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Sleep Disruption Among Older Men and Risk of Prostate Cancer

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Abstract

Background—While positive associations have consistently been reported between sleep disruption and breast cancer, less is known about its potential role in prostate cancer.

Methods—Within the prospective AGES-Reykjavik cohort study, we followed 2,102 men recruited in 2002–2006 until the end of 2009. Participants answered questions on sleep disruption. Information on the occurrence of prostate cancer was obtained through record-linkages across the Icelandic Cancer Registry. We used Cox regression models with 95% confidence intervals [CIs] to estimate hazard ratios [HR] of prostate cancer by symptoms of sleep disruption.

Results—During follow-up, 135 men (6.4%) were diagnosed with prostate cancer. Compared to men without sleep disruption, those with problems falling and staying asleep were at significantly increased risk of prostate cancer [HR, 1.7 (95% CI, 1.0–2.9) and 2.1 (95% CI, 1.2–3.7)], respectively, with increasing sleep disruption severity. When restricted to advanced prostate cancer (≥ stage T3 or lethal disease), these associations became even stronger [HRs 2.1 (95% CI, 0.7–6.2) and 3.2 (95% CI, 1.1–9.7)]. The results did not change after excluding from the analyses men who woke up during the night, indicative of nocturia, suggesting limited risk of reverse association.

Conclusions—Our data suggest that certain aspects of sleep disruption may confer an increased risk of prostate cancer and call for additional, larger studies with longer follow-up times.

Impact—Prostate cancer is one of the leading public health concerns in men; if confirmed in future studies the association between sleep disruption and prostate cancer risk may open new avenues for prevention.

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Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

Keywords

prostate cancer; circadian disruption; sleep disruption; cohort study; melatonin; light at night

Introduction

In 2007 the International Agency for Research on Cancer (IARC) designated shift work involving circadian disruption as a probable carcinogen in humans (Group 2A) (1). In addition to extensive animal and *in vitro* studies (2), the ruling was based primarily on data showing that breast cancer risk among women working night shifts was ~50% higher as compared to those who had not worked night shifts (3). While data examining this hypothesis for prostate cancer risk among men are more sparse (4), two Japanese cohort studies and two Canadian case-control studies have suggested an association between shift work and prostate cancer risk (5–8), although a Swedish cohort study reported no association (9).

One of the major behavioral consequences of night shift work is displacement of the sleep-wake cycle, which results in shift workers having difficulty falling asleep and staying asleep when they attempt to sleep during the day (10). Short night-time sleep has been shown to be associated with an increased risk of prostate cancer in non-shift working men (11), suggesting that sleep *per se* may be an important contributing risk factor. Further, current sleep problems seem to be indicative of persistent sleep disruption over time(12). We therefore examined the association between sleep disruption and prostate cancer risk in the population-based AGES-Reykjavik cohort. We hypothesized that men with disruption of sleep would have an increased risk of prostate cancer as compared to men without sleep disruption.

Materials and Methods

Study population and material

The AGES-Reykjavik study included 2,425 men aged 67 to 96 years who were randomly drawn from an established population-based cohort, the Reykjavik study, and recruited in 2002–2006. The AGES-Reykjavik study has been described in detail by Harris *et al.* (13). At study entry all men completed a detailed questionnaire, including the five following questions on sleep: (1) “How often do you take medicines to help you sleep?”; (2) “How often do you experience not getting to sleep within 30 minutes?”; (3) “How often do you wake up during the night having difficulty getting back to sleep?”; (4) How often do you wake up early in the morning having difficulty getting back to sleep?”, and; (5) “How often are you feeling unrested during the day no matter how many hours of sleep you had?”. We excluded Question #5 in our analysis as it did not address sleep behaviour specifically. There were 5 answer categories: “Never or almost never”, “Less than once a week”, “1–2 times per week”, “3–5 times per week”, or “6–7 times per week”. We combined the four sleep questions in various ways to group symptoms consistent with problems falling asleep, problems staying asleep, or both, and the severity of each (Figure 1). Our rationale for the combination of the sleep questions was based on the symptomology of different types of sleep problems. For example, Questions 1 and 2 are indicative of difficulty falling asleep, which might occur in sleep-onset insomnia, whereas Questions 3 and 4 denote problems staying asleep, a common compliant in sleep-maintenance insomnia. The combinations of three of more complaints was an attempt to assess severity of sleep complaints. While it is not possible to confirm a clinical sleep disorder in the current dataset, the combinations are based on logic consistent with known sleep disorders. Those with sleep problems of any

type were classified as having any answer other than “Never or almost never”, which was used for comparison.

Of the 2,425 men in the cohort we excluded 104 men who did not answer the questions on sleep and 215 men who had been diagnosed with prostate cancer before study entry. Thus, none of the participants had been diagnosed with prostate cancer at study entry. Further, 4 men who were censored at diagnosis of other cancer, leaving 2,102 men to form our base population.

Covariates

We collected information on several factors that could potentially confound the association between sleep disruption and prostate cancer. From the questionnaire at study enrollment we obtained information on age at study entry; family history of prostate cancer (father/brother/son); visit to doctor during previous 12 months for any type of illness, injury or health check-up; level of education (elementary school/secondary school/college/university); smoking status (never smoked/ past smoker of at least 100 cigarettes or 20 cigars in lifetime/ current smoker); alcohol use (g/week); and diagnosis of benign prostate disease (yes/no). We obtained information on body mass index (BMI, m/kg^2) from the clinical examination records and presence of diabetes mellitus was based on self-report, a fasting blood glucose of ≥ 126 mg/d, or medication use.

Follow-up and ascertainment of outcome

The men were followed through December 31, 2009 for the occurrence of prostate cancer and all-cause mortality. Using unique identification numbers assigned to all Icelandic citizens, we performed record linkages across: the nationwide Icelandic Cancer Registry (14–16) to obtain information on prostate cancer diagnoses (over 95% are histologically verified) (17), and; the Statistics Iceland for Causes of Death Register (18) to obtain information on prostate cancer-specific death and all-cause mortality. The cancer registry receives infomation on TNM stage of prostate cancer from medical records; the TNM stage was available for only 68% of the cases. We did not have information on Gleason grade. Advanced prostate cancer was defined as anatomic stage T3 or T4 or N1/M1 at diagnosis according to the TNM staging system, i.e. when the cancer has spread through the prostatic capsule, invaded nearby structures, or has spread to lymph nodes or other organs. To obtain a more complete picture of advanced disease, men who died from prostate cancer were also classified as having advanced disease, regardless of the stage at diagnosis; all of the death-specific diagnoses had previously been retreived from the cancer registry (Figure 2).

Statistics

We present the distribution of potential covariates according to categories of sleep disruption. We used Cox regression models to estimate age-adjusted hazard ratios [HRs] with 95% confidence intervals [CIs] for total and advanced incident prostate cancer, as well as added potential covariates in two additional multivariable models. The covariates selected were based on potential confounding effects or factors other than circadian disruption that may be related to sleep and prostate cancer. The second model was further adjusted for family history of prostate cancer, education, visit to a doctor in previous 12 months, diagnosis of benign prostate disease, BMI and diabetes mellitus; the third model additionally controlled for smoking and alcohol consumption. As age- and multivariate-adjusted results were similar and power was limited in the analyses, we present age-adjusted HRs as our main results. We imputed missing values of BMI and alcohol use using the mean. For ordinal variables, we used the missing indicator method for handling missing data by creating a separate category for missing data and a new indicator variable to designate missingness. The category with the most missing data was education with 55 missing values

(2.6% of all men). We used SPSS Software version 19.0 (SPSS Inc., 2010, IBM Chicago, IL, www.spss.com) for all statistical analysis.

To assess potential reverse association bias, whereby undiagnosed prostate cancer might cause sleep disturbance, we performed several sensitivity analyses. First, we repeated our analyses after excluding cases diagnosed within two years after study entry. Second, we excluded men who reported waking up during the night (Question #3) since men with nocturia related to undiagnosed prostate cancer may be more likely to wake up during the night, and hence report sleep disruption. Men reporting taking medication for sleep (Question #1) were also excluded in this sensitivity analysis. Therefore, in this secondary analysis, we limited sleep disruption to difficulties falling asleep (Question #2) and early morning awakening (Question #4).

Ethical approval

The study protocol was approved by the Icelandic Ethical Review Board and the Icelandic Data Protection Authority.

Results

Baseline characteristics

During the mean 5.0 years of follow-up, 135 of 2,102 eligible men (6.4%) were diagnosed with prostate cancer. Information on disease staging was available for 92 men (68%) of whom 16 (17%) had advanced TNM stage. In addition to the 16 men with advanced disease, 10 men who died from prostate cancer but had localized disease or unknown stage at diagnosis were classified as having advanced disease: leaving us with 26 men (19%) with advanced prostate cancer.

The characteristics of the participants are presented in Table 1, according to presence or absence of sleep disruption. Between 5.7 and 20.5 percent of the men were classified with sleep disruption, depending on the type of sleep problem. The comparison group consisted of 755 men (36% of total) who did not report any sleep disturbances for any of the four questions. The mean age of participants at baseline was 76.4 years and mean BMI 26.9 m/kg^2. Men with and without sleep problems were similar with respect to age, education, family history of prostate cancer, smoking status, and BMI but those with sleep disruption were more likely to have visited a doctor in the previous 12 months and to have been diagnosed with diabetes mellitus. The men with problems getting to sleep and staying asleep (see Figure 1 for definitions) were more likely to have benign prostatic disease. Only the men with very severe sleep problems were more likely to consume more alcohol.

Sleep disruption and risk of prostate cancer

Compared to men who did not report any sleep problems, in age-adjusted analyses, those who reported problems falling and staying asleep (Figure 1) were significantly at increased risk of prostate cancer with a hazard ratio of 1.6 (95% CI, 1.0–2.5), 1.7 (95% CI, 1.0–2.9), and 2.1 (95% CI, 1.2–3.7), respectively for increase in severity of problems falling or staying asleep (Table 2). The association did not change materially after adjustment for potential confounding factors. The association was stronger for advanced prostate cancer than for overall prostate cancer for all types of sleep problems, especially for very severe sleep problems (HR, 3.2; 95% CI, 1.1–9.7), when compared to men without sleep problems.

Sensitivity analyses

After excluding men who were diagnosed with prostate cancer within two years from study entry, too few advanced cases remained to conduct the 2-years lagged analyses. However,

the association between sleep disruption and prostate cancer remained after excluding men with potential symptoms of nocturia (men who reported waking up during the night), with an age-adjusted HR of 2.2 (95% CI, 1.3–3.7) for overall prostate cancer (68 cases) and and 3.3 (95% CI, 1.2–9.3) for advanced disease (15 cases).

Discussion

In this prospective cohort study we found that men with sleep disruption were at increased risk of prostate cancer, particularly advanced prostate cancer, when compared to men who did not report any sleep problems.

The association between sleep disruption and prostate cancer was stronger for advanced disease than for overall prostate cancer. This may be a chance finding due to limited number of cases in the analyses for advanced cases. It is also possible that underlying mechanisms of sleep disturbance, such as circadian disruption and reduced melatonin levels, affect prostate cancer progression to a greater extent than prostate cancer initiation (19). Nonetheless, our data support the hypothesis that some aspect related to sleep disruption may confer an increased risk of prostate cancer.

Most epidemiological studies to date on the effect of sleep or circadian rhythm disruption have focused on the impact of shift work on cancer risk. Consistent with the hypotheses for sleep disruption, four studies found an increased risk of prostate cancer among night shift workers (5–8), although one did not (9).

To our knowledge the role of sleep disruption *per se*, separate from the impact of shift work, has only been assessed in one study on prostate cancer risk. Kakizaki *et al.* reported that men who slept for 6 hours or less were at non-significant increased risk of prostate cancer (HR, 1.34; 95% CI, 0.83–2.17) and those who slept for 9 hours or more at lower risk (HR, 0.48; 95% CI, 0.29–0.79) when compared to men who slept for 7–8 hours (11). Our data are consistent with this finding and suggest that impairment of sleep, either through reduced sleep duration or greater sleep disruption, increases the risk of prostate cancer. Limited data are indeed available on the direct role of melatonin on prostate cancer risk. Shorter sleep duration and greater sleep disruption may be viewed as a proxy for increased melatonin suppression, given that individuals are likely to be exposed to light when not asleep at night. Bartsch *et al.* have reported that men with prostate cancer have lower melatonin levels when compared to men with benign prostate hyperplasia (BPH) and young men (20, 21). Interestingly blind men, who may also have reduced exposure to light, have lower prostate cancer incidence when compared to the general population (22, 23), similar to lower breast cancer risk in blind compared to sighted women (24). Further work to establish causality is required, however.

Sleep disruption induced by shift work induces a number of physiological changes that have been proposed as possible mechanisms underlying the observed increase in cancer risk. The endogenous circadian pacemaker, located in the suprachiasmatic nuclei (SCN) of the hypothalamus, is a major determinant of the timing, duration and structure of sleep (25) such that sleep propensity and consolidation are maximized when sleep occurs during the night. Further, disruption of the molecular components of circadian clocks, particularly expression of the *Period2* gene (*Per2*) is thought to have tumor-suppressive properties (26, 27). Notably, expression levels of *Per2* were significantly lower in all proliferative prostate diseases compared with normal prostate tissue (28). Also, a major consequence of shift work is light-induced inhibition of pineal melatonin secretion, which is acutely suppressed by the electric light required to enable night-shift work. Melatonin is produced only during the biological night and is the biochemical correlate of darkness; light exposure during the night

inhibits melatonin production (29). The presence of melatonin has been shown to inhibit or slow down tumor growth both *in vitro* and *in vivo*, including prostate cancer (30–35), whereas suppression of melatonin via constant light exposure or pinealectomy increases tumor growth in a dose-dependent manner in experimental models (36). Melatonin is also a potent free radical scavenger (37) and may facilitate reduction of oxidative stress implicated in prostate cancer progression (19).

The prospective design, complete follow-up and detailed information on a variety of potential confounders, constitute important strengths of our study. Nevertheless, several potential limitations should be considered. First, our definition of sleep disruption rests on the four questions included in the AGES entry questionnaire on problem falling asleep, staying asleep, early morning awakening (with difficulty falling back asleep) and use of sleep medication. These questions have not been validated against objective measures of sleep disruption. Morover, we have no information on the timing or duration of sleep, which can be important additonal factors when assessing sleep disruption. Second, we had limited clinical information at diagnosis, with stage information for only two-thirds of the cases. Our analyses showed that the association was particularly strong for advanced disease, but the small number of cases with advanced disease limited our statistical power and yielded wide confidence intervals. Third, despite inclusion of a wide variety of potential confounding factors in our models, we cannot exclude the possiblity that residual confounding unknown to us may account for these associations. Lastly, and importantly, observation time in our study was short (5 years) and the men only provided information on sleep problems during the prior few months, whereas the time from prostate cancer onset to clinical detection has been estimated to be a decade or more (38, 39). If the carcinogenic effect of sleep disruption on tumour progression was mediated through melatonin suppression, laboratory studies suggest that the impact of reduced melatonin could be quite rapid (36), although there is no parallel clinical evidence in humans. It is also plausible that reports about current sleep problems are indicative of persistent sleep disruption over time (12) that may underlie a longer-term disease process. Nevertheless, the short observation time in our study may raise concerns of reverse association bias; for example, that men with undiagnosed prostate cancer may have symptoms such as nocturia before diagnosis that consequently lead to sleep disturbances. Men with urinary symptoms (hence sleep disruption) related to prostate cancer, especially advanced cancer, often suffer from nocturia (waking up during the night). To address this concern, we conducted sensitivity analyses in which we exluded men with symptoms of sleep disturbance that might be indicative of nocturia. Notably, the point estimates remained essentially unchanged, to some extent alleviating these concerns, although the number of cases were few.

These data lend support to the hypothesis that sleep disruption may affect prostate carcinogenesis. Sleep disruption and light-induced melatonin suppression represent plausible biological explanations underlying cancer risk, although prospective studies are needed to substantiate their respective roles. Large cohort studies entailing longer observation times, allowing for closer investigatons of the temporality of the association between sleep disruption and prostate cancer, will be needed to address this hypothesis further.

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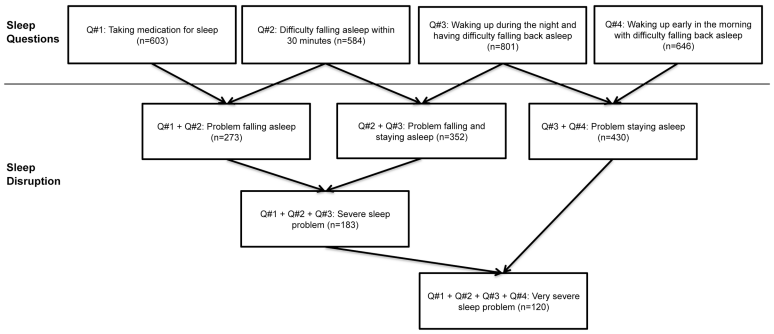

Figure 1.

Categorization of sleep disruption according to combination of four questions (Q) on sleep from the AGES-Reykjavik Cohort.

n=number of participants who have specified sleep problem (any other answer than “never or almost never”)

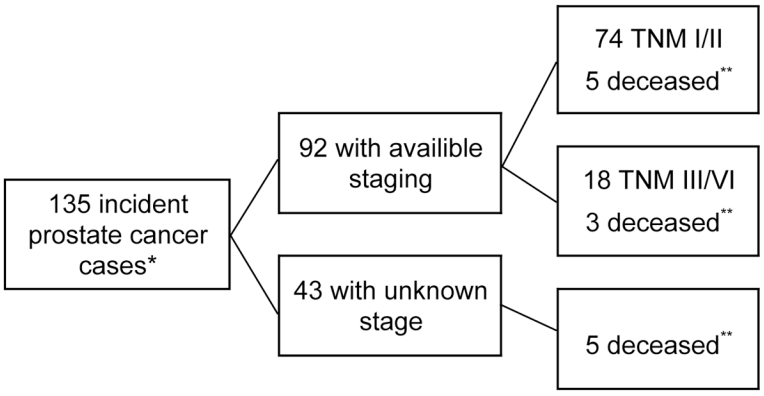

Figure 2.
Information on TNM staging and causes of death due to prostate cancer.
*All of the incident cases were identified through record linkage with the Icelandic Cancer Registry.
**Information on cause-specific death was obtained through record linkage with the Statistics Iceland.

Table 1

Characteristics of the Male Participants in the AGES-Reykjavik Cohort by Sleep Disruption (four sleep questions), Iceland, 2002–2009.

Category	Characteristic	Total (N= 2,102) No. (%) or Mean (SD)	Problem Falling Asleep[a] No. (%) or Mean (SD)	Problem Staying Asleep[a] No. (%) or Mean (SD)	Problem Falling and Staying Asleep[a] No. (%) or Mean (SD)	Severe Sleep Problem[a] No. (%) or Mean (SD)	Very Severe Sleep Problem[a] No. (%) or Mean (SD)	No Sleep Problem[b] (n=755) No. (%) or Mean (SD)
Prevalence of sleep problem		662 (31.5)	273 (13.0)	430 (20.5)	352 (16.7)	183 (8.7)	120 (5.7)	0
Number of cases		135	27	34	29	21	16	49
Age[c], years		76.4 (5.3)	77.3 (5.1)	76.8 (5.3)	76.9 (5.4)	77.0 (5.0)	77.2 (5.1)	76.0 (5.2)
Education	Elementary	339 (16.5)	44 (16.6)	70 (16.9)	60 (17.4)	29 (16.3)	18 (15.7)	125 (16.9)
	Secondary	1091 (53.2)	146 (55.1)	218 (52.5)	191 (55.4)	97 (54.5)	59 (51.3)	391 (52.8)
	College	255 (12.4)	33 (12.5)	47 (11.3)	36 (10.4)	21 (11.8)	15 (13.0)	101 (13.6)
	University	367 (17.9)	42 (15.8)	80 (19.3)	58 (16.8)	31 (17.4)	23 (20.0)	123 (16.6)
Family history of prostate cancer		194 (9.2)	25 (9.2)	33 (7.7)	33 (9.4)	16 (8.7)	6 (5.0)	70 (9.3)
Visit to doctor in previous 12 months		1714 (81.7)	237 (86.8)	375 (87.2)	302 (85.8)	159 (86.9)	105 (87.5)	569 (75.4)
Diagnosed as diabetic		365 (15.7)	57 (20.9)	76 (17.7)	68 (19.3)	39 (21.3)	21 (17.5)	115 (15.2)
Smoking status	Never	581 (28.2)	61 (23.0)	108 (26.0)	84 (24.3)	40 (22.5)	33 (28.7)	239 (32.3)
	Previously	1234 (60.0)	177 (66.8)	268 (64.4)	218 (63.2)	121 (68.0)	75 (65.2)	428 (57.8)
	Current	242 (11.8)	27 (10.2)	40 (9.6)	43 (12.5)	17 (9.6)	7 (6.1)	74 (10.0)
Benign prostate disease		723 (34.4)	116 (42.5)	157 (36.5)	133 (37.8)	77 (42.1)	47 (39.2)	231 (30.6)
Alcohol[c], g/week		22.4 (42.7)	24.2 (45.8)	24.3 (44.7)	24.7 (48.6)	26.5 (51.3)	29.4 (56.6)	20.8 (42.6)
Body mass index[c], m/kg^2		26.9 (3.8)	27.0 (3.8)	26.8 (3.8)	27.0 (3.8)	27.0 (3.6)	26.8 (3.6)	27.0 (3.9)

[a] Less than once per week up to 6 times per week;

[b] Never or almost never;

[c] Mean (Standard deviation)

Table 2

Estimated Risk of Prostate Cancer by Sleep Disruption[a] among Males in the AGES-Reykjavik Cohort.

Category	Characteristic	No. of Cases	Person years	Hazard Ratio[b] (95% CI)	Hazard Ratio[c] (95% CI)	Hazard Ratio[d] (95% CI)
Problem falling asleep	Total prostate cancer					
Q#1 + Q#2	No sleep disruption	49	3809	Ref	Ref	Ref
	Sleep disruption	27	1385	1.6 (1.0–2.5)	1.6 (1.0–2.6)	1.6 (1.0–2.6)
	Advanced disease					
	No sleep disruption	9	3809	Ref	Ref	Ref
	Sleep disruption	6	1385	1.7 (0.6–4.8)	1.9 (0.7–5.4)	1.8 (0.6–5.3)
Problem staying asleep	Total prostate cancer					
Q#3 + Q#4	No sleep disruption	49	3809	Ref	Ref	Ref
	Sleep disruption	34	2211	1.2 (0.8–1.9)	1.2 (0.8–1.9)	1.2 (0.8–1.9)
	Advanced disease					
	No sleep disruption	9	3809	Ref	Ref	Ref
	Sleep disruption	9	2211	1.6 (0.6–4.1)	1.7 (0.7–4.4)	1.7 (0.7–4.3)
Problem falling and staying asleep	Total prostate cancer					
Q#2 + Q#3	No sleep disruption	49	3809	Ref	Ref	Ref
	Sleep disruption	29	1807	1.3 (0.8–2.0)	1.3 (0.8–2.0)	1.3 (0.8–2.0)
	Advanced disease					
	No sleep disruption	9	3809	Ref	Ref	Ref
	Sleep disruption	8	1807	1.7 (0.6–4.4)	1.8 (0.7–4.8)	1.7 (0.7–4.6)
Severe sleep problem	Total prostate cancer					
Q#1 + Q#2 + Q#3	No sleep disruption	49	3809	Ref	Ref	Ref
	Sleep disruption	21	952	1.7 (1.0–2.9)	1.7 (1.0–2.9)	1.7 (1.0–2.9)
	Advanced disease					
	No sleep disruption	9	3809	Ref	Ref	Ref
	Sleep disruption	5	952	2.1 (0.7–6.2)	2.2 (0.7–6.8)	2.2 (0.7–6.9)
Very severe sleep problem	Total prostate cancer					
Q#1 + Q#2 + Q#3 + Q#4	No sleep disruption	49	3809	Ref	Ref	Ref
	Sleep disruption	16	606	2.1 (1.2–3.7)	2.1 (1.2–3.8)	2.2 (1.2–3.9)
	Advanced disease					

Category	Characteristic	No. of Cases	Person years	Hazard Ratio[b] (95% CI)	Hazard Ratio[c] (95% CI)	Hazard Ratio[d] (95% CI)
	No sleep disruption	9	3809	Ref	Ref	Ref
	Sleep disruption	5	606	3.2 (1.1–9.7)	3.5 (1.1–10.7)	3.8 (1.2–11.7)

[a] Four questions on sleep (Q#1, Q#2, Q#3, and Q#4) combined in different categories. See figure 1 for the definitions.

[b] Age-adjusted HR

[c] Additional adjustment for family history of prostate cancer, benign prostate disease, education, visit to a doctor in previous 12 months, BMI, and diabetes mellitus

[d] Additional adjustment for smoking and alcohol