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Night work and prostate cancer risk: results from the EPICAP Study

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ABSTRACT

Objective To investigate the role of night work in prostate cancer based on data from the EPICAP Study.

Methods EPICAP is a French population-based case-control study including 818 incident prostate cancer cases and 875 frequency-matched controls that have been interviewed face to face on several potential risk factors including lifetime occupational history. Detailed information on work schedules for each job (permanent or rotating night work, duration, total number of nights, length of the shift, number of consecutive nights) as well as sleep duration and chronotype, was gathered. Prostate cancer aggressiveness was assessed by Gleason Score.

Results Night work was not associated with prostate cancer, whatever the aggressiveness of prostate cancer, while we observed an overall increased risk among men with an evening chronotype (OR=1.83, 95% CI 1.05 to 3.19). A long duration of at least 20 years of permanent night work was associated with aggressive prostate cancer (OR=1.76, 95% CI 1.13 to 2.75), even more pronounced in combination with a shift length >10 hours or ≥ 6 consecutive nights (OR=4.64, 95% CI 1.78 to 12.13; OR=2.43, 95% CI 1.32 to 4.47, respectively).

Conclusion Overall, ever night work, either permanent or rotating, was not associated to prostate cancer. Nevertheless, our results suggest that a long duration of permanent night work in combination with a long shift length or at least six consecutive nights may be associated with prostate cancer, particularly with aggressive prostate cancer. Further studies are needed to confirm those findings.

Key messages

What is already known about this subject?
- A possible role of circadian disruption related to night work in prostate cancer risk was hypothesised based on the International Agency for Research on Cancer monograph that classified 'shift work leading to a disruption of circadian rhythm' as probably carcinogenic to humans.
- To date, 11 epidemiological studies have investigated night work in prostate cancer risk with conflicting results.

What are the new findings?
- Our results suggest that a long duration in combination with a long shift and/or at least six consecutive nights of permanent night work are associated with an increased risk of prostate cancer, and particularly aggressive prostate cancer.
- In addition, an overall increased risk of prostate cancer was also observed among night workers with an evening chronotype.

How might this impact on policy or clinical practice in the foreseeable future?
- The increasing prevalence of night shift work in the world population and the high incidence of prostate cancer make this research area a key issue for public and occupational health.
- Further studies are needed to enhance existing findings, and to identify night work patterns and individual characteristics that may have a strong impact on the internal circadian rhythm and therefore on cancer risk.

INTRODUCTION

Prostate cancer is the most common cancer in men in industrialised countries with more than 1 000 000 cases diagnosed worldwide in 2012,[1] and more than 50 000 cases of prostate cancer in France each year.[2] Despite its high incidence, only age, ethnic origin and family history of prostate cancer are well-established risk factors, leaving aetiology of prostate cancer largely unexplained. Migrant studies have shown that Asian men living in USA have much higher prostate cancer incidence rates than their counterparts living in their native country suggesting the importance of westernised lifestyle and environmental factors in prostate cancer aetiology.[3–5] Among those factors, a possible role of circadian disruption related to night work in prostate cancer risk has emerged,[6 7] especially since the publication of the International Agency for Research on Cancer (IARC) monograph that classified in 2007 'shift work leading to a disruption of circadian rhythm' as probably carcinogenic to humans.[8] This classification was based on sufficient evidence from experimental studies but limited evidence in humans, particularly for cancers other than breast cancer, including prostate cancer. Several biological mechanisms for how circadian disruption may be related to cancer have been hypothesised, among which: (A) exposure to light at night that suppresses the nocturnal peak of melatonin and its associated anticarcinogenic effects; (B) disruption of the circadian rhythm regulated by

several clock genes controlling apoptosis and cell proliferation; (C) repeated phase shifting leading to internal desynchronisation and defects in the regulation of the circadian cell cycle; (D) sleep deprivation that alters immune function; and (E) lower vitamin D and harmful lifestyle factors.[9–11]

To date, 11 epidemiological studies, including 3 population-based case-control studies[12–14] and 8 cohorts,[15–22] have investigated the relationship between night work and prostate cancer with inconsistent results even though a recent meta-analysis concluded a 24% increased risk of prostate cancer in men exposed to night shift work, based on 8 of these studies.[23] Several limitations in the epidemiological studies conducted so far may be pointed out: the different definitions of night work used (night work without any information, rotating shift, fixed and rotating night work) and few indicators studied (mostly duration). Moreover, very few studies took into account individual characteristics such as sleep patterns[13 16 18] or chronotype[13 17] as recommended by an IARC group of experts in 2011[24] and only one study investigated night work according to prostate cancer aggressiveness.[13]

In that context of a lack of evidence regarding night work and prostate cancer and given the large number of men involved in a non-standard day schedule (~20%),[25 26] our objective was to investigate the role of night work, either permanent or rotating, in prostate cancer taking into account prostate cancer aggressiveness and individual characteristics, based on data from the EPICAP (Epidemiology of Prostate CAncer) Study.

METHODS

Study population

EPICAP is a population-based case-control study; details of its study protocol have been published elsewhere.[27] Briefly, eligible cases were all men less than 75 years old newly diagnosed with histologically confirmed prostate cancer in 2012–2013 and residing in the Hérault region at the time of diagnosis. Controls were randomly selected from the general population and frequency-matched to the cases by 5-year age groups. They were free of prostate cancer history and were residing in the same Hérault region as the cases. Quotas by socioeconomic status (SES) were established to yield a control group similar to the general population in terms of SES to control for potential selection bias arising from differential participation rates across SES categories. These quotas were calculated using the census data available in the Hérault region to ensure that the distribution by SES among controls was similar to the SES distribution in the general population of men in Hérault of the same age.

In total, 819 incident cases of prostate cancer and 879 male population-based controls were enrolled in the study, which corresponds to a participation rate of 75% and 79%, respectively.

All participants provided a written consent. The EPICAP Study was approved by the review board of the French institute of health and medical research (INSERM, n°01–040, November 2010) and authorised by the French data protection authority (CNIL n°910485, April 2011).

Data collection

A face-to-face interview was conducted by trained clinical research nurses using a standardised computer-assisted questionnaire. During interview, we gathered information on sociodemographic characteristics such as educational level (highest diploma), personal and familial medical history, lifestyle factors including smoking status (never, former, current), physical activity (at least 1 hour per week during 1 year), alcohol drinking (at least once a month during 1 year), height and weight (measured during interview), sleep duration and individual chronotype.

Sleep duration was categorised into three groups according to the average number of sleep hours per night over the lifetime (<7 hours, 7–8 hours and >8 hours per night).

The individual chronotype was assessed using the Morningness-Eveningness Questionnaire[28] allowing us to classify cases and controls as a morning, evening or undifferentiated persons, according to the adapted classification from Taillard *et al*.[29]

Clinical information of prostate cancer cases were extracted from medical records including prostatic specific antigen (PSA) levels, Gleason Score and stage at diagnosis.

Night work exposure assessment

Cases and controls were asked to describe their entire work history for each job held for more than 6 months including general information on: beginning and ending dates, tasks involved, name and address of the company and if they had a non-day schedule for each given job. For each job for which a non-day schedule was indicated, they completed a specific 'night work' questionnaire gathering detailed information on their work time schedule. Night workers were defined as men who performed at least 270 hours of night work per year or three nights per month during at least 1 year, according to the French legal definition.[30]

Based on this definition, we categorised night work into permanent or rotating. We assigned men, who had performed both permanent and rotating night work during their entire work history, either to the permanent night work group when their duration of permanent night work was higher (24 cases, 19 controls) or to the rotating night work group when their duration of rotating night work was higher (7 cases, 19 controls). When the duration was equivalent for permanent and rotating night work (eight cases, five controls), men were assigned to both groups.

For each type of night work, overall, permanent or rotating, we were able to characterise several night work indicators: lifetime cumulative duration of night work (<10 years, 10–19 years, 20–29 years, ≥30 years), number of consecutive nights (<6 consecutive nights, ≥6 consecutive nights),[31] night shift length (<8 hours, 8–10 hours, >10 hours),[32] and lifetime cumulative number of nights according to the median values among controls (≤1314 nights, >1314 nights).

We also characterised night work as early morning shifts (shift *starting between midnight and 06:00)*, late evening shifts (shift *ending between 21:00 and 02:00)* and overnight shifts (*shift starting before 00:00 and ending after 05:00)*. Regarding rotating night work, we were also able to characterise the type of rotation (only forward, only backward, both) as well as the speed of rotation (≤3 days, 4–5 days, ≥6 days).

Statistical analysis

All analyses were performed using the statistical analysis software SAS (V.9.4). Occupational questionnaires were missing for one case and four controls, restricting, therefore, our analyses to 818 cases and 875 controls. Associations between night work indicators and prostate cancer were assessed using unconditional logistic regression models systematically adjusted for age, ethnic origin and family history of prostate cancer. In addition, several potential confounding factors such as educational level, body mass index, physical activity and sleep duration were also taken into account in our models. We calculated all p-trend values using the original continuous variables. All analyses have

been performed taking into account the aggressiveness of the tumour based on the Gleason Score at diagnosis (low aggressiveness: Gleason Score <7 or Gleason Score =7 including subjects for whom the two most commonly represented grades in the tumour are 3+4, as well as those for which the two grades are not known, high aggressiveness: Gleason Score >8 or Gleason Score =7 including subjects for whom the two grades are 4+3). Indeed, prostate cancer with a Gleason Score =7 (3+4) has been recognised to be less aggressive than prostate cancer with a Gleason Score =7 (4+3).

We also stratified analyses on individual characteristics such as sleep duration and chronotype.

RESULTS

Characteristics of the study population are reported in table 1. Age, ethnic origin, educational level, body mass index (BMI), physical activity, smoking status, alcohol consumption, chronotype and lifetime average sleep duration per night were identically distributed among cases and controls. As expected, a family history of prostate cancer in first-degree relatives was significantly higher in cases (22.2%) than in controls (8.8%) (p<0.0001).

Overall, 36% of the cases and controls had ever worked at night (OR=0.97, 95% CI 0.79 to 1.19), of which 28% on permanent night work (OR=1.04, 95% CI 0.82 to 1.32) and 15% on rotating night work (OR=0.81, 95% CI 0.59 to 1.16) (table 2). The type of night shift (early morning, late evening and overnight shift), total duration of night work, total frequency of night work and number of consecutive nights, either on permanent or rotating night work, were not associated to prostate cancer. However, a shift length longer than 10 hours was associated with an elevated risk of prostate cancer (OR=1.57, 95% CI 1.01 to 2.44), especially among permanent night workers (OR=1.88, 95% CI 1.08 to 3.26). Regarding rotating night work, neither the type of rotation nor the speed of rotation was associated with prostate cancer.

Table 3 shows associations between combined night work indicators and prostate cancer risk. A duration of night work of at least 20 years, in association with at least six consecutive nights or a shift length longer than 10 hours, slightly increased the risk of prostate cancer, even though not significantly (OR=1.45, 95% CI 0.99 to 2.13; OR=1.73, 95% CI 0.95 to 3.16, respectively). Those associations became significant for a duration of at least 30 years (OR=1.71, 95% CI 1.06 to 2.76; OR=2.49, 95% CI 1.11 to 5.61, respectively) and were more specifically observed for permanent night work. A shift length longer than 10 hours in association with a cumulative number of at least 1314 nights or at least 6 consecutive nights also increased the risk of prostate cancer (OR=1.76, 95% CI 1.03 to 3.03; OR=1.86, 95% CI 1.05 to 3.27, respectively), particularly for permanent night work (OR=2.36, 95% CI 1.21 to 4.56; OR=2.57, 95% CI 1.31 to 5.06, respectively).

A duration of at least 20 years, at least six consecutive nights and a shift length of more than 10 hours of permanent night work were associated with aggressive prostate cancer (OR=1.76, 95% CI 1.13 to 2.75; OR=1.87, 95% CI 1.13 to 3.11; OR=2.63, 95% CI 1.23 to 5.63, respectively) (table 4). Those associations were more pronounced when night work indicators were combined two by two for permanent night work and aggressive prostate cancer with an OR of 2.43, 95% CI 1.32 to 4.47 for a duration of at least 20 years and at least six consecutive nights, and an OR of 4.64, 95% CI 1.78 to 12.1 for a duration of at least 20 years and a shift length longer than 10 hours.

Table 1 Sociodemographic characteristics of the EPICAP Study population

	Cases	Controls	
	n=818 (%)	n=875 (%)	P values*
Gleason Score			
≤7 (3+4)	623 (77.4)	_	
≥7 (4+3)	182 (22.6)	_	
Age (years)			0.15
<55	48 (5.9)	59 (6.7)	
(55–60)	99 (12.1)	99 (11.3)	
(60–65)	216 (26.4)	200 (22.9)	
(65–70)	274 (33.5)	283 (32.3)	
≥70	181 (22.1)	234 (26.7)	
Race			0.41
Caucasian	794 (97.1)	855 (97.7)	
Other	24 (2.9)	20 (2.3)	
Family history of prostate cancer			<0.0001
No	632 (77.7)	796 (91.3)	
Yes	181 (22.3)	76 (8.7)	
Educational level			0.59
Primary or less	179 (21.9)	190 (21.7)	
High School	379 (46.3)	424 (48.5)	
University	260 (31.8)	260 (29.6)	
Body mass index			0.57
<25	230 (28.4)	247 (29.1)	
(25–30)	399 (49.2)	397 (46.7)	
≥30	182 (22.4)	206 (24.2)	
Physical activity			0.11
No	191 (23.4)	177 (20.1)	
Yes	626 (76.6)	698 (79.8)	
Smoking			0.27
Non-smoker	240 (29.4)	246 (28.1)	
Former smoker	454 (55.6)	475 (54.3)	
Current smoker	123 (15.1)	157 (17.6)	
Alcohol drinking			0.6
No	72 (8.8)	84 (9.6)	
Yes	745 (91.2)	791 (90.4)	
Chronotype			0.3
Neither chronotype	403 (49.3)	436 (49.8)	
Morning chronotype	301 (36.8)	297 (33.9)	
Evening chronotype	113 (13.8)	142 (16.2)	
Lifetime average sleep duration/night (hours)			0.9
<7	174 (21.3)	186 (21.3)	
7	288 (35.3)	301 (34.4)	
≥8	354 (43.4)	388 (44.3)	

*Age-adjusted p values (except for age).

No association was observed with rotating night work, either for aggressive or less aggressive prostate cancer.

Stratified analyses by chronotype (table 5) showed an elevated risk of prostate cancer among ever night workers with an evening chronotype (OR=1.83, 95% CI 1.05 to 3.19). The risk of prostate cancer also increased with the increase in duration of night work (p *trend*=0.01) among men with an evening chronotype.

Table 2 Associations between night work indicators and prostate cancer risk

	Ever night work		Permanent night work		Rotating night work	
	Cases (n=818) / controls (n=875)	OR*†	Cases (n=742) / controls (n=769)	OR*†	Cases (n=616) / controls (n=667)	OR*†
Never night work	532/556	1.0 (reference)	532/556	1.0 (reference)	532/556	1.0 (Rreference)
Ever night work	286/319	0.97 (0.79 to 1.19)	210/213	1.04 (0.82 to 1.32)	84/111	0.81 (0.59 to 1.16)
Early morning shifts‡	97/119	0.87 (0.64 to 1.18)	61/76	0.87 (0.60 to 1.25)	36/43	0.84 (0.52 to 1.35)
Late evening shifts§	119/131	0.98 (0.74 to 1.30)	69/66	1.10 (0.76 to 1.59)	50/66	0.82 (0.55 to 1.23)
Overnight shifts¶	161/190	0.90 (0.70 to 1.16)	108/122	0.92 (0.68 to 1.23)	58/70	0.86 (0.59 to 1.26)
Total duration of night work (years)						
<20	145/176	0.90 (0.70 to 1.17)	102/107	1.02 (0.75 to 1.38)	50/76	0.72 (0.49 to 1.07)
<10	87/113	0.86 (0.63 to 1.18)	54/65	0.91 (0.62 to 1.35)	39/53	0.79 (0.50 to 1.22)
10–19	58/63	0.98 (0.66 to 1.44)	48/42	1.17 (0.76 to 1.83)	11/23	0.57 (0.27 to 1.21)
≥20	141/143	1.05 (0.80 to 1.38)	108/106	1.06 (0.78 to 1.44)	34/35	0.99 (0.60 to 1.65)
20–29	50/58	0.94 (0.63 to 1.42)	39/48	0.87 (0.56 to 1.37)	19/14	1.29 (0.62 to 2.68)
≥30	91/85	1.12 (0.80 to 1.56)	69/58	1.22 (0.83 to 1.79)	15/21	0.78 (0.39 to 1.55)
p-trend		*0.37*		*0.26*		*0.46*
Total frequency of night work (number of cumulative nights)						
<1314	132/159	0.90 (0.69 to 1.18)	90/88	1.05 (0.76 to 1.46)	54/82	0.71 (0.49 to 1.04)
≥1314	154/160	1.04 (0.80 to 1.35)	120/125	1.03 (0.77 to 1.38)	30/29	1.08 (0.63 to 1.87)
p-trend		*0.94*		*0.89*		*0.92*
Number of consecutive nights						
<6	144/173	0.90 (0.69 to 1.17)	95/98	1.01 (0.74 to 1.39)	58/83	0.77 (0.53 to 1.11)
≥6	124/108	1.24 (0.93 to 1.67)	93/76	1.33 (0.95 to 1.87)	26/27	0.98 (0.55 to 1.74)
p-trend		*0.25*		*0.25*		*0.83*
Shift length (hours)						
<8	18/46	0.44 (0.25 to 0.78)	11/37	0.32 (0.16 to 0.64)	3/9	0.42 (0.11 to 1.57)
8 to 10	97/131	0.79 (0.59 to 1.07)	23/30	0.86 (0.48 to 1.53)	69/92	0.79 (0.56 to 1.12)
>10	54/38	1.57 (1.01 to 2.44)	38/22	1.88 (1.08 to 3.26)	12/10	1.29 (0.54 to 3.07)
p-trend		*0.94*		*0.29*		*0.28*
Direction of shift rotation						
Forward					55/71	0.82 (0.56 to 1.21)
Backward					11/13	0.85 (0.37 to 1.98)
Forward and backward					18/27	0.74 (0.40 to 1.39)
Speed of shift rotation (days)						
Short (≤3)					13/16	0.80 (0.37 to 1.72)
Intermediate (4–5)				41/57	0.82 (0.53 to 1.26)	
Long (≥6)					20/20	0.95 (0.49 to 1.83)
Short/intermediate/long					14/21	0.62 (0.28 to 1.37)

*Adjusted for age, family history of prostate cancer, race, education level.
†95% CI.
‡Shifts starting before 05:00.
§Shifts ending between 21:00 and 02:00.
¶Shifts running from at least 00:00 to 05:00.

DISCUSSION

The EPICAP Study showed that a long duration of permanent night work in combination with a long shift length or at least six consecutive nights was associated with prostate cancer, particularly in men with aggressive prostate cancer. We also observed an overall increased risk among ever night workers in men with an evening chronotype.

Based on the existing epidemiological literature, the evidence of an association between night work and prostate cancer is still conflicting from one study to another.[12–22] Overall, there seems to be a slight association between ever night work and prostate cancer,[12 14 16 20] although other studies did not find any association in men who had ever worked at night.[13 15 17–19 21 22] The difference in assessment and definition of night work used across studies may explain some of the inconsistencies, and may represent different degrees of circadian disruption.

Overall, we did not find any association between night work indicators examined separately, either for permanent or rotating night work, and prostate cancer risk. However, we observed an increased risk of prostate cancer when night work indicators were jointly examined, particularly for a duration of at least 20 years of night work in combination with at least six consecutive nights or a shift length longer than 10 hours. Associations with a long duration of night work were observed in four studies with durations ranging from 10 years to 34 years,[12–14 16] out of the five which reported the duration of night work.[12–16] We observed a more pronounced association with a duration of at least 20 years for aggressive prostate cancer as also shown by the Spanish multicase-control study (MCC-Spain) (OR=1.63, 95% CI 1.08 to 2.45).[13] MCC-Spain was the only study to characterise intensity of night work and observed a slightly increased, but not significant, risk of prostate cancer in men who had worked at

Table 3 Associations between combined night work indicators and prostate cancer risk

	Ever night work		Permanent night work		Rotating night work	
	Cases (n=818)/ controls (n=875)	OR*†	Cases (n=742)/ controls (n=769)	OR*†	Cases (n=616)/ controls (n=667)	OR*†
Never night work	532/556	1.0 (reference)	532/556	1.0 (reference)	532/556	1.0 (reference)
Duration and number of consecutive nights						
<20 years and < 6 nights	87/106	0.89 (0.65 to 1.23)	57/56	1.06 (0.71 to 1.58)	34/57	0.68 (0.43 to 1.06)
<10 years and < 6 nights	56/73	0.84 (0.58 to 1.23)	32/36	0.95 (0.57 to 1.57)	27/41	0.74 (0.44 to 1.23)
10–19 years and < 6 nights	31/33	0.97 (0.57 to 1.63)	25/20	1.24 (0.67 to 2.31)	7/16	0.50 (0.20 to 1.24)
<20 years and ≥ 6 nights	49/53	1.01 (0.67 to 1.54)	35/33	1.21 (0.74 to 2.00)	16/19	0.86 (0.42 to 1.74)
<10 years and ≥ 6 nights	24/28	0.94 (0.53 to 1.67)	14/17	0.96 (0.46 to 2.00)	12/12	0.92 (0.39 to 2.16)
10–19 years and ≥ 6 nights	25/25	1.07 (0.60 to 1.92)	21/16	1.46 (0.75 to 2.86)	4/7	0.74 (0.21 to 2.58)
≥20 years and < 6 nights	57/67	0.87 (0.59 to 1.29)	38/42	0.91 (0.57 to 1.46)	24/26	0.94 (0.52 to 1.71)
20–29 years and < 6 nights	23/27	0.86 (0.48 to 1.55)	14/20	0.74 (0.36 to 1.50)	14/10	1.25 (0.53 to 2.95)
≥30 years and < 6 nights	34/40	0.88 (0.54 to 1.43)	24/22	1.09 (0.59 to 1.99)	10/16	0.72 (0.32 to 1.63)
≥20 years and ≥ 6 nights	75/55	1.45 (0.99 to 2.13)	58/43	1.42 (0.92 to 2.18)	10/8	1.27 (0.49 to 3.33)
20–29 years and ≥ 6 nights	23/23	1.14 (0.62 to 2.08)	19/19	1.08 (0.56 to 2.10)	5/4	1.34 (0.35 to 5.17)
≥30 years and ≥ 6 nights	52/32	1.71 (1.06 to 2.76)	39/24	1.75 (1.01 to 3.03)	5/4	1.22 (0.31 to 4.75)
Duration and shift length						
<20 years and ≤ 10 hours	55/102	0.60 (0.42 to 0.85)	14/27	0.61 (0.31 to 1.20)	41/71	0.63 (0.42 to 0.96)
<10 years and ≤ 10 hours	39/62	0.71 (0.46 to 1.09)	8/11	0.89 (0.35 to 2.26)	32/49	0.70 (0.44 to 1.13)
10–19 years and ≤ 10 hours	16/40	0.42 (0.22 to 0.77)	6/16	0.43 (0.17 to 1.13)	9/22	0.48 (0.21 to 1.06)
<20 years and > 10 hours	24/19	1.39 (0.74 to 2.59)	16/12	1.46 (0.68 to 3.16)	9/5	1.95 (0.64 to 6.00)
<10 years and > 10 hours	13/11	1.31 (0.57 to 3.01)	6/7	1.06 (0.35 to 3.23)	7/4	1.73 (0.49 to 6.11)
10–19 years and > 10 hours	11/8	1.47 (0.58 to 3.74)	10/5	1.99 (0.66 to 5.94)	2/1	2.76 (0.25 to 30.78)
≥20 years and ≤ 10 hours	60/75	0.83 (0.57 to 1.21)	20/40	0.51 (0.29 to 0.90)	31/30	1.03 (0.60 to 1.77)
20–29 years and ≤ 10 hours	23/25	0.94 (0.52 to 1.71)	4/14	0.28 (0.09 to 0.87)	18/12	1.43 (0.66 to 3.08)
≥30 years and ≤ 10 hours	37/50	0.77 (0.48 to 1.22)	16/26	0.65 (0.34 to 1.25)	13/18	0.75 (0.36 to 1.59)
≥20 years and > 10 hours	30/19	1.73 (0.95 to 3.16)	22/10	2.35 (1.08 to 5.11)	3/5	0.63 (0.15 to 2.75)
20–29 years and > 10 hours	10/10	1.07 (0.43 to 2.66)	8/5	1.69 (0.53 to 5.34)	1/2	0.41 (0.03 to 4.94)
≥30 years and > 10 hours	20/9	2.49 (1.11 to 5.61)	14/5	3.07 (1.07 to 8.80)	2/3	0.82 (0.13 to 4.95)
Shift length and total frequency of night work (cumulative number of nights)						
≤10 hours and < 1314 nights	55/94	0.64 (0.45 to 0.93)	12/17	0.77 (0.36 to 1.66)	47/77	0.66 (0.45 to 0.98)
≤10 hours and ≥ 1314 nights	60/83	0.74 (0.51 to 1.08)	22/50	0.47 (0.27 to 0.80)	25/24	1.06 (0.59 to 1.93)
>10 hours and < 1314 nights	17/14	1.24 (0.59 to 2.58)	9/8	1.13 (0.42 to 3.02)	7/5	1.39 (0.43 to 4.53)
>10 hours and ≥ 1314 nights	37/24	1.76 (1.03 to 3.03)	29/14	2.36 (1.21 to 4.56)	5/5	1.16 (0.33 to 4.13)
Shift length and number of consecutive nights						
≤10 hours and < 6 nights	65/105	0.68 (0.48 to 0.96)	13/26	0.54 (0.27 to 1.09)	50/76	0.72 (0.49 to 1.06)
≤10 hours and ≥ 6 nights	49/62	0.81 (0.54 to 1.22)	18/33	0.58 (0.32 to 1.07)	22/24	0.93 (0.50 to 1.71)
>10 hours and < 6 nights	15/15	1.10 (0.52 to 2.32)	4/7	0.60 (0.16 to 2.15)	8/7	1.24 (0.44 to 3.55)
>10 hours and ≥ 6 nights	35/21	1.86 (1.05 to 3.27)	30/13	2.57 (1.31 to 5.06)	4/3	1.36 (0.29 to 6.26)

*Adjusted for age, family history of prostate cancer, race, education level.
†95% CI.

least 2857 nights over their lifetime (OR=1.30, 95%CI 0.97 to 1.74),[13] while our results did not show any association with the total number of nights worked except when total number of nights worked was combined with a shift length longer than 10 hours.

In our study, we were able to characterise night work with other indicators already studied in many breast cancer studies, as the number of cumulative nights and type (early morning, late evening and overnight) or length of the shift, but not yet studied in prostate cancer studies. Among those indicators, we observed an increased risk of aggressive prostate cancer in men working at least six consecutive nights and in men with a shift length longer than 10 hours, as already observed for breast cancer.[31 32] Our results, more specifically observed in aggressive prostate cancer, may suggest that circadian disruption due to night work may play a role in cancer promotion, as observed in experimental animal studies.[33]

To date, our study is the first to include detailed information on rotating night work such as direction and speed of the rotation, as recommended by the IARC group of experts.[24] We did not find any association with those rotating night work indicators.

Taking into account individual characteristics such as the individual chronotype, we found an association between ever night work and prostate cancer among men with an evening chronotype, as observed in two previous studies.[13 17] This finding was surprising and did not support the hypothesis of a better adaptation or tolerance to night work in evening types.[34 35] Indeed, evening types usually got asleep more easily than morning types after night work and sleep more extensively.[35] Therefore, chronotype may influence the individual sensitivity to circadian

Table 4 Association of night work indicators and prostate cancer risk, by prostate cancer aggressiveness

	Permanent night work				Rotating night work			
	Gleason Score ≤7 (3+4) n=566		Gleason Score ≥7 (4+3) n=165		Gleason Score ≤7 (3+4) n=478		Gleason Score ≥7 (4+3) n=127	
	Cases (n=566)/ controls (n=769)	OR*†	Cases (n=165)/ controls (n=769)	OR*†	Cases (n=478)/ controls (n=667)	OR*†	Cases (n=127)/ controls (n=667)	OR*†
Never night work	416/566	1.0 (Reference)	107/556	1.0 (Reference)	416/556	1.0 (Reference)	107/556	1.0 (Reference)
Ever night work	150/213	0.97 (0.75 to 1.25)	58/213	1.41 (0.98 to 2.04)	62/111	0.78 (0.55 to 1.11)	20/111	0.92 (0.54 to 1.58)
Total duration of night work (in years)								
<20	79/107	1.05 (0.76 to 1.47)	23/107	1.09 (0.66 to 1.81)	36/76	0.69 (0.45 to 1.07)	12/76	0.78 (0.40 to 1.51)
≥20	71/106	0.89 (0.63 to 1.25)	35/106	1.76 (1.13 to 2.75)	26/35	0.96 (0.55 to 1.67)	8/35	1.26 (0.55 to 2.89)
p-trend		0.97		0.003		0.37		0.11
Total frequency of night work (number of cumulative nights)								
<1314	63/88	1.04 (0.72 to 1.49)	27/88	1.27 (0.78 to 2.05)	40/82	0.70 (0.46 to 1.06)	12/82	0.75 (0.39 to 1.44)
≥1314	85/125	1.01 (0.74 to 1.40)	33/125	1.14 (0.73 to 1.77)	22/29	1.00 (0.55 to 1.82)	8/29	1.41 (0.61 to 3.24)
p-trend		*0.97*		*0.79*		*0.96*		*0.56*
Number of consecutive nights								
<6	67/98	0.95 (0.67 to 1.35)	27/98	1.46 (0.90 to 1.37)	39/83	0.67 (0.44 to 1.01)	19/83	1.23 (0.70 to 2.16)
≥6	66/76	1.20 (0.83 to 1.73)	26/76	1.87 (1.13 to 3.11)	23/27	1.18 (0.65 to 2.14)	1/27	0.16 (0.02 to 1.23)
p-trend		*0.28*		*0.35*		*0.75*		*0.85*
Shift length (hours)								
≤10	23/67	0.48 (0.29 to 0.80)	11/67	0.88 (0.44 to 1.74)	54/101	0.75 (0.52 to 1.09)	16/101	0.83 (0.46 to 1.48)
>10	25/22	1.65 (0.90 to 3.01)	12/22	2.63 (1.23 to 5.63)	8/10	1.07 (0.40 to 2.82)	4/10	1.76 (0.52 to 5.97)
p-trend		*0.75*		*0.04*		*0.21*		*0.95*
Duration (years) × number of consecutive nights								
<20 × <6	43/56	1.08 (0.70 to 1.66)	14/56	1.30 (0.68 to 2.47)	23/57	0.60 (0.36 to 1.01)	11/57	1.00 (0.50 to 2.00)
<20 × ≥6	27/33	1.23 (0.72 to 2.10)	8/33	1.30 (0.57 to 2.93)	13/19	0.96 (0.45 to 2.03)	1/19	0.22 (0.03 to 1.71)
≥20 × <6	24/42	0.76 (0.45 to 1.30)	13/42	1.61 (0.82 to 3.16)	16/26	0.78 (0.40 to 1.54)	8/26	1.77 (0.75 to 4.17)
≥20 × ≥6	39/43	1.16 (0.72 to 1.87)	18/43	2.43 (1.32 to 4.47)	10/8	1.69 (0.64 to 4.46)	0/8	–
Duration (years) × shift length (hours)								
<20 × ≤10	9/27	0.53 (0.24 to 1.17)	5/27	1.04 (0.39 to 2.81)	30/71	0.62 (0.39 to 0.99)	9/71	0.64 (0.31 to 1.35)
<20 × >10	13/12	1.57 (0.70 to 3.52)	3/12	1.11 (0.30 to 4.10)	6/5	1.59 (0.46 to 5.41)	3/5	2.49 (0.55 to 11.26)
≥20 × ≤10	14/40	0.45 (0.23 to 0.86)	6/40	0.77 (0.31 to 1.90)	24/30	1.01 (0.56 to 1.81)	7/30	1.31 (0.54 to 3.16)
≥20 × >10	12/10	1.76 (0.73 to 4.23)	9/10	4.64 (1.78 to 12.13)	2/5	0.54 (0.10 to 2.99)	1/5	0.99 (0.11 to 8.81)
Shift length (hours) × total frequency of night work (cumulative number of nights)								
≤10 × < 1314	6/17	0.50 (0.19 to 1.32)	6/17	2.01 (0.76 to 5.30)	34/77	0.63 (0.41 to 0.99)	11/77	0.74 (0.38 to 1.47)
≤10 × ≥ 1314	17/50	0.48 (0.26 to 0.84)	5/50	0.52 (0.20 to 1.35)	20/24	1.09 (0.58 to 2.07)	5/24	1.09 (0.40 to 2.99)
>10 × < 1314	7/8	1.21 (0.42 to 3.45)	2/8	0.95 (0.19 to 4.81)	6/5	1.57 (0.46 to 5.37)	1/5	0.77 (0.08 to 7.12)
>10 × ≥ 1314	18/14	1.97 (0.94 to 4.09)	10/14	3.79 (1.58 to 9.12)	2/5	0.55 (0.10 to 3.02)	3/5	2.86 (0.65 to 12.50)
Shift length (hours) × number of consecutive nights								
≤10 × <6	8/26	0.45 (0.20 to 1.04)	5/26	1.03 (0.38 to 2.80)	35/76	0.66 (0.42 to 1.02)	15/76	1.08 (0.59 to 1.99)
≤10 × ≥6	13/33	0.53 (0.27 to 1.04)	5/33	0.82 (0.31 to 2.18)	19/24	1.10 (0.57 to 2.09)	1/24	0.19 (0.02 to 1.42)
>10 × <6	3/7	0.71 (0.18 to 2.83)	1/7	0.51 (0.06 to 4.43)	4/7	0.76 (0.21 to 2.78)	4/7	2.50 (0.69 to 9.03)
>10 × ≥6	19/13	2.12 (1.02 to 4.44)	10/13	4.30 (1.77 to 10.44)	4/3	1.74 (0.37 to 8.06)	0/3	–
Direction of shift rotation								
Forward					42/71	0.82 (0.54 to 1.25)	12/71	0.86 (0.45 to 1.69)
Backward					5/13	0.73 (0.28 to 1.91)	3/13	1.10 (0.30 to 4.04)
Forward and backward					13/27	0.70 (0.34 to 1.40)	5/27	0.97 (0.36 to 2.62)
Speed of shift rotation (in days)								
Short (≤3)					9/19	0.70 (0.29 to 1.65)	4/16	1.16 (0.37 to 3.62
Intermediate (4–5)					27/57	0.71 (0.43 to 1.15)	13/57	1.26 (0.65 to 2.43)
Long (≥6)					18/20	1.18 (0.60 to 2.34)	1/20	0.20 (0.03 to 1.52)
Short/intermediate/ long					8/18	0.62 (0.26 to 1.47)	2/18	0.64 (0.14 to 2.85)

*Adjusted for age, family history of prostate cancer, race, education level.
† 95% CI.

disruption due to night work and is one important component of circadian disruption to take into account in future studies.

To improve our understanding of the role of night work in prostate cancer risk, epidemiological studies need to better capture all aspects of circadian disruption. This includes identifying night work patterns and individual characteristics that may have a strong impact on the internal circadian rhythm and studying clock genes polymorphisms. Indeed, clock genes polymorphisms have been associated with chronotype,[36] and they may also modify the association between night work and cancer.[37 38] Consideration of these polymorphisms in epidemiological studies on night work and cancer is therefore important.

Besides the circadian disruption driven by the biological clock, we also need to consider short sleep by itself, as a potential risk factor for cancer, especially on a long-term basis.[9 39] Night work is associated daily with a sleep deficit of about 1 hour compared with day workers. It may be hypothesised, considering the role of slow wave sleep on immunity than sleep deficit by itself may promote cancer and increase its severity.

Our findings are based on a large carefully designed population-based case-control study conducted to specifically assess the

Table 5 Association between night work indicators and prostate cancer risk, stratified by chronotype

	Morning chronotype		Neither chronotype		Evening chronotype	
	n=598		n=839		n=255	
	Cases (n=301)/ controls (n=297)	OR*†	Cases (n=403)/ controls (n=436)	OR*†	Cases (n=113)/ controls (n=142)	OR*†
Never night work	202/181	1.0 (Reference)	270/282	1.0 (Reference)	60/93	1.0 (Reference)
Ever night work	99/116	0.77 (0.54 to 1.10)	133/154	0.96 (0.51 to 1.78)	53/49	1.83 (1.05 to 3.19)
Permanent night work	76/68	1.02 (0.68 to 1.54)	94/109	0.93 (0.67 to 1.30)	39/36	1.71 (0.93 to 3.14)
Rotating night work	23/48	0.43 (0.25 to 0.75)	43/48	1.02 (0.64 to 1.62)	17/15	1.95 (0.84 to 4.53)
Total duration of night work (in years)						
<20	47/68	0.64 (0.42 to 1.00)	72/80	0.99 (0.68 to 1.44)	25/28	1.57 (0.79 to 3.12)
<10	22/42	0.47 (0.26 to 0.82)	49/51	1.11 (0.71 to 1.72)	16/20	1.45 (0.65 to 3.22)
10–19	25/26	0.97 (0.53 to 1.78)	23/29	0.80 (0.44 to 1.45)	9/8	1.80 (0.62 to 5.19)
≥20	52/48	0.96 (0.60 to 1.54)	61/74	0.92 (0.62 to 1.36)	28/21	2.14 (1.06 to 4.30)
20–29	19/16	1.11 (0.54 to 2.29)	22/34	0.74 (0.42 to 1.32)	9/8	1.64 (0.56 to 4.82)
≥30	33/32	0.90 (0.51 to 1.58)	39/40	1.07 (0.66 to 1.74)	19/13	2.46 (1.07 to 5.61)
p-trend		*0.74*		*0.78*		*0.01*
Total frequency of night work (number of cumulative nights)						
<1314	41/61	0.60 (0.38 to 0.95)	64/72	0.98 (0.66 to 1.44)	26/26	1.79 (0.90 to 3.55)
≥1314	58/55	0.98 (0.63 to 1.54)	69/82	0.94 (0.65 to 1.37)	27/23	1.87 (0.93 to 3.75)
p-trend		*0.89*		*0.57*		*0.26*
Number of consecutive nights						
<6	46/56	0.74 (0.47 to 1.17)	71/93	0.83 (0.58 to 1.21)	27/24	1.91 (0.96 to 3.78)
≥6	49/46	1.01 (0.63 to 1.62)	51/41	1.33 (0.84)	23/21	2.00 (0.95 to 4.24)
p-trend		*0.67*		*0.24*		*0.95*
Shift length (hours)						
≤10	34/68	0.44 (0.27 to 0.71)	57/83	0.79 (0.53 to 1.16)	23/26	1.57 (0.77 to 3.22)
>10	24/14	1.70 (0.83 to 3.47)	22/18	1.37 (0.71 to 2.67)	8/6	2.08 (0.65 to 6.62)
p-trend		*0.51*		*0.94*		*0.07*
Duration (years) × number of consecutive nights						
<20 × <6 nights	25/39	0.59 (0.34 to 1.03)	45/50	0.98 (0.62 to 1.54)	17/17	1.63 (0.74 to 3.58)
≥20 × <6 nights	21/17	1.09 (0.53 to 2.22)	26/43	0.65 (0.38 to 1.11)	10/7	2.16 (0.73 to 6.37)
<20 × ≥6 nights	20/21	0.93 (0.48 to 1.80)	22/23	1.01 (0.54 to 1.89)	6/9	1.25 (0.37 to 4.29)
≥20 × ≥6 nights	29/25	1.09 (0.59 to 2.02)	29/18	1.74 (0.93 to 3.26)	17/12	2.26 (0.93 to 5.49)
Duration (years) x shift length (hours)						
<20 × ≤10	13/41	0.30 (0.15 to 0.59)	31/42	0.83 (0.50 to 1.38)	10/19	1.02 (0.41 to 2.54)
≥20 × ≤10	21/27	0.65 (0.33 to 1.25)	26/41	0.73 (0.42 to 1.26)	13/7	2.77 (0.99 to 7.78)
<20 × >10	11/6	1.97 (0.69 to 5.60)	10/11	1.01 (0.41 to 2.50)	3/2	1.92 (0.30 to 12.24)
≥20 × >10	13/8	1.52 (0.60 to 3.88)	12/7	1.91 (0.73 to 5.04)	5/4	2.12 (0.50 to 9.02)
Shift length (hours) × total frequency of night work (number of cumulative nights)						
≤10 × < 1314 nights	14/37	0.35 (0.18 to 0.68)	27/40	0.78 (0.46 to 1.33)	13/17	1.45 (0.60 to 3.48)
≤10 × ≥ 1314 nights	20/21	0.52 (0.27 to 0.98)	30/43	0.79 (0.47 to 1.33)	10/9	1.75 (0.60 to 5.07)
>10 × < 1314 nights	7/5	1.46 (0.44 to 4.79)	8/6	1.36 (0.45 to 4.14)	2/3	0.75 (0.11 to 4.93)
>10 × ≥ 1314 nights	17/9	1.93 (0.80 to 4.63)	14/12	1.33 (0.59 to 3.00)	6/3	3.70 (0.82 to 16.67)
Shift length (hours) × number of consecutive nights						
≤10 × <6 nights	18/37	0.43 (0.23 to 0.79)	33/54	0.72 (0.44 to 1.17)	14/14	1.72 (0.71 to 4.19)
≤10 × ≥6 nights	16/28	0.48 (0.24 to 0.95)	23/22	1.13 (0.60 to 2.11)	9/12	1.35 (0.49 to 3.76)
>10 × <6 nights	4/5	0.85 (0.22 to 3.29)	7/8	1.01 (0.34 to 2.93)	4/2	2.52 (0.42 to 15.19)
>10 × ≥6 nights	17/9	1.92 (0.81 to 4.58)	14/9	1.62 (0.68 to 3.90)	4/3	2.57 (0.53 to 12.54)

*Adjusted for age, family history of prostate cancer, race, education level.
†95% CI.

role of circadian disruption, including night work, in prostate cancer. The study has been implemented in the Hérault region of France, owing to the existence of a general Cancer Registry created since 1983, thus facilitating the exhaustive identification of all incident prostate cancer cases. In 2011, the Hérault Cancer Registry observed 770 new cases of prostate cancer, of which 575 were under 75 years of age. Considering that the number of cases observed in 2011 was identical, approximately 1150 new cases were expected during the study period (2012–2013). Overall, we identified 1098 eligible cases suggesting that the recruitment of cases in the EPICAP Study was exhaustive, thus limiting a potential selection bias. Controls were randomly selected from the general population of the Hérault region using quotas on age (5-year age groups) to reflect the age distribution of the cases. Moreover, quotas by SES have been established to yield a control group similar to the general population of the

same age in the Hérault region, in terms of SES. After the selection process, we compared the distribution by SES between our control group and the male general population of the Hérault region and found no difference, indicating that no major selection bias by SES had occurred. In addition, the prevalence of night work in the EPICAP Study controls (~35%) is quite similar to that observed in the general population of men in France[25] or in Europe.[26] Despite the high overall prevalence of night work in our study, our results may have suffered from a lack of power in some subanalyses such as those stratified by chronotype or rotating night work according to prostate cancer aggressiveness.

Recall bias cannot be totally ruled out although it has been minimised by the use of standardised questionnaires and the similar interviewing conditions for cases and controls. Information on lifetime occupational history and on work time schedule has been self-reported by cases and controls which may have induced a classification bias. However, a recent study has compared working time information based on payroll data and questionnaires, highly validating self-reported assessment of shift work with night work and permanent night shifts,[40] therefore strongly supporting our exposure assessment method.

All models were systematically adjusted for well-established risk factors of prostate cancer (age, ethnic origin and family history of prostate cancer in first-degree relatives) and our results remained unchanged after adjustment for potential confounders. Nevertheless, exposure to light at night during the sleep period of the cases and controls and night shift was not available in our data, therefore, we were not able to take into account those important variables for our analyses.

In conclusion, there was no overall association of ever night work, either permanent or rotating, to prostate cancer. Nevertheless, our results suggest that a long duration of permanent night work in combination with a long shift length or at least six consecutive nights may be associated with prostate cancer, particularly in men with aggressive prostate cancer. They also suggest that, overall, prostate cancer risk may be higher in men with an evening chronotype. Further studies, taking into account individual characteristics to circadian disruption such as individual chronotype, clock genes polymorphisms and prostate cancer aggressiveness, are needed to deeply understand role of circadian disruption related to night work in prostate cancer risk.

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