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Original Contribution

Rotating Night-Shift Work and Lung Cancer Risk Among Female Nurses in the United States

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The risk of lung cancer among night-shift workers is unknown. Over 20 years of follow-up (1988–2008), we documented 1,455 incident lung cancers among 78,612 women in the Nurses' Health Study. To examine the relationship between rotating night-shift work and lung cancer risk, we used multivariate Cox proportional hazard models adjusted for detailed smoking characteristics and other risk factors. We observed a 28% increased risk of lung cancer among women with 15 or more years spent working rotating night shifts (multivariate relative risk (RR) = 1.28, 95% confidence interval (CI): 1.07, 1.53; $P_{trend} = 0.03$) compared with women who did not work any night shifts. This association was strongest for small-cell lung carcinomas (multivariate RR = 1.56, 95% CI: 0.99, 2.47; $P_{trend} = 0.03$) and was not observed for adenocarcinomas of the lung (multivariate RR = 0.91, 95% CI: 0.67, 1.24; $P_{trend} = 0.40$). Further, the increased risk associated with 15 or more years of rotating night-shift work was limited to current smokers (RR = 1.61, 95% CI: 1.21, 2.13; $P_{trend} < 0.001$), with no association seen in nonsmokers ($P_{interaction} = 0.03$). These results suggest that there are modestly increased risks of lung cancer associated with extended periods of night-shift work among smokers but not among nonsmokers. Though it is possible that this observation was residually confounded by smoking, our findings could also provide evidence of circadian disruption as a "second hit" in the etiology of smoking-related lung tumors.

circadian disruption; lung cancer; night work; rotating shift work; smoking

Abbreviations: BMI, body mass index; CI, confidence interval; RR, relative risk.

Light exposure during night-shift work affects the circadian system of shift workers in several unfavorable ways, including by desynchronizing their 24-hour bodily rhythms and suppressing nocturnal melatonin secretion (1). Melatonin, a hormone closely linked to the circadian system, regulates the sleep/wake cycle in humans and has antimutagenic and oncostatic properties (2). Both lower melatonin levels (3) and sleep disruption (4) have been linked to increased cancer risk. Today, there is a growing body of literature that indicates an association between rotating night-shift work and increased risk of several malignancies, including breast (5), endometrial (6), prostate (7–10), and colorectal (10, 11) cancer, as well as non-Hodgkin lymphoma (12).

Despite remarkable gains in treatment and prevention (primarily by means of smoking-reduction efforts), lung cancer remains the second most common cancer and number 1 cancer killer in the United States (13). Some evidence has suggested that smoking rates are higher among shift workers (14), yet the few previous studies that examined lung cancer risk in this group mostly used occupational registers with no information on smoking habits (15, 16). By contrast, nursing, an occupation with a high prevalence of night-shift workers, has been associated with lung cancer risk (17, 18) even after adjustment for smoking (18). Most recently, Parent et al. (10) described significantly increased risks of a number of cancers, including lung cancer, among men who reported having ever worked at night; however, the lung cancer risk was not significant for those who had been engaged in night work for more than 10 years, casting some doubt on the potential for causality of the observed association. To examine whether night-shift work increases the risk of lung cancer in women above and beyond the risk imposed by cigarette smoking, we used data from the prospective Nurses'

Health Study (19–21), a large cohort study of nurses in the United States.

MATERIALS AND METHODS

Study population

A total of 121,701 female registered nurses between 30 and 55 years of age were enrolled in the Nurses' Health Study in 1976. Participants have completed biennial mailed questionnaires to update information on exposure status and to identify newly diagnosed case subjects of cancer and other medical conditions, and the response rate has been at least 90% for each cycle. The current study population was drawn from the 85,197 women who reported their duration of night-shift work on the 1988 questionnaire. After excluding women with a previous report of cancer, 78,612 women remained for analysis. The study was approved by the Brigham and Women's Hospital Institutional Review Board in Boston, Massachusetts. In addition, this study was approved by the Connecticut Department of Public Health Human Investigations Committee.

Ascertainment of lung cancer

Cases of lung cancer were self-reported by the participants or identified on their death certificates and were subsequently confirmed by medical records. A total of 3,083 cases of lung cancer were reported in the entire cohort over the follow-up period of the present analysis (June 1988 to June 2008). We were able to obtain medical records for 2,574 of these reports, and we confirmed primary lung cancer by pathological reports for 2,243 (87%). After all exclusions, there were 1,297 primary lung cancer cases among the 78,612 women who formed our study population. Because lung cancers were well-reported in this cohort, we included 148 reports that were reconfirmed by the participant but for which we had no pathological report, bringing the total to 1,445 lung cancer cases for analysis. Of these, 44% were adenocarcinoma, 14% were squamous carcinoma, 14% were small-cell carcinoma, 16% were cancers with other histologies (large-cell and non–small-cell carcinoma, carcinoid, or papillary, mixed sarcoma), and 12% were of unknown histology.

Assessment of rotating night-shift work and covariates

On the 1988 questionnaire, study participants were asked to supply their total number of years spent working rotating night shifts, which was characterized as at least 3 nights per month in addition to days or evenings in that month Data were gathered in 8 prespecified categories: 1, 1–2, 3–5, 6–9, 10–14, 15–19, 20–29, and 30 or more years.

Information on age, smoking status, and weight was updated according to the biennial follow-up questionnaire. Participants were asked whether they were current smokers, and if so, their number of cigarettes smoked per day. Adult height was asked on the 1976 questionnaire, and body mass index was calculated by dividing weight in kilograms by height in meters squared. Questions about environmental tobacco exposure were included in the 1982 questionnaire. Participants were asked whether one or both of their parents smoked, whether they were exposed to second-hand smoke at work and/or at home, and the number of years they lived with someone who smoked. Fruit and vegetable (22) intake was first assessed in 1984, and information was updated in alternate cycles on a questionnaire that included 15 fruits and 30 vegetables.

Statistical analysis

Women contributed person-time from the return of their 1988 questionnaire and were censored at first report of any cancer (except non-melanoma skin cancer), the date of a diagnosis of lung cancer, the date of death, or the end of follow-up in June 2008. We collapsed the data on years spent working a rotating night shift into 4 categories (never, 1–5 years, 6–14 years, and 15 or more years) and calculated *P* values for trend based on the median of these categories. For the category of 15 or more years of rotating night-shift work, we conservatively used 20 years because this category was the combination of 15–10, 20–29, and 30 or more years. Cox proportional hazard models were used to calculate age-adjusted relative risks and 95% confidence intervals in each exposure category compared with the reference category. In multivariate analyses, we further adjusted for risk factors for lung cancer, including smoking status, age at the start of smoking, cigarettes smoked per day (among current smokers), time since quitting smoking, environmental smoking exposure, fruit/vegetable intake, body mass index, use of oral contraceptives or postmenopausal hormones (23), and menopausal status. Because adjustment for alcohol consumption and husband's educational status (a surrogate for socioeconomic status) did not alter risks, these variables were not retained in our primary model. In secondary analyses, we adjusted for pack-years of smoking (0, 1–9, 10–19, 20–39, and ≥40 pack-years).

In addition, we performed a stratified analysis to explore the whether smoking status (never, former, or current) had a modifying effect on the association between rotating night shifts and lung cancer. The *P* value for interaction was calculated using the likelihood ratio test, which compares the models with and without the interaction term of rotating night-shift work and smoking status along with the same covariates. We then estimated relative risk separately by histology subtype of lung cancer (adenocarcinoma, squamous-cell carcinoma, and small-cell carcinoma). The *P* value for differences between the histological types was tested using polytomous logistic regression models. All statistical analyses were performed using SAS software, version 9.1.3 (SAS Institute, Inc., Cary, North Carolina), and all statistical tests are 2-sided.

RESULTS

Participant characteristics at baseline in 1988 are presented in Table 1. Women who had never worked rotating night shifts accounted for 40.4% of the study population, and those with 15 or more years of rotating night-shift work accounted for 7.4%. Women with longer histories of rotating night-shift work were older, were more likely to be current smokers, had a higher mean body mass index, and had more often encountered environmental smoking exposure (except for exposure to passive smoking via parents who smoked) than women without any rotating night-shift work.

Table 1. Age and Age-adjusted Characteristics by Number of Years Working Rotating Night Shifts Among 78,612 Women in the Nurses' Health Study, 1988[a]

Characteristic	Years Working Rotating Night Shifts							
	0 (n = 31,777)		1–5 years (n = 31,990)		6–14 years (n = 9,032)		≥15 years (n = 5,813)	
	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%
Age, years[b]	54.3 (7.2)		54.5 (7.1)		55.4 (7.1)		57.1 (6.7)	
Body mass index[c]	25.4 (4.8)		25.5 (4.8)		26.3 (5.3)		27.0 (5.5)	
Servings of vegetables per day	3.0 (1.5)		3.1 (1.6)		3.1 (1.7)		3.1 (1.8)	
Servings of fruit per day	2.1 (1.3)		2.2 (1.4)		2.2 (1.4)		2.1 (1.4)	
Postmenopausal		71		71		72		75
Current postmenopausal hormone use[d]		34		35		32		29
Oral contraceptive use for >5 years		17		16		16		15
Age at start of smoking, years[b]	19.4 (3.5)		19.5 (3.6)		19.7 (3.8)		19.9 (4.1)	
Smoking status								
Never		46		44		41		42
Past		37		38		36		33
Current		17	18	18		23		25
Months since quitting smoking[e]	195 (141)		197 (143)		191 (155)		178 (138)	
Pack-years of smoking[f]	23.1 (19.6)		22.6 (19.2)		25.0 (19.9)		25.8 (19.9)	
≥25 cigarettes smoked per day[g]		25		25		24		24
Regular smoking exposure[h]								
At home		19		19		22		25
At work		25		23		31		38
Both parents smoked[h]		17		17		16		15
Living ≥20 years with someone who smoked[h]		29		29		32		36

Abbreviation: SD, standard deviation.
[a] Values are standardized to the age distribution of the study population.
[b] Value is not age-adjusted; among ever smokers.
[c] Weight (kg)/height $(m)^2$.
[d] Among postmenopausal women.
[e] Among former smokers.
[f] Among ever smokers.
[g] Among current smokers.
[h] As assessed in 1982.

The relationship between total years spent working rotating night shifts and the risk of lung cancer is shown in Table 2. In age-adjusted analyses, we observed a significantly increased risk of lung cancer with increasing years of rotating night-shift work (for women with ≥15 years of rotating night shifts compared with women who never worked any night shifts, relative risk (RR) = 1.44, 95% CI: 1.20, 1.71; $P_{trend} < 0.0001$). This risk was slightly attenuated after adjustment for age, cigarette smoking, fruit/vegetable intake, body mass index, and environmental smoking exposure. Women who had worked rotating night shifts for 15 or more years had a 28% higher risk of lung cancer (RR = 1.28; 95% CI: 1.07, 1.53; $P_{trend} = 0.03$) than did women who never worked rotating night shifts, and these results were essentially unchanged when pack-years were used to control for smoking instead of age at start, years since quitting, and cigarettes per day (RR = 1.29, 95% CI: 1.08, 1.55). Restricting our analyses to women who engaged in rotating night-shift work only slightly attenuated the P values for trend (for the age-adjusted model, $P_{trend} = 0.0002$; for the age- and smoking-adjusted model, $P_{trend} = 0.11$; and for the multivariate-adjusted model, $P_{trend} = 0.09$).

In analyses stratified by smoking status, we found that the positive association between rotating night-shift work and overall lung cancer risk was restricted to current smokers (Table 2). Among current smokers, 15 or more years of rotating night-shift work was associated with a 61% increase in the risk of lung cancer (RR = 1.61, 95% CI: 1.21, 2.13; $P_{trend} = 0.0006$). By contrast, never or former smokers experienced no or little

Table 2. Relative Risks of Lung Cancer by Number of Years Working Rotating Night Shifts Stratified by Smoking Status Among 78,612 Women in the Nurses' Health Study, 1988–2008

Time Working Rotating Night Shifts, years	All Women							Never Smokers				
	No.	RR[a]	95% CI	RR[b]	95% CI	RR[c]	95% CI	No.	RR[a]	95% CI	RR[d]	95% CI
0	542	1.00	Referent	1.00	Referent	1.00	Referent	52	1.00	Referent	1.00	Referent
1–5	572	1.03	0.91, 1.16	1.02	0.90, 1.14	1.03	0.91, 1.16	63	1.22	0.84, 1.77	1.19	0.82, 1.73
6–14	177	1.09	0.92, 1.29	0.95	0.80, 1.13	0.96	0.81, 1.14	11	0.79	0.41, 1.51	0.75	0.39, 1.45
≥15	164	1.44	1.21, 1.72	1.23	1.03, 1.47	1.28	1.07, 1.53	11	1.06	0.55, 2.05	1.00	0.51, 1.94
P for trend			<.0001		0.07		0.03			0.78		0.65
	Former Smokers							Current Smokers				
	No.	RR[a]	95% CI	RR[e]	95% CI			No.	RR[a]	95% CI	RR[f]	95% CI
0	289	1.00	Referent	1.00	Referent			191	1.00	Referent	1.00	Referent
1–5	292	0.96	0.81, 1.13	0.99	0.83, 1.16			203	0.99	0.81, 1.22	1.01	0.82, 1.24
6–14	78	0.89	0.69, 1.14	0.86	0.66, 1.10			84	1.12	0.86, 1.46	1.16	0.89, 1.52
≥15	68	1.15	0.88, 1.51	1.06	0.81, 1.38			80	1.53	1.17, 2.01	1.61	1.21, 2.13
P for trend			0.52		0.92					0.001		0.0006

Abbreviation: CI, confidence interval; RR, relative risk.

[a] Adjusted for age (continuous) and time period.

[b] Adjusted for age (continuous), time period, smoking status (never, past, or current), cigarettes smoked per day among current smokers (1–4, 5–14, 15–24, 25–34, 35–44, and ≥45 cigarettes/day), and time since quitting among past smokers (<3, 3–5, 6–9, 10–14, 15–19, and ≥20 years ago).

[c] Adjusted for age (continuous), smoking status (never, past, or current), age at start of smoking (continuous), cigarettes smoked per day among current smokers (1–4, 5–14, 15–24, 25–34, 35–44, and ≥45 cigarettes/day), time since quitting among past smokers (<3, 3–5, 6–9, 10–14, 15–19, and ≥20 years ago), fruit intake (<1.5, 1.5–1.99, 2.0–2.49, 2.5–2.99, and ≥3.0 servings/day), vegetable intake (<2.0, 2.0–2.49, 2.5–2.99, 3.0–3.99, and ≥4.0 servings/week), and body mass index, measured as weight in kilograms divided by height in meters squared (<20, 20–21.9, 22–23.9, 24–26.9, 27–29.9, and >30), as well as environmental smoking exposures: parents smoking while living with them (no, mother only, father only, or both parents), years living with someone who smoked (<1, 1–9, 10–19, 20–29, and ≥30 years), exposure to smoking at work (no, occasionally, and regularly), and exposure to smoking at home (no, occasionally, and regularly).

[d] Adjusted for age (continuous), fruit intake (<1.5, 1.5–1.99, 2.0–2.49, 2.5–2.99, and ≥3.0 servings/day), vegetable intake (<2.0, 2.0–2.49, 2.5–2.99, 3.0–3.99, and ≥4.0 servings/week), and body mass index, measured as weight in kilograms divided by height in meters squared (<20, 20–21.9, 22–23.9, 24–26.9, 27–29.9, and >30), as well as environmental smoking exposures: parents smoking while living with them (no, mother only, father only, or both parents), years living with someone who smoked (<1, 1–9, 10–19, 20–29, and ≥30 years), exposure to smoking at work (no, occasionally, and regularly), and exposure to smoking at home (no, occasionally, and regularly).

[e] Adjusted for age (continuous), age at start of smoking (continuous), time since quitting (<3, 3–5, 6–9, 10–14, 15–19, and ≥20 years ago), fruit intake (<1.5, 1.5–1.99, 2.0–2.49, 2.5–2.99, and ≥3.0 servings/day), vegetable intake (<2.0, 2.0–2.49, 2.5–2.99, 3.0–3.99, and ≥4.0 servings/week), body mass index, measured as weight in kilograms divided by height in meters squared (<20, 20–21.9, 22–23.9, 24–26.9, 27–29.9, and >30), menopausal status (premenopausal vs. postmenopausal), hormone use among postmenopausal women (never, past, and current user), oral contraceptive use (never, <5 years, and ≥5 years), as well as environmental smoking exposures: parents smoking while living with them (no, mother only, father only, or both parents), years living with someone who smoked (<1, 1–9, 10–19, 20–29, and ≥30 years), exposure to smoking at work (no, occasionally, and regularly), and exposure to smoking at home (no, occasionally, and regularly).

[f] Adjusted for age (continuous), age at start smoking (continuous), cigarettes smoked per day (1–4, 5–14, 15–24, 25–34, 35–44, and ≥45 cigarettes/day), fruit intake (<1.5, 1.5–1.99, 2.0–2.49, 2.5–2.99, and ≥3.0 servings/day), vegetable intake (<2.0, 2.0–2.49, 2.5–2.99, 3.0–3.99, and ≥4.0 servings/week), body mass index, measured as weight in kilograms divided by height in meters squared (<20, 20–21.9, 22–23.9, 24–26.9, 27–29.9, and >30), menopausal status (premenopausal vs. postmenopausal), hormone use among postmenopausal women (never, past, and current user), and oral contraceptive use (never, <5 years, and ≥5 years), as well as environmental smoking exposures: parents smoking while living with them (no, mother only, father only, or both parents), years living with someone who smoked (<1, 1–9, 10–19, 20–29, and ≥30 years), exposure to smoking at work (no, occasionally, and regularly), and exposure to smoking at home (no, occasionally, and regularly).

increase in the risk of lung cancer even after 15 or more years of rotating night-shift work (for never smokers, RR = 1.00, 95% CI: 0.51, 1.94, and for former smokers, RR = 1.06, 95% CI: 0.81, 1.38). The interaction between night-shift work and smoking (current smokers vs. nonsmokers) was significant ($P_{\text{interaction}} = 0.03$).

Risks varied by histological subtype of lung cancer (Table 3). Compared with women who never worked any rotating night shifts, women in the category of longest night-shift work (≥15 years) had a 56% higher risk of small-cell lung cancer (RR = 1.56, 95% CI: 0.99, 2.47; $P_{\text{trend}} = 0.03$) and a 45% higher risk of squamous-cell carcinoma (RR = 1.45, 95% CI: 0.92, 2.30; $P_{\text{trend}} = 0.13$). By contrast, no significant association was observed between 15 or more years of rotating night-shift work and adenocarcinoma of the lung (RR = 0.91, 95% CI: 0.67, 1.24; $P_{\text{trend}} = 0.34$). Results for adenocarcinoma and

Table 3. Relative Risks of Lung Cancer Histology Subtypes by Rotating Night Shifts in the Nurses' Health Study, 1988–2008

Time Working Rotating Night Shifts, years	Adenocarcinoma						
	No.	RR[a]	95% CI	RR[b]	95% CI	RR[c]	95% CI
Never	249	1.00		1.00		1.00	
1–5 years	263	1.02	0.86, 1.21	1.02	0.85, 1.21	1.03	0.87, 1.24
6–14 years	74	0.99	0.76, 1.28	0.89	0.68, 1.15	0.92	0.71, 1.20
≥15 years	50	0.97	0.71, 1.32	0.85	0.63, 1.16	0.91	0.67, 1.24
P for trend[d]			0.79		0.20		0.40
	Squamous Cell Carcinoma						
	No.	RR[a]	95% CI	RR[b]	95% CI	RR[c]	95% CI
Never	75	1.00		1.00		1.00	
1–5 years	75	0.98	0.71, 1.75	0.96	0.70, 1.33	0.96	0.69, 1.33
6–14 years	25	1.11	0.71, 1.76	1.00	0.63, 1.58	1.01	0.64, 1.60
≥15 years	26	1.58	1.01, 2.48	1.37	0.87, 2.16	1.45	0.92, 2.30
P for trend[d]			0.04		0.19		0.13
	Small Cell Carcinoma						
	No.	RR[a]	95% CI	RR[b]	95% CI	RR[c]	95% CI
Never	65	1.00		1.00		1.00	
1–5 years	73	1.10	0.79, 1.54	1.06	0.76, 1.49	1.11	0.79, 1.57
6–14 years	34	1.73	1.14, 2.63	1.39	0.91, 2.13	1.40	0.91, 2.15
≥15 years	29	2.15	1.38, 3.34	1.66	1.05, 2.60	1.56	0.99, 2.47
P for trend[d]			<0.0001		0.01		0.03

Abbreviations: CI, confidence interval; RR, relative risk.

[a] Adjusted for age (continuous) and time period.

[b] Adjusted for age (continuous), time period, smoking status (never, past, or current), cigarettes smoked per day among current smokers (1–4, 5–14, 15–24, 25–34, 35–44, and ≥45 cigarettes/day), and time since quitting among past smokers (<3, 3–5, 6–9, 10–14, 15–19, and ≥20 years ago).

[c] Adjusted for age (continuous), age at start smoking (continuous), cigarettes smoked per day among current smokers (1–4, 5–14, 15–24, 25–34, 35–44, and ≥45 cigarettes/day), time since quitting among past smokers (<3, 3–5, 6–9, 10–14, 15–19, and ≥20 years ago), fruit intake (<1.5, 1.5–1.99, 2.0–2.49, 2.5–2.99, and ≥3.0 servings/day), vegetable intake (<2.0, 2.0–2.49, 2.5–2.99, 3.0–3.99, and ≥4.0 servings/week), body mass index, measured as weight in kilograms divided by height in meters squared (<20, 20–21.9, 22–23.9, 24–26.9, 27–29.9, and >30), menopausal status (premenopausal vs. postmenopausal), hormone use among postmenopausal women (never, past, and current user), and oral contraceptive use (never, <5 years, and ≥5 years), as well as environmental smoking exposures: parents smoking while living with them (no, mother only, father only, or both parents), years living with someone who smoked (<1, 1–9, 10–19, 20–29, and ≥30 years), exposure to smoking at work (no, occasionally, and regularly), and exposure to smoking at home (no, occasionally, and regularly).

[d] *P* for differences between the histological types tested using a polytomous logistic regression model. For adenocarcinoma versus squamous-cell carcinoma $P = 0.25$; for adenocarcinoma versus small-cell carcinoma, $P = 0.02$; and for squamous-cell carcinoma versus small-cell carcinoma $P = 0.33$.

small-cell carcinoma were statistically different ($P_{\text{difference}} = 0.02$).

We further explored the potential modifying effects of smoking by histological lung cancer subtype. Among current smokers, 15 or more years of rotating night-shift work was associated with a 22% increased risk of adenocarcinoma of the lung (RR = 1.22, 95% CI: 0.74, 2.01; $P_{\text{trend}} = 0.26$), a 57% higher risk of small-cell lung cancer (RR = 1.57, 95% CI: 0.85, 2.89; $P_{\text{trend}} = 0.10$), and 48% higher risk of squamous-cell carcinoma (RR = 1.48, 95% CI: 0.68, 3.23; $P_{\text{trend}} = 0.24$). Among past smokers, 15 or more years of rotating night-shift work was not associated with an increased risk of adenocarcinoma of the lung (340 cases; RR = 0.78, 95% CI: 0.50, 1.22; $P_{\text{trend}} = 0.10$) but was associated with a 78% higher risk of small-cell lung cancer (72 cases; RR = 1.78, 95% CI: 0.82, 3.86; $P_{\text{trend}} = 0.10$) and a 40% higher risk of squamous-cell carcinoma (114 cases; RR = 1.40, 95% CI: 0.75, 2.62; $P_{\text{trend}} = 0.35$). We did not have enough power to examine lung cancer risks by histological subtype among never smokers.

DISCUSSION

To our knowledge, the present study is the first prospective cohort study to examine lung cancer risk in women who worked night shift, with adjustment for a variety of potential confounders, including a detailed smoking history, and with information on histological subtypes of lung cancer. We found a significantly higher risk of lung cancer that was limited to women who currently smoked and reported having worked 15 or more years of rotating night-shift work. That the risk elevation appeared to be restricted to lung cancer types that were more strongly linked to smoking (squamous-cell carcinoma and small-cell carcinoma) than adenocarcinoma of the lung lends some support to an interaction between smoking behavior and working rotating night shifts, which suggests that women who smoke might be at an even higher risk of lung cancer if they simultaneously work rotating night shifts. Assuming a causal relationship between shift work and lung cancer, the population attributable risk percent is 5.9 among current smokers; this would imply that roughly 6% of all lung cancer cases among smokers (i.e., 33 of 558 cases) are attributable to longer durations (≥15 years) of night-shift work. However, given the lack of an association between rotating night-shift work and the risk of lung cancer among the never smokers in our study, residual confounding by smoking needs to be considered as an alternate explanation for the increased risk of lung cancer among rotating night-shift workers who smoke.

Our findings are largely compatible with the small body of previous literature on this topic. Only few studies, mostly register-based cohort or case-control studies, have attempted to examine the risk of lung cancer in various occupations associated with shift work. Data from Nordic countries were summarized by Pukkala et al. (15), who evaluated all cancer risk associated with a variety of occupations, covering 2.8 million incident cancer cases over 45 years of follow-up. Lung cancer was not elevated among shift workers in that large population-based cohort study (15), although the analyses were not adjusted for smoking. Similarly, a French population-based smoking-adjusted case-control study did not find any occupations that involve shift work to be associated with a higher risk of lung cancer (16). By contrast, 2 more recent studies found nursing (an occupation with traditionally high rates of rotating night-shift workers) to be associated with an increased risk of lung cancer. The first study, a US-based study of over 4.5 million women who died between 1984 and 1998, showed nursing to be significantly associated with higher rates of lung cancer even after adjustment for smoking status (18). The second, a recent study conducted in New Zealand, found nursing as an occupation to be highly associated with lung cancer risk (17). There were several studies of airline personnel in which investigators reported a lower risk of lung cancer related to that occupation (24–26), but whether the decreased risk is related to the lifestyle of airline personnel currently remains unclear (27). Studies have also linked increasing satellite-determined nightly light in 164 countries to higher rates breast (28) and prostate cancer (29), but not to those of lung cancer (29); however, conclusions on individual-level risks may not agree with these aggregate-level findings.

The most convincing evidence to date for an association between night-shift work and lung cancer risk comes from a Canadian population-based case-control study. Parent et al. (10) conducted a retrospective study to examine the association between night-shift work and a range of cancer outcomes in men. On the basis of 761 lung cancer cases and after adjustment for smoking status, β-carotene levels, and occupational exposure to asbestos and silica, they found a 76% increased risk of lung cancer (95% CI: 1.25, 2.47). The risk was largely comparable among all histological subtypes (for squamous-cell carcinoma, smoking-adjusted odds ratio =1.91; for small-cell carcinoma, OR = 1.62; and for adenoma carcinoma, OR = 1.46). However, Parent et al. (10) did not observe a dose–response relationship for the reported association and did not present their data stratified by smoking status.

Animal data support the existence of anticarcinogenic associations of melatonin, a prime marker of the circadian system, with a number of different kinds of tumors, including tumors in the lung (30). Although human data from prospective studies are still lacking, previous research has suggested that melatonin levels are suppressed in patients with lung cancer (31). More recent experimental evidence supported the hypothesis that circadian disruption in the form of chronic jet lag accelerated tumor progression and metastasis in mice that were inoculated with Lewis lung carcinoma cells (32); likewise, lung tumor growth was stimulated by circadian disruption in rats (33). In humans, a small cross-sectional study of 30 patients with non–small-cell lung cancer showed that they had significantly lower melatonin levels than did their healthy controls (34). Further, in humans, flattened cortisol rhythms as an indicator of a disturbed circadian system have repeatedly been linked to faster tumor progression in lung cancer patients (35, 36). Our results provide some plausibility to influence of shift work on lung cancer risk, especially in populations that are particularly vulnerable to developing the disease, such as smokers. Whether this supports circadian disruption as a "second hit" in the etiology of smoking-related lung tumors warrants further study. Alternate explanations for the observed associations among smokers include other factors that might be related to smoking, for example, chronotype, amount of sleep (37), and vitamin D level (38).

Our study had several limitations of note. Information on rotating night-shift work exposure was collected only once and may have been misclassified in some instances; for example, we do not have information on which precise work schedule to which each nurse adhered or whether she continuously worked the night shift. Further, the way we asked for information on life-time night work on the 1988 questionnaire may have misled some of the nurses. In the United States, a significant portion of nurses worked on permanent night shifts during the period of our investigation. These nurses may not have classified themselves as working on rotating shifts, but instead characterized themselves as "never-rotating workers" because they may have perceived permanent night work as "non-rotating" night work. Measurements of melatonin profiles in night workers show great variability in the timing of melatonin secretion, and because permanent night workers do not completely entrain to their circadian shift rhythm, the average serum melatonin levels among these women would be lower than those of never workers. However, women who worked rotating shifts would still remain at the highest overall risk because they would not be able to entrain to their circadian shift rhythm at all and therefore would have the lowest melatonin levels. Finally,

rotating night-shift work was defined as "at least 3 nights per month, in addition to evenings and afternoons in that month" in our study. However, from a small pilot study of approximately 60 women from within the Nurses' Health Study 2 cohort (E. Schernhammer, unpublished data, 2013), we expect a relatively large spread of number of nights worked: Among rotating night workers, the average number of nights worked per month was 6.4 (standard deviation, 4.1), with a range of 1–21 nights per month, whereas among permanent night workers, the average number of nights worked per month was 12.3 (standard deviation, 4.8), with a range of 3–30 nights per month. However, despite all of these limitations of our crude exposure assessment, we anticipate that any misclassification would have biased our results only towards the null.

Further, even though we adjusted for all known or suspected risk factors for lung cancer, including active and passive smoking exposures, the possibility for uncontrolled confounding remains. Strengths of our study include its large size, prospective nature, high prevalence of rotating night-shift workers, and detailed information on smoking exposure and histological type of lung cancer, as well as regularly updated information on confounders.

In summary, we found a higher risk of lung cancer in women with longer durations of rotating night-shift work that was limited to current smokers. Although we cannot rule out the possibility of this observation being confounded by smoking or of chance as an explanation for our findings, additional large prospective studies with detailed smoking assessments are needed to further explore the role of circadian disruption in lung cancer risk.

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