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ARTICLE

Shiftwork and Prostate-Specific Antigen in the National Health and Nutrition Examination Survey

Erin E. Flynn-Evans, Lorelei Mucci, Richard G. Stevens, Steven W. Lockley

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Correspondence to: Erin E. Flynn-Evans, PhD, Division of Sleep Medicine, Brigham and Women's Hospital, 221 Longwood Ave BLI 438, Boston, MA 02115 (e-mail: erin.flynn-evans@mail.harvard.edu).

Background Shiftwork has been implicated as a risk factor for prostate cancer. Results from prior studies have been mixed but generally support an association between circadian disruption and prostate cancer. Our aim was to investigate the relationship between shiftwork and prostate-specific antigen (PSA) test obtained as part of the National Health and Nutrition Examination Survey (NHANES) study.

Methods We combined three NHANES surveys (2005–2010) to obtain current work schedule among employed men aged 40 to 65 years with no prior history of cancer (except nonmelanoma skin cancer). Men who reported working regular night shifts or rotating shifts were considered shiftworkers. We obtained the total and percentage free PSA test results for these men and dichotomized total PSA into less than 4.0 ng/mL or 4.0 ng/mL or greater and total PSA of 4.0 ng/mL or greater combined with percentage free PSA less than or equal to 25%. Using multivariable logistic regression models, we compared PSA level among current shiftworkers and nonshiftworkers. All statistical tests were two-sided.

Results We found a statistically significant, age-adjusted association between current shiftwork and elevated PSA at the 4.0 ng/mL or greater level (odds ratio = 2.48, 95% confidence interval [CI] = 1.08 to 5.70; $P = .03$). The confounder-adjusted odds ratio was 2.62 (95% CI = 1.16 to 5.95; $P = .02$). The confounder-adjusted odds ratio for those with total PSA of 4.0 ng/mL or greater and free PSA less than or equal to 25% was 3.13 (95% CI = 1.38 to 7.09; $P = .01$).

Conclusions We observed a strong positive association with shiftwork and elevated PSA level. Our data support the notion that sleep or circadian disruption is associated with elevated PSA, indicating that shiftworking men likely have an increased risk of developing prostate cancer.

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Circadian disruption experienced during shiftwork may increase the risk of prostate cancer (1). Night-work is associated with increased exposure to light at night, which leads to two distinct biological consequences. First, exposure to light at night phase shifts the circadian system, creating an internal "jet-lag," affecting not only the sleep–wake cycle but also other systems, including metabolism and gastrointestinal function, release of cortisol and other hormones, and immune response (2). Second, the hormone melatonin is acutely suppressed through ocular light exposure. Melatonin has been implicated in conferring antiproliferation effects in prostate cancer cells in vivo and in vitro (3). Studies in women have consistently demonstrated that both insufficient sleep and shiftwork are associated with an increased risk of breast cancer (4,5) and lower melatonin levels (6). Although it has been suggested that a common mechanism may be shared in hormone-dependent cancers in both men and women, there has been little research investigating such an association in men.

Prior studies examining the association between insufficient sleep or shiftwork and prostate cancer have been mixed and have often included few cases or obvious misclassification. A study examining Nordic Airline pilots reported an elevated risk of prostate cancer among men reporting more than 10 000 hours of transmeridian flights as an occupational proxy for insufficient sleep and shiftwork (7). A retrospective cohort study by the same group found that public safety workers and waiters, presumed to work at night or have occupations associated with short sleep, also had an elevated risk of prostate cancer (8). A Canadian group conducted a retrospective cohort study among airline pilots and reported an increased risk of prostate cancer in that group; however, the sample only included 34 cases of prostate cancer (9). A separate Canadian group reported findings from a case–control study that demonstrated an association between history of shiftwork and prostate cancer among 760 cases (10). A Japanese group reported findings from a prospective study, in which they found an increased risk of prostate cancer with rotating shiftwork (11), and in a retrospective cohort of rotating shiftworkers, they found a non-statistically significant elevated risk of prostate cancer, although that study only included 17 cases of prostate cancer (12). The same group conducted a small prospective cohort study and found an elevated but non-statistically significant

increased risk in prostate cancer among Japanese men who slept 6 hours or less a night compared with those who slept 9 hours or more a night (13). Recently, a case–control study demonstrated that cancer at several sites, including the prostate, is increased among night workers compared with men who never worked night shifts (14). While these studies generally support an association between shiftwork and prostate cancer, additional studies are needed to evaluate the nature of the relationship.

Although prostate-specific antigen (PSA) testing is no longer recommended for all men as an immediate screening test for prostate cancer, there is evidence that PSA level in serum is a marker of future risk of prostate cancer development (15). In addition, accumulating research suggests that assessing percentage of free PSA in addition to total PSA improves the specificity of the test and is an indicator of aggressive disease (16). As such, we examined data obtained from the National Health and Nutrition Examination Survey (NHANES) to determine whether total PSA level was higher in shiftworking men than in day-working men. We further hypothesized that shiftworkers would be more likely to have a combined high total PSA and low percent free PSA compared with nonshiftworkers.

Methods

Survey Selection

All data were extracted from the US Centers for Disease Control NHANES database. The NHANES database is a cross-sectional biennial survey administered to a new subset of the US population each year by a trained interviewer. NHANES includes a standardized medical exam component as well as a laboratory component. The questions of interest for this study were included on the occupational questionnaire in three consecutive surveys, 2005 to 2006, 2007 to 2008, and 2009 to 2010. These surveys were combined to increase the sample size and improve statistical power.

Participant Selection

NHANES data are based on a randomly selected, nationally representative sample of approximately 11 000 men and women at each survey. Only men aged 40 years or older were asked to consent to PSA testing; therefore the present analysis is restricted to those aged 40 years or older. In addition, this analysis was restricted to men of working age and excludes men aged greater than 65 years. To ensure the control group was comparable with the exposure group, the analysis was further limited to those men who were currently employed. Finally, participants were also excluded if they reported prior history of any cancer (including prostate cancer) except nonmelanoma skin cancer, leaving an eligible sample size of 2136. Of these, 119 participants had missing PSA values, leaving a final sample size of 2017.

Exposure

The exposure of interest for this study was shiftwork. The NHANES occupational questionnaire included the following question: "Which best describes hours worked?" Response options for this question included: a regular daytime schedule, a regular evening schedule, a regular night shift, a rotating shift, another schedule. For the purposes of this analysis, a participant was considered a shiftworker if he reported working regular night shifts or a rotating schedule. All other working groups were included in the comparison group.

Outcome

The primary outcome for this study was the PSA test result. A single PSA test was obtained as part of the NHANES laboratory examination after the participant completed the NHANES interview. The continuous total PSA value obtained from the laboratory section of the NHANES medical exam was collapsed into binary outcomes of less than 4.0 ng/mL and of 4.0 ng/mL or greater for the primary analysis. The cutpoint of PSA result of 4.0 ng/mL or greater was selected a priori because this value has historically been used as the clinical threshold for screening (17). In addition, we examined the relationship between shiftwork and PSA value using sextile categories (<1.01, 1.01–2.00, 2.01–3.00, 3.01–4.00, 4.01–10.00, >10.00) that have been shown to be predictive of future prostate cancer development (18).

Low percentage free PSA has recently been shown to better predict aggressive disease and to improve the specificity in predicting disease compared with using total PSA alone (16). To further evaluate the relationship between shiftwork and PSA level, we created a combined variable to define those with high risk of developing aggressive disease, including only those with percentage of free PSA less than or equal to 25% and total PSA of 4.0 ng/mL or greater compared with those defined as low risk, including only those with percentage free PSA greater than 25% and total PSA less than 4.0 ng/mL (16).

Statistical Analysis

To account for the survey design and oversampling in some populations during the three survey cycles, all analyses incorporated the primary sampling unit variable, the stratum variable, and the weighting variable. The sample weighting is based on three factors—the 2000 Census, the probability of selection for the study, and nonresponse. The weighting factor was divided by three for analyses using combined survey cycles. The weighting of NHANES data allows for extrapolation of study findings to the national population.

Study participants were only asked about their history of having a PSA test in the 2005 to 2006 survey cycle. Therefore, a subset analysis was conducted on this survey cycle to evaluate the impact of PSA testing history on current PSA level.

Univariate summary measures of demographic characteristics were calculated for shiftworkers compared with nonshiftworkers. All categorical variables were compared using χ^2 tests, and all continuous variables were compared using two-sided t tests. Multivariable logistic regression was used to generate odds ratios adjusted for age and for covariables with either a statistical or a hypothesized a priori relationship with the PSA test and shiftwork. Unweighted means and standard deviations are presented in the tables and text. Sample weighting, as described above, was included for all tests of statistical significance.

All analyses were completed using the survey procedures in SAS software (SAS Inc, Cary, NC) or SAS-callable SUDAAN software (RTI, Research Triangle Park, NC). A P value of less than .05 was considered statistically significant.

This analysis was approved by the Partners Healthcare Institutional Review Board (protocol 2012-P-002333). Informed consent was obtained from all study participants by designated NHANES staff.

Results

2005 to 2010 Surveys Combined

This analysis included 2017 working men aged 40 to 65 years, which may be extrapolated to represent approximately 31 576 504 men in the United States. Shiftworkers differed from nonshiftworkers in several ways. Shiftworkers were slightly younger, less likely to have been married, had a higher frequency of education at the high school and some college level, worked longer hours, and more often fell into low-income categories (Table 1). Nonshiftworkers were also more likely to be covered by health insurance than shiftworkers. Shiftworkers were similar to nonshiftworkers in body mass index (BMI), but nonshiftworkers had a statistically significant longer average sleep duration than shiftworkers ($P < .001$).

Three percent of men had a total PSA level of 4.0 ng/mL or greater, including 5.6% of shiftworkers and 2.8% of nonshiftworkers; this could be interpreted as an absolute risk of high PSA in shiftworkers of 0.056 compared with a risk of high PSA in nonshiftworkers of 0.028. The mean total PSA among shiftworkers was 1.32 ng/mL (standard deviation [SD] = ±2.06) and among nonshiftworkers was 1.18 ng/mL (SD = ±1.34). The age-adjusted odds ratio for having a total PSA resultof 4.0 ng/mL or greater among shiftworkers compared with nonshiftworkers was 2.48 (95% confidence interval [CI] = 1.08 to 5.70; $P = .03$). The multivariable model odds ratio adjusted for age, BMI, race/ethnicity, health insurance, average hours of sleep per night, and months on the current job was 2.62 (95% CI = 1.16 to 5.95; $P = .02$) (Table 2).

In comparisons of high and low risk for aggressive disease, 5.6% of shiftworkers fell into the high risk category compared with 2.6% of nonshiftworkers. The age-adjusted odds ratio for having a total PSA result of 4.0 ng/mL or greater and a free PSA result less than or equal to 25% was 3.10 (95% CI = 1.32 to 7.31; $P = .01$). The multivariable model odds ratio adjusted for age, BMI, race/ethnicity, health insurance, average hours of sleep per night, and months on the current job was 3.13 (95% CI = 1.38 to 7.09; $P = 0.01$) (Table 2).

The confounder-adjusted odds ratio for the association between shiftwork and categorical level of total PSA followed a generally increasing pattern (Table 3).

Table 1. Baseline characteristics among shiftworkers compared with nonshiftworkers*

Characteristics	Nonshiftworkers, mean (SD)	Shiftworkers, mean (SD)	*P*
No.	1784	233	
Age, y	51.4 (6.7)	50.4 (6.8)	.03
Height, cm	174.8 (7.8)	175.1 (7.3)	.49
Weight, kg	88.5 (18.7)	89.7 (17.9)	.34
BMI, kg/m^2	28.9 (5.4)	29.2 (5.3)	.41
Average sleep duration, h	6.7 (1.2)	6.2 (1.5)	<.001
Hours worked last week, h	44.3 (12.9)	47.3 (16.2)	.02
Total PSA, ng/mL	1.2 (1.3)	1.3 (2.1)	.32
	No. (%)	**No. (%)**	
Marital status			
Married	1286 (72.1)	138 (60.0)	<.001
Widowed	20 (1.1)	5 (2.1)	
Divorced	188 (10.5)	37 (16.0)	
Separated	51 (2.9)	12 (5.2)	
Never married	113 (6.3)	27 (11.7)	
Living with partner	125 (7.0)	12 (5.2)	
Race ethnicity			
White	834 (46.8)	80 (34.3)	<.001
Black	317 (17.8)	69 (29.6)	
Hispanic	552 (30.9)	71 (30.5)	
Other	81 (4.5)	13 (5.6)	
Education			
Less than 9th grade	226 (12.7)	31 (13.3)	.002
9th–11th grade	235 (13.2)	35 (15.0)	
High school graduate	403 (22.6)	65 (27.9)	
Some college	449 (25.2)	68 (29.2)	
College graduate	470 (26.4)	34 (14.6)	
Annual household income			
<$20 000	204 (14.9)	43 (21.7)	.02
$20 001–55 000	575 (41.9)	90 (45.5)	
$55 001–75 000	237 (17.3)	32 (16.2)	
>$75 000	356 (26.0)	33 (16.7)	
Ever smokers	927 (52.0)	120 (51.5)	.57
Covered by health insurance	1346 (75.5)	153 (65.6)	<.001
Have ≥12 alcoholic drinks/yr	1416 (84.9)	173 (83.2)	.52

* Continuous variables were analyzed using two-sided t-tests and categorical variables were analyzed using χ^2 tests. BMI = body mass index; PSA = prostate-specific antigen; SD = standard deviation.

Table 2. Association between shiftwork and total prostate-specific antigen (PSA) of 4.0 ng/mL or greater and between shiftwork and total PSA of 4.0 ng/mL or greater with free PSA less than or equal to 25%*

Exposure	Total PSA ≥ 4.0, odds ratio (95% CI)	P†
Shiftwork, age-adjusted	2.48 (1.08 to 5.70)	.03
Shiftwork, confounder adjusted‡	2.62 (1.16 to 5.95)	.02
	Total PSA ≥ 4.0, free PSA ≤ 25%, odds ratio (95% CI)	**P†**
Shiftwork, age-adjusted	3.10 (1.32 to 7.31)	.01
Shiftwork, confounder adjusted‡	3.13 (1.38 to 7.09)	.01

* CI = confidence interval.

† All statistical tests were two-sided; *P* values were calculated using logistic regression models. Nonshiftworkers were the reference group.

‡ Adjusted for age (continuous), body mass index (continuous), race (white, black, Hispanic, other), health insurance (yes/no), hours of sleep per night (continuous), and months on the current job (continuous).

Table 3. Association between shiftwork and total prostate-specific antigen (PSA) by category*

PSA value	OR	(95% CI)	P
<1.01	1.00	(referent)	—
1.01–2.00	1.03	(0.68 to 1.56)	.89
2.01–3.00	0.75	(0.35 to 1.64)	.47
3.01–4.00	1.39	(0.41 to 4.71)	.60
4.01–10.00	2.68	(1.01 to 7.12)	.05
>10.00	3.78	(0.87 to 16.37)	.08

* All statistical tests were two-sided. *P* values were calculated using logistic regression models. Adjusted for age (continuous), body mass index (continuous), race (white, black, Hispanic, other), health insurance (yes/no), hours of sleep per night (continuous), and months on the current job (continuous). CI = confidence interval.

Table 4. History of prostate-specific antigen (PSA) screening among participants in the 2005 to 2006 National Health and Nutrition Examination Survey*

Characteristics	Nonshiftworkers, mean (SD)	Shiftworkers, mean (SD)
No.	506	67
Age, y	51.0 (6.9)	50.6 (6.9)
Age of first PSA test, y	47.9 (7.6)	45.1 (7.2)
Months since last PSA test	658 (847)	1146 (1650)
Number of PSA tests in the last 5 years	2.4 (2.2)	2.5 (2.4)
	No. (%)	**No. (%)**
Ever had a PSA test	199 (41.6)	27 (40.9)
Ever had an abnormal PSA test	7 (3.5)	2 (7.4)

* SD = standard deviation.

PSA Testing History Comparison

The 2005 to 2006 survey cycle included several questions on PSA testing history. History of PSA testing characteristics obtained from the 2005 to 2006 survey are described in Table 4. To evaluate the impact of PSA testing history on PSA level, we restricted the analysis to those men participating in the 2005 to 2006 survey cycle. In this subgroup, the age-adjusted odds ratio for total PSA of 4.0 ng/mL or greater was 4.58 (95% CI = 1.10 to 19.14; *P* = .04), and when adjusted for confounders, including ever/never had a PSA test, the odds ratio was 5.11 (95% CI = 1.59 to 16.38; *P* = .006) (Table 5). The age-adjusted odds ratio for total PSA of 4.0 ng/mL or greater and free PSA less than or equal to 25% was 5.16 (95% CI = 1.25 to 21.31; *P* = .02), and the confounder-adjusted odds ratio, including ever/never had a PSA test, was 5.58 (95% CI = 1.87 to 16.68; *P* = .002).

Discussion

We found a strong positive association with having a total PSA test result of 4.0 ng/mL or greater among shiftworkers compared with nonshiftworkers aged 40 to 65 years. These findings were similar when we examined low percentage of free PSA and high total PSA combined. Our findings are consistent with prior reports that suggest shiftwork is a risk factor for prostate cancer and extend these findings by demonstrating that PSA level is elevated among shiftworkers compared with nonshiftworkers. The World Health Organization categorized shiftwork involving circadian desynchrony as a "probable carcinogen" based on studies of breast cancer risk in female shiftworkers (19). This study supports the notion that shiftwork may relate to an increased risk in prostate cancer among men. Approximately 25% of the United States population is currently engaged in nondaytime or rotating shiftwork (20). Given the magnitude of our findings, prospective studies should be conducted on this topic to examine whether the elevated PSA we observe in shiftworkers ultimately leads to prostate cancer.

It has been suggested that the increased risk of prostate cancer among shiftworkers may operate through internal desynchronization of circadian rhythms (21), through reduction in levels of the pineal hormone melatonin (22), and/or through inadequate sleep duration, all of which are interrelated and are caused by exposure to light at night (23). The endogenous circadian pacemaker, located in the suprachiasmatic nuclei of the hypothalamus, is a major determinant of the timing, duration, and structure of sleep such that sleep is maximized when it occurs during the night (24). When attempting to sleep during the day, shiftworkers are trying to sleep at a time when the circadian system is promoting wakefulness, and consequently it is difficult to fall asleep and stay asleep, often reducing total sleep time (20).

Table 5. Association between shiftwork and total prostate-specific antigen (PSA) of 4.0 ng/mL or greater and between shiftwork and total PSA of 4.0 ng/mL or greater with free PSA less than or equal to 25% among 2005 to 2006 National Health and Nutrition Examination Survey participants*

Exposure	Total PSA ≥ 4.0, odds ratio (95% CI)	*P*†
Shiftwork, age-adjusted	4.58 (1.10 to 19.14)	.04
Shiftwork, confounder adjusted‡	5.11 (1.59 to 16.38)	.006
	Total PSA ≥ 4.0, free PSA ≤ 25%, odds ratio (95% CI)	***P*†**
Shiftwork, age-adjusted	5.16 (1.25 to 21.31)	.02
Shiftwork, confounder adjusted‡	5.58 (1.87 to 16.68)	.002

* CI = confidence interval.

† All statistical tests were two-sided. *P* values were calculated using logistic regression models. Nonshiftworkers were the reference group.

‡ Adjusted for age (continuous), body mass index (continuous), race (white, black, Hispanic, other), health insurance (yes/no), hours of sleep per night (continuous), months on the current job (continuous), and history of PSA test (ever/never).

It is not only sleep that is affected; meal times are also altered such that feeding occurs at an inappropriate circadian phase, during the biological night, a time known to impair postprandial glucose regulation and lipid metabolism (25). Shiftwork also causes desynchronization of the internal circadian system. It has recently been discovered that, in addition to a "central" circadian pacemaker in the suprachiasmatic nuclei, most peripheral tissues are also capable of generating circadian rhythms to maintain appropriate timing of local events (26). These clocks have been found in most tissues, including the heart, liver, lungs, kidney, pancreas, ovary, stomach, and intestine, and appear to be less sensitive to light, the major environmental time cue resetting the hypothalamic clock, and more sensitive to feeding time or other "nonphotic" time cues. The altered exposure to light–dark and feeding cycles induced by shiftwork cause not only desynchronization between the circadian system and environmental time but also desynchronization among internal timing systems, which impacts the temporal alignment of genetic and metabolic processes.

Melatonin has a 24-hour circadian rhythm that is synchronized to the external light–dark cycle and under normal conditions peaks during the night (27). Light exposure at night both acutely suppresses melatonin production and shifts the timing of the rhythm. Although it is possible for a dedicated night shiftworker to shift his circadian rhythms to become nocturnal, it is unlikely in most cases because it requires a stable pattern of daytime sleep with night-time wakefulness, along with careful control of light exposure during the commute home (28). It is not possible for a rotating shiftworker to adapt to changing shifts of any frequency, especially when they revert to a day-active pattern of activity on days off. Shiftworkers are therefore likely to have their melatonin suppressed or only partially shifted, thereby potentially reducing 24-hour output (29). It has also been reported that 44% of shiftworkers obtain 6 hours or less of sleep a day (20), which would allow for more hours of light exposure and melatonin suppression along with a cascade of physiological changes associated with sleep loss itself.

Although the PSA test has been questioned as a screening tool for current prostate cancer, total PSA level has been shown to be predictive of future prostate cancer and mortality (18). In our sextile analysis, we used cutpoints based on a report that demonstrated that prostate cancer risk and prostate cancer mortality increase stepwise by category of total PSA obtained at baseline (18). This study found that the absolute risk of future prostate cancer and mortality was less than 1.6% for men aged 45 years or older with total PSA levels of 1.00 ng/mL or less. In contrast, for men with a PSA value of 10.00 ng/mL or greater, the risk of developing prostate cancer was 35% for men aged less than 45 years, 41% for men aged 45 to 49 years, and increased stepwise to 88% for men aged greater than 75 years. Likewise, the absolute risk of mortality for men with a PSA value of 10.00 ng/mL or greater was 9.8% for men aged less than 45 years, 16% for men aged 45 to years 49, and increased to a peak risk of 52% among men aged 60 to 64 years. Based on these projections, it is likely that a greater proportion of the shiftworkers in our dataset will develop and die from prostate cancer in their lifetimes.

Our study is not without limitations. As with any analysis of NHANES data, this is a secondary use, publically available dataset; therefore the survey was not designed to test the hypothesis specifically. Shiftworkers may be different from nonshiftworkers in ways that could not be assessed in this analysis. For example, possible vitamin D deficiency and lifestyle differences could not be assessed in this study. Furthermore, diurnal preference and genetic polymorphisms associated with circadian rhythms and sleep could not be measured. In addition, PSA level may be elevated because of benign prostatic hyperplasia or prostatitis, so it is possible that shiftwork may differentially increase the risk of one of these other conditions. We are not able to differentiate between these conditions in this study, but because the PSA test is a predictor of future development of prostate cancer (15), we believe our results reflect an important difference among shiftworkers compared with nonshiftworkers. In addition, the use of the PSA test as a screening tool has been questioned in recent years because of concerns over a positive test result causing psychological distress among those with nonlethal disease (30). As such, we conducted additional analyses using the percentage of free PSA in combination with total PSA because this method has been shown to improve the specificity of the prostate cancer screening and low percentage free PSA has been associated with aggressive disease (16).

In our sample, nonshiftworkers were more likely to have health insurance than shiftworkers, so it is possible that the

association between shiftwork and elevated PSA test could be a function of access to care, but model adjustment for this association did not statistically significantly alter our results. It is unclear whether the duration of years of shiftwork increases a man's risk of prostate cancer. In this study there were insufficient cases to stratify based on years of shiftwork with the current employer, and type of shift worked with former employers was not assessed in this survey.

In summary, we found a strong positive association with current shiftwork and having a PSA test result of 4.0 ng/mL or greater and a combined PSA test result of 4.0 ng/mL or greater with free PSA less than or equal to 25% among working men aged 40 to 65 years. This study extends current knowledge about prostate cancer risk and circadian disruption. Future studies should examine these associations prospectively to determine the extent to which elevated PSA leads to aggressive or lethal prostate cancer development.

References

1. Zhu Y, Zheng T, Stevens RG, Zhang Y, Boyle P. Does "clock" matter in prostate cancer? *Cancer Epidemiol Biomarkers Prev*. 2006;15(1):3–5.
2. Czeisler CA, Gooley JJ. Sleep and circadian rhythms in humans. *Cold Spring Harb Symp Quant Biol*. 2007;72:579–597.
3. Jung-Hynes B, Schmit TL, Reagan-Shaw SR, Siddiqui IA, Mukhtar H, Ahmad N. Melatonin, a novel Sirt1 inhibitor, imparts antiproliferative effects against prostate cancer in vitro in culture and in vivo in TRAMP model. *J Pineal Res*. 2011;50(2):140–149.
4. Pukkala E, Auvinen A, Wahlberg G. Incidence of cancer among Finnish airline cabin attendants, 1967–92. BMJ. 1995;311(7006):649–652.
5. Schernhammer ES, Laden F, Speizer FE, et al. Rotating night shifts and risk of breast cancer in women participating in the nurses' health study. *J Natl Cancer Inst*. 2001;93(20):1563–1568.
6. Schernhammer ES, Hankinson SE. Urinary melatonin levels and breast cancer risk. *J Natl Cancer Inst*. 2005;97(14):1084–1087.
7. Pukkala E, Aspholm R, Auvinen A, et al. Incidence of cancer among Nordic airline pilots over five decades: occupational cohort study. BMJ. 2002;325(7364):567.
8. Pukkala E, Martinsen JI, Lynge E, et al. Occupation and cancer—follow-up of 15 million people in five Nordic countries. *Acta Oncol*. 2009;48(5):646–790.
9. Band PR, Le ND, Fang R, et al. Cohort study of Air Canada pilots: mortality, cancer incidence, and leukemia risk. *Am J Epidemiol*. 1996;143(2):137–143.
10. Conlon M, Lightfoot N, Kreiger N. Rotating shiftwork and risk of prostate cancer. *Epidemiology*. 2007;18(1):182–183.
11. Kubo T, Ozasa K, Mikami K, et al. Prospective cohort study of the risk of prostate cancer among rotating-shiftworkers: findings from the Japan collaborative cohort study. *Am J Epidemiol*. 2006;164(6):549–555.
12. Kubo T, Oyama I, Nakamura T, et al. Industry-based retrospective cohort study of the risk of prostate cancer among rotating-shiftworkers. *Int J Urol*. 2011;18(3):206–211.
13. Kakizaki M, Inoue K, Kuriyama S, et al. Sleep duration and the risk of prostate cancer: the Ohsaki Cohort Study. *Br J Cancer*. 2008;99(1):176–178.
14. Parent ME, El-Zein M, Rousseau MC, Pintos J, Siemiatycki J. Night work and the risk of cancer among men. *Am J Epidemiol*. 2012;176(9):751–759.
15. Orsted DD, Nordestgaard BG, Jensen GB, Schnohr P, Bojesen SE. Prostate-specific antigen and long-term prediction of prostate cancer incidence and mortality in the general population. *Eur Urol*. 2012;61(5):865–874.
16. Catalona WJ, Partin AW, Slawin KM, et al. Use of the percentage of free prostate-specific antigen to enhance differentiation of prostate cancer from benign prostatic disease: a prospective multicenter clinical trial. JAMA. 1998;279(19):1542–1547.
17. Welch HG, Schwartz LM, Woloshin S. Prostate-specific antigen levels in the United States: implications of various definitions for abnormal. *J Natl Cancer Inst*. 2005;97(15):1132–1137.
18. Orsted DD, Nordestgaard BG, Jensen GB, Schnohr P, Bojesen SE. Prostate-specific antigen and long-term prediction of prostate cancer incidence and mortality in the general population. *Eur Urol*. 2012;61(5):865–874.
19. Straif K, Baan R, Grosse Y, et al. Carcinogenicity of shift-work, painting, and fire-fighting. *Lancet Oncol*. 2007;8(12):1065–1066.
20. Luckhaupt SE, Tak S, Calvert GM. The prevalence of short sleep duration by industry and occupation in the National Health Interview Survey. *Sleep*. 2010;33(2):149–159.
21. Stevens RG, Blask DE, Brainard GC, et al. Meeting report: the role of environmental lighting and circadian disruption in cancer and other diseases. *Environ Health Perspect*. 2007;115(9):1357–1362.
22. Stevens RG, Davis S, Thomas DB, Anderson LE, Wilson BW. Electric power, pineal function, and the risk of breast cancer. FASEB J. 1992;6(3):853–860.
23. Brainard GC, Hanifin JP. Photons, clocks, and consciousness. *J Biol Rhythms*. 2005;20(4):314–325.
24. Dijk DJ, Czeisler CA. Paradoxical timing of the circadian rhythm of sleep propensity serves to consolidate sleep and wakefulness in humans. *Neurosci Lett*. 1994;166(1):63–68.
25. Morgan L, Hampton S, Gibbs M, Arendt J. Circadian aspects of postprandial metabolism. *Chronobiol Int*. 2003;20(5):795–808.
26. Richards J, Gumz ML. Advances in understanding the peripheral circadian clocks. *FASEB* J. 2012;26(9):3602–3613.
27. Arendt J. Melatonin: characteristics, concerns, and prospects. *J Biol Rhythms*. 2005;20(4):291–303.
28. Crowley SJ, Lee C, Tseng CY, Fogg LF, Eastman CI. Combinations of bright light, scheduled dark, sunglasses, and melatonin to facilitate circadian entrainment to night shiftwork. *J Biol Rhythms*. 2003;18(6):513–523.
29. Dumont M, Lanctot V, Cadieux-Viau R, Paquet J. Melatonin production and light exposure of rotating night workers. *Chronobiol Int* .2012;29(2):203–210.
30. Lin K, Lipsitz R, Miller T, Janakiraman S. Benefits and harms of prostate-specific antigen screening for prostate cancer: an evidence update for the US Preventive Services Task Force. *Ann Intern Med*. 2008;149(3):192–199.

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Affiliations of authors: Division of Sleep Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA (EEF, SWL); Division of Sleep Medicine, Department of Medicine, Harvard Medical School, Boston, MA (EEF, SWL); Department of Epidemiology, Harvard School of Public Health, Boston, MA (LM); Department of Community Medicine, University of Connecticut Health Center, Farmington, CT (RGS).