Work Schedule, Sleep Duration, Insomnia, and Risk of Fatal Prostate Cancer

Susan M. Gapstur, PhD, W. Ryan Diver, MSPH, Victoria L. Stevens, PhD, Brian D. Carter, MPH, Lauren R. Teras, PhD, Eric J. Jacobs, PhD

Background: Studies of breast cancer in women and laboratory studies provide evidence that shift work involving circadian rhythm disruption is a probable human carcinogen. However, evidence linking shift work and other circadian disruption factors to prostate cancer risk is limited.

Purpose: To examine associations of work schedule (i.e., rotating shift work, fixed night and fixed afternoon/evening shift work); sleep duration; and insomnia frequency with prostate cancer mortality.

Methods: The Cancer Prevention Study–II is a large prospective cohort study of U.S. adults. Work schedule, sleep duration, insomnia frequency, and other information was self-reported in 1982. Among 305,057 employed men, aged ≥29 years who were cancer free at baseline, there were 4974 prostate cancer deaths during follow-up through 2010. In 2013, multivariable-adjusted relative risks (RRs) and 95% CIs were computed using Cox proportional hazards regression.

Results: Work schedule and insomnia frequency were not associated with risk of fatal prostate cancer. Short sleep duration was associated with higher risk of prostate cancer during the first 8 years of follow-up, compared to 7 hours/night, the RRs (95% CIs) for 3–5 and 6 hours/night were 1.64 (1.06, 2.54), and 1.28 (0.98, 1.67), respectively. There was no association between sleep duration and fatal prostate cancer during later follow-up.

Conclusions: These results do not support associations of work schedule or insomnia frequency with prostate cancer mortality. The association between short sleep duration and higher risk of fatal prostate cancer only during the first 8 years of follow-up suggests that short sleep duration could affect later stages of prostate carcinogenesis.

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Introduction

Shift work is a method of organizing work schedules that includes hours other than fixed daytime hours and often results in exposure to light at night and circadian rhythm disruption. An expert panel organized by the International Agency for Research on Cancer (IARC) in 2007 concluded that "shiftwork that involves circadian disruption is probably carcinogenic to humans."[1] This conclusion was based on studies of female night shift workers and flight attendants employed at least 10 years showing increased risk of breast cancer, and on animal studies supporting a carcinogenic effect for light exposure during the daily dark period.

The IARC panel also noted that "evidence related to the role of circadian rhythm disruption in causing prostate cancer is weak."[1] Recently, Sigurdardottir et al.[2] reviewed the epidemiologic evidence on circadian disruption and prostate cancer risk. Although most early studies of male airline pilots were suggestive of significant positive trends between number of long-haul flights and prostate cancer incidence, results of other studies comparing prostate cancer incidence rates in men employed in rotating or night shift work to men in the general population or between occupations where at least 40% of employees work rotating shifts and occupations where less than 30% work rotating shifts were inconsistent.

From the Epidemiology Research Program, American Cancer Society, Atlanta, Georgia

Address correspondence to: Susan M. Gapstur, PhD, Epidemiology Research Program, American Cancer Society, National Home Office, 250 Williams Street, NW, Atlanta GA 30303-1002. E-mail: susan.gapstur@cancer.org.

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Case–control[3,4] and prospective cohort studies[5] showed significant higher risks of prostate cancer associated with rotating shift work and night shift work. The only study of sleep duration in relation to risk showed an inverse association.[6] Further, in an ecologic analysis of associations of light at night exposure (as estimated using GIS methods from satellite images of nighttime illumination) with age-standardized colorectal, lung, and prostate cancer incidence rates across 164 countries, only the association with prostate cancer incidence was significant.[7] A causal association between shift work and circadian rhythm disruption and prostate cancer risk is biologically plausible and could be due, in part, to suppression of melatonin, a hormone secreted by the pineal gland that reduces the growth rate of prostate cancer in vivo and in vitro.[8]

Although results of epidemiologic studies of circadian disruption–related factors and prostate cancer risk are intriguing, some limitations should be considered. First, studies of shift work comparing men in specific occupations to the general population should be interpreted cautiously because of higher screening rates in employed men. Second, studies of total prostate cancer might be less relevant because many prostate cancers detected through screening would never have become clinically apparent. Third, in the only published prospective cohort study of rotating shift work and prostate cancer risk,[5] there were only 31 total cases, and therefore results could be due to chance. Additionally, the IARC panel noted the need for further research on factors that affect circadian rhythm such as sleep duration and quality.[9]

The Cancer Prevention Study–II (CPS–II) is a large, long-term prospective cohort study of cancer mortality in which self-reported information on work schedule, sleep duration, and frequency of insomnia was collected in 1982 and has been followed for cause-specific mortality through 2010.[10] Using data collected from more than 305,000 employed men in this cohort, in 2013 associations of work schedule, sleep duration and insomnia frequency with prostate cancer mortality were examined. Sensitivity analyses examining associations stratified on follow-up period, and excluding men who reported frequent or painful urination, were conducted. Corroboration of associations of circadian rhythm–related factors with fatal prostate cancer risk in this cohort would strengthen the evidence that circadian disruption is a carcinogen in men.

Methods

The Cancer Prevention Study–II Cohort

Detailed methods for the enrollment of participants and data collection in the CPS–II were reported previously.[10] Briefly, CPS–II was designed to identify risk factors for cancer and ways to prevent it. Approximately 77,000 American Cancer Society (ACS) volunteers in all 50 U.S. states, the District of Columbia, and Puerto Rico invited their friends, neighbors, and relatives to complete a four-page self-administered questionnaire that queried participants for information on demographic, medical, occupational, and behavioral factors; dietary intake of major food groups; height and weight; and a detailed history of current and past use of cigarettes (and in men cigars, pipes, and smokeless tobacco). Nearly 1.2 million adults (508,227 men) were enrolled in 1982 and 1983. The CPS–II is approved by the IRB of Emory University.

Men were excluded from analysis if they reported a history of cancer other than nonmelanoma skin cancer (n=25,232); reported no current occupation at the time they completed the questionnaire in 1982 (n=138,009); left rotating shift work blank (n=26,833); and among nonrotating shift workers, if they did not report the time they started work (n=13,096). A total of 305,057 men were included in this analysis.

Assessment of Work Schedule, Sleep Duration, Insomnia Frequency, and Other Risk Factors

The 1982 CPS–II baseline self-administered questionnaire queried participants for information on current occupation, and participants were asked, *Do you work rotating shifts?* and *What time of day do you start working?* The rotating shift work and time-of-day variables were combined to create a five-level variable for work schedule. Men who responded *yes* to working rotating shifts were classified as rotating shift workers whereas, consistent with the hours of shift work described by McMenamin,[11] fixed day workers (reference group) were those who responded "no" to working rotating shifts and reported starting work during the hours of 6:00AM to 10:00AM; fixed afternoon/evening workers reported starting work during the hours of 2:00PM to 4:00PM; fixed night workers reported starting work during the hours of 9:00PM to 12MN; and all other nonrotating shift workers were classified as "other."

The 1982 questionnaire also included the questions *On the average, how many hours do you sleep each night?* and *On the average, how many times per month do you have insomnia?* Sleep duration was categorized as 3–5, 6, 7 (reference), 8, 9, and 10–12 hours/night; men were classified as missing if they did not respond to the question or if they reported ≤ 2 or ≥ 13 hours/night because these values were considered implausible. Consistent with previous publications of insomnia and death from this cohort,[12] the frequency of insomnia was classified as never; infrequent or 1, 2, 3–9, and ≥ 10 nights/month; or missing if left blank.

Mortality Follow-up

Vital status of CPS–II participants was determined using two approaches. First, in September 1984, 1986, and 1988, ACS volunteers made personal inquiries to determine whether the participants they had enrolled were alive or dead, and then they recorded the dates and places of deaths. Reported deaths were verified by obtaining death certificates. At completion of the 1988 follow-up, vital status was known for 98.2% of the cohort. Subsequently, linkage to the National Death Index (NDI) was used to identify deaths that occurred from September 1988 through December 2010, and to identify deaths among the

21,704 participants lost to follow-up between 1982 and 1988. Death certificates or codes for cause of death were obtained for more than 99% of all known deaths. A death was counted as a prostate cancer death if the underlying cause of death was coded as prostate cancer (ICD-9 code 185 and ICD-10 code C61).[13,14] Among the 305,057 men included in this analysis, 4974 died of prostate cancer during follow-up through 2010.

Statistical Analysis

Means and distributions of sociodemographic and other factors across categories of work schedule, sleep duration, and frequency of insomnia were examined to assess potential confounding. Person-years of follow-up were computed for each participant as the amount of time since completion of the baseline questionnaire until date of death or until December 31, 2010. Cox proportional hazards regression[15] was used to compute multivariable-adjusted relative risks (RRs) and 95% CIs to examine associations with work schedule, sleep duration, and insomnia frequency. All models were adjusted for age using the stratified Cox procedure. Multivariable-adjusted models included dummy variables for race, education, BMI, smoking history, family history of prostate cancer, and frequent or painful urination. Although prescription sleeping pill use was associated with sleep duration and insomnia, it was not associated with risk of fatal prostate cancer and did not confound the associations of work schedule, sleep duration, or insomnia frequency with risk in this study; therefore it was not included in the final models. *P* values for trends were determined using the median value within categories for sleep duration and insomnia frequency. Additional multivariable models mutually adjusted for all of the main exposure variables but results were unchanged and therefore are not presented.

A sensitivity analysis stratified on follow-up time was conducted. Multivariable-adjusted RRs (95% CIs) for the main exposure variables were compared between the follow-up time from 1982 through 1990, 1991 through 2000, and 2001 through 2010; results for the latter two follow-up times were nearly identical and therefore were combined (data not shown). Therefore, effect modification by follow-up time from 1982 to 1990 and 1991 to 2010 was assessed by computing *p*-values for multiplicative interactions using likelihood ratio tests comparing Cox multivariable models with and without cross-product terms for categories of the main exposure variables and follow-up time. To address possible reverse causality, sensitivity analyses excluding the first 3 years of follow-up and men who reported frequent or painful urination were conducted. All analyses were performed using Statistical Analysis Software (SAS, version 9.2), and all tests of significance are two-sided, with the level of significance set at $p<0.05$.

Results

Among participants included in this analysis, nearly 6% worked rotating shifts, 1% worked a fixed afternoon/evening shift, and 0.5% worked a fixed night shift (Table 1). Men who worked fixed day shifts were slightly older and had a lower BMI than men who worked other shifts. The proportion of men who reported working a fixed day shift was lowest among men who were black, did not complete high school, were not currently married, and were current/former smokers. There were no meaningful associations of family history of prostate cancer or frequency/painful urination with work schedule. As expected, men employed in the emergency/security, food service, janitorial/maintenance, manufacturing, and transportation industries were less likely to report working a fixed day shift than men in other industries/occupations. For sleep duration (Appendix A, available online at www.ajpmonline.org), men who reported fewer hours/night of sleep were younger and experienced more frequent insomnia. In addition, a higher proportion of men who reported fewer hours of sleep were black, had a lower education, were not currently married, were current or ever smokers, experienced frequent/painful urination, and worked fixed night shifts. Men with frequent/painful urination were more likely to report insomnia than other men (Appendix B, available online at www.ajpmonline.org).

In age-adjusted adjusted analyses, rotating and fixed afternoon/evening shift work, but not fixed night work, were associated with a significantly higher risk of fatal prostate cancer compared to fixed day work (Table 2). After adjustment for race, education, frequent/painful urination and other risk factors, the RRs were attenuated and no longer significant. Neither sleep duration nor frequency of insomnia was associated with prostate cancer mortality in either the age- or multivariable-adjusted analyses.

In sensitivity analyses stratified on follow-up time, there were no associations of work schedule or insomnia with prostate cancer mortality for either follow-up period from 1982 through 1990 or 1991 through 2010 (Table 3). However, during follow-up from 1982 through 1990 there was an inverse association between sleep duration and risk. Compared to 7 hours/night of sleep, there was a 64% higher risk of fatal prostate cancer associated with 3–5 hours/night and a 28% higher risk associated with 6 hours/night ($p_{trend}=0.05$). There was no evidence of an association between sleep duration and prostate cancer mortality for the follow-up time from 1991 to 2010. The test for interaction between sleep duration and follow-up time was borderline significant ($p_{interaction}=0.05$). After excluding the first 3 years of follow-up time from analyses of the 1982 through 1990 follow-up period, the RRs (95% CIs) for 3–5, 6, 8, 9, and 10–12 hours/night compared to 7 hours/night were 1.78 (1.14, 2.78); 1.30 (0.99, 1.72); 1.05 (0.83, 1.32); 0.90 (0.55, 1.48); and 1.13 (0.50, 2.57), respectively ($p_{trend}=0.03$). Analyses were repeated after excluding men who reported frequent/painful urination (a potential cause of short sleep duration and a symptom of prostate cancer) and results were unchanged (data not shown).

Table 1. Characteristics by work schedule in the Cancer Prevention Study–II, % unless otherwise noted

Variable	N[a]	Work schedule				
		Fixed day (*n*=274,702)	Rotating (*n*=18,126)	Fixed afternoon/ evening (*n*=2921)	Fixed night (*n*=1612)	Other fixed shift (*n*=7696)
Age (years; M [SD])	305,057	53.4 (7.8)	51.4 (8.5)	52.4 (8.4)	51.9 (9.0)	53.2 (8.8)
BMI (M [SD])	299,385	26.0 (3.3)	26.5 (3.7)	26.3 (3.7)	26.7 (3.9)	26.6 (3.9)
Sleep duration (hours/night; M [SD])	302,350	7.2 (0.9)	7.1 (1.1)	7.2 (1.1)	6.8 (1.3)	6.9 (1.2)
Insomnia (nights/ week; M [SD])	294,495	1.0 (2.9)	1.0 (3.0)	0.8 (2.6)	0.9 (3.0)	0.9 (3.0)
Race						
White	288,738	90.6	5.7	0.9	0.5	2.4
Black	9,387	78.0	12.7	2.6	1.5	5.2
Other	6,932	85.3	8.9	1.4	0.7	3.8
Education						
<High school	31,571	81.6	9.6	2.2	1.2	5.5
High school	58,781	84.4	9.0	1.6	0.8	4.1
Some college	82,657	88.3	7.2	1.2	0.6	2.7
College grad	129,995	95.9	2.8	0.2	0.2	0.9
Missing	2,053	84.6	9.3	1.3	0.9	4.0
Currently married						
No	14,921	85.8	8.0	1.6	0.8	3.8
Yes	288,839	90.3	5.8	0.9	0.5	2.5
Missing	1,297	85.2	9.3	1.1	0.9	3.5
Smoking status						
Never	80,441	91.3	5.1	0.7	0.5	2.4
Former	110,709	91.1	5.4	0.9	0.4	2.1
Current	80,132	87.3	7.5	1.3	0.8	3.1
Ever	3,008	83.1	11.0	1.0	0.8	4.1
Cigar/pipe	24,276	91.7	4.9	0.6	0.4	2.3
Missing	6,491	86.9	7.6	1.1	0.5	3.8
Family history of prostate cancer						
No	296,194	90.0	6.0	1.0	0.5	2.5
Yes	8,863	91.1	5.1	0.8	0.4	2.6
Painful/frequent urination in last month						
No	289,140	90.0	5.9	1.0	0.5	2.5
Yes	15,917	90.0	5.9	1.1	0.4	2.5
Industry/occupation						
Agriculture	11,586	90.3	2.8	0.1	0.1	6.6

(continued on next page)

Table 1. Characteristics by work schedule in the Cancer Prevention Study–II, % unless otherwise noted *(continued)*

Variable	N[a]	Work schedule				
		Fixed day (*n*=274,702)	Rotating (*n*=18,126)	Fixed afternoon/ evening (*n*=2921)	Fixed night (*n*=1612)	Other fixed shift (*n*=7696)
Construction	12,004	92.9	4.4	0.9	0.4	1.5
Education	19,246	97.0	1.7	0.2	0.1	1.0
Emergency/ security	4,023	46.6	42.6	3.5	3.1	4.3
Engineering	16,945	95.8	3.0	0.3	0.1	0.7
Food service	1,403	62.9	15.3	3.0	1.9	17.0
Healthcare	16,382	87.3	10.0	0.7	0.5	1.4
Janitorial/ maintenance	5,548	80.7	6.4	4.9	1.8	6.2
Management	65,686	93.9	3.6	0.5	0.3	1.7
Manufacturing	10,335	82.8	10.4	3.0	1.0	2.8
Retail	25,404	91.8	4.7	0.4	0.4	2.7
Transportation	14,660	80.2	10.4	2.0	1.1	6.3
Other/unknown	101,835	89.7	6.2	1.0	0.6	2.4

[a]Total number of participants for each variable may not add to 305,057 because of missing data.

Discussion

In this large prospective study, there was no evidence that work schedule or frequency of insomnia were associated with fatal prostate cancer. Although there was no relationship between sleep duration and risk during the full 28-year follow-up time, compared to 7 hours/night of sleep, there was a significant 64% higher risk associated with 3–5 hours/night and a borderline significant 28% higher risk associated with 6 hours/night during the first 8 years of follow-up.

Most epidemiologic studies of rotating or night shift work and prostate cancer risk have been occupational studies, and results of those studies are inconsistent.[2] However, case–control studies of shift work have shown significant higher risks of prostate cancer among rotating shift workers[3] and night workers[4] compared to fixed day workers. Similarly, a Japanese prospective study[5] showed a significant threefold higher risk of prostate cancer associated with rotating shift work compared to day work and the risk associated with fixed night shift also was elevated although not significant. However, there were only 31 total prostate cancer cases in that study and associations with advanced or metastatic disease were not examined. In this CPS–II analysis, which included nearly 5000 fatal prostate cancer cases, there was no association with work schedule after adjustment for confounding factors. The absence of an association between work schedule and fatal prostate cancer in CPS–II, despite its large size, might be due to the fact that no information was available on specific aspects of shift work such as duration or individual adaptability to rotating or night shift work. Therefore, possible associations with long duration of shift work or among individuals less able to adapt to shift work cannot be ruled out.

In CPS–II, frequency of insomnia was not related to fatal prostate cancer risk; no other study has examined this relationship. It is possible that the insomnia frequency might not adequately measure sleep quality. Further research using more detailed measures is needed to understand whether sleep quality is associated with risk. For example, a recent study showing a positive association between insomnia and risk of thyroid cancer in women used an insomnia score that was based on five questions related to insomnia, early morning awakening, and sleep latency, maintenance, and quality.[16]

Short sleep duration was associated with higher risk of fatal prostate cancer during the first 8 years of follow-up in CPS–II. These results are similar to the only one other study that examined this association.[6] In a cohort study including 22,320 Japanese men, only 127 developed prostate cancer during 6 years of follow-up, and the RR between short sleep duration (i.e., for 4–6 hours/night compared to 7–8 hours/night) and overall prostate cancer risk was 1.38 (95% CI=0.77, 2.48), whereas for

Table 2. Age- and multivariable-adjusted associations of circadian rhythm–related factors and fatal prostate cancer

Variable	N deaths[a]	Person-years	Age-adjusted RR (95% CI)	Multivariable-adjusted[b] RR (95% CI)
Work schedule				
Fixed day	4497	6,465,182	1.00	1.00
Rotating	268	422,487	1.13 (1.00, 1.28)	1.08 (0.95, 1.22)
Fixed afternoon/evening	55	65,955	1.35 (1.04, 1.76)	1.27 (0.97, 1.65)
Fixed night	16	36,017	0.78 (0.47, 1.27)	0.72 (0.44, 1.18)
Sleep duration (hours/night)				
3–5	155	223,835	1.10 (0.93, 1.29)	1.03 (0.87, 1.21)
6	801	1,206,882	1.04 (0.96, 1.13)	1.01 (0.93, 1.10)
7 (ref)	1859	2,833,291	1.00	1.00
8	1842	2,515,594	1.05 (0.98, 1.12)	1.04 (0.98, 1.11)
9	226	263,463	1.12 (0.98, 1.29)	1.10 (0.96, 1.26)
10–12	46	59,435	1.02 (0.76, 1.37)	0.97 (0.72, 1.30)
			p_{trend}=0.61	p_{trend}=0.32
Frequency of insomnia (nights/month)				
Never	3578	5,130,613	1.00	1.00
1	280	503,331	0.86 (0.76, 0.97)	0.87 (0.77, 0.99)
2	340	490,252	1.04 (0.93, 1.16)	1.05 (0.94, 1.17)
3–9	453	642,871	1.01 (0.92, 1.12)	1.02 (0.93, 1.13)
≥10	123	160,897	1.04 (0.87, 1.25)	1.06 (0.88, 1.27)
			p_{trend}=0.56	p_{trend}=0.40

[a]Total number of deaths for each exposure variable do not add to 4974 because results for the categories "other" for work schedule and "missing" for sleep duration or frequency of insomnia are not included in the table.
[b]Multivariable models are adjusted for age, race, education, BMI, smoking status, family history of prostate cancer, and painful/frequent urination.
RR, relative risk

advanced or metastatic disease the RR was 1.82 (95% CI=0.82, 4.05).

It is unclear why short sleep duration was associated with a higher risk of fatal prostate cancer in CPS–II only during the first 8 years of follow-up. Reverse causality appears unlikely because the elevated RRs for short sleep duration were unchanged when the first 3 years of follow-up and men who reported frequent/painful urination were excluded. Because the first 8 years of follow-up (i.e., 1982–1990) preceded widespread screening for prostate cancer using prostate-specific antigen (PSA) testing, confounding by PSA screening also is unlikely to explain the elevated RRs observed. However, chance and confounding by unmeasured factors associated with both short sleep duration and prostate cancer mortality cannot be ruled out. Reasons for the lack of association between sleep duration and prostate cancer mortality during the later follow-up period are unclear. It is possible that short sleep duration promotes later stages of prostate carcinogenesis but has little effect on earlier stages.

The biologic mechanism underlying a possible association between short sleep duration and a higher risk of fatal prostate cancer is likely complex and not fully understood. Short sleep duration can affect the circadian clock resulting in the dysregulation of a number of genes involved in tumor suppression.[17] Sleep deprivation and the associated presence of light at night can inhibit the production of melatonin,[18] and a link between melatonin and carcinogenesis was recognized at least 30 years ago.[19] Suppression of melatonin could result in increased mutagenesis and oxidative damage, reduced DNA repair, and enhanced immune suppression with a shift in the regulation of inflammatory cytokines to those more likely to promote cancer.[20,21] For prostate cancer, melatonin inhibits cell proliferation and/or induces cell

Table 3. Multivariable-adjusted associations of circadian rhythm–related factors and fatal prostate cancer by follow-up time

Variable	Follow-up 1982–1990			Follow-up 1991–2010		
	N deaths[a]	Person-years	Multivariable-adjusted[b] RR (95% CI)	N deaths[a]	Person-years	Multivariable-adjusted[b] RR (95% CI)
Work schedule						
Fixed day	420	2,219,117	1.00	4077	4,246,065	1.00
Rotating	20	146,040	0.81 (0.52, 1.28)	248	276,447	1.11 (0.97, 1.26)
Fixed afternoon/evening	5	23,507	1.09 (0.45, 2.65)	50	42,448	1.29 (0.97, 1.70)
Fixed night	1	12,872	0.40 (0.06, 2.87)	15	23,144	0.76 (0.46, 1.26)
Sleep duration (hours/night)						
3–5	24	79,127	1.64 (1.06, 2.54)	131	144,708	0.96 (0.81, 1.15)
6	87	415,976	1.28 (0.98, 1.67)	714	790,906	0.99 (0.90, 1.08)
7 (reference)	150	958,612	1.00	1709	1,874,679	1.00
8	170	870,124	1.07 (0.86, 1.33)	1672	1,645,470	1.04 (0.97, 1.11)
9	20	95,188	0.89 (0.55, 1.42)	206	168,276	1.13 (0.98, 1.30)
10–12	7	22,473	1.14 (0.53, 2.45)	39	36,961	0.94 (0.69, 1.30)
			p_{trend}=0.05			p_{trend}=0.09
Frequency of insomnia (nights/month)						
Never	329	1,765,635	1.00	3249	3,364,978	1.00
1	15	168,545	0.55 (0.33, 0.92)	265	334,786	0.90 (0.80, 1.02)
2	25	166,750	0.86 (0.57, 1.30)	315	323,502	1.07 (0.95, 1.20)
3–9	53	221,472	1.26 (0.94, 1.69)	400	421,398	1.00 (0.90, 1.11)
≥10	9	56,280	0.77 (0.40, 1.50)	114	104,617	1.09 (0.90, 1.31)
			p_{trend}=0.94			p_{trend}=0.36

[a]Total number of deaths for each of the main exposure variables do not add to 4974 because results for the categories "other" for work schedule and "missing" for sleep duration or frequency of insomnia are not included in the table.
[b]Multivariable models are adjusted for age, race, education, BMI, smoking status, family history of prostate cancer, and painful/frequent urination.
RR, relative risk

differentiation of androgen-sensitive and androgen-insensitive prostate cancer cells in vitro.[8,22] In the transgenic adenocarcinoma of mouse prostate (TRAMP) model, physiologic doses of melatonin also showed antiproliferative effects.[8]

The major strengths of this study include its prospective design, and very large, nationwide sample of employed men. The strengths include the collection of information on work schedule, sleep duration, and frequency of insomnia, which allowed for a detailed analysis of multiple factors related to circadian rhythm disruption. Moreover, we were able to adjust for potentially important confounding factors, including education, smoking, obesity, and frequent or painful urination. Despite these strengths, the principal limitations include the use of self-reported information. However, the distributions of circadian rhythm–related factors across categories of race and industry/occupation were consistent with those reported elsewhere.[11,23] Because exposure information was collected only once, it is unlikely to reflect long-term patterns, and given the long follow-up period, there is likely to be nondifferential misclassification of circadian rhythm–related factors over time, potentially resulting in attenuated associations. Misclassification over time is of concern since the men in this study were employed, and during the long-follow-up period many of them likely retired, which might affect their sleep duration and quality and exposure to light at night.

In summary, shift work and insomnia were not associated with fatal prostate cancer in this large prospective cohort study, whereas short sleep duration was

associated with higher risk but only during the first 8 years of follow-up. Further research is warranted to confirm and better understand the biologic basis for this relationship.

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Appendix

Supplementary data

Supplementary data associated with this article can be found at http://dx.doi.org/10.1016/j.amepre.2013.10.033.