Self-reported sleep disturbances and prostate cancer morbidity and mortality in Swedish men: A longitudinal study over 40 years

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Summary
The present study, with an observational period of about 40 years, examined the association between self-reported sleep disturbances (i.e. problems with falling and staying asleep; use of hypnotics) and prostate cancer morbidity and mortality in initially 2322 men (all 50 years old at baseline). Self-reported sleep disturbances and established risk factors (e.g. age, lower urinary tract symptoms, smoking and family history of cancer) were measured at ages 50 and 70 years. Information about prostate cancer diagnosis and deaths as a result of prostate cancer was available from the National Cancer Registry and the Swedish Civil Registry of Morbidity. During the observational period, 263 participants developed prostate cancer (11% of the total cohort); 146 of them died as a result of prostate cancer. There was no association between sleep disturbances and prostate cancer morbidity or mortality (hazard ratio 1.09, 95% confidence interval (CI) 0.79, 1.52, and hazard ratio 1.21, 95% CI 0.77, 1.91, respectively). Similar findings were observed when examining associations between single sleep disturbance parameters and prostate cancer morbidity and mortality. Our study does not provide evidence that reports of sleep disturbances increase the risk of prostate cancer morbidity or mortality in middle to older-aged men. Therefore, assessing subjective sleep problems may not meaningfully help to identify men at risk of developing prostate cancer or dying of this devastating condition.

KEYWORDS
longitudinal study, prostate cancer morbidity, prostate cancer mortality, sleep disturbances

1 | INTRODUCTION

According to a US survey performed between 2002 and 2012, approximately 15% of American men aged ≥18 years suffer from symptoms of insomnia, including problems with falling and staying asleep (Ford, Cunningham, Giles, & Croft, 2015). Moreover, about 3.1% of American men aged 20+ regularly use prescription sleep aids (Chong, Fryer, & Gu, 2013). Alarmingly, chronic sleep disturbances have been shown to increase the risks of several major causes of death in men, including prostate cancer. For instance, in a cohort of 2,102 Icelandic men (aged 67–96 years), it was observed that compared with men without reports of sleep disruption, those reporting difficulties initiating and maintaining sleep had a 70% higher risk of prostate cancer during the mean 5.0 years of follow-up (Sigurdardottir et al., 2013). Supporting a role of poor sleep in carcinogenesis, a recent study in mice showed that chronically fragmented sleep leads to accelerated tumor growth (Hakim et al., 2014). However, findings from other cohorts did not show an association between reports of...
sleep disturbances or insufficient sleep duration and the risk of prostate cancer in men (Dickerman et al., 2016; Markt et al., 2015, 2016). With these inconsistent results in mind, the present study sought to investigate in initially middle-aged men (50 years at baseline) whether self-reported sleep disturbances and use of hypnotics would increase the risk of incident and fatal prostate cancer during an observational period of more than 40 years (1970–2013). It is noteworthy that our study is the first to shed light on this putative association over such a long observational period. Prostate cancer, in general, is a slow growing cancer. Hence, results of the present study may further expand our understanding regarding the impact of sleep disturbances and use of hypnotics on prostate cancer development.

2 | MATERIALS AND METHODS

2.1 | Population

Variables for the present analysis were taken from the Uppsala longitudinal study of adult men (ULSAM; http://www.pubcare.uu.se/ulsam/). The main objective of ULSAM was to identify metabolic risk factors for cardiovascular disease in middle-aged men. A total of 2,322 men living in Uppsala, Sweden (82% of those invited), participated in the baseline investigation at age 50 in 1970. Participants attended several consecutive follow-up investigations. For the present analysis, data from the baseline and age-70 investigations were utilized, as reports on sleep disturbances (effect variable) were only collected at these time-points. All participants gave written informed consent and the study was approved by the regional ethical review board in Uppsala.

2.2 | Sleep disturbance variables

Three ‘yes’ or ‘no’ questions related to sleep disturbances were asked at the examination at ages 50 and 70, including: (a) Do you have difficulties falling asleep at night? (b) Do you often wake up in early hours, unable to get back to sleep? (c) Do you take sleeping pills more than three times per week? Having sleep disturbance at each time-point was defined as answering ‘yes’ to a minimum of one of the three questions.

2.3 | Prostate cancer

The primary endpoints were the diagnosis of prostate cancer and whether prostate cancer was the primary cause of death. Information about prostate cancer diagnosis and mortality was available from the National Cancer Registry and the Swedish Civil Registry of Morbidity until 31 December 2013. No participant had been diagnosed with prostate cancer at baseline.

2.4 | Covariates

Covariates, including presence of smoking (categorical), presence of diabetes (defined as fasting blood glucose ≥ 6.1 mM/L and/or use of oral hypoglycaemic agents or insulin; categorical), level of physical activity during leisure time (‘Do you do any active sport or heavy gardening for at least 3 hr every week?’; categorical), body mass index (BMI), and exact age at investigation, were collected from the investigations at age 50 and 70 years.

Family history of cancer in ULSAM was assessed by three yes/no questions at both the age-50 and age-70 investigations (Did your father die of cancer? Did your mother die of cancer? Did any of your siblings die of cancer?). Answering ‘yes’ to a minimum of one of the three questions was defined as having a relative who died of cancer. The National Cancer Registry and the Swedish Civil Registry of Morbidity were also used to adjust our statistical analysis for cancers other than prostate cancer (e.g. lung cancer).

At ages 50 and 70, the following two yes/no questions were asked related to lower urinary tract symptoms (LUTS): Do you have difficulty in passing water? Has the flow of urine become thin and weak? Answering ‘yes’ to a minimum of one of these questions was defined as having LUTS.

2.5 | Statistical analysis

Cox regression analysis was used to investigate the association between sleep disturbances and risk of prostate cancer. If available, the analysis used time-updated exposure and covariate information for each individual. Otherwise, individual exposure and covariate information from the baseline investigation was utilized (for a detailed description see Table 1). Time at risk of morbidity was calculated from the exact age at the age-50 investigation to the age of prostate cancer diagnosis or death, or exact age at last follow-up (31 December 2013), whichever came first. Time at risk of mortality was calculated from the exact age at the age-50 investigation to the age of death, or exact age at last follow-up, whichever came first. Proportional hazards assumptions were confirmed using graphical evaluation. Overall, a two-sided p value of less than 0.05 was regarded as statistically significant. Analyses were performed with SPSS 22.0 (SPSS, Inc., Chicago, IL, USA).

3 | RESULTS

Cohort characteristics are summarized in Table 1. The investigated cohort had a total of 67,119 years at risk. Sleep disturbances were reported by approximately 21% of participants at age 50 and 24% at age 70. During the observation period, 263 participants developed prostate cancer (11% of the total cohort), among whom 146 had prostate cancer as their primary cause of death.

Time-updated self-reported sleep disturbances did not increase the risk of morbidity or mortality from prostate cancer (Table 2). Similar findings were observed when examining associations between individual sleep disturbance parameters (i.e. problems falling asleep, problems staying asleep and use of hypnotics) and morbidity or mortality from prostate cancer (Table 2). Finally, separate Cox regression analyses, performed either in the group with time-
updated information on covariates or those who only had full data on covariates from the age-50 investigation, confirmed the null results of the above-mentioned main analyses (i.e. including both groups) ($p \geq 0.10$ for all subgroup analyses).

**TABLE 1** Characteristics of men with and without sleep disturbances

|                                             | Sleep disturbances | No sleep disturbance |
|---------------------------------------------|--------------------|----------------------|
| Those who reported sleep data only at age-50 investigation |                    |                      |
| No. of participants                         | 267                | 905                  |
| Age (years), mean (SD)                      | 49.6 (0.6)         | 49.7 (0.6)           |
| BMI (kg/m²), mean (SD)                      | 25.1 (3.6)         | 25.3 (3.4)           |
| Smoking (no/yes)                            | 95/172             | 399/506              |
| Diabetes (no/yes)                           | 259/8              | 886/19               |
| LUTS (no/yes/unknown)                       | 237/30/0           | 857/40/8             |
| Leisure time PA $\geq$3 hr/week (no/yes/unknown) | 151/101/15         | 466/394/45           |
| Relatives died of cancer (no/yes)           | 200/67             | 674/231              |
| No. of cancers other than prostate cancer   | 78                 | 271                  |
| No. of prostate cancer events               | 22                 | 78                   |
| Age (years) at prostate cancer diagnosis, mean (SD) | 67.3 (5.4)         | 71.7 (7.3)           |
| No. of deaths due to prostate cancer        | 11                 | 51                   |
| Age (years) at death due to prostate cancer, mean (SD) | 72.7 (9.7)         | 76.1 (9.3)           |
| Those who reported sleep data at both the age-50 and age-70 investigations |                    |                      |
| Age-50 investigation                        |                    |                      |
| No. of participants                         | 221                | 929                  |
| Age (years), mean (SD)                      | 49.6 (0.6)         | 49.6 (0.6)           |
| BMI (kg/m²), mean (SD)                      | 24.7 (2.6)         | 24.8 (3.0)           |
| Smoking (no/yes)                            | 120/101            | 523/406              |
| Diabetes (no/yes)                           | 219/2              | 924/5                |
| LUTS (no/yes/unknown)                       | 202/16/3           | 873/52/4             |
| Leisure time PA $\geq$3 hr/week (no/yes/unknown) | 112/99/10          | 398/484/47           |
| Relatives died of cancer (no/yes)           | 165/56             | 701/228              |
| No. of cancers other than prostate cancer   | 10                 | 38                   |
| No. of prostate cancer events               | 6                  | 21                   |
| Age (years) at prostate cancer diagnosis, mean (SD) | 67.4 (1.6)         | 67.4 (2.9)           |
| Age-70 investigation                        |                    |                      |
| No. of participants                         | 271$^a$            | 879$^a$              |
| Age (years), mean (SD)                      | 71.0 (0.6)         | 71.0 (0.6)           |
| BMI (kg/m²), mean (SD)                      | 26.7 (3.9)         | 26.1 (3.2)           |
| Smoking (no/yes/unknown)                    | 206/54/11          | 686/176/17           |
| Diabetes (no/yes)                           | 226/45             | 762/117              |
| LUTS (no/yes/unknown)                       | 144/103/24         | 598/224/57           |
| Leisure time PA $\geq$3 hr/week (no/yes/unknown) | 119/144/8          | 316/544/19           |
| Relatives died of cancer (no/yes/unknown)   | 132/127/12         | 480/350/49           |
| No. of cancers other than prostate cancer   | 68                 | 203                  |
| No. of prostate cancer events               | 23                 | 113                  |
| Age (years) at prostate cancer diagnosis, mean (SD)$^b$ | 75.9 (3.7)         | 79.0 (4.9)           |
| No. of deaths due to prostate cancer        | 10                 | 74                   |
| Age (years) at death due to prostate cancer, mean (SD) | 82.8 (5.4)         | 82.9 (4.9)           |

Notes: BMI, body mass index; LUTS, lower urinary tract symptoms; PA, physical activity; SD, standard deviation. $^a$Including those who developed prostate cancer prior to the age-70 investigation. $^b$New events after age-70 investigation.

Our findings suggest that self-reported insomnia symptoms and use of hypnotics in middle-aged men do not identify those who later in
TABLE 2  Risk of prostate cancer diagnosis and mortality in relation to self-reported sleep disturbances

|                     | Model 1 Hazard ratio for prostate cancer (95% CI) | Model 2 Hazard ratio for prostate cancer (95% CI) |
|---------------------|--------------------------------------------------|--------------------------------------------------|
| Prostate cancer diagnosis |                                                 |                                                 |
| Any sleep disturbance           | 1.16 (0.85, 1.58)                              | 1.09 (0.79, 1.52)              |
| Difficulty initiating sleep     | 1.19 (0.79, 1.78)                              | 1.19 (0.77, 1.83)              |
| Early morning awakenings        | 1.13 (0.79, 1.61)                              | 1.07 (0.73, 1.56)              |
| Use of hypnotic                | 1.55 (0.69, 3.49)                              | 1.62 (0.67, 3.94)              |
| Prostate cancer mortality      |                                                 |                                                 |
| Any sleep disturbance           | 1.23 (0.80, 1.90)                              | 1.21 (0.77, 1.91)              |
| Difficulty initiating sleep     | 1.24 (0.70, 2.20)                              | 1.27 (0.70, 2.30)              |
| Early morning awakenings        | 1.07 (0.66, 1.72)                              | 1.06 (0.64, 1.76)              |
| Use of hypnotic                | 1.22 (0.45, 3.29)                              | 1.49 (0.47, 4.70)              |

Note: Model 1, adjusted for age; Model 2, adjusted for age, body mass index, diabetes, smoking, level of leisure-time physical activity, other cancer diagnoses, lower urinary tract symptoms, and deaths due to cancer in relatives.

life develop or even die of prostate cancer. These findings are in line with some, but not all, previous observational studies (Dickerman et al., 2016; Gapstur et al., 2014; Markt et al., 2015, 2016). For instance, a study involving 3,241 men followed over 23 years found no association between reports of waking up during the night, difficulty falling asleep or waking up too early and risk of any prostate cancer outcomes (e.g. lethal prostate cancer and different grades of prostate cancer) (Markt et al., 2016). In a separate study, no connection between sleep duration and fatal prostate cancer has been demonstrated by a study involving 305,057 employed men, aged ≥29 years who were cancer free at baseline (observational period, ≥28 years) (Gapstur et al., 2014). On the other hand, by utilizing data from the National Health Insurance system of Taiwan (n = 2,000,000), it has been shown that the risk of prostate cancer morbidity is about 3.7-fold higher in patients with obstructive sleep apnea (OSA) than patients without OSA (Fang, Miao, Chen, Sithole, & Chung, 2015). Moreover, reported sleep duration of ≥9 hr/day has been linked with a lower risk of prostate cancer in a cohort of 22,320 Japanese men (Kakizaki et al., 2008). However, sleep duration and OSA were not measured in the present study.

When interpreting our results, several limitations must be kept in mind. First, our analysis was based on a relatively small population. Second, chronic night-shift work exposure, which has been proposed to accelerate prostate carcinogenesis (Behrens et al., 2017), was not measured. Third, our sleep variables were based on self-reports. Finally, nocturia, which occurs at a higher frequency in prostate cancer (Gourova, van de Beek, Spigt, Nieman, & van Kerrebroeck, 2006; Tikkinen et al., 2009) and therefore may contribute to poor sleep quality (Asplund, 2002; Rembratt, Norgaard, & Andersson, 2003), was not measured.

Notwithstanding the above-mentioned limitations, a major strength of our study is the long observational period. Studies utilizing objectively measured sleep quality (e.g. actigraphy and polysomnography) are needed to fully disentangle the connection between sleep disturbances and prostate cancer in men.

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CONFLICT OF INTEREST

No conflicts of interest declared.

AUTHOR CONTRIBUTIONS

XT and CB conceived the study. XT, JC, LAF and CB analyzed data. All authors drafted the article. All authors approved the final version for submission.

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