this large cohort of men. *Cancer Epidemiol Biomarkers Prev; 25(2); 302–8. ©2015 AACR.*

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Introduction

Sleep disruption and insufficient sleep are major public health problems in the United States with more than 1 in 4 American adults experiencing less than 7 hours of sleep per night and an estimated 1 in 5 with chronic sleep or wakefulness disorders (1). Poor sleep may have broader health effects given that insufficient sleep has been associated with an increased risk of cardiovascular disease, obesity, diabetes, and total mortality (2–7).

Shift work involving circadian disruption was designated a probable human carcinogen by the International Agency for Research on Cancer (IARC) in 2007 and is hypothesized to increase cancer risk through at least three interrelated pathways: (i) internal desynchronization of circadian rhythms, (ii) suppression of the pineal hormone melatonin, and (iii) inadequate sleep duration or sleep disruption. Risk of prostate cancer is increased among occupations with exposure to some degree of night shift work, including airline pilots, physicians, and law enforcement personnel (8, 9). In addition, men who ever worked at night had an increased risk of prostate cancer compared with men who had never worked at night (10), and shift work has been associated with elevated PSA levels among men without known prostate cancer (11).

Inadequate sleep duration or sleep disruption may be risk factors for prostate cancer, although few epidemiologic studies have addressed this question. A prospective cohort study in Japan showed a 64% reduced risk of overall prostate cancer for men who reported sleeping ≥9 hours per night compared with those who slept 7 to 8 hours per night (12). The Cancer Prevention Study-II (CPS-II) found that short sleep duration was associated with an increased risk of fatal prostate cancer, but only during the first 8 years of follow-up (13). Recently, we showed within an Icelandic population that men with problems falling and staying asleep had a significantly higher risk of advanced prostate cancer compared with men without sleep problems (14).

In this prospective study, we address the hypothesis that altered sleep patterns or reduced sleep duration influence risk of prostate

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cancer, with a focus on more aggressive disease in the Health Professionals Follow-up Study (HPFS).

Materials and Methods

Study population

The HPFS included 51,529 male health professionals in the United States ages 40 to 75 in 1986, when the study began. The men have been followed with biennial questionnaires to obtain updated demographic, lifestyle, and disease endpoint information. Usual diet was assessed every 4 years using a validated food frequency questionnaire.

The first sleep duration question was asked in a special survey in 1987, and we limited this analysis to men who completed that questionnaire ($n = 33{,}685$). We further excluded participants with a diagnosis of cancer (except nonmelanoma skin cancer) before 1987. Our final study population included 32,141 men who were followed prospectively for prostate cancer incidence until 2010. The HPFS is approved by the Institutional review board at the Harvard T.H. Chan School of Public Health (Boston, MA).

Assessment of sleep duration and disruption

Men were asked to indicate the "total hours of actual sleep in a typical 24-hour period" on the 1987, 2000, and 2008 questionnaires, and response categories were $\leq$5, 6, 7, 8, 9, 10, and $\geq$11 hours. For our primary analysis, sleep duration was categorized into $\leq$5 hours, 6 hours, 7 hours, 8 hours, 9 hours, and 10+ hours with 8 hours per night as the reference group. For comparison with a recent study (12), we combined the sleep duration categories into $\leq$6 hours and $\geq$9 hours compared with 7 to 8 hours per night. In 1987 and 2000, participants were additionally asked "do you snore?"; response options were: every night, most nights, a few nights a week, occasionally, and almost never. We defined snorers as those who reported snoring every night or most nights.

In 2004, men were asked "how often do you have difficulty falling asleep?," "how often do you have trouble with waking up during the night?," "how often are you troubled by waking up too early and not being able to fall asleep again?," and "how often do you feel really rested when you wake up in the morning?." The three response choices for each question were: most of the time (always), sometimes, and rarely/never. We limited the analysis to men with responses to the sleep disruption questions and excluded participants with a diagnosis of cancer before 2004, leaving 19,639 men we followed prospectively for prostate cancer incidence.

Prostate cancer ascertainment

Cancer and other disease outcomes were initially obtained from self-report by participants or their next of kin on the biennial questionnaires. For each report, medical records and pathology reports are obtained to confirm the diagnosis; the current analysis includes only confirmed cases. Deaths were ascertained from family members and the National Death Index. Cause of death was assigned by an endpoint committee of four study physicians using data included in medical history, medical reports, registry information, and death certificates.

Beginning in 2000, men with prostate cancer were followed with an additional prostate-cancer–specific questionnaire every year to assess disease progression and metastases. For this analysis, we assessed total prostate cancer incidence (excluding stage T1a, cases discovered incidentally during treatment for benign prostatic hypertrophy). In addition, because accumulating evidence suggests that lethal and indolent prostate cancer may have distinct etiologies (15, 16), we assessed advanced, lethal, or nonadvanced cancers separately. Advanced cancers were defined as those that had spread beyond the prostate; they included men with stage T3b, T4, N1, or M1 at diagnosis, men who developed lymph node or distant metastases, and men who died of prostate cancer before the end of follow-up. Lethal cancers were defined as men who died of prostate cancer or who developed distant metastases. Nonadvanced cancers were those stage T1/T2 and N0 and M0 at diagnosis and did not progress to metastases or death over follow-up. We further assessed high grade (Gleason sum 8–10), grade 7, or low grade (Gleason sum 2–6) at diagnosis based on prostatectomy, biopsy pathology reports, or patient self-report.

Statistical analysis

We used Cox proportional hazards regression models to calculate hazard ratios (HRs) and 95% confidence intervals (CI) for the association between sleep duration and our outcomes, using age as the underlying time scale. We calculated person-time for each participant from return of the 1987 questionnaire return until prostate cancer diagnosis, death, or end of follow-up (January 31, 2010), whichever came first. Nutritional information was updated every other questionnaire cycle; all other confounding covariates except race, height, and body mass index (BMI) at age 21 were updated every questionnaire cycle. In multivariable models, we adjusted for race (White, African American, Asian American, other), vigorous physical activity (quintiles, metabolic equivalents-hours/week), smoking (never, former quit > 10 years ago, former quit $\leq$10 years ago, current), diabetes (yes or no), family history of prostate cancer in father or brother (yes or no), multivitamin use (yes or no), energy and alcohol intake (quintiles), history of PSA testing (yes or no, lagged by one period, collected beginning in 1994), β-blocker use (never, past, current), snoring status (snorer or nonsnorer), coffee intake (none, <1cup/day, 1–3 cups/day, 4–5 cups/day, and $\geq$6 cups/day), marital status (never married, married, widowed, divorced), and number of urinations per night (none, 1–2 times/night, 3+ times/night). We also conducted analyses additionally adjusting for height (quartiles), BMI at age 21 (<20, 20–22.5, 22.5-<25, $\geq$25 kg/m^2), lifetime average ejaculation frequency per month (continuous), working status (working, retired, disabled), and current BMI (<21, 21-<23, 23-<25, 25-<27.5, 27.5-<30, $\geq$30 kg/m^2), but results were similar.

We performed complementary secondary analyses. First, we used baseline (1987) sleep duration only, rather than updating over time. To assess possible reverse causation due to symptoms of subclinical disease that affect sleep, we also performed the analysis lagged by 2 and 4 years and restricted to men who reported never urinating at night. To further control for possible confounding by PSA testing, we evaluated the association in the pre-PSA (1987–1993) and PSA eras (1994–2010) separately, and examined a subgroup of men who reported PSA testing in 1994 and 1996, with follow-up from 1994 until 2010.

We then assessed change in sleep duration between 1987 and 2000. For this analysis, person-time was calculated from return of the 2000 questionnaire return until prostate cancer diagnosis, death, or end of follow-up (January 31, 2010), whichever came first. Change in sleep duration was categorized into no change, a decrease or increase of 1 hour, or a decrease or increase of $\geq$2 hours. We used Cox proportional hazards regression models to

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calculate HRs and 95% CIs for the association between change in sleep duration and our outcomes, using no change in duration as the reference group.

Finally, we evaluated the association between prostate cancer and sleep disruption, as defined by how often the participants reported symptoms consistent with difficulty falling asleep, waking up during the night, waking up too early and not being able to fall back asleep, and feeling rested in the morning. Person-time calculation began at the age of return of the 2004 questionnaire. We calculated multivariable HRs and 95% CIs, adjusting for race, height, BMI, vigorous activity level, smoking, diabetes, family history of prostate cancer, β-blocker use, PSA testing, multivitamin use, snoring, marital status, work status, coffee intake, and sleep duration.

All analyses were performed using SAS version 9.3 (SAS Institute, Inc). All *P* values were two-sided, with a value <0.05 considered to be statistically significant.

Results

We confirmed 4,261 total prostate cancer cases among the 32,141 men during 23 years of follow-up. Of these, 563 were lethal, 742 were advanced (563 lethal and 179 additional extraprostatic cancers), and 522 were Gleason grade ≥8. A quarter of the men ($n = 8{,}328$, 26%) reported getting 8 hours of sleep per night at baseline in 1987, and 2% ($n = 701$) reported less than or equal to 5 hours per night. Table 1 shows the characteristics of the study population according to categories of sleep duration in 1987. Men who were short sleepers (≤5 hours) tended to be more physically active, currently working, and or unmarried. Men reporting longer sleep duration (≥10 hours) tended to smoke more, retired, and report urinating at least 2 times per night. Frequency of PSA testing was similar between short sleepers and those sleeping 8 hours per night, however, those sleeping more than 10 hours per night reported less PSA testing. Longer sleep duration was also associated with higher intakes of energy and alcohol.

We did not find a clear pattern of association between sleep duration and incidence of prostate cancer (Table 2). Men who reported sleeping 10+ hours per night had a 30% reduced risk of overall prostate cancer, compared with men who slept 8 hours per night (RR, 0.70; 95% CI, 0.50–0.99). Baseline sleep duration was not associated with our prostate cancer outcomes (≤5 hours vs. 8 hours in 1987; RR, 0.95; 95% CI, 0.54–1.67; 10+ hours vs. 8 hours in 1987; RR, 1.16; 95% CI, 0.50–2.70, for lethal prostate cancer).

We repeated the analysis comparing sleep duration ≤6 hours and ≥9 hours to 7 to 8 hours per night, respectively. We found longer sleep duration was associated with a reduced risk of overall (≥9 hours vs. 7–8 hours; RR, 0.84; 95% CI, 0.74–0.95) and advanced prostate cancer (≥9 hours vs. 7–8 hours; RR, 0.70; 95% CI, 0.52–0.95); however, the association was not significant for lethal or high-grade disease. Similarly, we found men who slept ≤6 hours had a statistically significant reduced risk of overall prostate cancer compared with 7 to 8 hours (RR, 0.90; 95% CI, 0.83–0.97) and advanced (RR, 0.76; 95% CI, 0.63–0.92); however, there was no association with lethal, or high-grade disease. In addition, the association between sleep duration and prostate cancer did not qualitatively differ when stratified by snoring status (data not shown).

To examine whether confounding by PSA testing might influence our results, we evaluated the pre-PSA and PSA eras separately. The association between sleep duration and each of our prostate cancer outcomes was similar in both time periods (data not shown). We also did not find evidence of a consistent association when restricted to a subcohort of men with PSA tests in 1994 and 1996 (≤5 hours vs. 8 hours; RR, 0.86; 95% CI,0.60–1.24; 10+ hours vs. 8 hours; RR, 0.58; 95% CI, 0.31–1.07; for overall

Table 1. Age-standardized characteristics of the HPFS at baseline in 1987 by categories of sleep duration

	Sleep duration categories					
Characteristic	**< = 5 hours (*n* = 701)**	**6 hours (*n* = 6,257)**	**7 hours (*n* = 15,220)**	**8 hours (*n* = 8,328)**	**9 hours (*n* = 1,432)**	**10+ hours (*n* = 203)**
Mean age, y[a]	58	55	55	57	61	64
Mean BMI, kg/m^2	25.8	25.4	25.2	25.3	25.5	25.9
White race, %	93	94	97	97	97	88
Former smoker, quit > 10 years ago, %	28	30	31	30	30	31
Former smoker, quit ≤ 10 years ago, %	11	12	12	13	15	18
Current smoker, %	9	8	8	9	11	15
Married, %	84	89	91	91	90	91
Currently working, %	89	88	87	84	78	75
Vigorous activity (% highest quintile)	18	17	15	14	10	10
Family history of prostate cancer, %	15	13	13	14	14	5
History of diabetes, %	4	3	3	3	4	7
Snoring regularly, %	28	28	27	28	27	33
Current β-blocker users, %	11	10	9	10	13	16
Current multivitamin user, %	44	42	41	40	39	34
Antidepressant user, 1990, %	3	2	2	2	2	7
2+ times urinate at night, 1992, %	21	22	22	24	31	35
PSA test, 1994, %	40	44	43	42	38	30
PSA test, 2006, %	67	70	72	72	70	60
Coffee intake, 3+ cups/day, %	11	11	10	9	10	6
Mean dietary intakes						
Total calories, kcal/day	1907	1917	1952	1976	2012	2004
Alcohol use, g/d	9.7	10.1	10.8	12.4	15.0	18.6
Vitamin E, mg/d	48.2	39.9	36.7	34.1	29.9	32.1

Abbreviations: BMI, body mass index; PSA, prostate-specific antigen.

[a]All variables (except age) are standardized to the age distribution of the cohort at baseline.

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Table 2. RR and 95% confidence interval (95% CI) of prostate cancer according to hours of sleep per day in the HPFS, 1987–2010

	≤5 hours	6 hours	7 hours	8 hours	9 hours	10+ hours
All prostate cancer, no.	99	752	1894	1235	246	35
Age-adjusted RR (95% CI)	0.85 (0.69–1.05)	0.91 (0.83–1.00)	1.03 (0.95–1.10)	Ref.	0.87 (0.76–1.00)	0.68 (0.48–0.95)
Multivariable-adjusted RR (95% CI)	0.88 (0.72–1.09)	0.93 (0.85–1.02)	1.03 (0.96–1.11)	Ref.	0.88 (0.76–1.01)	0.70 (0.50–0.99)
Lethal prostate cancer, no.	18	83	250	170	32	10
Age-adjusted RR (95% CI)	1.27 (0.77–2.08)	0.80 (0.61–1.05)	1.09 (0.89–1.33)	Ref.	0.75 (0.51–1.11)	1.25 (0.64–2.42)
Multivariable-adjusted RR (95% CI)	1.20 (0.72–1.98)	0.81 (0.62–1.06)	1.08 (0.89–1.33)	Ref.	0.75 (0.51–1.11)	1.17 (0.60–2.28)
Advanced prostate cancer, no.	21	110	353	210	38	10
Age-adjusted RR (95% CI)	1.15 (0.73–1.81)	0.84 (0.66–1.06)	1.20 (1.01–1.44)	Ref.	0.75 (0.52–1.06)	1.07 (0.56–2.05)
Multivariable-adjusted RR (95% CI)	1.10 (0.70–1.75)	0.84 (0.66–1.07)	1.21 (1.01–1.44)	Ref.	0.75 (0.53–1.07)	1.04 (0.54–2.00)
Nonadvanced prostate cancer, no.	64	546	1303	857	175	18
Age-adjusted RR (95% CI)	0.78 (0.60—1.01)	0.94 (0.84—1.05)	1.00 (0.92—1.09)	Ref.	0.91 (0.77—1.07)	0.52 (0.32—0.83)
Multivariable-adjusted RR (95% CI)	0.82 (0.64—1.07)	0.97 (0.87—1.08)	1.01 (0.93—1.11)	Ref.	0.91 (0.77—1.08)	0.54 (0.34—0.87)
Grade 8–10 prostate cancer, no.	11	86	245	143	33	4
Age-adjusted RR (95% CI)	0.86 (0.46–1.60)	0.96 (0.73–1.26)	1.23 (0.99–1.51)	Ref.	0.97 (0.66–1.42)	0.63 (0.23–1.72)
Multivariable-adjusted RR (95% CI)	0.90 (0.48–1.68)	1.02 (0.77–1.34)	1.25 (1.01–1.54)	Ref.	0.98 (0.67–1.45)	0.61 (0.22–1.68)
Grade 7 prostate cancer, no.	37	234	600	389	75	10
Age-adjusted RR (95% CI)	0.97 (0.68–1.36)	0.86 (0.73–1.01)	0.99 (0.87–1.13)	Ref.	0.88 (0.68–1.13)	0.70 (0.37–1.33)
Multivariable-adjusted RR (95% CI)	1.01 (0.71–1.42)	0.88 (0.74–1.03)	1.00 (0.88–1.14)	Ref.	0.88 (0.68–1.13)	0.75 (0.40–1.42)
Grade 2–6 prostate cancer, no.	35	344	822	540	100	14
Age-adjusted RR (95% CI)	0.70 (0.49–0.99)	0.95 (0.82–1.08)	0.99 (0.89–1.11)	Ref.	0.85 (0.69–1.06)	0.64 (0.37–1.10)
Multivariable-adjusted RR (95% CI)	0.75 (0.53–1.07)	0.97 (0.85–1.12)	1.01 (0.90–1.13)	Ref.	0.86 (0.70–1.07)	0.68 (0.39–1.17)

NOTE: Multivariable: Adjusted for age, race, vigorous activity level, smoking, diabetes, family history of prostate cancer, snoring status, multivitamin use, energy intake, history of PSA testing, β-blocker use, marital status, coffee intake, alcohol intake, and number of urinations per night. Lethal: N1/M1, bone or organ mets over follow-up or death from prostate cancer. Advanced: T3b/T4/N1/M1 + N1 or M1 or mets to other organs over follow-up or death from prostate cancer.

prostate cancer; ≤5 hours vs. 8 hours; RR, 1.18; 95% CI, 0.40–3.50; 10+ hours vs. 8 hours; RR, 0.92; 95% CI, 0.20–4.10, for lethal prostate cancer). Finally, we did not find evidence of reverse causation as our results were similar when lagged by 2 years and 4 years, and when restricted to men who reported never urinating at night (data not shown).

We then assessed whether change in sleep duration from 1987 to 2000 was associated with risk or progression of prostate cancer (Table 3). Compared with those who reported no change in sleep duration, there was a nonstatistically significant increased risk of lethal disease (RR, 2.08; 95% CI, 0.90–4.81) for those whose sleep duration decreased at least 2 hours, and a reduced risk of lethal disease (RR, 0.34; 95% CI, 0.10–1.11) for an increase in sleep duration at least 2 hours. We did not find an association for men who reported short (≤6 hours) or long (≥9 hours) sleep duration on both questionnaires compared with men who reported consistently normal sleep duration (7–8 hours; data not shown).

Of the 19,639 men with information on sleep disruption from the 2004 questionnaire, 24% ($n = 5{,}095$) reported always having trouble waking during the night, 4% ($n = 835$) difficulty falling asleep, 8% ($n = 1{,}499$) waking up too early, and 6% ($n = 1{,}243$) reported never feeling rested when they wake up. Among these

Table 3. RR and 95% CI of prostate cancer according to change in sleep duration from 1987 to 2000 in the HPFS, 2000–2010

	Decreased by 2+ hours	Decreased by 1 hour	Remained the same	Increased by 1 hour	Increased by 2+ hours
All prostate cancer, no.	36	336	985	468	82
Age-adjusted RR (95% CI)	0.86 (0.62–1.21)	1.12 (0.99–1.27)	Ref.	1.08 (0.97–1.21)	0.87 (0.69–1.09)
Multivariable-adjusted RR (95% CI)	0.89 (0.63–1.25)	1.11 (0.97–1.25)	Ref.	1.06 (0.95–1.19)	0.87 (0.69–1.10)
Lethal prostate cancer, no.	7	12	65	32	3
Age-adjusted RR (95% CI)	2.10 (0.93–4.72)	0.60 (0.32–1.12)	Ref.	1.03 (0.67–1.59)	0.40 (0.13–1.30)
Multivariable-adjusted RR (95% CI)	2.08 (0.90–4.81)	0.56 (0.30–1.05)	Ref.	0.91 (0.58–1.43)	0.34 (0.10–1.11)
Advanced prostate cancer, no.	8	23	104	42	4
Age-adjusted RR (95% CI)	1.52 (0.72–3.18)	0.73 (0.46–1.15)	Ref.	0.90 (0.62–1.29)	0.35 (0.13–0.96)
Multivariable-adjusted RR (95% CI)	1.53 (0.71–3.26)	0.69 (0.44–1.10)	Ref.	0.86 (0.59–1.26)	0.33 (0.12–0.90)
Nonadvanced prostate cancer, no.	27	268	762	367	65
Age-adjusted RR (95% CI)	0.86 (0.58–1.27)	1.16 (1.00–1.33)	Ref.	1.09 (0.96–1.24)	0.91 (0.70–1.18)
Multivariable-adjusted RR (95% CI)	0.90 (0.61–1.32)	1.14 (0.99–1.32)	Ref.	1.07 (0.94–1.21)	0.92 (0.71–1.19)
Grade 8–10 prostate cancer, no.	8	42	121	70	8
Age-adjusted RR (95% CI)	1.42 (0.69–2.94)	1.15 (0.80–1.64)	Ref.	1.21 (0.90–1.63)	0.68 (0.33–1.40)
Multivariable-adjusted RR (95% CI)	1.36 (0.65–2.85)	1.07 (0.75–1.54)	Ref.	1.15 (0.85–1.56)	0.63 (0.30–1.30)
Grade 7 prostate cancer, no.	7	115	360	169	26
Age-adjusted RR (95% CI)	0.44 (0.21–0.94)	1.04 (0.84–1.29)	Ref.	1.07 (0.89–1.29)	0.75 (0.50–1.13)
Multivariable-adjusted RR (95% CI)	0.46 (0.22–0.98)	1.05 (0.85–1.30)	Ref.	1.07 (0.88–1.29)	0.75 (0.50–1.14)
Grade 2–6 prostate cancer, no.	17	152	416	189	36
Age-adjusted RR (95% CI)	1.05 (0.64–1.71)	1.19 (0.99–1.44)	Ref.	1.05 (0.88–1.25)	0.97 (0.68–1.36)
Multivariable-adjusted RR (95% CI)	1.11 (0.68–1.82)	1.17 (0.97–1.42)	Ref.	1.01 (0.84–1.20)	1.00 (0.70–1.41)

NOTE: Multivariable: Adjusted for age, race, vigorous activity level, smoking, diabetes, family history of prostate cancer, snoring status, multivitamin use, energy intake, history of PSA testing, beta-blocker use, marital status, coffee intake, alcohol intake, and number of urinations per night. Lethal: N1/M1, bone or organ mets over follow-up or death from prostate cancer; Advanced: T3b/T4/N1/M1 + N1 or M1 or mets to other organs over follow-up or death from prostate cancer.

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men, there were 930 incident cases of prostate cancer, including 50 lethal cases. We did not find an association between waking up during the night, difficulty falling asleep or waking up too early and risk of any of our prostate cancer outcomes (Table 4). We also did not find an association when these questions were combined into "severe sleep problems" (ref. 14; data not shown). Men who reported never feeling rested when they wake up ($n = 1{,}243$) were less likely to sleep 8+ hours per night, be less physically active, and have a higher BMI; they were more likely to report snoring regularly and more likely to take β-blockers. Men who reported never feeling rested when they wake up had an increased risk of lethal prostate cancer (RR, 3.05; 95% CI, 1.15–8.10) compared with those who reported always feeling rested when they wake up (Table 5). Associations between restfulness were similar, although not significant, for high grade and advanced stage. When we combined sometimes and never feeling rested and compared with most of the time, our results were attenuated and no longer statistically significant (RR, 1.67; 95% CI, 0.88–3.18; Supplementary Table S1).

Discussion

In this prospective cohort study of U.S. health professional men, we found that sleep duration and change in sleep duration was not associated with risk of prostate cancer. While we hypothesized there would be an inverse association between sleep duration and prostate cancer, particularly for advanced disease, we found no evidence of a clear association with more aggressive disease, defined by lethal, advanced, or high-grade cancer. We did find, however, that men who woke up never feeling rested had an increased risk of lethal disease compared with men who reported always feeling rested. We did not find an association between symptoms consistent with difficulty falling asleep, waking up during the night, or waking up too early, and prostate cancer risk or progression.

Few prior studies have evaluated the association between sleep duration and prostate cancer risk. The CPS-II study did not find an association between sleep duration and fatal prostate cancer risk over the entire study period, but they did find an elevated risk in the first 8 years of follow-up for men sleeping 3–5 and 6 hours per night compared with those sleeping 7 hours (13). A Japanese study, with 7 years of follow-up, also found an increased, but not statistically significant, risk of overall prostate cancer for short sleepers ($\leq$6 hours) compared with those sleeping 7–8 hours per night (12). In addition, they found a 64% reduced risk of overall prostate cancer for long sleepers ($\geq$9 hours) compared with those who slept 7 to 8 hours per night (12). When we categorized sleep duration similarly, we found a reduced risk of overall prostate cancer for long sleepers; however, we also found a reduced risk for short sleepers. Similar to our population, the Japanese short sleepers were more likely to be never smokers and longer sleepers were less likely to be employed. Contrary to the Japanese cohort, however, the HPFS short sleepers were more likely to exercise and were less likely to be married. Interestingly, we found short sleepers in HPFS exhibited several "healthy" habits, such as more exercise, less smoking, and consumed fewer calories and less alcohol.

Studies of the association between sleep duration and overall cancer risk have shown conflicting results. In the EPIC-Potsdam cohort, sleep duration of less than 6 hours was associated with an increased risk of overall cancer compared with 7 to 8 hours of

Table 4. RR and 95% CI of prostate cancer according to sleep disruption in the HPFS, 2004–2010

	Waking up during the night, how often			Difficulty falling asleep, how often			Waking up too early, how often		
	Never	Sometimes	Always	Never	Sometimes	Always	Never	Sometimes	Always
All prostate cancer, no.	268	405	257	688	210	32	456	409	65
Age-adjusted RR (95% CI)	Ref.	0.99 (0.84–1.16)	1.06 (0.89–1.27)	Ref.	0.92 (0.79–1.08)	0.85 (0.59–1.22)	Ref.	1.02 (0.89–1.17)	0.95 (0.73–1.24)
Multivariable-adjusted RR (95% CI)	Ref.	0.99 (0.84–1.16)	1.07 (0.89–1.28)	Ref.	0.93 (0.79–1.09)	0.92 (0.64–1.33)	Ref.	1.02 (0.89–1.17)	0.98 (0.75–1.28)
Lethal prostate cancer, no.	12	27	11	32	16	2	26	21	3
Age-adjusted RR (95% CI)	Ref.	1.59 (0.79–3.18)	0.95 (0.41–2.18)	Ref.	1.34 (0.72–2.48)	0.92 (0.22–3.90)	Ref.	0.94 (0.53–1.69)	0.66 (0.20–2.20)
Multivariable-adjusted RR (95% CI)	Ref.	1.70 (0.83–3.51)	1.09 (0.46–2.62)	Ref.	1.40 (0.73–2.70)	1.07 (0.23–4.94)	Ref.	1.02 (0.55–1.89)	0.89 (0.25–3.19)
Advanced prostate cancer, no.	22	34	15	51	18	2	39	28	4
Age-adjusted RR (95% CI)	Ref.	1.01 (0.58–1.74)	0.75 (0.39–1.47)	Ref.	0.95 (0.55–1.65)	0.67 (0.16–2.79)	Ref.	0.83 (0.51–1.36)	0.60 (0.21–1.69)
Multivariable-adjusted RR (95% CI)	Ref.	1.03 (0.59–1.82)	0.82 (0.41–1.64)	Ref.	0.96 (0.54–1.71)	0.80 (0.18–3.47)	Ref.	0.86 (0.52–1.44)	0.69 (0.23–2.04)
Grade 8–10 prostate cancer, no.	28	63	36	92	33	2	61	59	7
Age-adjusted RR (95% CI)	Ref.	1.48 (0.94–2.32)	1.32 (0.80–2.18)	Ref.	1.00 (0.67–1.50)	0.40 (0.10–1.62)	Ref.	1.13 (0.78–1.62)	0.77 (0.35–1.70)
Multivariable-adjusted RR (95% CI)	Ref.	1.47 (0.93–2.33)	1.29 (0.77–2.15)	Ref.	1.00 (0.66–1.52)	0.42 (0.10–1.75)	Ref.	1.15 (0.79–1.66)	0.82 (0.36–1.84)

NOTE: Multivariable: Adjusted for age, sleep duration, race, vigorous activity level, smoking, diabetes, family history of prostate cancer, snoring status, beta blocker use, PSA testing, marital status, coffee intake, multivitamin use, energy intake, alcohol intake, and number of urinations per night. Lethal: N1/M1, bone or organ mets over follow-up or death from prostate cancer. Advanced: T3b/T4/N1/M1 + N1 or M1 or mets to other organs over follow-up or death from prostate cancer.

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Table 5. Association between feeling rested when wake up and prostate cancer in the HPFS, 2004–2010

	Most of the time	Sometimes	Never
All prostate cancer, no.	685	185	60
Age-adjusted RR (95% CI)	Ref.	0.85 (0.72–1.01)	1.08 (0.83–1.42)
Multivariable-adjusted RR (95% CI)	Ref.	0.88 (0.74–1.04)	1.12 (0.85–1.47)
Lethal prostate cancer, no.	33	11	6
Age-adjusted RR (95% CI)	Ref.	1.04 (0.52–2.07)	2.49 (1.01–6.10)
Multivariable-adjusted RR (95% CI)	Ref.	1.27 (0.61–2.63)	3.05 (1.15–8.10)
Advanced prostate cancer, no.	49	15	7
Age-adjusted RR (95% CI)	Ref.	0.92 (0.51–1.66)	1.81 (0.81–4.09)
Multivariable-adjusted RR (95% CI)	Ref.	0.99 (0.54–1.83)	2.08 (0.88–4.88)
Grade 8–10 prostate cancer, no.	95	22	10
Age-adjusted RR (95% CI)	Ref.	0.75 (0.47–1.19)	1.58 (0.81–3.06)
Multivariable-adjusted RR (95% CI)	Ref.	0.74 (0.46–1.19)	1.66 (0.84–3.29)

NOTE: Multivariable: Adjusted for age, sleep duration, race, vigorous activity level, smoking, diabetes, family history of prostate cancer, snoring status, beta blocker use, PSA testing, marital status, coffee intake, multivitamin use, energy intake, alcohol intake, and number of urinations per night. Lethal: N1/M1, bone or organ mets over follow-up or death from prostate cancer. Advanced: T3b/T4/N1/M1 + N1 or M1 or mets to other organs over follow-up or death from prostate cancer.

sleep per day (17). A recent meta-analysis of prospective cohort studies found neither short nor long sleep duration was associated with risk of overall cancer (18). In the HPFS, Zhang and colleagues found a statistically significant increased risk of colorectal cancer for men sleeping ≥9 hours compared with 7 hours, particularly among those who reported snoring regularly (19). Although we found a slight increased risk of overall prostate cancer for snorers compared with nonsnorers, our results for sleep duration and prostate cancer were similar when stratified by snoring status.

There are little epidemiologic data on sleep disruption and prostate cancer risk. Icelandic men who reported sleep disruption, such as problems falling and staying asleep, had a significantly increased risk of advanced prostate cancer, compared with those who reported no sleep problems (14). We did not find an association with problems falling asleep or staying asleep in this cohort. However, our findings for an increased risk of lethal prostate cancer for those who never feel rested when they wake up, while based on small numbers, are broadly in line with the hypothesis that sleep disruption increases risk of more aggressive disease. In our population, 6% of men reported never feeling rested, and they were more likely to report fewer hours of sleep per night. Similarly, a survey from the Centers for Disease Control and Prevention in 2009 showed 7% of U.S. adults more than 65 years old reported feeling they did not get enough sleep at least 14 of 30 days in the past month (1). These findings support the notion that short sleep duration alone may not lead to an increased risk of prostate cancer. If short sleep in itself is associated with an increased risk of prostate cancer, then it is possible that those in our cohort who report short sleep did not experience a sleep deficit. Our findings suggest that disturbances of physiologic processes during sleep rather than duration may play a role in increasing prostate cancer risk. Future studies with additional follow-up and more cases should further investigate the association between sleep disruption and prostate cancer risk.

Light exposure during the night, such as during night shift work, is associated with reduced production and secretion of the nocturnal hormone melatonin (20–22). Melatonin is the biochemical signal of darkness and under normal conditions production peaks at night. Sleep disruption and reduced sleep duration have also been associated with lower melatonin levels, presumably through increased exposure to light at night (23, 24). We did not have information on melatonin levels in this study.

Several strengths of this study include the prospective nature of our study design, complete follow-up for prostate cancer incidence and mortality, large case numbers, and longitudinal questionnaires which allow us to capture change in sleep duration over time. Questionnaires capture rich covariate data to adjust for potential confounding, including PSA testing, and we have cases diagnosed both pre- and post-PSA screening. Our assessment of change in sleep duration and sleep disruption with risk of incident prostate cancer was limited by smaller sample sizes as follow-up started in 2000 and 2004, respectively. There was adequate power to evaluate the association between sleep duration and risk of overall prostate cancer; however, our power was limited for the association between feeling rested and lethal prostate cancer (40%).

A limitation of our study is the reliance on accurate self-reporting of sleep duration and disruption via questionnaires, rather than objective measures. This method may have led to misclassification of our exposure, but it is likely that any misclassification would be nondifferential with respect to the outcome, as sleep duration and disruption information was collected prior to development of prostate cancer. Moreover, when we restricted analyses to men without urinary symptoms, which may be an early indicator of prostate cancer, the results were unchanged. Objective estimation of rest-activity cycles through actigraphy or polysomnography, while not always practical in large epidemiologic studies, would potentially offer more accurate measures of sleep duration and quality. Moderate correlation (0.45–0.57) has been seen between self-reported and objective measures of sleep duration, with one study reporting an overestimation (25) and another an underestimation (26) of self-reported mean sleep duration compared with the objectively measured marker. Finally, we cannot rule out the possibility of unmeasured confounding, although we controlled for several proposed prostate cancer risk factors.

In conclusion, we did not find support for an association between self-reported sleep duration and risk of advanced or lethal prostate cancer in this large cohort of men from the HPFS. Further prospective studies should investigate the interplay between sleep duration and disturbance on risk of prostate cancer.

Disclosure of Potential Conflicts of Interest

C.A. Czeisler has received research support from Philips Respironics, and has an ownership interest in Vanda Pharmaceuticals. C.A. Czeisler has received consulting fees or served as a paid member of scientific advisory boards for Bose Corporation, Merck and Company, Quest Diagnostics, Samsung Electronics, Teva Pharmaceuticals, and Vanda Pharmaceuticals.

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C.A. Czeisler has also served as an expert witness on various legal matters, including Purdue Pharma L.P. and Philips Respironics. No other authors report conflicts of interest.

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The authors assume full responsibility for analyses and interpretation of these data.

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