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Cancer Epidemiology, Biomarkers & Prevention

Review

Circadian Disruption, Sleep Loss, and Prostate Cancer Risk: A Systematic Review of Epidemiologic Studies

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Abstract

Disruption of the circadian system has been hypothesized to increase cancer risk, either because of direct disruption of the molecular machinery generating circadian rhythms or because of disruption of parameters controlled by the clock such as melatonin levels or sleep duration. This hypothesis has been studied in hormone-dependent cancers among women, but data are sparse about potential effects of circadian disruption on the risk of prostate cancer. This review systematically examines available data evaluating the effects of light at night, sleep patterns, and night shift work on prostate cancer risk. *Cancer Epidemiol Biomarkers Prev; 21(7); 1002–11. ©2012 AACR.*

Introduction

In 2007, the International Agency for Research on Cancer of the World Health Organization designated shift work involving circadian disruption as "probably carcinogenic to humans" (1). The main rationale for this classification is evidence from experimental animal models and limited evidence from human epidemiologic studies describing an increased risk of breast cancer among long-term female night shift workers, including flight attendants, as compared with women who do not work during the night (2, 3).

Shift work and transmeridian travel induce a number of physiologic changes that have been proposed as possible mechanisms underlying this observed increase in cancer risk. First, disruption and reduction of sleep is inherent in shift work. 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 such that sleep is maximized when it occurs during the night (4). When attempting to sleep during the day, shift workers 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, reducing total sleep time.

Shift work also causes disruption and desynchronization of the internal circadian system. It has recently been discovered that, in addition to a "central" circadian pacemaker in the hypothalamus, most peripheral tissues are also capable of generating circadian rhythms to maintain appropriate timing of local events (5). These clocks have been found in most places including the heart, liver, lungs, kidney, pancreas, ovary, stomach, and intestine and seem to be less sensitive to light, the major environmental time cue resetting the hypothalamic clock, and more sensitive to feeding time or other "non-photic" time cues. The altered exposure to light-dark and feeding cycles induced by shift work not only cause desynchronization between the circadian system and environmental time but also desynchronization among internal timing systems that impacts the temporal alignment of genetic and metabolic processes (6). Disruption of the molecular components of circadian clocks, particularly expression of the *Period2* gene (*Per2*), has been shown to increase breast cancer tumor growth rates (7), whereas overexpression of *Per2* is thought to have tumor-suppressive properties (8, 9). Notably, expression levels of *Per2* were significantly lower in all proliferative prostate diseases compared with normal prostate tissue (10).

Finally, 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 at night and is the biochemical correlate of darkness (4). Melatonin secretion requires an intact projection from the circadian pacemaker in the SCN to the pineal gland via the Superior Cervical Ganglion, severance of which, as occurs in tetraplegia, abolishes melatonin production (11, 12). Ocular light exposure during the night also temporarily inhibits melatonin production (4). The presence of melatonin has

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been shown to inhibit or slow down tumor growth, both *in vitro* and *in vivo*, including prostate cancer (13–19), whereas suppression of melatonin via constant light exposure or pinealectomy increases tumor growth in a dose-dependent manner in experimental models (20, 21). The oncostatic actions of melatonin can be explained by its potential modulation of cell-cycle length through control of the p53/p21 pathway (22) and its antimitotic and antioxidant activity (23). Melatonin is a potent free radical scavenger (24) and may facilitate reduction of oxidative stress implicated in prostate cancer progression (25). Moreover, melatonin secretion may be reduced in prostate cancer patients as compared with men diagnosed with prostate cancer *in situ* or benign prostatic hyperplasia (26, 27), and in a single case report, exogenous melatonin has been shown to inhibit prostate cancer progression temporarily (28). Moreover, totally blind individuals who theoretically may have a less disturbed melatonin secretion profile because of light exposure have lower risks of prostate and breast cancer (29–32).

The principal aim of this study is to systematically review evidence from epidemiologic studies evaluating the effects of light at night, sleep loss, and night shift work (main factors known to affect the circadian system) on prostate cancer risk. Previous reviews among men have mainly focused on one specific exposure, such as shift work or airline occupation, with respect to cancer incidence (33–36).

Materials and Methods

Search strategy

The electronic database PubMed was searched through November 2011 for studies examining the hypothesis that light at night, sleep pattern, or night shift work might be associated with prostate cancer. For night shift work, we included occupational studies conducted among airline pilots, navigators, waiters, firefighters, policemen, and public safety workers, as their working schedule likely includes night shift work: we did not include cabin attendants, an occupation with few males, most of whom are below 50 years. The following search terms were used along with "prostate cancer": "Shift work," "circadian," "sleep," "insomnia," "melatonin," "jet lag," "chronodisruption," and "pineal gland."

Eligible studies

The inclusion criteria of reviewed papers were as follows: (i) Observational studies on humans including case–control, cohort, or ecologic studies, (ii) presenting original data on the above-mentioned hypothesis, and (iii) published in English.

Ineligible studies

Altogether, 336 articles were sent to the collection (My NCBI). All abstracts were reviewed, of which 252 were uninformative on the hypothesis or published in a language other than English. Of the 84 remaining papers, we excluded 9 commentaries or hypothesis-generating reports and 18 reviews that did not include original data. Three letters to the editor not presenting original data were also excluded. Furthermore, we excluded 2 studies on visual impairment, as the exposure does not specifically involve circadian disruption. Finally, 40 experimental studies in genetics, cell lines, animal models, case series, or interventions were excluded.

Studies identified

Twelve epidemiologic studies that provided data on light at night, sleep patterns, or night shift work and prostate cancer risk were included; 2 were meta-analyses that included a total of 4 eligible individual studies on airline occupation related to the hypothesis. We used the combined estimates derived in the meta-analyses and reviewed the original articles. Therefore, a total of 16 epidemiologic studies, including the meta-analyses as single studies, were reviewed.

Results

All of the studies included in this systematic review presented data on prostate cancer incidence, either as a single outcome (37–40) or along with other cancers (35, 36, 41–47). Four of the studies presented data on prostate cancer mortality, all of which were conducted among airline pilots (36, 44, 48, 49). The studies addressed various proxies of circadian disruption: light at night distribution (41), sleep duration (37), rotating shift work (38–40, 42), and occupations likely to include night shift work, such as firefighters (47, 50), policemen (50), public safety workers (46), waiters (46), and airline pilots (35, 36, 43–45, 48, 49).

The main characteristics of the 16 observational studies and risk estimates for 15 studies on the association between proxies for circadian disruption and prostate cancer risk are summarized in Table 1. The ecologic study (41) does not present risk estimates.

Light at night and prostate cancer

The only ecologic study published to date (41) addressing exposure to light at night and cancer risk among men compared age-standardized incidence rates of prostate, lung, and colon cancer among men residing in 164 different countries using population-weighted light at night as their main exposure. Population-weighted refers to calculating light at night exposure while taking both geographic population distribution of a country and its local light at night intensities into account. Geographic Information System technology was used for matching country-specific cancer rates with the light at night levels obtained from satellite images. Several developmental and environmental indicators, including per capita income, percent urban population, and electricity consumption were also compared. Among the 3 cancers analyzed, only prostate cancer exhibited a significant positive correlation with light at night exposure and per capita electricity consumption. An increase of light at

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Table 1. Main characteristics and risk estimates of the 16 epidemiologic studies on circadian disruption or sleep loss and prostate cancer risk

Study; Country	Study design, population (participation rate) and time period under observation	Source of information for exposure (i.e., circadian disruption or sleep loss)	Adjusted covariates	Number of prostate cancer cases	Risk estimate (95% CI)
Light at night					
Kloog and colleagues (2009); United States	Ecologic study of 164 different countries; 2002.	Per capita light at night obtained from the U.S. Defense Meteorologic Satellite Program. Per capita GDP[a], percent urban population, and per capita electricity consumption obtained from the ESRI ArcCI Sdatabase and the CIA[b] World Fact Book, 1998–1999.	Income level and percent urban population.		
Sleep duration					
Kakizaki and colleagues (2008); Japan	Prospective cohort study of 22,320 men from the general population of Miyagi (94%); 1995–2001.	Sleep duration obtained from questionnaires and categorized into 3 groups: 6 $\leq$,7–8, $\geq$9 hours per day. Those who slept less than 4 h or more than 12 h were excluded.	Age, marital status, education, job status, history of disease, family history of cancer, body mass index, cigarette smoking, alcohol consumption, and walking status.	21 ($\leq$6 h) 19 ($\geq$9 h)	HR 1.38 (0.77–2.48) HR 0.36 (0.18–0.72)
Shift work					
Kubo and colleagues (2011); Japan	Retrospective cohort study of 4,995 male workers; 1981–2009.	Industry-based health-care database of a Japanese corporation that had recorded the results of annual health check-ups and the work schedule of every employee since 1981. Exposue classified as having worked on continuous counter-clockwise 3-shift system for >80% of their career.	Age, body mass index, alcohol intake, smoking, exercise and marriage status.	17	OR 1.56 (0.51–4.80)

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Table 1. Main characteristics and risk estimates of the 16 epidemiologic studies on circadian disruption or sleep loss and prostate cancer risk (Cont'd)

Study; Country	Study design, population (participation rate) and time period under observation	Source of information for exposure (i.e., circadian disruption or sleep loss)	Adjusted covariates	Number of prostate cancer cases	Risk estimate (95% CI)
Schwartzbaum and colleagues (2007); Sweden	Historical population-based occupational cohort study of 2,102,126 employed men (84% in ULF[c]); 1971–1989.	Cohort member's occupation obtained from the 1960 and 1970 censuses. Occupation classified as shift work if at least 40% were engaged in rotating shifts or working any hour 0100–0400 at least once a week during 1977–1981 according to the ULF[c]. Occupations with <30% of people engaged in shift work used as comparison.	Age, socioeconomic status, occupational position, county of residence, marital status, and urbanization.	1,319	SIR[d] 1.04 (0.99–1.10)
Kubo and colleagues (2006); Japan	Prospective population-based cohort study of 14,052 employed men (83%); 1991–1997.	The longest held work schedule obtained from questionnaires of the JACC[e] Study in 1988–1990, grouped into daytime, fixed night, or rotating shift work.	Age, study area and family history	7 (rotating) 3 (fixed)	HR 3.0 (1.2–7.7) HR 2.3 (0.6–9.2)
Conlon and colleagues (2007); Canada	Case–control study of 760 cases and 1,632 controls; 1995–1998.	Ever having worked rotating full-time shift work for 1 year or more. Usual work time obtained from questionnaires. Categories of all subjects and age 23–29 years when first working full-time rotating shift work (other categories of exposure omitted.)	Age and family history of prostate cancer.	760 (all subjects) 107 (young when started shift work)	OR 1.19 (1.00–1.42) OR 1.38 (1.05–1.80)
Proxy for shift work					
Pukkala and colleagues (2009); Nordic countries	Retrospective cohort study of 14.9 million persons in the 5 Nordic countries.	Study base consisted of persons participating in any computerized population	Gender, age (5-year categories) and calendar (5-year periods).	4,893 (public safety	SIR 1.11 (1.08–1.14) SIR 1.10 (1.01–1.20)

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Table 1. Main characteristics and risk estimates of the 16 epidemiologic studies on circadian disruption or sleep loss and prostate cancer risk (Cont'd)

Study; Country	Study design, population (participation rate) and time period under observation	Source of information for exposure (i.e., circadian disruption or sleep loss)	Adjusted covariates	Number of prostate cancer cases	Risk estimate (95% CI)
		census 1960–1990 grouped into 54 occupational categories: we present data for public safety workers and waiters. Followed until December 31st 2005 at latest.		workers) 490 (waiters)	
Bates (2007); California	Case–Control study of 3,659 firefighters diagnosed with cancer.	Firefighters aged 21–80 and diagnosed with prostate cancer during 1988–2003. Subjects with all other cancers, except outcome measure and cancers that were associated with firefighter occupation, used as a comparison group.	Age (5-year categories), year of diagnosis (4-year categories), ethnicity, socioeconomic status.	1,144	OR 1.22 (1.12–1.33)
Buja and colleagues (2005); Italy	Meta-analysis of 9 studies of which 5 include prostate cancer incidence; 1943–1996.	Pilots (3 studies) and male flight attendants (not included).		104	SIR 1.47 (1.06–2.05)
Pukkala and colleagues (2002); Nordic countries	Retrospective cohort study of 10,032 male airline pilots; 1943–1997.	Male pilots with number of block hours. Aircrafts classified into low altitude, intermediate distance, and long distance categories; total and age >60 years with more than 10,000 block hours.	Calendar periods and broad age categories.	64 (total)	SIR 1.21 (0.93–1.54)
				8 (>10,000 h)	SIR 3.88 (1.26–11.9)
Ballard and colleagues (2000); Italy	Meta-analysis of 6 studies of which 4 include prostate cancer; 1986–1998.	Civilian pilots (2 mortality studies and 2 incidence studies) and female flight attendants.	Correction factor of 1.1 for socioeconomic status.	23	SMR 1.11 (0.70–1.75)
				40	SIR 1.65 (1.19–2.29)

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Study; Country	Study design, population (participation rate) and time period under observation	Source of information for exposure (i.e., circadian disruption or sleep loss)	Adjusted covariates	Number of prostate cancer cases	Risk estimate (95% CI)
Irvine and colleagues (1999); Britain	6,209 male pilots and 1,153 male flight engineers employed for at least 1 year; 1950–1992.	Male British Airways flight deck crew compared with the general population of England and Wales.		15	SMR 1.11 (0.62–1.83)
Nicholas and colleagues (1998); United States	Case–control study of 1,538 diseased pilots and navigators; 1984–1991.	Death certificates of commercial pilots and navigators. Expected numbers based on the 24-state data for all occupations.	Race, gender, age, and region.	38	MOR 1.46 (1.06–2.03)
Krstev and colleagues (1998); United States	Case–control study of 60,878 men diagnosed with prostate cancer, by occupation; 1984–1993.	Death certificate-based occupational mortality data, with prostate cancer as an underlying cause of death. Comparison group subjects who died of all other causes except cancer.	5-year age groups and race.	37 (pilots and navigators) 140 (firefighters) 20 (police and detectives)	MOR 1.4 (1.0–2.0) MOR 1.2 (1.0–1.4) MOR 1.6 (1.0–2.5)
Band and colleagues (1996); Canada	Retrospective cohort study of 2,680 pilots (97.8%); 1950–1992.	All male pilots employed for at least one year since 1950.	5-year age groups and 5-year calendar periods.	34 7	SIR 1.87 (1.38–2.49) SMR 1.52 (0.71–2.85)
Band and colleagues (1990); Canada	Retrospective cohort study of 891 pilots (97.6%); 1950–1988.	All male pilots employed since 1950.	5-year age groups and 5-year calendar periods.	6	SIR 1.54 (0.70–3.00)[f]

[a]GDP, gross domestic products; [b]CIA, Central Intelligence Agency; [c]ULF, annual Survey of Living Condition conducted by Statistics Sweden; [d]SIR, standardized incidence ratio; [e]JACC, Japan Collaborative Cohort, [f]90% CI.

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night from 8.60 nanowatts/cm^2/sr (countries with minimal light at night exposure) to 28 nanowatts/cm^2/sr (countries with average light at night exposure) corresponded to an increase of 30% in prostate cancer age-standardized rates. A further increase in light at night value to 99.21 (the maximum light at night exposure) corresponded to an 80% increase.

Several techniques were used to reduce the possibility of ecologic confounding, including grouping by geographic areas and adjusting for some potential confounders, such as income levels and percent urban population. Still, results have to be viewed with caution, as different income of residents as well as higher diagnostic intensity and access to medical procedures in the "high resource" societies are likely to explain at least some of the observed association (41). Furthermore, differences in cancer registration completeness can bias the results because the developing countries with less nighttime illumination are more likely to have incomplete cancer registration. In sum, although the observed parallel increase in risk and exposure to light at night is in line with an increase in electricity consumption following the industrial revolution, results from this group-level study are subject to ecologic fallacy.

Sleep duration and prostate cancer

To date, only one epidemiologic study has examined sleep duration in relation to prostate cancer risk. In a cohort of Japanese men, sleep duration was inversely associated with risk of prostate cancer (37). Compared with those who slept an average number of hours (7–8 hours), those sleep deprived (6 hours or less) were at nonsignificantly increased risk (multivariate HR, 1.38, 95% Confidence Interval (CI), 0.77–2.48) of developing prostate cancer, whereas those who slept for longer than average (9 or more hours) were at lower risk for prostate cancer (multivariate HR, 0.36; 95% CI, 0.18–0.72; $P_{\text{trend}} = 0.001$). The association between short sleep duration and prostate cancer risk was stronger for advanced disease defined as prostate cancer stage T3/T4 and/or metastasized (HR, 1.82; 95% CI, 0.82–4.05), although this was based on 8 cases only. The inverse association of sleep duration and prostate cancer risk in this study is in line with observed increased nocturnal melatonin secretion with longer sleep duration (51) and decreased melatonin levels in prostate cancer patients (26). Limitations of this study, however, might include self-reported sleep duration (52), small case number ($n = 127$), and short follow-up that does not preclude the potential for reverse causality, although lag-time analyses (3 years) showed the same results.

Shift work and prostate cancer

Four studies on shift work and prostate cancer risk have been published, with mixed results. In a population-based cohort study in Sweden (42), there was no increased risk of prostate cancer among shift workers [standardized incidence ratio (adjusted for age, socioeconomic status, country of residence, and occupational position), 1.04; 95% CI, 0.99–1.10] compared with the general population of Swedish men. The definition of shift work used in the study was based on another survey from which shift work classification was based on job-title and industry combination with at least 40% shift workers and compared with occupations with less than 30% shift workers and daytime workers, respectively. Classification of shift work was based on occupation rather than individual level data. Occupations having 40% of men engaged in shift work classified as shift work could have led to as many as 60% of the men being misclassified as shift workers. Hence, nondifferential misclassification of exposure to shift work may have been substantial in this study which could have biased results to the null. Furthermore, shift work did not have to include night work even though night shift work is more strongly linked to circadian disruption, reduced sleep duration, and melatonin suppression than any other alternate shift (53).

In contrast, a Japanese prospective cohort study (38) reported that rotating shift workers (alternating between a day and/or afternoon shift and a night shift) were at 3-fold increased risk of prostate cancer (multivariate RR, 3.0; 95% CI, 1.2–7.7), and fixed-night work was associated with a smaller and nonsignificantly increased risk (multivariate RR, 2.3; 95% CI, 0.6–9.2) when compared with day workers. Potential confounding factors taken into consideration included perceived job stress, which did not alter the results. In this study, participants were classified as night shift workers based on self-report. A limitation of this study is that the increase in risk of developing prostate cancer observed among rotating shift workers is based on 7 cases only. The same group subsequently published results from a cohort study of 4,995 male workers of whom 824 had undertaken rotating shift work for more than 80% of their career (40). In this study, with only 17 prostate cancer cases, shift workers were at nonsignificantly increased risk of prostate cancer when compared with daytime workers (multivariate RR, 1.79; 95% CI, 0.57–5.68).

In a Canadian population-based case–control study (39), a 20% increased risk of prostate cancer (RR, 1.19; 95% CI, 1.00–1.42) was reported among men who normally worked full-time rotating shifts, when compared with men who had never worked full-time shift work. Men who became full-time rotating shift workers in their mid 20s seemed to be at highest risk (RR, 1.38; 95% CI, 1.05–1.80). Even though the investigators had information on a variety of potential confounders from their mailed questionnaire, only age and family history were adjusted for in these preliminary analyses, and thus there may be some residual confounding explaining the observed association, although such an adjustment has not been shown to affect the association between circadian disruption and prostate cancer.

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Occupations as a proxy for shift work

A 2005 meta-analysis on cancer incidence among male airline pilots (35), an occupation associated with circadian disruption due to transmeridian travel, includes 3 studies reporting data on prostate cancer incidence. In a Nordic study of 5 countries (43), a nearly 4-fold higher prostate cancer risk (RR, 3.88; 95% CI, 1.26–11.9) was found among pilots aged more than 60 with more than 10,000 block hours in long-haul aircrafts, when compared with pilots with less than 5,000 hours. Block hours are defined as a cumulative service hour, measured as an hour after leaving the departure gate and before arriving at the destination gate. Similarly, 2 Canadian cohort studies reported 87% (44) and 54% (45) increased risks of prostate cancer among pilots, respectively, when compared with the Canadian male population. The summary relative risk of the meta-analysis (35) suggested a 47% increased risk of prostate cancer among pilots (95% CI, 1.06–2.05). A significant higher risk of prostate cancer among pilots is supported by another, earlier meta-analysis from 2000 (36) that also included both of the Canadian studies (44, 45), with information on prostate cancer incidence and mortality, and, in addition, one British flight deck mortality study (49). This increase in risk might be explained by circadian rhythm disruption to which pilots are exposed, although cosmic radiation and electromagnetic fields (54) are possible alternate causal factors. Healthy worker effect might have deflated relative risk estimates (55, 56) relative to the comparison group; alternatively, pilots have regular health check and are therefore more likely to be diagnosed with disease than the general population.

In a large occupational Nordic study (46), public safety workers and waiters were at 11% and 10% increased risk of prostate cancer (95% CI, 1.08–1.14 and 1.01–1.20), respectively. Similarly, in a U.S. case–control study (50), firefighters were at 20% increased risk of prostate cancer death (95% CI, 1.0–1.4) and African American policemen at 60% increased risk (95% CI, 1.0–2.5), when compared with men who died of all other causes except cancer. A case–control study of Californian firefighters (47) found that men aged 21 to 80 were at 22% increased risk of prostate cancer when compared with controls with other cancer types (95% CI, 1.12–1.29). When the data were restricted to subjects aged 21 to 60 at diagnosis and stratified into 2 study periods, the risk increased to 50% (Table 1).

Discussion

This systematic review includes 16 epidemiologic studies that addressed the association between proxies of circadian disruption, sleep loss, and prostate cancer risk, of which 15 (35–41, 43–50) were suggestive of a positive association, with 10 of these providing statistically significant results. The studies supporting an increase in prostate cancer risk are in line with the vast majority of the studies on shift work and breast cancer risk, which have focused primarily on nurses and flight attendants (2).

Both positive as well as negative studies must be considered in light of some potential for bias or confounding. The proxies for circadian disruption and sleep loss considered herein attempt to reflect the association with prostate cancer in different ways. For light at night exposure, individual level data are needed to overcome the limitations of an ecologic study (41). Sleep duration in nonshift workers has been proposed as a proxy for exposure to light at night (57) because sleep (dark) duration is related to melatonin duration (51). Even though the only study published to date to examine the association between sleep duration and prostate cancer risk suggests a higher risk with shorter sleep duration, more evidence is needed.

Night shift work exposure is a good proxy for circadian, sleep, and melatonin disruption, and occupational shift work history might be considered a reasonable proxy for night shift work. Using occupational titles from registers to derive shift work precludes recall bias, but it also entails a potentially substantial amount of misclassification.

The basis of using airline occupational studies to estimate circadian disruption exposure relies on the employees who work on long-haul flights, as crossing several time zones is more likely to be associated with circadian disruption than short-haul flights. Pilots undergo regular and thorough health check-ups that can result in detection bias when comparing prostate incidence rates to the general population.

As noted, multiple physiologic, metabolic, and behavioral changes are associated with shift work, including sleep disruption, circadian disruption, and melatonin disruption. These factors and their relative contribution to prostate cancer risk are difficult to differentiate, given that they often occur simultaneously. Although there is sufficient evidence in experimental animal studies for the carcinogenicity of artificial light during the biologic night, which causes circadian, sleep, and melatonin disruption, direct evidence for the carcinogenicity of these factors is still limited in humans (1). Three of the 4 published studies on shift work and prostate cancer risk, however, as well as majority of the other studies on occupations with proxy for shift work show increased risk of prostate cancer among pilots and other occupations, in support of a potential effect of circadian disruption on prostate cancer risk.

Conclusion

This systematic review illustrates that although the circadian rhythm disruption hypothesis is plausible, based on the epidemiologic evidence discussed herein, more studies with individual level, prospectively collected, stringent exposure measurements are needed to draw definite conclusions on the potential impact of circadian disruption, sleep deficiency, melatonin suppression, or even clinical sleep disorders and use of sleeping medication on prostate cancer risk and, ultimately, progression.

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Disclosure of Potential Conflicts of Interest

Steven W. Lockley has expert Testimony for Armstrong Management Lawyers regarding effects of work shifts on health and safety, expert Testimony for Hicks Morley Hamilton Stewart Storie LLP regarding effects of work shifts on health and safety, and expert Testimony for Rothstein Law Firm regarding effects of work shifts on health and safety, No potential conflicts of interest were disclosed by the other authors.

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