American Journal of Epidemiology

Vol. 176, No. 9
DOI: 10.1093/aje/kws318
Advance Access publication:
October 3, 2012

Original Contribution

Night Work and the Risk of Cancer Among Men

Marie-Élise Parent*, Mariam El-Zein, Marie-Claude Rousseau, Javier Pintos, and Jack Siemiatycki

* Correspondence to Dr. Marie-Élise Parent, Epidemiology and Biostatistics Unit, INRS-Institut Armand-Frappier, Institut national de la recherche scientifique (INRS), University of Quebec, 531 Boulevard des Prairies, Laval, Quebec H7V 1B7, Canada (e-mail: marie-elise.parent@iaf.inrs.ca).

Initially submitted October 12, 2011; accepted for publication February 2, 2012.

Night work might influence cancer risk, possibly via suppression of melatonin release. In a population-based case-control study conducted in Montreal, Quebec, Canada, between 1979 and 1985, job histories, including work hours, were elicited from 3,137 males with incident cancer at one of 11 anatomic sites and from 512 controls. Compared with men who never worked at night, the adjusted odds ratios among men who ever worked at night were 1.76 (95% confidence interval (CI): 1.25, 2.47) for lung cancer, 2.03 (95% CI: 1.43, 2.89) for colon cancer, 1.74 (95% CI: 1.22, 2.49) for bladder cancer, 2.77 (95% CI: 1.96, 3.92) for prostate cancer, 2.09 (95% CI: 1.40, 3.14) for rectal cancer, 2.27 (95% CI: 1.24, 4.15) for pancreatic cancer, and 2.31 (95% CI: 1.48, 3.61) for non-Hodgkin's lymphoma. Equivocal evidence or no evidence was observed for cancers of the stomach (odds ratio (OR) = 1.34, 95% CI: 0.85, 2.10), kidney (OR = 1.42, 95% CI: 0.86, 2.35), and esophagus (OR = 1.51, 95% CI: 0.80, 2.84) and for melanoma (OR = 1.04, 95% CI: 0.49, 2.22). There was no evidence of increasing risk with increasing duration of night work, with risks generally being increased across all duration categories. Results suggest that night work may increase cancer risk at several sites among men.

case-control studies; circadian rhythm; men; neoplasms; night work; occupations; shift work

Abbreviation: CI, confidence interval.

Editor's note: *An invited commentary on this article appears on page 760, and the authors' response appears on page 764.*

Exposure to light at night suppresses the release of melatonin, a hormone which typically peaks in the middle of the night (1). Such suppression has been associated with disruption of circadian rhythms, a reduction in nonspecific oncostatic (anticancer) effects of the pineal gland, and an increase in reproductive hormone levels (2–9). According to these experimental observations, night work, which typically entails exposure to light at night, induces physiologic changes that might influence tumor development. The International Agency for Research on Cancer recently designated shift work that involves circadian disruption as a probable cause of human cancer (Group 2A) on the basis of sufficient experimental evidence and limited epidemiologic evidence (10, 11). The melatonin hypothesis remains the most widely cited etiologic mechanistic pathway for the putative increased risk of cancer among night-shift workers (2, 8, 9). Several studies have assessed the possible association between night work, particularly among nurses, and breast cancer (12–20), but little evidence has been accrued regarding cancer at other sites (21) or among males. To address this issue, we assessed whether night work was associated with an increased risk of cancer at several sites in the context of a large population-based case-control study of occupational factors and cancer carried out in Montreal, Quebec, Canada, in the 1980s among men with different occupational profiles.

MATERIALS AND METHODS

The design and data collection methods of this multicancer study, the Montreal Multisite Case-Control Cancer

Study, have been described in detail elsewhere (22–26). It was originally designed to explore possible associations between occupational exposures and cancer among men. The study protocol was approved by the ethics committees of all participating institutions, and all subjects provided informed consent.

Case series

Cases were male patients aged 35–70 years residing in the greater Montreal area who had been diagnosed at any of the 18 major Montreal hospitals with incident, pathologically confirmed cancer. Participation of all large hospitals in this area ensured virtually complete (97%) population-based ascertainment of cases. Between 1979 and 1985, a total of 4,576 eligible cancer patients were accrued, and 3,730 of these patients (82%) were successfully interviewed. Eighty-one percent of patients responded for themselves; proxies, mainly the spouse, provided information for the rest. Although the main study included cancers diagnosed at 23 anatomic sites, we report here on 3,137 patients diagnosed with the 11 most frequent cancers: that is, cancers of the lung ($n = 761$), colon ($n = 439$), bladder ($n = 439$), prostate ($n = 400$), rectum ($n = 236$), stomach ($n = 228$), kidney ($n = 158$), pancreas ($n = 94$), and esophagus ($n = 91$) and melanoma ($n = 94$), as well as non-Hodgkin's lymphoma ($n = 197$).

Control series

Controls were recruited from the general population using electoral lists. In the province of Quebec, the electoral list is maintained through an active, ongoing registration process and is considered an almost complete list of citizens of voting age. Controls were randomly selected from the same age groups (±5 years) and residential areas (districts of about 40,000 electors) as the cases in order to obtain good representation of the base population. Of 740 population controls ascertained, 533 (72%) were successfully interviewed.

Data collection

Interviews were conducted, mostly face-to-face, by trained interviewers from 1979 to 1986. The interviews, requiring between 30 minutes and 2 hours, included a structured section inquiring about sociodemographic and lifestyle characteristics and a semistructured section eliciting a detailed description of each job held by the subject in his working lifetime. The expert-based approach developed by our group (27) was applied to each participant's work history in order to determine exposure to some 300 workplace chemicals. In addition, an occupational physical activity level was assigned by attributing metabolic equivalents to main tasks within each job (28).

Ascertainment of night work

For each job held, a subject was asked whether the job entailed shift work and, if so, the start and finish times of his work shift. In our analyses, a job entailing night work was defined as one that included working between 1:00 AM and 2:00 AM for at least 6 months. We calculated a cumulative index of night work exposure by totaling the number of years of night work in all jobs held.

Statistical analyses

Analyses were restricted to subjects who provided information about night work: 512 controls (96% of controls) and 3,137 cancer patients (84% of patients). Unconditional logistic regression was used to estimate odds ratios and 95% confidence intervals for the risk of cancer among men who had ever held a job entailing night work. We also conducted analyses according to the cumulative duration (<5, 5–10, or >10 years) and timing (recent, distant) of night work over the participant's lifetime. Recent night work exposure was attributed when jobs entailing night work had been held within the 20 years prior to the date of diagnosis or interview, whereas distant night work exposure was related to night jobs that had been held further in the past.

A separate regression model was fitted for each type of cancer. Each model included a set of known or potential nonoccupational and occupational confounding factors specific to each cancer type (Table 1). Age, ancestry, educational level, family income, and respondent status were included in all models. Other covariates retained for one or more of the cancer types included birthplace, used as a correlate of *Helicobacter pylori* exposure; coffee, tea, beer, and alcohol consumption; a β-carotene index; farming; occupational exposure to crystalline silica, asbestos, and aromatic amines; body mass index; recreational and occupational physical activity; and smoking history. The latter was entered as 3 variables: ever smoking, number of cigarette-years of smoking, and number of years since quitting smoking (29).

We also fitted a multivariate polytomous regression model (30) which simultaneously included all cancer types, using a set of core regression confounders (age, ancestry, income, educational level, the above-mentioned 3-pronged variable for smoking history, and respondent status). Since results were very similar using both modeling approaches, we opted for presenting the results derived from the use of a separate logistic regression model for each cancer site, allowing for tailored adjustment by relevant site-specific covariates. Analyses were performed using SPSS, version 16 (SPSS Inc., Chicago, Illinois).

RESULTS

Table 2 shows the distribution of cases and controls according to selected characteristics. Cancer cases and controls were generally similar in terms of age. Lung, prostate, and esophageal cancer cases were more often of French ancestry than controls, whereas this tendency was reversed for other cancer sites. In general, cases tended to have had fewer years of schooling, to have a lower family income, and to have been heavier smokers than controls and were more likely to have had a proxy respondent.

Table 1. Potential Nonoccupational and Occupational Confounders Retained for Analyses of Night Work and Cancer Risk, by Cancer Type/Site, Montreal Multisite Case-Control Cancer Study, 1979–1985

Cancer Type or Site	No. of Subjects	Potential Confounders Included in Regression Models[b]
All[a]		Age, ancestry, educational level, family income, respondent status
Lung	761	Smoking, β-carotene, occupational exposure to asbestos and silica
Small-cell carcinoma	142	
Adenocarcinoma	149	
Squamous cell carcinoma	314	
Other	156	
Colon	439	Smoking, BMI, alcohol, β-carotene, occupational physical activity
Bladder	439	Smoking, coffee, β-carotene, occupational exposure to aromatic amines
Prostate	400	Smoking, alcohol, BMI, farming, occupational physical activity
Rectum	236	Smoking, beer, BMI
Stomach	228	Smoking, alcohol, β-carotene, birthplace
Non-Hodgkin's lymphoma	197	
Kidney	158	Smoking, coffee, alcohol, BMI
Melanoma	94	β-carotene, sports and/or outdoor activities
Pancreas	94	Smoking, coffee, alcohol, β-carotene, BMI
Esophagus	91	Smoking, coffee, tea, alcohol, β-carotene

Abbreviation: BMI, body mass index.

[a] All models included age (years; continuous), ancestry (French, Anglo, Italian, Jewish, other European, or other), educational level (elementary, secondary, or postsecondary), family income (Canadian dollars; continuous), and respondent status (self or proxy).

[b] Additional site-specific covariates were entered as follows: birthplace (Montreal, Quebec excluding Montreal, Canada excluding Quebec, United States, Southern Europe, Northern Europe, Asia/Africa, or other), coffee or tea consumption (cup-years; continuous), beer or alcohol consumption (drink-years; continuous), β-carotene index (derived from the frequency of consumption of 10 β-carotene-rich foods, in tertiles), body mass index (weight (kg)/height $(m)^2$; <25, 25–<30, or ≥30, in tertiles), farming (never vs. ever), occupational exposure to crystalline silica, asbestos, or aromatic amines (never vs. ever), occupational physical activity (low, medium, or high), participation in sports and/or outdoor activities (not often or never vs. often), and smoking (entered as a 3-pronged variable: ever smoking, number of cigarette-years, and number of years since quitting).

The proportion of men who had ever held a job entailing night work for at least 6 months was 14.5% among controls and 25.5% among all cases combined (Table 3). Examples of occupations that often entailed night work included drivers, mechanics, machine operators, security guards, maintenance workers, boiler room operators, railway workers, firemen, policemen, waiters, cooks, hospital workers, dockworkers, and bakers.

Table 4 shows odds ratios and 95% confidence intervals for the various cancer types among men who reported ever having worked at night, as compared with those who never had. Odds ratios above unity were observed for all cancer sites, and most of these odds ratios were above 1.50. Statistically significant excess risks were observed for cancers of the lung, prostate, colon, bladder, rectum, and pancreas and for non-Hodgkin's lymphoma. Cancer sites showing equivocal evidence or no evidence of an association with ever working at night included the stomach, kidney, and esophagus and melanoma. For lung cancer, we further explored the effect of having ever worked at night, according to main histologic subtype. Adjusted odds ratios were 1.91 (95% confidence interval (CI): 1.27, 2.87) for squamous cell carcinoma, 1.62 (95% CI: 1.25, 2.47) for small-cell carcinoma, and 1.46 (95% CI: 0.86, 2.50) for adenocarcinoma.

For none of the cancer sites was there evidence of a duration-response relation, with risks generally being elevated across all categories of duration. Considering men who had been engaged in night work for more than 10 years, the association was statistically significant only for cancers of the prostate, colon, and bladder, as well as for non-Hodgkin's lymphoma.

The timing of exposure to night work during a participant's work history did not appear to be associated with the level of risk, as men who had worked at night within the 20 years preceding the index date had similar relative risks as those who had held night jobs further in the past.

DISCUSSION

While there is a substantial body of experimental and epidemiologic evidence that points to an association between night work and breast cancer, the hypothesis remains controversial, with disagreement about the potential role of bias, chance, or confounding (31). For other cancer sites, previous evidence is even less compelling. Our study provides new evidence concerning possible associations that have not previously been well investigated, namely between night work and risks of several types of cancer among males. Our findings are perplexing. On the one hand, they suggest elevated risks for many cancer sites among men working at night. The sites for which the statistical evidence is strongest are the lung, prostate, colon, bladder, rectum, and pancreas and non-Hodgkin's lymphoma. On the other hand, the absence of duration-response relations, and the very fact of ostensible excess risks across such a wide array of tumor types, might raise questions about the credibility of these findings and possible methodological artifacts. The absence of a duration-response pattern could possibly reflect favorable chronotypes among subjects in the longer-duration exposure categories or constancy of exposure; men who engage in night work will usually do it for most of their careers. One thing is certain: If our findings are valid, it would signal an important systemic cancer hazard.

Table 2. Selected Characteristics of Cases and Controls in a Study of Night Work and Cancer Risk, by Cancer Type/Site, Montreal Multisite Case-Control Cancer Study, 1979–1985

Participant Group	Mean Age, years	French Ancestry, %	Mean Duration of Schooling, years	Mean Annual Family Income (in Thousands), Can$	Use of a Proxy Respondent, %	Ever Smoking, %	Mean Intensity of Smoking, cigarette-years[a]	Mean Time Since Quitting Smoking, years[b]
Controls	59.6 (7.9)[c]	64.1	10.0 (4.6)	26.5 (8.7)	12.9	80.3	810 (707)	12.6 (10.4)
Cancer type or site (cases)								
Lung	59.2 (7.0)	69.0	8.5 (3.8)	22.4 (8.0)	23.9	98.4	1,494 (830)	5.1 (6.4)
Colon	59.4 (7.6)	54.9	9.9 (4.2)	26.0 (8.9)	14.4	80.9	802 (731)	11.8 (9.7)
Bladder	59.2 (7.6)	57.9	10.0 (4.7)	25.8 (10.0)	12.5	91.6	1,035 (704)	9.8 (9.9)
Prostate	63.0 (5.0)	65.2	9.3 (4.4)	24.7 (9.0)	11.0	83.0	969 (810)	11.8 (10.6)
Rectum	58.7 (8.0)	58.5	9.3 (4.5)	26.2 (9.1)	15.7	80.1	791 (762)	11.7 (10.7)
Stomach	58.3 (8.2)	58.3	8.8 (4.0)	24.2 (8.3)	16.7	87.7	967 (849)	10.0 (10.1)
Non-Hodgkin's lymphoma	55.0 (9.7)	63.5	10.2 (4.2)	26.2 (8.3)	18.8	82.7	757 (665)	11.3 (10.5)
Kidney	58.2 (7.6)	53.8	9.4 (4.3)	26.3 (9.0)	10.8	80.4	804 (692)	9.1 (8.7)
Melanoma	52.9 (10.1)	36.2	12.3 (4.5)	29.7 (8.9)	12.8	64.9	484 (593)	13.1 (11.4)
Pancreas	58.9 (7.5)	57.4	8.5 (4.1)	25.8 (9.7)	43.6	87.2	992 (770)	9.2 (8.7)
Esophagus	59.7 (7.6)	64.8	8.9 (3.7)	24.4 (8.0)	27.5	93.4	1,255 (843)	9.6 (11.1)

[a] Among ever smokers, based on 20 cigarettes per packet.
[b] Among ex-smokers.
[c] Numbers in parentheses, standard deviation.

In general, the odds ratios were of approximately the same magnitude regardless of duration or timing of exposure. In previous studies of breast cancer (16, 18, 32, 33) prolonged night-shift work (over 20 or 30 years) was found to be an important determinant of increased risk. We observed an effect of long-term night work (beyond 10 years' duration) for cancers of the prostate, colon, and bladder and for non-Hodgkin's lymphoma, whereas the evidence was

Table 3. Lifetime Prevalence, Cumulative Duration, and Timing of Night Work Among Cases and Controls in a Study of Night Work and Cancer Risk, by Cancer Type/Site, Montreal Multisite Case-control Cancer Study, 1979–1985

Participant Group	Total No. of Participants	Ever Performing Night Work				Cumulative Duration of Night Work, years						Timing of Night Work[a]			
		Never		Ever		<5		5–10		>10		Recent Past[b]		Distant Past[c]	
		No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Controls	512	438	85.5	74	14.5	36	7.0	19	3.7	19	3.7	29	6.2	30	6.4
Cancer type or site (cases)															
Lung	761	545	71.6	216	28.4	110	14.5	52	6.8	54	7.1	91	14.3	79	12.7
Colon	439	329	74.9	110	25.1	61	13.9	20	4.6	29	6.6	53	13.9	45	12.0
Bladder	439	333	75.9	106	24.1	62	14.1	15	3.4	29	6.6	54	14.0	42	11.2
Prostate	400	268	67.0	132	33.0	68	17.0	27	6.8	36	9.0	55	17.0	57	17.5
Rectum	236	178	75.4	58	24.6	35	14.8	10	4.2	12	5.1	25	12.3	26	12.7
Stomach	228	185	81.1	43	18.9	24	10.5	7	3.1	12	5.3	14	7.0	23	11.1
Non-Hodgkin's lymphoma	197	150	76.1	47	23.9	21	10.7	15	7.6	11	5.6	25	14.3	13	8.0
Kidney	158	128	81.0	30	19.0	15	9.5	9	5.7	6	3.8	13	9.2	11	7.9
Melanoma	94	82	87.2	12	12.8	7	7.4	5	5.3	0	0.0	8	8.9	2	2.4
Pancreas	94	70	74.5	24	25.5	10	10.6	6	6.4	8	8.5	14	16.7	7	9.1
Esophagus	91	70	76.9	21	23.1	10	11.0	4	4.4	7	7.7	11	13.6	8	10.3

[a] Men who had worked at jobs entailing night work in both time periods were excluded from these analyses.
[b] Defined as ≤20 years prior to the date of diagnosis (cases) or interview (controls).
[c] Defined as >20 years prior to the date of diagnosis (cases) or interview (controls).

Table 4. Adjusted[a] Odds Ratios for Cancer According to Employment Involving Night Work, Montreal Multisite Case-Control Cancer Study, 1979–1985

Cancer Type or Site	Ever Performing Night Work			Cumulative Duration of Night Work, years						Timing of Night Work[b]			
	Never (OR = 1)[c]	Ever		<5		5–10		>10		Recent Past[d]		Distant Past[e]	
		OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI	OR	95% CI
Lung	1.00	1.76	1.25, 2.47	1.93	1.22, 3.03	1.51	0.80, 2.85	1.67	0.90, 3.09	1.76	1.07, 2.89	1.88	1.13, 3.14
Colon	1.00	2.03	1.43, 2.89	2.32	1.47, 3.68	1.43	0.73, 2.80	2.11	1.13, 3.94	2.50	1.51, 4.14	2.08	1.24, 3.47
Bladder	1.00	1.74	1.22, 2.49	1.98	1.24, 3.16	1.06	0.51, 2.20	1.98	1.05, 3.76	2.19	1.30, 3.66	1.80	1.06, 3.04
Prostate	1.00	2.77	1.96, 3.92	3.13	1.98, 4.95	2.11	1.11, 3.99	2.68	1.45, 4.95	3.17	1.89, 5.31	3.01	1.83, 4.93
Rectum	1.00	2.09	1.40, 3.14	2.58	1.53, 4.33	1.42	0.64, 3.18	1.67	0.77, 3.61	2.27	1.27, 4.05	2.35	1.32, 4.20
Stomach	1.00	1.34	0.85, 2.10	1.50	0.83, 2.70	0.89	0.34, 2.33	1.45	0.64, 3.26	1.04	0.51, 2.13	1.93	1.03, 3.58
Non-Hodgkin's lymphoma	1.00	2.31	1.48, 3.61	2.25	1.23, 4.12	2.41	1.14, 5.10	2.32	1.03, 5.23	2.51	1.36, 4.64	1.91	0.94, 3.90
Kidney	1.00	1.42	0.86, 2.35	1.43	0.73, 2.79	1.81	0.77, 4.29	1.05	0.39, 2.80	1.51	0.73, 3.13	1.34	0.63, 2.86
Melanoma	1.00	1.04	0.49, 2.22	1.16	0.44, 3.11	2.77	0.89, 8.58	—[f]	—	2.24	0.84, 5.95	0.51	0.11, 2.23
Pancreas	1.00	2.27	1.24, 4.15	1.91	0.81, 4.52	2.77	0.97, 7.90	2.43	0.91, 6.47	3.81	1.75, 8.28	1.49	0.55, 4.06
Esophagus	1.00	1.51	0.80, 2.84	1.53	0.64, 3.63	1.27	0.38, 4.28	1.71	0.59, 4.93	1.92	0.82, 4.52	1.59	0.59, 4.27

Abbreviations: CI, confidence interval; OR, odds ratio.

[a] Regression models included the site-specific potential confounders listed in Table 1.

[b] Men who had worked at jobs entailing night work in both time periods were excluded from these analyses.

[c] Reference category.

[d] Defined as ≤20 years prior to the date of diagnosis (cases) or interview (controls).

[e] Defined as >20 years prior to the date of diagnosis (cases) or interview (controls).

[f] No men with melanoma worked at jobs entailing night work for more than 10 years.

weaker for other cancer types. Too few men in our study had worked in jobs involving night work for over 20 years to conduct analyses for such durations.

Findings in the context of prior studies

Lung cancer. To our knowledge, there is no current epidemiologic evidence suggesting that night work influences lung cancer development. Two ecologic studies have investigated the link between levels of light at night and the incidence of a few types of cancer (34, 35). In the first, using female breast and lung cancer rates and light-at-night intensity data for 147 individual urban localities in Israel, Kloog et al. (34) found a strong positive association between light-at-night exposure and breast cancer but not lung cancer. In the second study, correlating male prostate, lung, and colon cancer rates and population-weighted light-at-night levels in 164 countries, Kloog et al. (35) found a significant positive association between light-at-night exposure and prostate cancer but not lung or colon cancer. We observed a significantly elevated risk of lung cancer in relation to having ever been engaged in night work, with excesses apparent across all main histologic subtypes.

Prostate and colon cancers. We observed significantly increased risks of cancer in the prostate and colon irrespective of the duration or timing of night work. Three previous studies showed nonsignificant positive associations between night-shift work and colon cancer (36–38). For prostate cancer, 2 studies found elevated risk (39, 40) and one did not (38). Recently, the main characteristics, dissimilarities, and findings of these studies were critically reviewed (11, 31, 41). The issues highlighted were mostly related to the diversity of shift-work ascertainment methods, varying exposure durations, different definitions of critical exposure windows, assessment of changes in night-shift work schedules throughout the working lifetime, and adjustment for confounders. Our study addressed some of these concerns by 1) including the period between 1:00 AM and 2:00 AM in the definition of night work, thereby excluding the possibility of evening shift work being considered night-work exposure; 2) calculating a cumulative index of night-work exposure; and 3) incorporating adequate analytic control for several potential confounders.

Non-Hodgkin's lymphoma. Our study is the second to suggest that night work predisposes to non-Hodgkin's lymphoma. Exposure to night work for 10 years was previously found to be modestly associated with an increased risk of non-Hodgkin's lymphoma among men (odds ratio = 1.10, 95% CI: 1.03, 1.19) (42). Unlike in our study, the definition of night-work exposure in that study was based not on individual data but on a job-exposure matrix.

Other cancers. We observed suggestive associations between night work and the risks of bladder and pancreatic cancers, as well as equivocal evidence for esophageal and stomach cancers. To our knowledge, no prior studies have investigated such associations. It was recently postulated that the light-at-night hypothesis may apply to melanoma (43). Two previous studies have investigated this. No relation between shift work and melanoma among women was reported in a study based on 11 cases (38). Another study among 318 female nurses with incident melanoma found that working for 10 years or more on rotating night shifts lowered the risk of this cancer (adjusted hazard ratio = 0.56, 95% CI: 0.36, 0.87) (44). Overall, our findings provide little support for an association with melanoma.

Potentially carcinogenic consequences of night work have been ascribed to light-at-night exposure, phase shift, sleep disruption, lifestyle factors (diet, physical activity, or body mass index), and vitamin D exposure (45, 46). Mechanisms could be specific to specific cancer types. However, our findings of increased risks across a wide array of cancer types are more in line with a common underlying mechanism. The anticancer effects of melatonin remain the most often evoked theory; its effects on reproductive hormone levels would influence risks of breast, prostate, and colon cancers. Direct oncostatic effects of melatonin, through inhibition of and repair of oxidative damage in DNA, could be involved as well (47–49).

Strengths and possible limitations

This study had several strengths. It allowed us to present evidence regarding a large number of cancer sites and to compare risks across sites within a common study base using a common methodology. It contributes additional information in a research area where the available evidence—the potential effects of night work on cancer risk in men—is very limited and inconsistent. Other advantageous attributes include: a virtually complete population-based case ascertainment system; histologic confirmation of primary cancers; relatively high participation rates; relatively large numbers of cancer cases; collection of detailed lifetime job histories across multiple professions and a wide range of occupations; collection of comprehensive information on potential covariates; and the likelihood that our operational definition of night work captured a nighttime period that could be pertinent to the hypothetical mechanism of carcinogenesis.

However, studies such as this are subject to a number of potential limitations or biases. Response rates were over 80% for most cases series and over 70% for controls. While differentially biased participation of subjects with a history of night work is theoretically possible, it is unlikely. First, given the high response rates, very imbalanced participation would be required in order to induce detectable bias. Second, if there were such a bias operating, it would probably have the greatest effect among subjects who were currently or recently working at night, whereas we saw no difference in risk patterns between subjects with recent night-work exposure and those with distant night-work exposure. Third, restricting analyses to men who were retired from work at the time of contact, and therefore were unlikely to have their participation influenced by their work hours, did not alter the results.

Differential quality of response between cases and controls is unlikely. The study was presented to subjects as a general study of health, lifestyle, and environment, with a wide-ranging questionnaire that elicited an occupational history. Night-shift work was not a central focus of the interview, nor was it suspected to be important in cancer

etiology at the time of interview. It was rather an incidental piece of information that was collected. Accordingly, it seems implausible that popular beliefs would have influenced subjects' reporting of night work or the manner in which the information was elicited by the interviewers. The one feature of our study that could have led to differential information quality is the fact that 17.6% of case interviews and 12.9% of control interviews were with proxy respondents, most often the spouse of the subject. Results (not shown) of analyses restricting the data to self-respondents were very similar to those shown in Table 4. Nondifferential exposure misclassification would have attenuated rather than exaggerated the results of any case-control comparisons.

We dealt with possible confounding by accounting for several relevant covariates for which information was collected with varying levels of detail. For instance, our regression models included in-depth information on smoking parameters, such as amount, duration, and time since quitting, but limited information on body mass index, which was based on self-reported weight at one point in time "while in good health." The possibility of residual confounding by smoking or the possibility that our adjustment for body size was suboptimal cannot be ruled out, regardless of the amount of information collected. The possibility that there was an unmeasured confounder that could have distorted the associations for approximately 10 cancer sites is most implausible, since that unmeasured confounder would have to be a powerful yet unrecognized risk factor for cancer at all of those sites and would have to be strongly correlated with night work. Finally, some cancer sites had small numbers of cases, which influenced statistical precision.

There are different ways in which night work might be ascertained in epidemiologic studies, and these measures may have different degrees of validity (50). By contrast with some other studies, which used indirect methods, our ascertainment of night work was based on a complete lifetime history of night work as reported explicitly by the individual. On the basis of such data, we were able to compute the lifetime cumulative duration of night work exposure for each subject—an important dimension to consider (50). Unfortunately, the questionnaire did not collect data on light intensity levels (12, 17), type of shifts (fixed vs. rotating) (39), or other aspects of night work, such as direction and rate of shift rotation, rest periods after shift work, light-at-night exposure during sleep and during leisure time, and characteristics of the individual, such as chronotype (morning person vs. evening person) (50). Moreover, we did not elicit information about the frequency of night work within a given job. However, considering the reported jobs that entailed shift work in this population, we can suppose that shift work tended to be more often frequent than occasional, as these jobs typically entail regular night work.

In order to evaluate whether the control group was somehow unrepresentative of the base population, we compared the distribution of job titles held by control subjects with the distribution of occupations registered in the Canadian censuses of the base population over the years covered by the study (unpublished results). Our sample and the base population were very similar in terms of their occupational profiles, suggesting that selection bias is an unlikely explanation for the positive associations observed.

A final observation that is germane to the question of the "validity" of the control group is that our research team has carried out hundreds of analyses of occupational associations in this data set over the years (24–26, 28, 51, 52), and in these analyses there has not been a tendency for indiscriminately high risks to be observed in case-control comparisons. Some high risks were detected for some occupational agents, but these tended to be localized at one or two cancer sites.

While it remains possible that some methodological factors might have led to the high odds ratios we observed for many sites, none of the sensitivity analyses we conducted provided indications in this direction. Statistical fluctuation is always a possible explanation for unexpected findings. In our case, confidence intervals have to be interpreted with more caution than is often the case, because in reality the results for different sites are not independent of each other. If the proportion of night workers happened to be low by chance among the sample of 512 controls in this study, that would have manifested in systematically elevated odds ratios for all cancer sites. Nevertheless, the proportion of shift workers (14.5%) in the control group did not appear to be unlike what would be expected in the general male population of Canada (53). Our best speculation is either that our results reflect a chance-induced low proportion of night workers among the 512 participating controls or that there was an indication of excess risk of cancer at several sites in relation to night work. One line of evidence that can be seen in support of the hypothesis that light exposure could have a systemic effect on cancer risk stems from a Swedish report that blind people have a reduced risk of cancer at several sites (54).

With accruing epidemiologic and experimental evidence, and because of the increasing prevalence of night work, further exploration of the hypothesis is warranted. Future epidemiologic studies should incorporate better and more precise methods of systematically assessing exposure to night work and nocturnal light and melatonin levels (55). Sleep deprivation and disruption of circadian rhythms are other factors related to the significant features of night work (41) that might play an etiologic role and should be taken into consideration.

Conclusion

Several studies have documented night-shift work to be associated with an increased risk of breast cancer, and a few have documented associations with prostate and colorectal cancer. The observation here of elevated risks for several other types of cancer is novel. The consistent positive association could not be ascribed to an identifiable methodological bias, but chance cannot be ruled out as an explanation for these findings. Our results lend some support to the hypothesis that night work might lead to an increase in cancer risk.

ACKNOWLEDGMENTS

Author affiliations: INRS-Institut Armand-Frappier, Institut national de la recherche scientifique (INRS), University of Quebec, Laval, Quebec, Canada (Marie-Élise Parent, Mariam El-Zein, Marie-Claude Rousseau); University of Montreal Hospital Research Centre (CRCHUM), Montreal, Quebec, Canada (Marie-Élise Parent, Marie-Claude Rousseau, Javier Pintos, Jack Siemiatycki); and Department of Social and Preventive Medicine, Faculty of Medicine, University of Montreal, Montreal, Quebec, Canada (Marie-Élise Parent, Marie-Claude Rousseau, Jack Siemiatycki).

This study was supported by research and personnel support grants from Health Canada, the National Cancer Institute of Canada, the Institut de recherche en santé et sécurité au travail du Québec, and the Fonds de la recherche en santé du Québec (FRSQ). M. E. P. is the recipient of a Career Award from the FRSQ. M. C. R. holds a New Investigator Award from the Canadian Institutes of Health Research. J. S. holds the Guzzo-CRS Research Chair in Environment and Cancer.

The authors acknowledge Martine Shareck and Marie Désy for coding the night-work covariates from the participants' work histories. The fieldwork for the study was coordinated by Lesley Richardson.

Conflict of interest: none declared.

REFERENCES

1. Zeitzer JM, Dijk DJ, Kronauer R, et al. Sensitivity of the human circadian pacemaker to nocturnal light: melatonin phase resetting and suppression. *J Physiol*. 2000;526(3):695–702.
2. Stevens RG, Davis S. The melatonin hypothesis—electric power and breast cancer. *Environ Health Perspect*. 1996;104(suppl 1):135–140.
3. Reddy AB, Wong GK, O'Neill J, et al. Circadian clocks: neural and peripheral pacemakers that impact upon the cell division cycle. *Mutat Res*. 2005;574(1-2):76–91.
4. Bartsch C, Bartsch H. The anti-tumor activity of pineal melatonin and cancer enhancing life styles in industrialized societies. *Cancer Causes Control*. 2006;17(4):559–571.
5. Jasser SA, Blask DE, Brainard GC. Light during darkness and cancer: relationships in circadian photoreception and tumor biology. *Cancer Causes Control*. 2006;17(4):515–523.
6. Anisimov VN. Light pollution, reproductive function and cancer risk. *Neuroendocrinol Lett*. 2006;27(1-2):35–52.
7. Haus E, Smolensky M. Biological clocks and shift work: circadian dysregulation and potential long-term effects. *Cancer Causes Control*. 2006;17(4):489–500.
8. Reiter RJ, Gultekin F, Manchester LC, et al. Light pollution, melatonin suppression and cancer growth. *J Pineal Res*. 2006;40(4):357–358.
9. Arendt J. Shift work: coping with the biological clock. *Occup Med (Lond)*. 2010;60(1):10–20.
10. Straif K, Baan R, Grosse Y, et al. Carcinogenicity of shift-work, painting, and fire-fighting. *Lancet Oncol*. 2007;8(12):1065–1066.
11. International Agency for Research on Cancer. *Painting, Fire-Fighting and Shiftwork*. (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, vol 98). Lyon, France: International Agency for Research on Cancer; 2010.
12. Davis S, Mirick DK, Stevens RG. Night shift work, light at night, and risk of breast cancer. *J Natl Cancer Inst*. 2001;93(20):1557–1562.
13. Hansen J. Risk of breast cancer after night- and shift work: current evidence and ongoing studies in Denmark. *Cancer Causes Control*. 2006;17(4):531–537.
14. Stevens RG. Artificial lighting in the industrialized world: circadian disruption and breast cancer. *Cancer Causes Control*. 2006;17(4):501–507.
15. Megdal SP, Kroenke CH, Laden F, et al. Night work and breast cancer risk: a systematic review and meta-analysis. *Eur J Cancer*. 2005;41(13):2023–2032.
16. Schernhammer ES, Kroenke CH, Laden F, et al. Night work and risk of breast cancer. *Epidemiology*. 2006;17(1):108–111.
17. O'Leary ES, Schoenfeld ER, Stevens RG, et al. Shift work, light at night, and breast cancer on Long Island, New York. *Am J Epidemiol*. 2006;164(4):358–366.
18. Lie JAS, Roessink J, Kjaerheim K. Breast cancer and night work among Norwegian nurses. *Cancer Causes Control*. 2006;17(1):39–44.
19. Patel D. Shift work, light at night and risk of breast cancer. *Occup Med (Oxford)*. 2006;56(6):433. (doi:10.1093/occmed/kql078).
20. Stevens RG. Light-at-night, circadian disruption and breast cancer: assessment of existing evidence. *Int J Epidemiol*. 2009;38(4):963–970.
21. Davis S, Mirick DK. Circadian disruption, shift work and the risk of cancer: a summary of the evidence and studies in Seattle. *Cancer Causes Control*. 2006;17(4):539–545.
22. Siemiatycki J, Wacholder S, Richardson L, et al. Discovering carcinogens in the occupational environment: methods of data collection and analysis of a large case-referent monitoring system. *Scand J Work Environ Health*. 1987;13(6):486–492.
23. Rousseau MC, Parent ME, Pollak MN, et al. Diabetes mellitus and cancer risk in a population-based case-control study among men from Montreal, Canada. *Int J Cancer*. 2006;118(8):2105–2109.
24. Siemiatycki J. *Risk Factors for Cancer in the Workplace*. Boca Raton, FL: CRC Press; 1991.
25. Rousseau MC, Parent ME, Nadon L, et al. Occupational exposure to lead compounds and risk of cancer among men: a population-based case-control study. *Am J Epidemiol*. 2007;166(9):1005–1014.
26. Parent ME, Rousseau MC, Boffetta P, et al. Exposure to diesel and gasoline engine emissions and the risk of lung cancer. *Am J Epidemiol*. 2007;165(1):53–62.
27. Siemiatycki J. Discovering occupational carcinogens in population-based case-control studies: review of findings from an exposure-based approach and a methodologic comparison of alternative data collection strategies. *Recent Results Cancer Res*. 1990;120:25–38.
28. Parent ME, Rousseau MC, El-Zein M, et al. Occupational and recreational physical activity during adult life and the risk of cancer among men. *Cancer Epidemiol*. 2011;35(2):151–159.
29. Leffondré K, Abrahamowicz M, Siemiatycki J, et al. Modeling smoking history: a comparison of different approaches. *Am J Epidemiol*. 2002;156(9):813–823.
30. Hosmer DW, Lemeshow S. *Applied Logistic Regression*. New York, NY: John Wiley & Sons, Inc; 1989.
31. Kolstad HA. Nightshift work and risk of breast cancer and other cancers—a critical review of the epidemiologic evidence. *Scand J Work Environ Health*. 2008;34(1):5–22.

32. Schernhammer ES, Laden F, Speizer FE, et al. Rotating night shifts and risk of breast cancer in women participating in the Nurses' Health Study. *J Natl Cancer Inst*. 2001;93(20): 1563–1568.
33. Pesch B, Harth V, Rabstein S, et al. Night work and breast cancer—results from the German GENICA study. *Scand J Work Environ Health*. 2010;36(2):134–141.
34. Kloog I, Haim A, Stevens RG, et al. Light at night co-distributes with incident breast but not lung cancer in the female population of Israel. *Chronobiol Int*. 2008;25(1): 65–81.
35. Kloog I, Haim A, Stevens RG, et al. Global co-distribution of light at night (LAN) and cancers of prostate, colon, and lung in men. *Chronobiol Int*. 2009;26(1):108–125.
36. Schernhammer ES, Laden F, Speizer FE, et al. Night-shift work and risk of colorectal cancer in the Nurses' Health Study. *J Natl Cancer Inst*. 2003;95(11):825–828.
37. Tynes T, Hannevik M, Andersen A, et al. Incidence of breast cancer in Norwegian female radio and telegraph operators. *Cancer Causes Control*. 1996;7(2):197–204.
38. Schwartzbaum J, Ahlbom A, Feychting M. Cohort study of cancer risk among male and female shift workers. *Scand J Work Environ Health*. 2007;33(5):336–343.
39. Kubo T, Ozasa K, Mikami K, et al. Prospective cohort study of the risk of prostate cancer among rotating-shift workers: findings from the Japan Collaborative Cohort Study. *Am J Epidemiol*. 2006;164(6):549–555.
40. Conlon M, Lightfoot N, Kreiger N. Rotating shift work and risk of prostate cancer. *Epidemiology*. 2007;18(1): 182–183.
41. Costa G, Haus E, Stevens R. Shift work and cancer—considerations on rationale, mechanisms, and epidemiology. *Scand J Work Environ Health*. 2010;36(2):163–179.
42. Lahti TA, Partonen T, Kyyronen P, et al. Night-time work predisposes to non-Hodgkin lymphoma. *Int J Cancer*. 2008;123(9):2148–2151.
43. Kvaskoff M, Weinstein P. Are some melanomas caused by artificial light? *Med Hypotheses*. 2010;75(3):305–311.
44. Schernhammer ES, Razavi P, Li TY, et al. Rotating night shifts and risk of skin cancer in the Nurses' Health Study. *J Natl Cancer Inst*. 2011;103(7):602–606.
45. Fritschi L. Shift work and cancer [editorial]. *Br Med J*. 2009;339:b2653. (doi:10.1136/bmj.b2653).
46. Fritschi L, Glass DC, Heyworth JS, et al. Hypotheses for mechanisms linking shiftwork and cancer. *Med Hypotheses*. 2011;77(3):430–436.
47. Santoro R, Marani M, Blandino G, et al. Melatonin triggers p53(Ser) phosphorylation and prevents DNA damage accumulation. *Oncogene*. 2012;31(24):2931–2942.
48. Blask DE, Dauchy RT, Sauer LA, et al. Growth and fatty acid metabolism of human breast cancer (MCF-7) xenografts in nude rats: impact of constant light-induced nocturnal melatonin suppression. *Breast Cancer Res Treat*. 2003;79(3):313–320.
49. Sliwinski T, Rozej W, Morawiec-Bajda A, et al. Protective action of melatonin against oxidative DNA damage: chemical inactivation versus base-excision repair. *Mutat Res*. 2007; 634(1-2):220–227.
50. Stevens RG, Hansen J, Costa G, et al. Considerations of circadian impact for defining 'shift work' in cancer studies: IARC Working Group Report. *Occup Environ Med*. 2011; 68(2):154–162.
51. Fritschi L, Siemiatycki J. Melanoma and occupation: results of a case-control study. *Occup Environ Med*. 1996;53(3): 168–173.
52. Aronson KJ, Siemiatycki J, Dewar R, et al. Occupational risk factors for prostate cancer: results from a case-control study in Montreal, Quebec, Canada. *Am J Epidemiol*. 1996;143(4): 363–373.
53. Williams C. *Work-Life Balance of Shift Workers*. (Statistics Canada catalogue no. 75-001-X). Ottawa, Ontario, Canada: Statistics Canada; 2008.
54. Feychting M, Osterlund B, Ahlbom A. Reduced cancer incidence among the blind. *Epidemiology*. 1998;9(5):490–494.
55. Hsing AW, Meyer TE, Niwa S, et al. Measuring serum melatonin in epidemiologic studies. *Cancer Epidemiol Biomarkers Prev*. 2010;19(4):932–937.