American Journal of Epidemiology

Vol. 188, No. 10
DOI: 10.1093/aje/kwz167
Advance Access publication: July 30, 2019

Original Contribution

Night-Shift Work and Risk of Prostate Cancer: Results From a Canadian Case-Control Study, the Prostate Cancer and Environment Study

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Initially submitted April 12, 2019; accepted for publication July 12, 2019.

Night-shift work involving disruption of circadian rhythms has been associated with breast cancer risk. A role in prostate cancer is also suspected, but evidence is limited. We investigated the association between night-shift work and prostate cancer incidence in the Prostate Cancer and Environment Study (PROtEuS), a population-based case-control study conducted in 2005–2012 in Montreal, Quebec, Canada. Participants were 1,904 prostate cancer cases (432 high-grade cancers) and 1,965 population controls. Detailed work schedules for each job held for at least 2 years ($n = 15{,}724$) were elicited in face-to-face interviews. Night-shift work was defined as having ever worked ≥3 hours between midnight and 5:00 AM ≥3 nights/month for ≥1 year. Unconditional logistic regression was used to estimate odds ratios and 95% confidence intervals for the association between night-shift work and prostate cancer, adjusting for age, ancestry, and education. No association was found between overall prostate cancer and night-shift work metrics, including ever exposure, duration, intensity, cumulative exposure, rotating shifts, and early-morning shifts. For none of the exposure indices was there evidence of heterogeneity in odds ratios between low- and high-grade cancers. Sensitivity analyses restricting exposures to ≥7 nights/month or considering screening history yielded similar results. Our findings lend no support for a major role of night-shift work in prostate cancer development.

case-control studies; circadian rhythm disruption; circadian rhythms; night-shift work; prostate cancer; workplace

Abbreviations: CI, confidence interval; IARC, International Agency for Research on Cancer; OR, odds ratio; PROtEuS, Prostate Cancer and Environment Study.

Prostate cancer is the most frequently diagnosed solid tumor among men in industrialized countries (1). The global burden of the disease is still rising, and more than 2 million men are predicted to be affected worldwide by 2040 (1). Factors other than screening probably contribute to geographical disparities in incidence (2). Age, African ancestry, and a first-degree family history of prostate cancer are the only confirmed risk factors for the disease. Identifying modifiable factors which could be targeted by public health measures for prostate cancer prevention remains a considerable research challenge. A role for Western-related environmental influences, including diet, other lifestyle factors, and workplace exposures, has been suggested in various studies investigating the spatiotemporal trends in prostate cancer (2, 3) and disease risk in Asian migrant populations (4).

Night-shift work is increasingly suspected to be involved in cancer development through a number of compelling mechanisms, including disruption of circadian rhythms. Other mechanisms have been advanced as well (5). Initially proposed for breast cancer, the night-shift work hypothesis was recently extended to prostate cancer. In its 2007 evaluation, the International Agency for Research on Cancer (IARC) classified shift work that involves circadian rhythm disruption as probably carcinogenic to humans on the basis of sufficient evidence from animal models but limited evidence in humans (6). Inadequate and inconsistent exposure assessment was felt to play a key role in the uncertainty around the overall body of evidence on night-shift work and cancer. In response to this, an IARC Working Group issued recommendations to standardize the aspects or domains of night-shift work that were

captured across studies in order to better understand what specific aspects of night-shift work are carcinogenic (7). In its 2018 review (8), the National Toxicology Program concluded that persistent night-shift work that causes circadian rhythm disruption is known to be a human carcinogen. A peer-review panel judged that the evidence for breast cancer was sufficient, while for prostate cancer it was found to be limited. For the latter, several issues were raised, including the small number of methodologically strong investigations, poor characterization of night-shift work exposure across studies, and the fact that few studies have evaluated disease aggressiveness or the role of screening.

The possible role of night-shift work in cancer development continues to be of high scientific and public health interest. Our objective in the present study was to investigate the association between night-shift work, early-morning shifts, and the risk of prostate cancer, applying recommendations for a rigorous exposure assessment protocol.

METHODS

Study design and population

The present work was based on data from the Prostate Cancer and Environment Study (PROtEuS), a large population-based case-control study on prostate cancer conducted in Montreal, Quebec, Canada, in 2005–2012. PROtEuS was primarily conceived to study the role of occupational exposures in prostate cancer. The study design has been described previously (9–11). In brief, eligible cases were patients aged ≤75 years who were diagnosed with a histologically confirmed primary tumor of the prostate in one of the 7 largest French-language hospitals (out of 9) in Montreal during 2005–2009. These patients represented more than 80% of all cases in the study base, according to the tumor registry. Concomitantly, population controls were randomly selected from the electoral list of French-speaking men residing in Montreal, which is continually updated. Eligible controls with a history of prostate cancer were excluded. Cases and controls were frequency-matched by age (±5 years). Among eligible subjects, 79% of cases ($n = 1,937$) and 56% of controls ($n = 1,994$) participated in the study. Refusal (86%) and untraceability (11%) were the main reasons for nonparticipation. Overall, 1,904 cases (1,472 low-grade prostate cancers and 432 high-grade prostate cancers) and 1,965 controls contributed to the analyses.

Data collection

Subjects were interviewed face-to-face by trained interviewers. Data on sociodemographic characteristics, lifestyle habits, medical history, and anthropometric variables and a detailed occupational history were collected. For each job held for at least 2 years, information on work schedules, along with information on tasks, workplace characteristics, equipment used, and protective measures, was elicited. For complex occupations (industrial mechanics, firefighting, etc.), specialized questionnaires ($n = 32$) were also used. Occupations and industries were coded according to Canadian classifications (12, 13).

The PROtEuS protocol was approved by the ethics boards of all participating institutions. All participants provided written informed consent.

Assessment of night-shift work and early-morning shifts

Work schedules and schedule changes (hours, duration, etc.) within each of the 15,724 jobs held were recorded. On the basis of recommendations from the IARC Working Group (7), we defined night-shift work as having ever worked for at least 3 hours between midnight and 5:00 AM. We then restricted our sample of night workers to men who had ever worked at night for at least 1 year with a minimum frequency of 3 nights per month, on average, over the course of their night-shift jobs. Subjects who had never worked at night constituted the reference category in all analyses in which night-shift work was considered.

We assessed exposure to night-shift work through several metrics: 1) ever engaging in night-shift work; 2) engaging in night-shift work with rotation, defined as having ever worked in night shifts involving a rotation with at least 1 other shift; 3) the number of night shifts worked in rotation, categorized as no night-shift work, no rotation, 2 rotations, or 3 rotations; 4) the direction of night-shift work rotation—that is, always forward, always backward, or both; 5) the rate of night-shift work rotation, based on the rate performed the longest over the course of the worker's lifetime—categorized as no night-shift work, daily or 2–4 days/week, weekly, or more than weekly; 6) the cumulative number of days of night-shift work, expressed as the sum of duration times intensity over the course of the worker's career; 7) the total duration of night-shift work, corresponding to the number of years of having worked at least 3 nights/month over the course of the worker's career; 8) the average intensity of night-shift work over the worker's career, expressed as the sum of the product of the number of days per year and the number of years of each job period in night-shift work, divided by the total number of years in night-shift work; and 9) work in night shifts only, without rotation (i.e., permanent night shifts).

Finally, we investigated the role of working in early-morning shifts—that is, starting work after 2:00 AM but before 6:00 AM—at least 3 times per month for at least 1 year. Consistently with the night-shift work metrics, we examined ever exposure, total duration, intensity, and cumulative exposure to early-morning shifts. For the latter analyses, subjects who had never worked in early-morning shifts and night shifts constituted the reference category.

In the main analyses, continuous variables were categorized according to approximate quartiles of the distributions among exposed controls.

Confounding factors

We identified potential confounders using a directed acyclic graph (see Web Figure 1, available at https://academic.oup.com/aje) based on the current knowledge and assumptions about the causal structure of the associations under investigation. Accordingly, our main models included covariates for age at diagnosis (cases) or interview (controls), expressed as <65 years or ≥65 years, ancestry (sub-Saharan African, Asian, French, other European, greater Middle Eastern, Latino, or other), and educational level (primary school or less, high school, college (2–3 years post–high school),

university degree, or other). We had information on several lifestyle and occupational variables, but these were not retained for adjustment based on the directed acyclic graph.

Statistical analysis

Multivariable unconditional logistic regression was used to estimate the association between the different schedule variables and the risk of prostate cancer and to calculate odds ratios and 95% confidence intervals. Assuming that missing data on night-shift work and early-morning shifts (approximately 8% of jobs) were missing at random, and including occupational codes as predictors, we performed multiple imputation by chained equations (14) using 15 data sets. Distributions in the latter were similar to those in observed data. Dose-response relationships were tested by modeling each category as a continuous variable. Polytomous logistic regression models were used to investigate associations with prostate cancer aggressiveness according to the Gleason score at diagnostic biopsy. Gleason scores of ≤6 or 7 (with 3 as the primary score and 4 as the secondary score) defined low-grade tumors (referred to as less aggressive cancers), while scores of ≥8 or 7 (with 4 as the primary score and 3 as the secondary score) defined high-grade (aggressive) cancers (15). The Wald test was used to detect heterogeneity in odds ratios between the two groups.

Because prostate cancer is generally asymptomatic in its early stage, we conducted sensitivity analyses excluding controls who had not been screened in the 2-year period before the interview ($n = 473$), thereby reducing the likelihood of latent cancers in the control series. Moreover, because the cutoff of ≥3 nights/month, which was previously used in other studies of rotating night-shift work and cancer (16, 17), is arbitrary and represents a low frequency of night-shift work, we conducted sensitivity analyses with a higher cutoff (≥7 nights/month for at least 1 year) to capture night-shift workers with higher exposures.

We also explored the timing of night-shift work over the course of the participants' careers—that is, whether the last job entailing night-shift work had been held within the 20 years prior to the index date or further in the past.

All analyses were performed using SAS (version 9.4; SAS Institute, Inc., Cary, North Carolina). Statistical tests were 2-sided.

RESULTS

The main characteristics of cases and controls are presented in Table 1. Most subjects were of French descent. As expected, a greater proportion of cases than of controls were of sub-Saharan African ancestry and had a positive family history of prostate cancer. Controls were generally more educated and were older by 1 year, on average, than cases owing to the slightly longer time required to secure interviews. Reported night-shift jobs involved mainly protective services (16.4% of jobs), materiel handling (6.0%), and motor transport operations (5.7%). More specifically (Table 2), night-shift work occurred most frequently among firefighters (88.3% of jobs), persons in distilling, subliming, and carbonizing occupations (81.8%), deck officers (80.0%), and airline pilots and flight workers (68.8%).

Associations between night-shift work and overall prostate cancer risk are shown in Table 3. Compared with men who had never engaged in night-shift work, there was no clear evidence that those who had were at increased risk of prostate cancer for any of the metrics evaluated, including categories representing the highest exposures. Some risk estimates were slightly above 1, but confidence intervals included the null value in all metric categories, and no dose-response patterns emerged. A modest increase in risk was observed among men who had always worked on night-shift schedules involving forward rotation (odds ratio (OR) = 1.23, 95% confidence interval (CI): 0.96, 1.58).

In additional analyses, we investigated whether associations with the different metrics varied according to tumor aggressiveness (Table 4). For low-grade cancers, some elevated risks were apparent in the highest category of intensity of rate of rotation (OR = 2.10, 95% CI: 0.99, 4.47), based on small numbers, but other associations were not elevated. No clear patterns emerged for aggressive tumors. *P* values for heterogeneity between low- and high-grade cancers varied between 0.15 and 0.94.

Odds ratios for overall prostate cancer based on the timing of the last night-shift job were 1.07 (95% CI: 0.82, 1.40) when the last night-shift job occurred within 20 years of the index date and 0.95 (95% CI: 0.65, 1.38) when it was further in the past. Among current/recent night-shift workers (last night-shift job within 2 years of the index date), the odds ratio was 1.28 (95% CI: 0.85, 1.91). Timing of exposure was not associated with tumor aggressiveness (data not shown).

In additional analyses, we examined associations with early-morning shifts (Table 5). We found no increased risks with duration or intensity of exposure or with cumulative exposure. There was no heterogeneity in odds ratios between tumor grades.

We conducted several sensitivity analyses. Increasing the cutoff defining exposure to night-shift work from ≥3 nights/month to ≥7 nights/month did not substantially alter results (Web Table 1).

When restricting controls to men who had been screened for prostate cancer during the 2 years prior to interview, risk estimates for overall prostate cancer and according to tumor aggressiveness remained largely unchanged for night-shift work or early-morning shifts (Web Tables 2 and 3).

Complete-case analyses without imputations generated findings consistent with those from our main analyses. Results based on tertiles of exposure, which allowed for greater numbers of subjects in individual categories, were also consistent with those of our main analyses (data not shown).

DISCUSSION

In this large population-based case-control study, we investigated associations between night-shift work, early-morning shifts, and prostate cancer risk. Our results were generally consistent with the absence of associations with prostate cancer overall, as well as associations stratified by disease aggressiveness. The only suggestive positive associations, albeit weak, were for night-shift schedules with forward rotation and for a high rate of rotation (based on small numbers), especially for low-grade tumors.

Table 1. Sociodemographic Characteristics of Cases and Controls in a Study of Night-Shift Work and Risk of Prostate Cancer, PROtEuS, Montreal, Quebec, Canada, 2005–2012

Characteristic	Prostate Cancer Cases (n = 1,904)		Controls (n = 1,965)	
	No.	%	No.	%
Age group, years				
<65	989	51.9	878	44.7
≥65	915	48.1	1,087	55.3
Mean age, years[a]	63.6 (6.8)		64.9 (6.9)	
Ancestry				
Sub-Saharan African	129	6.8	89	4.6
Asian	24	1.3	72	3.7
French	1,422	75.2	1,224	62.6
Other European	243	12.8	434	22.3
Greater Middle Eastern	45	2.4	99	5.1
Latino	28	1.5	31	1.5
Other	1	0.1	3	0.2
Educational level				
Primary school or less	442	23.2	421	21.4
High school	569	29.9	570	29.0
College (2–3 years post–high school)	308	16.2	368	18.7
University degree	580	30.5	604	30.7
Other	5	0.3	2	0.1
First-degree family history of prostate cancer				
No	1,396	76.1	1,717	90.0
Yes	439	23.9	190	10.0

Abbreviation: PROtEuS, Prostate Cancer and Environment Study.
[a] Values are expressed as mean (standard deviation).

The possible mechanisms linking night-shift work and cancer have been reviewed (5, 18). These could explain associations with breast cancer in particular, for which the evidence is most consistent (19), or with cancers at other sites, including the prostate gland, another hormone-dependent organ. There is substantial evidence from animal and experimental studies that exposure to light at night triggers circadian rhythm dysfunction by suppressing melatonin levels and altering expression of clock genes. Both are key protectors against tumor development through inhibition of tumor growth and maintenance of tissue homeostasis. Multiple biological pathways in the carcinogenicity process, such as DNA repair, cell proliferation, and apoptosis, might be involved. There is a line of evidence for a potential link between circadian disruption and prostate cancer risk more specifically (20).

Research evaluating this relationship in humans has been limited. In a 2015 meta-analysis based on 5 cohort studies and 3 case-control studies, Rao et al. (21) reported an overall meta–relative risk of 1.24 in night workers, but differences in definitions of night-shift work and the large heterogeneity across studies weakened this finding. Since then, 4 investigations (2 cohort studies and 2 case-control studies) have found positive associations (22–25), while 2 cohort studies have not (26, 27).

The lack of a consistent definition of night-shift work involving circadian disruption across studies has hampered the ability to draw conclusions from the overall evidence. To our knowledge, ours is the only case-control study to have applied IARC's definition of night-shift work (i.e., work for at least 3 hours between midnight and 5:00 AM). In one cohort study, Hammer et al. (22) also did, reporting no evidence of higher risks among rotating shift workers exposed to night shifts. In another cohort study (23), night-shift work was defined as a shift that included work between midnight and 5:00 AM, although it was not explicit in the report that at least 3 hours of work had to occur within this period.

Most of the cohort studies investigating the association between night-shift work and prostate cancer risk have reported null findings for ever exposure (26–31) or for duration of night-shift work (27), in line with our results. In only 1 German prospective cohort study did researchers report elevated risks among participants with the longest duration of night-shift work, with an indication of a dose-response relationship (23). In the 5 case-control studies conducted to date (24, 25, 32–34), results have been mixed. Some found elevated odds ratios, sometimes marginally elevated, for ever exposure (24, 32–34), and most also did for selected metrics. Our findings are consistent with the absence of a clear association with overall prostate

Table 2. Most Common Jobs Involving Night-Shift Work and Early-Morning Shifts, PROtEuS, Montreal, Quebec, Canada, 2005–2012

Occupation[a]	No. of Persons	% of Jobs Involving Exposure
Occupations involving night-shift work		
Police officers and detectives working for the government	170	50.6
Guards and related security occupations	135	49.6
Physicians and surgeons	87	27.6
Baking, confectionery-making, and related occupations	81	27.2
Fire-fighting occupations	60	88.3
Mail and postal clerks	53	43.4
Musicians	46	43.5
Electronic data-processing equipment operators	39	28.2
Textile-knitting occupations	29	58.6
Bartenders	26	50.0
Molding occupations, rubber, plastic, and related products	25	44.0
Stationary engine and auxiliary equipment operating and maintaining occupations	23	56.5
Occupations in laboring and other elemental work, NEC	23	30.4
Nurses with a nursing diploma, except supervisors	22	31.8
Marine craft fabricating, assembling and repairing occupations	21	33.3
Air transport operations support occupations	20	50.0
Foremen/women, materiel handling and related occupations, NEC	19	31.6
Textile-weaving occupations	19	26.3
Rail transport equipment mechanics and repairmen	18	33.3
Deck crew, ship	17	52.9
Inspecting and testing occupations, equipment repair, NEC	17	35.3
Airline pilots, flight officers, and flight engineers	16	68.8
Electronic equipment fabricating and assembling occupations	16	25.0
Molding, core-making, and metal-casting occupations	15	40.0
Fabricating, assembling, and repairing occupations involving rubber, plastic, and related products, NEC	15	26.7
Supervisors in reception, information, mail, and message distribution occupations	14	42.9
Hotel clerks	13	53.9
Milk processing and related occupations	12	25.0
Distilling, subliming, and carbonizing occupations, chemicals and related materials	11	81.8
Printing and related occupations, NEC	11	27.3
Deck officers	10	80.0
Metal processing and related occupations, NEC	10	60.0
Foremen, metal processing and related occupations	10	40.0
Travel and related attendants, except food and beverage workers	10	40.0
Typists and clerk-typists	10	40.0
Occupations involving early-morning shifts		
Bus drivers	89	28.1
Armed forces	51	27.5
Air transport operations support occupations	20	30.0
General farm workers	19	31.6
Livestock farmers	18	27.8
Deck crew, ship	17	41.2
Airline pilots, flight officers, and flight engineers	16	50.0
Travel and related attendants, except food and beverage workers	10	50.0

Abbreviations: NEC, not elsewhere classified; PROtEuS, Prostate Cancer and Environment Study.

[a] Based on 4-digit codes from the *Canadian Classification and Dictionary of Occupations* (12). Occupations presented had at least 10 jobs and at least 25% exposure to night-shift work or early-morning shifts.

Table 3. Association Between Night-Shift Work and Risk of Overall Prostate Cancer, PROtEuS, Montreal, Quebec, Canada, 2005–2012

Night-Shift Work Metric	No. of Controls	No. of Cases	OR[a]	95% CI
Never engaged in night-shift work	1,548	1,453	1.00	Referent
Ever engaged in night-shift work	403	439	1.07	0.92, 1.26
Cumulative duration of night-shift work, years				
≤4.00	106	120	1.10	0.84, 1.44
4.01–11.00	112	111	1.01	0.76, 1.34
11.01–21.00	87	105	1.17	0.86, 1.59
>21.00	98	103	1.04	0.77, 1.38
P for trend				0.61
Intensity of night-shift work, nights/year				
≤83.33	97	108	1.10	0.82, 1.47
83.34–122.50	106	133	1.20	0.92, 1.56
122.51–240.00	103	92	0.91	0.68, 1.22
>240.00	97	106	1.09	0.81, 1.46
P for trend				0.69
Cumulative no. of night shifts				
≤588	101	119	1.10	0.84, 1.46
589–1,332	100	116	1.20	0.90, 1.59
1,333–2,575	101	115	1.10	0.83, 1.46
>2,575	101	89	0.88	0.65, 1.20
P for trend				0.97
Permanent night-shift work without rotation	7	12	1.22	0.76, 1.95
Night-shift work with rotation				
Never	170	192	1.12	0.89, 1.40
Ever	233	247	1.04	0.86, 1.27
Cumulative duration of night-shift work with rotation, years				
≤4.00	67	59	0.90	0.63, 1.27
4.01–11.00	63	64	1.04	0.72, 1.50
11.01–21.00	46	56	1.10	0.74, 1.64
>21.00	57	68	1.19	0.83, 1.72
P for trend				0.64
Intensity of night-shift work with rotation, nights/year				
≤81.67	68	81	1.14	0.81, 1.59
81.68–84.00	51	63	1.14	0.78, 1.65
84.01–125.00	65	62	0.96	0.65, 1.40
>125.00	49	41	0.93	0.60, 1.44
P for trend				0.67
Cumulative no. of night shifts with rotation				
≤490	59	61	0.99	0.68, 1.44
491–1,111	57	60	1.10	0.75, 1.63
1,112–2,292	59	68	1.07	0.75, 1.53
>2,292	58	58	1.02	0.69, 1.49
P for trend				0.93
Direction of shift rotation				
Always forward	131	158	1.23	0.96, 1.58
Always backward	3	1	0.29	0.03, 2.80
Both	78	69	0.92	0.66, 1.29
Not classifiable	21	19	0.94	0.50, 1.77

Table continues

Table 3. Continued

Night-Shift Work Metric	No. of Controls	No. of Cases	OR[a]	95% CI
Rate of shift rotation				
Daily or 2–4 days/week	12	19	1.70	0.81, 3.57
Weekly	171	169	1.00	0.80, 1.27
More than weekly	28	39	1.40	0.85, 2.31
Not classifiable	22	20	0.94	0.50, 1.75
No. of night shifts with rotation				
0 (no rotation)	170	192	1.12	0.89, 1.40
2	90	80	0.89	0.64, 1.24
3	143	167	1.14	0.89, 1.46

Abbreviations: CI, confidence interval; OR, odds ratio; PROtEuS, Prostate Cancer and Environment Study.
[a] ORs were adjusted for age, ancestry, and education and based on the imputed data for night-shift work metrics (8%).

cancer, notwithstanding the metric used, including total duration, intensity, and cumulative exposure to night-shift work. These results concur with those from other studies based on the duration of night-shift work (25, 32) and/or cumulative exposure (25, 34). However, they contrast with previous observations among workers with the longest durations of night-shift work (odds ratios of 1.38 and 2.68 based on ≥28 years and ≥10 years, respectively) (33, 34) and results obtained when long duration was combined with a longer shift length (OR = 2.49) or a higher number of consecutive nights worked (OR = 1.71) (25).

We observed no excess risk among men performing night-shift work in rotation with another shift. While 2 prospective cohort studies found higher risks among rotating shift workers (22, 28), most studies did not replicate this finding (25, 30, 31, 34). There was weak evidence in our data of elevated risks among night-shift workers with forward rotation schedules and those with the highest rate of shift rotation. Studies evaluating these metrics reported negative findings (22, 25). Forward rotating shifts reportedly have a lesser circadian impact than backward ones (7).

To date, only 2 studies have examined whether early-morning shifts (based on different definitions) are associated with prostate cancer (25, 33), with divergent results. In our study, employment in early-morning shifts, defined as starting work between 2:00 AM and 6:00 AM, was not associated with prostate cancer risk. We did not include workers who started work between midnight and 2:00 AM in our definition, so early-morning workers and night-shift workers were mutually exclusive in our study. However, had we expanded our definition to include subjects starting work at midnight instead of 2:00 AM, this would have added only 11 controls and 7 cases to our exposed group.

Different patterns of risk have been observed between less aggressive and more aggressive prostate tumors with factors such as alcohol (35) or obesity (36), suggesting that different types of tumors may have different sets of risk factors and etiology. In support of this, low-grade and high-grade cancer foci progress largely in parallel, diverging early from a common progenitor. Moreover, there appears to be no direct progression from low-grade disease to metastatic disease (37). We evaluated the possibility that night-shift work and early-morning shift work would be related to risk differently according to disease aggressiveness. This did not appear to be the case. For all exposure metrics, formal statistical testing revealed no heterogeneity in odds ratios between low- and high-grade cancers. Three previous studies have presented odds ratios separately by aggressiveness, although none reported on heterogeneity testing (22, 25, 34). In two of them, most positive findings observed for prostate cancer overall were also found for aggressive tumors (25, 34). While our analyses were based on a relatively large number of aggressive cases, the numbers of exposed subjects in the different metric categories were sometimes limited, possibly reducing the ability to detect associations.

Our study had some limitations. Misclassification of night-shift work and early-morning shifts inevitably occurred, which might have brought risk estimates towards the null. However, several factors likely mitigated this to some extent. PROtEuS was specifically conceived to test hypotheses around workplace exposures and prostate cancer. Subjects provided detailed descriptions of each job held, including specific tasks, which may have helped situate them in their context and may have improved reporting. Interviews were conducted face-to-face by interviewers specially trained for occupational studies. Work schedules were coded by industrial hygienists using full job descriptions.

Assessment of specific work metrics at the population level for over 15,000 jobs proved to be quite challenging, in light of changes in schedules within jobs, irregular schedules (such as on-call and emergency work), and complex schedule information, even using the detailed job descriptions industrial hygienists had access to. Unlike studies conducted in homogeneous occupational groups (e.g., nurses), which are typically characterized by fewer types of schedules, the variability in work hours encountered here across a wide range of occupations complicated the exposure assessment considerably. This was particularly the case when assessing the direction and rate of shift rotation, for which confidence in the assessment was lower than for other metrics. Nevertheless, reports of work histories have been shown to be valid

Table 4. Association Between Night-Shift Work and Prostate Cancer Risk, by Tumor Aggressiveness, PROtEuS, Montreal, Quebec, Canada, 2005–2012

Night-Shift Work Metric	No. of Controls	Low-Grade Prostate Cancer			High-Grade Prostate Cancer		
		No. of Cases	OR[a]	95% CI	No. of Cases	OR[a]	95% CI
Never engaged in night-shift work	1,548	1,127	1.00	Referent	326	1.00	Referent
Ever engaged in night-shift work	403	338	1.08	0.91, 1.28	101	1.07	0.82, 1.39
Cumulative duration of night-shift work, years							
≤4.00	106	93	1.08	0.81, 1.44	27	1.17	0.73, 1.87
4.01–11.00	112	83	0.98	0.72, 1.34	28	1.08	0.69, 1.68
11.01–21.00	87	81	1.20	0.87, 1.66	24	1.09	0.68, 1.75
>21.00	98	81	1.08	0.79, 1.47	22	0.91	0.56, 1.48
P for trend				0.49			0.88
Intensity of night-shift work, nights/year							
≤83.33	97	85	1.12	0.83, 1.52	23	1.03	0.63, 1.67
83.34–122.50	106	106	1.25	0.94, 1.66	27	1.03	0.66, 1.61
122.51–240.00	103	71	0.90	0.65, 1.24	21	0.95	0.58, 1.56
>240.00	97	76	1.03	0.75, 1.43	30	1.25	0.80, 1.94
P for trend				0.83			0.56
Cumulative no. of night shifts							
≤588	101	94	1.10	0.83, 1.47	25	1.11	0.68, 1.82
589–1,332	100	85	1.14	0.84, 1.56	31	1.37	0.88, 2.12
1,333–2,575	101	91	1.15	0.85, 1.56	24	0.95	0.60, 1.52
>2,575	101	68	0.90	0.65, 1.26	21	0.83	0.50, 1.36
P for trend				0.83			0.72
Permanent night-shift work without rotation	7	10	1.27	0.78, 2.09	2	1.02	0.46, 2.25
Night-shift work with rotation							
Never	170	140	1.06	0.83, 1.36	52	1.29	0.92, 1.83
Ever	233	198	1.09	0.88, 1.34	49	0.90	0.64, 1.28
Cumulative duration of night-shift work with rotation, years							
≤4.00	67	49	0.93	0.65, 1.35	10	0.77	0.39, 1.52
4.01–11.00	63	48	1.02	0.69, 1.51	16	1.10	0.62, 1.94
11.01–21.00	46	46	1.19	0.78, 1.80	10	0.85	0.43, 1.69
>21.00	57	55	1.29	0.88, 1.89	13	0.91	0.49, 1.69
P for trend				0.38			0.51
Intensity of night-shift work with rotation, nights/year							
≤81.67	68	67	1.22	0.86, 1.73	14	0.89	0.48, 1.65
81.68–84.00	51	49	1.16	0.77, 1.73	14	1.07	0.59, 1.93
84.01–125.00	65	50	1.02	0.68, 1.52	12	0.77	0.40, 1.50
>125.00	49	32	0.93	0.58, 1.50	9	0.90	0.44, 1.86
P for trend				0.92			0.38
Cumulative no. of night shifts with rotation							
≤490	59	49	1.00	0.68, 1.48	12	0.94	0.49, 1.83
491–1,111	57	48	1.16	0.77, 1.74	12	0.94	0.48, 1.82
1,112–2,292	59	52	1.08	0.74, 1.59	16	1.04	0.59, 1.82
>2,292	58	49	1.13	0.75, 1.70	9	0.68	0.33, 1.40
P for trend				0.17			0.48
Direction of shift rotation							
Always forward	131	122	1.25	0.95, 1.63	36	1.18	0.80, 1.76
Always backward	3	1	0.36	0.04, 3.51	0		
Both	78	59	1.05	0.73, 1.49	10	0.55	0.28, 1.07
Not classifiable	21	16	1.03	0.53, 2.02	3	0.63	0.19, 2.15

Table continues

Table 4. Continued

Night-Shift Work Metric	No. of Controls	Low-Grade Prostate Cancer			High-Grade Prostate Cancer		
		No. of Cases	OR[a]	95% CI	No. of Cases	OR[a]	95% CI
Rate of shift rotation							
Daily or 2–4 days/week	12	18	2.10	0.99, 4.47	1	0.39	0.05, 3.01
Weekly	171	130	1.02	0.79, 1.30	39	0.97	0.66, 1.41
More than weekly	28	34	1.61	0.96, 2.70	5	0.75	0.29, 2.70
Not classifiable	22	16	0.98	0.51, 1.91	4	0.79	0.27, 2.33
No. of night shifts with rotation							
0 (no rotation)	170	140	1.06	0.83, 1.36	52	1.29	0.92, 1.83
2	90	66	0.95	0.68, 1.34	14	0.70	0.38, 1.27
3	143	132	1.17	0.90, 1.53	35	1.03	0.69, 1.54

Abbreviations: CI, confidence interval; OR, odds ratio; PROtEuS, Prostate Cancer and Environment Study.
[a] ORs were adjusted for age, ancestry, and education and based on the imputed data for night-shift work metrics (8%).

(38), and in a recent validity study in which self-reported exposure to night-shift work was investigated, self-reports of night-shift work showed the best performance compared with other factors (39).

Another limitation was our lack of information on sleep patterns, rest periods after night-shift work, light-at-night exposure during sleep and during leisure time, and chronotype. A few studies have incorporated information about the latter

Table 5. Association Between Early-Morning Shift Work and Risk of Prostate Cancer, PROtEuS, Montreal, Quebec, Canada, 2005–2012

Early-Morning Shift Metric	No. of Controls	All Prostate Cancer			Low-Grade Prostate Cancer			High-Grade Prostate Cancer		
		No. of Cases	OR[a]	95% CI	No. of Cases	OR[a]	95% CI	No. of Cases	OR[a]	95% CI
Never worked in early-morning shift and night shift	1,497	1,383	1.00	Referent	1,078	1.00	Referent	305	1.00	Referent
Ever worked in early-morning shift	112	137	1.19	0.91, 1.56	103	1.19	0.89, 1.59	34	1.21	0.80, 1.83
Cumulative duration of early-morning shifts, years										
≤4.00	32	37	1.14	0.69, 1.90	29	1.17	0.67, 2,01	8	1.08	0.47, 2.48
4.01–9.00	26	34	1.17	0.69, 1.98	22	1.01	0.56, 1.81	12	1.68	0.84, 3.38
9.01–20.00	27	40	1.51	0.88, 2.61	31	1.56	0.89,2.72	9	1.41	0.60, 3.30
>20.00	27	26	0.93	0.53, 1.63	21	1.01	0.56, 1.84	5	0.69	0.26,1.82
P for trend			0.30			0.30			0.58	
Intensity of early-morning shifts, days/year										
≤137.88	29	31	1.05	0.62, 1.77	27	1.20	0.70, 2.05	4	0.62	0.22, 1.71
137.89–245.00	28	46	1.59	0.98, 2.59	34	1.58	0.94, 2.65	12	1.64	0.80, 3,33
245.01–301.30	27	34	1.05	0.62, 1.77	22	0.89	0.50, 1,58	12	1.58	0.74, 3.39
>301.30	28	26	1.04	0.60, 1.82	20	1.05	0.58, 1.90	6	0.99	0.37, 2.66
P for trend			0.33			0.52			0.26	
Cumulative no. of early-morning shifts										
≤900	29	39	1.31	0.78, 2.19	32	1.41	0.82, 2.42	7	1.08	0.62, 1.88
901–1,920	29	36	1.16	0.70, 1.91	26	1.08	0.62, 1.88	10	1.42	0.67, 3.00
1,921–3,904	26	25	1.00	0.56, 1.79	18	0.95	0.50, 1.79	7	1.16	0.49, 2.72
>3,904	28	37	1.26	0.75, 2.11	27	1.24	0.71, 2.15	10	1.32	0.62, 2.82
P for trend			0.31			0.44			0.31	

Abbreviations: CI, confidence interval; OR, odds ratio; PROtEuS, Prostate Cancer and Environment Study.
[a] ORs were adjusted for age, ancestry, and education and based on the imputed data for early-morning metrics (8%).

(23, 25, 26, 34), but its role has yet to be fully explored (40). Participation rates were good in our study population, albeit lower among controls. No information on exposure to night-shift work and early-morning shifts was available for nonparticipants. However, according to census data based on area of residence, participants and nonparticipants were found to be very similar in terms of the proportions of recent immigrants, unemployment, educational level, and household income among both cases and controls, which reduces concerns about possible selection bias. The proportions of workers involved in night-shift work and early-morning shifts represented about 22% and 7% of our study population, respectively, which were slightly lower than those in other population-based case-control studies (e.g., 31%–36% (25, 34) and 11% (25), respectively). However, these proportions are expected to vary across studies, as they reflect different regional industrial activities, age distributions, and definitions of night-shift work and early-morning shifts.

Detailed job descriptions enabling assessment of night-shift work and early-morning shifts were collected only for jobs lasting 2 years or more, in order to decrease interview burden, since some subjects reported up to 12 jobs. However, jobs lasting under 2 years represented less than 4% of overall work years, on average (41). Imputation was applied to a low percentage of jobs, and results were similar to those from complete-case analyses.

Epigenetic studies on prostate cancer have found positive associations between some polymorphisms of genes involved in circadian rhythm (42–49) or the aggregate variation in circadian genes (48) and prostate cancer. We could not evaluate this aspect of the relationship in our study.

Several study strengths reinforce the robustness of our findings. The present study is one of a very few, and the largest based on the number of cases (to our knowledge), to have applied an exact definition of night-shift work involving circadian disruption based on work hours following IARC's recommendation (7). We were able to investigate night-shift work through several dimensions. The possibility of residual confounding cannot be totally excluded, although very few risk factors for this cancer, including occupational risk factors, have been clearly established (50). The wide range of occupations covered here may reduce the likelihood of strong confounding by a commonly shared factor, occupational or other, as compared with that in a specific occupation or industry. Finally, information on screening enabled us to evaluate the role of undiagnosed prostate cancers among controls in our findings.

In conclusion, results from this study lend no support for a major role of night-shift work or early-morning shifts in prostate cancer development.

ACKNOWLEDGMENTS

Author affiliations: Epidemiology and Biostatistics Unit, Centre Armand-Frappier Santé Biotechnologie, Institut national de la recherche scientifique, Université du Québec, Laval, Québec, Canada (Christine Barul, Hugues Richard, Marie-Elise Parent); and École de santé publique, Université de Montréal, Montréal, Québec, Canada (Marie-Elise Parent).

This work was funded by the Canadian Cancer Society (grants 13149, 19500, 19864, and 19865), the Canadian Institutes of Health Research (grant 399507), the Cancer Research Society, the Fonds de Recherche du Québec–Santé (FRQS), the FRQS–Réseau de recherche en santé environnementale, and the Ministère du Développement Économique, de l'Innovation et de l'Exportation du Québec.

We thank Dr. Louise Nadon, Mounia Senhaji Rhazi, and Jennifer Yu for exposure assessment, the urologists who collaborated in access to patients, and the entire PROtEuS fieldwork team for their contributions to this study.

Conflict of interest: none declared.

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