Minireview

Cancer Epidemiology, Biomarkers & Prevention

Circadian Disruption and Prostate Cancer Risk: An Updated Review of Epidemiological Evidences

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Abstract

Since the publication of the International Agency for Research on Cancer Monograph in 2007 classifying night shift work leading to a disruption of circadian rhythm as probably carcinogenic to humans, there is an increasingly growing interest in understanding how circadian disruption may play a role in cancer development.

This systematic review provides a comprehensive update on epidemiologic evidences on circadian disruption and prostate cancer since the last review published in 2012. We identified 12 new studies evaluating the effects of several circadian disruptors such as night shift work, sleep patterns, and circadian genes in prostate cancer risk. In contrast, no new studies have focused on exposure to light at night.

Several convincing and biologically plausible hypotheses have been proposed to understand how circadian disruption may be related to cancer. However, the current difficulty of concluding on the role of circadian disruption on prostate cancer risk requires further studies including a better characterization of the different night shift systems, data on sleep patterns and chronotype, measurement of biomarkers, and investigations of polymorphisms in the genes regulating the biological clock. *Cancer Epidemiol Biomarkers Prev; 26(7); 985–91. ©2017 AACR.*

Introduction

Prostate cancer is the most common cancer in westernized countries with more than 900,000 cases diagnosed worldwide (1), and approximately 60,000 new cases in France each year (2). Despite a relatively high morbidity and mortality, only age, ethnic origin, and family history of prostate cancer are well-established prostate cancer risk factors which etiology remains largely unexplained. Nevertheless, migrant studies have shown that Asian men living in the United States have much higher prostate cancer rates than their counterparts living in native lands, suggesting the importance of environmental and lifestyle factors in prostate cancer etiology and pathogenesis (3–5).

Since late eighties, increasing evidence has linked circadian rhythm dysfunction with the pathogenesis of cancer (6). Many physiologic functions (respiration, metabolism, cardiovascular, digestive, and immune system) and biological activities (hormonal secretions, sleep-wake cycle, cell division, apoptosis, DNA repair) display rhythms with a period close to 24 hours (7). These rhythms are called circadian and are controlled by a central clock in suprachiasmatic nucleus of the hypothalamus and peripheral clocks in other brain regions and most peripheral tissues (8). These clocks are regulated endogenously at the molecular level by periodic transcription of genes that form a network of self-regulated feedback loop (6, 9, 10). There are, to date, 8 known circadian core genes [*CLOCK*, neuronal PAS domain protein 2 (*NPAS2*), aryl hydrocarbon receptor nuclear translocator-like (*ARNTL*), cryptochrome 1 and 2 (*CRY1*, *CRY2*), period 1, 2, and 3 (*PER1*, *PER2*, *PER3*), casein kinase 1-E (*CSNK1ϵ*), *TIMELESS*, *MTNR1A*, and *MTNR1B*] that have been directly involved in the regulation of prostate tumorigenesis (11–13).

In 2007, the International Agency for Research on Cancer (IARC) classified "shift work leading to a disruption of circadian rhythm" as probably carcinogenic to humans (Group 2A; ref. 14; Straif and colleagues, 2007). This classification was based on sufficient evidence from experimental animal models but limited evidence from epidemiologic studies in humans, the majority focusing on breast cancer and specific occupation groups such as nurses, flight attendance, radio, and telegraph operators. Several mechanistic hypotheses for how circadian disruption may be related to cancer have been proposed, among them: (a) exposure to light at night (LAN) that suppresses the nocturnal peak of melatonin and its associated anticarcinogenic effects; (b) disruption of the circadian rhythm regulated by several clock genes controlling cell proliferation and apoptosis; (c) repeated phase shifting leading to internal desynchronization and defects in the regulation of the circadian cell-cycle and physiologic processes; and (d) sleep deprivation that alters immune function (15–17).

The IARC Monograph has raised a growing interest in understanding the role of circadian disruption, including night shift work, particularly in breast cancer occurrence with the publication of several new studies since its publication, including one carried out by our team (18–20), four meta-analyses published in 2013 (21–24), and a recent meta-analysis including three cohort studies (25). On the other hand, there is a limited epidemiologic evidence for prostate cancer even though Sigurdardottir and

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colleagues reviewed, in 2012, the lean literature on "circadian disruption, sleep loss and prostate cancer risk" (26).

Thus, the aim of this article was to update the review of Sigurdardottir and colleagues on the effects of night shift work, sleep patterns, and LAN in prostate cancer risk. We also completed this review with publications regarding the effect of circadian genes in prostate cancer risk, not included in Sigurdardottir's review.

Materials and Methods

Search strategy

We focused on studies that examined night shift work, sleep patterns, LAN exposure and circadian genes (main factors known to affect the circadian rhythm), and prostate cancer risk. All studies published since the review of Sigurdardottir and colleagues (26) have been identified mainly from the electronic database PubMed from November 2011 through September 2016. Studies on circadian genes published before November 2011 were taken into account. Search terms used were "*prostate cancer*," "*prostate tumor*," "*prostate carcinoma*," and "*prostatic neoplasms*" to specify the outcome of interest and "*night work*," "*shift work*," "*night shift work*," "*shiftworking*," "*shifworker*," "*chronobiology disorders*," "*occupational diseases*," "*circadian clocks*," "*circadian rythms*," "*light at night*," "*sleep disorders*," "*sleep deprivation*," "*insomnia*," "*dyssomnias*," "*circadian gene*," "*clock gene*," and "*clock gene polymorphism*" to specify the exposures.

Eligible studies

Only human-based epidemiologic studies matching with the following criteria were included: (a) studies with clearly defined research objectives, design, and statistical methods; (b) case-control, cohort, or ecological studies; (c) individual exposure assessment; (d) original data presented; (e) publications in English. Overall, a total of 134 articles have been identified, and all abstracts have been reviewed (Fig. 1). Among them, 99 articles were not relevant for detailed evaluation. Thirty-five articles have been reviewed in detail, of which 23 were excluded. Finally, 12 epidemiologic studies that provided results on night shift work, sleep patterns, and circadian genes and prostate cancer risk were included in our review. In contrast, no new studies have focused on exposure to LAN.

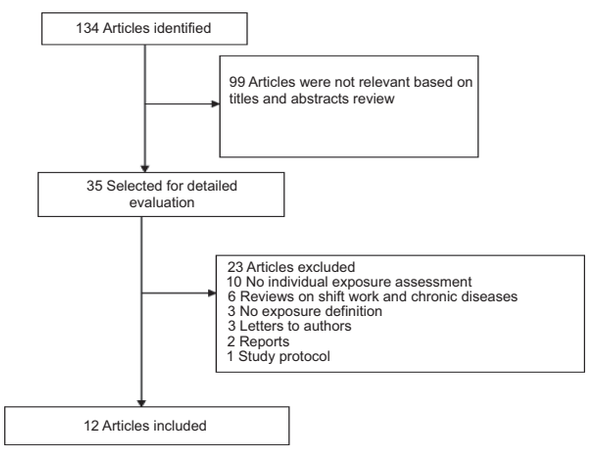

Figure 1.
Flowchart for articles selection.

Results

We reviewed 12 studies, including 2 meta-analyses, which are carefully described in Tables 1 to 3 regarding the following information: authors, country, time period under observation, study design, study sample size, number of prostate cancer cases and controls for case-control studies, exposure assessment, outcome and exposure data source, adjusted covariables, and adjusted relative risk (RR), odds ratio (OR), hazard ratio (HR) and their 95% confidence interval (CI).

Night shift work and prostate cancer (Table 1)

Four studies published before 2012 were included in Sigurdardottir's review presenting conflicting results as there was a significantly increased risk of prostate cancer in two studies (27, 28) while no association was observed in others (29, 30). Since that review, six studies have been published including two population-based case-control studies, three cohort studies, and one meta-analysis.

A Canadian population-based case-control study evaluating the role of night work in the risk of several cancers in men observed that night workers were at 3-fold increased risk of prostate cancer (OR = 2.77; 95% CI, 1.96–3.92; ref. 31). In contrast, a Spanish population-based case-control study reported that night workers were at nonsignificantly increased risk of prostate cancer (OR = 1.14; 95% CI, 0.94–1.37) compared with those who had never worked at night (32). Interestingly, authors observed an association for men who worked at night more than 28 years (OR = 1.38; 95% CI, 1.05–1.81), especially if they were of morning chronotype (OR = 1.79; 95% CI, 1.16–2.76). In addition, night shift workers had a higher prostate tumor risk according to the d'Amico classification (PSA more than 20, Gleason score equal or larger than 8, or clinical stage T2c-3a; RR = 1.40, 95% CI, 1.05–1.86). Conversely, a U.S. prospective cohort study on fatal prostate cancer did not find any association for rotating shift workers or fixed night workers (RR = 0.72; 95% CI, 0.44–1.18) compared with fixed day workers (RR = 1.08; 95% CI, 0.95–1.22; ref. 33). Similarly, a German industrial workers retrospective cohort study and a prospective cohort study of Finnish Twins did not find any association neither with rotating shift work (HR = 0.93; 95% CI, 0.71–1.21) in the German cohort (34) nor in fixed night workers (HR = 0.50; 95% CI, 0.10–1.90) and rotating shift workers (HR = 1.00; 95% CI, 0.70–1.20) in the Finish cohort (35).

Finally, a recent meta-analysis including eight studies (three case-control studies and five cohorts), of which four were included in Sigurdardottir's review, observed a 24% increased risk of prostate cancer for night shift workers (meta-RR = 1.24; 95% CI, 1.05–1.46; $P = 0.011$; ref. 36).

Sleep patterns and prostate cancer (Table 2)

Only one study, a Japanese cohort, was included in Sigurdardottir's review suggesting an inverse association between sleep duration and prostate cancer risk (37). Since this review, five new studies have investigated the role of sleep patterns in prostate cancer risk. Sleep patterns may be defined as sleep duration, sleep quality, and sleep problems or disorders such as insomnia (38). An Iceland prospective cohort study examining sleep disruption

Table 1. Characteristics of studies on night shift work and prostate cancer risk

Author, country	Study design, population	Number of prostate cancer	Data collection	Adjusted covariables	Exposure definition	Risk estimate (95% CI)
Parent et al. (2012), Québec, Canada	Population-based case-control study	400 cases 512 controls	Face-to-face interview	Age, ancestry, educational level, family income, smoking, alcohol, BMI, farming, occupational physical activity	Shift workNight work: working between 1:00 AM and 2:00 AM for at least 6 months	OR = 2.77 (1.96–3.92)
Gaptsur et al. (2014), United States	Cancer Prevention Study–II cohort American Cancer Society volunteers friends, neighbors, and relatives	4,974 cases	Self-administered questionnaire	Age, race, education, BMI, smoking history, family history of prostate cancer, and frequent or painful urination	Fixed night shift = 9:00 PM to 12:00 PM Rotating shift	RR = 0.72 (0.44–1.18) RR = 1.08 (0.95–1.22)
Yong et al. (2014), Germany	Cohort Study of male chemical production workers	337 cases	Personnel files Occupational health records	Age, smoking, professional status, and duration of employment	Shift patterns = "3 × 12 hours" or "4 × 12 hours" in which workers alternate day shifts, night shifts, and free periods	HR = 0.93 (0.71–1.21)
Papantoniou et al. (2015), Spain	Population-based case-control study	1,095 cases 1,338 controls	Face-to-face and phone interviews	Age, family history of prostate cancer, leisure, time physical activity, smoking status, past sun exposure, meat consumption, center, and educational level	Night shift = partly or entirely between 00:00 AM and 06:00 AM at least three times per month	OR = 1.14 (0.94–1.37)
Dickerman et al. (2016), Finland	Prospective cohort study of Finnish same-sex twin pairs	602 cases	Mailed questionnaire	Age, education, BMI, physical activity, social class, social class, smoking status, alcohol use, snoring, zygosity, chronotype	Last or current work Fixed night Rotating shift	 HR = 0.50 (0.10–1.90) HR = 1.00 (0.70–1.20)
Rao et al. (2015)	Meta-analysis	9,669 cases			Night shift work	RR = 1.24 (1.05–1.46)

Abbreviation: BMI, body mass index.

among older men residing in Reykjavik reported that men with severe and very severe sleep problems regarding falling and staying asleep were at a significantly increased risk of prostate cancer compared with men without sleep problems (HR = 1.7; 95% CI, 1.0–2.9 for severe sleep problems and HR = 2.2; 95% CI, 1.2–3.9 for very severe sleep problems; ref. 39). A large prospective cohort study of cancer mortality in U.S. adults observed that men who slept 3 to 5 hours per night or those who slept 6 hours per night had a significant 64% or 28%, respectively, higher risk of fatal prostate cancer compared with men who slept 7 hours per night during the first 8 years of follow-up (33). Similarly, the U.S. Health Professional Follow-up Study showed a 30% significant reduced risk of prostate cancer for long sleepers ($\geq$ 10 hours per night) compared with those who slept 8 hours per night (RR = 0.70; 95% CI, 0.50–0.99; ref. 40). Moreover, men who reported never feeling resting when they wake up were at more than 3-fold increased risk of fatal prostate cancer compared with those always feeling rested (RR = 3.05; 95% CI, 1.15–8.10) in that study. In contrast, a Swedish National Cohort study did not find any association neither with sleep duration nor with sleep restorative power or sleep quality (41). Likewise, no association between sleep duration and prostate cancer risk was observed in the cohort study of Finnish Twins (35).

Circadian genes and prostate cancer (Table 3)

Very few studies have examined the role of circadian genes in prostate cancer risk, and none has studied the influence of those genes in the association between night shift work and prostate cancer.

Five circadian genes variants were analyzed in a Chinese population-based case-control study. Men with the cryptochrome 2 (*CRY2*)-variant C allele had a significant 1.7-fold increased risk of prostate cancer (95% CI, 1.1–2.7) relative to those with the GG genotype (42).

An American population-based case-control study among Caucasian men analyzed 41 tagging SNPs in 10 circadian-related genes among which 17 SNPs located in three core genes (i.e., *ARNTL*, *CSNKIE*, and *NPAS2*) were significantly associated with prostate cancer (13). Recently, a meta-analysis of 3 cohort studies [the AGES-Reykjavik cohort, the Health Professionals Follow-Up Study (HPFS), and the Physicians' Health Study (PHS)] evaluated the association of 96 SNPs across 12 circadian-related genes with fatal prostate cancer (43). None of the 96 SNPs analyzed individually were associated with fatal prostate cancer across the 3 cohorts. Nevertheless, gene-based analyses showed that variation in the *CRY1* gene was nominally associated with fatal prostate cancer in each cohort (*P* values = 0.01, 0.01, and 0.05 for AGES-Reykjavik, HPFS, and PHS, respectively).

Discussion

This review gathered information on 12 studies (4 case-control studies, 6 cohort studies, and 2 meta-analyses) that addressed the association between circadian disruption indicators (night shift work, sleep patterns, and circadian genes) and prostate cancer risk.

Evidence of a possible association between night shift work and prostate cancer remains to date inconclusive even though results of a recent meta-analysis concluded to a 24% increase risk of prostate cancer. Indeed, the meta-analysis provided a meta-OR for eight studies that provide very different definitions and assessments of night shift work across studies. Moreover, only three studies of eight were of high quality according to the Newcastle–

Table 2. Characteristics of studies on sleep patterns and prostate cancer risk

Author, country	Study design, population	Number of prostate cancer	Data collection	Adjusted covariables	Exposure definition	Risk estimate (95% CI)
Sigurdardottir et al. (2013), Iceland	AGES-Reykjavik prospective cohort study	135 cases	Self-administered questionnaire	Age at study entry, family history of PCA, visit to doctor during previous 12 months, injury or health check-up, level of education, smoking status, alcohol use, diagnosis of benign prostate disease, BMI	Q1: Taking medication for sleep Q2: Difficulty falling asleep within 30 minutes Q3: Waking up during the night and having difficulty falling back asleep Q4: Waking up early in the morning and having difficulty falling back asleep Severe sleep problem = Q1+Q2+Q3 Very severe sleep problem = Q1+Q2+Q3+Q4	HR = 1.70 (1.0–2.9) HR = 2.2 (1.2–3.9)
Gaptsur et al. (2014), United States	Cancer Prevention Study–II cohort American Cancer Society volunteers friends, neighbors, and relatives	4,974 cases	Self-administered questionnaire	Age, race, education, BMI, smoking history, family history of prostate cancer, and frequent or painful urination	3–5 hours per night 6 hours per night	RR = 1.64 (1.06–2.54) RR=1.28 (0.98–1.67)
Markt et al. (2015a), United States	Health Professional Follow-up Study (HPFS)	4,261 cases	Self-administered questionnaire	Age, race, vigorous activity level, smoking, diabetes, family history of PCA, snoring status, multivitamin use, energy intake, history of PSA testing, beta-blocker use, marital status, coffee intake, alcohol intake, number of urination per night	$\geq$ 10 hours per night Never feeling rested when wake up	RR = 0.70 (0.50–0.99) RR = 3.05 (1.15–8.10)
Markt et al. (2015b), Sweden	National Cohort	785 cases	Self-administered questionnaire	Age, BMI, employment status, snoring, smoking, alcohol use, depressive symptoms, physical activity, coffee intake, multivitamin use, diabetes	Poor restorative power of sleep	HR = 1.23 (0.93–1.62)
Dickerman et al. (2016), Finland	Prospective cohort study of Finnish same-sex twin pairs	602 cases	Mailed questionnaire	Age, education, BMI, physical activity, social class, social class, smoking status, alcohol use, snoring, zygosity, chronotype	8 hours per night Fairly poor/poor quality of sleep	HR = 0.90 (0.70–1.20) HR = 1.00 (0.7–1.3)

Abbreviations: BMI, body mass index; PCA, prostate cancer.

Ottawa Scale criteria (45). Out of those eight studies, four were included in Sigurdardottir's review (27–30) and four are part of ours (31–34). Among the five more recent studies included in our review, two were suggestive of an association between night shift work and prostate cancer (31, 32) while three studies did not (33–35). Even though those five studies presented several positive features that should be emphasized: high quality exposure information with detailed lifetime job histories, large population size studies, information on sleep patterns, and chronotype in two studies of five, several limitations to an overall interpretation should also be highlighted: lack of standardization in both definition of night shift work and exposure assessment; different potential confounding factors taken into account; different prostate cancer outcomes either incidence or mortality; differences in populations studied some of them being population-based while others focused on specific occupational groups; few studies with information on prostate cancer aggressiveness, and few studies taking into account other occupational exposures that may also play a role in prostate cancer (45).

Some epidemiologic studies suggested that sleep patterns, such as a short duration of sleep or a poor quality of sleep (i.e., problems of falling and remaining asleep), may increase the risk of several cancer including prostate cancer (33, 39, 40). However, some potential limitations susceptible to affect those epidemiologic results should be considered, such as self-report of sleep information (33, 40) and a lack of information on sleep medication use. Short sleep duration and sleep disruption have been associated with lower melatonin levels and increase the exposure to LAN (46, 47). The role of melatonin as a tumor cells proliferation inhibitor, the impact of LAN exposure during sleep period or night shift work, and sleep patterns on melatonin levels also raised questions on a possible mediation of their carcinogenic effect through the suppression of the melatonin nocturnal pic (48).

To our knowledge, only one ecological study, included in Sigurdardottir's review, investigated at a large-scale population level the effect of LAN exposure in the risk of prostate, lung, and colon cancer in men, using the available age-standardized rates of

Table 3. Characteristics of studies on circadian genes and prostate cancer risk

Author, country	Study design, population	Number of prostate cancer	Data collection	Adjusted covariables	Exposure definition	Risk estimate (95% CI)
Chu et al. (2008), China	Population-based case-control study	187 cases 242 controls	Face-to-face interview Blood sample for DNA genotyping	Age	5 variants in 5 circadian genes *PER3* (54-base pair repeat length variant) *CRY2* (rs1401417:G>C) *CSNK1E* (rs1005473:A>C) *NPAS2* (rs2305160:G) *PER1* (rs2585405:G>C)	OR = 1.70 (1.1–2.7)
Zhu et al. (2009), Washington, United States	Population-based case-control study in residents of King County in Washington	1,308 cases 1,266 controls	Face-to-face interview Blood sample for DNA genotyping	Age, family history of PCA	Genotyping of 41 tag-SNPs in 10 circadian genes *PER1, PER2, PER3* *CSNK1E* *CRY1, CRY2* *ARNTL* (rs 969485) *CLOCK* *NPAS2* (rs10206435) *TIMELESS*	OR = 0.52 (0.30–0.91) OR = 0.62 (0.38–1.01)
Markt et al (2015c)	Meta-analysis of 3 cohort studies: AGES-Reykjavik, HPFS (United States), Physician Health Study (United States)	283 cases	Blood sample for DNA genotyping	_	Genotyping of 12 circadian genes *PER1, PER2, PER3* *CSNK1E* *CRY1, CRY2* *ARNTL* *CLOCK* *NPAS2* *TIMELESS* *MTNR1A, MTNR1B*	OR = 0.92 (0.71–1.19) OR = 1.00 (0.59–1.68)

Abbreviation: PCA, prostate cancer.

those male cancers for 164 countries (49). Authors observed that the more countries were exposed to LAN, the higher was the increase in prostate cancer age-standardized rates. To date, no new study has examined the role of LAN and prostate cancer risk, whereas six studies have already been published on LAN and breast cancer (50–55) since the publication of Stevens in 2009 (56).

A growing interest in circadian genes as a potential carcinogenesis pathway has emerged as they play a key role in the regulation of cells proliferation, cell-cycle control, *DNA* damage repair, and apoptosis (13). Two studies (13, 42) had suggested a significant association with susceptibility to prostate cancer, for an intronic *CRY2* variant, *ARNTL*, *CSNK1ϵ*, and *NPAS2*, whereas Markt and colleagues' meta-analysis failed to confirm any association between the SNPs evaluated and risk of fatal prostate cancer. However, within the individual cohorts included in the meta-analysis, two SNPs in *CRY1* (rs7297614 and sr1921126) were associated with risk of fatal prostate cancer in both AGES-Reykjavik and HPFS (43). The relatively large size of the study population in those studies, quality control measures, selection as well as misclassification of genotyping bias control, the test of Hardy–Weinberg equilibrium for each SNP in the control population to ensure that genotype frequencies did not differ from those expected in general population denoted the extent in which genotyping data and therefore the results may be reliable. Nevertheless, the major common limitation of all studies was related to homogeneity within study population and differences in population type across studies, restraining therefore results generalizability. However, those results are partially giving support to the possible role of circadian genes in hormone-related cancers, as circadian genes have been associated with high concentrations of sex steroid hormones (57).

Influence of circadian genes should also be taken into account when studying night shift work in prostate cancer risk, as it has been shown that circadian genes may modulate the role of night shift work in breast cancer (20, 58).

In conclusion, this review, an update to that of Sigurdardottir's (26), provides an overview of epidemiologic evidences on the role of circadian disruption indicators in prostate cancer risk. The mechanistic hypotheses that have been proposed to understand how circadian disruption may be related to cancer are convincing and biologically plausible. However, to better capture all aspects of circadian disruption and to improve our understanding of its carcinogenic effects, key domains should be investigated in future epidemiologic studies, as recommended by an IARC group of experts: better characterization of the different night shift systems; need to collect new data on sleep patterns and chronotype; measurement of biomarkers; and investigations of polymorphisms in the genes regulating the biological clock at the molecular level (circadian genes; ref. 59).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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