Night Work and Risk of Breast Cancer

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Background: Melatonin shows potential oncostatic activity and is acutely suppressed by light exposure. Some evidence suggests an association between night work and breast cancer risk, possibly through the melatonin pathway.

Methods: In a cohort of premenopausal nurses, we prospectively studied the relation between rotating night shift work and breast cancer risk. Total number of months during which the nurses worked rotating night shifts was first assessed at baseline in 1989 and periodically updated thereafter. We used Cox proportional hazards models to calculate relative risks (RRs) and 95% confidence intervals (CIs).

Results: Among 115,022 women without cancer at baseline, 1,352 developed invasive breast cancer during 12 years of follow up. Women who reported more than 20 years of rotating night shift work experienced an elevated relative risk of breast cancer compared with women who did not report any rotating night shift work (multivariate RR = 1.79; 95% CI = 1.06–3.01). There was no increase in risk associated with fewer years of rotating night work.

Conclusion: Our results suggest a modestly elevated risk of breast cancer after longer periods of rotating night work. Additional studies are warranted to rule out small sample size or uncontrolled sources for confounding as alternative explanations.

Environmental lighting powerfully influences the circadian system in humans.[1] In particular, light exposure may have an adverse effect on breast cancer risk through suppression of melatonin, a hormone that is intimately linked to the circadian system and demonstrates cancer-protective capability in experimental models.[2] Observational studies have consistently associated night work with an increase in breast cancer risk,[3] but these studies were mostly retrospective in design. The only prospective study[4] on the possible link between night shift work and breast cancer was the original Nurses' Health Study, which comprised primarily postmenopausal women.

METHODS

The Nurses' Health Study II is a prospective cohort study that began in 1989, when 116,671 registered female U.S. nurses of ages 25 to 42 years were enrolled. Since 1989, they have completed biennial mailed questionnaires that include items about their health status and known or suspected risk factors for cancer.[5] Response rates to questionnaires are at 90%. Further details of the Nurses' Health Study II are described elsewhere.[6]

Assessment of Night Shift Working Status

The 1989 questionnaire included detailed questions on total months during which study participants had worked on rotating night shifts for at least 3 nights per month in addition to having worked days or evenings in that month. This information was updated in 1991, 1993, and 1997. The prespecified categories for total numbers of months working on rotating night shifts were none, 1–4, 5–9, 10–14, 15–19, and 20 or more. Because the 1995 and 1999 questionnaires did not assess night work information, women were queried retrospectively in 2001 for the time periods 1993–1995 and 1997–1999. Questions were asked regarding both rotating night shifts, as previously described, and permanent night shifts for 6 or more months.

Documentation of Breast Cancer and Deaths

We identified breast cancer cases as cases occurring between 1 June 1989 and 1 June 2001. Nurses who reported breast cancer were asked for permission to review their medical records, and breast cancer was confirmed through review of these records. In addition, approximately two thirds of the deaths among cohort members were reported to us by next of kin or the postal system in response to follow-up questionnaires. We also searched the National Death Index to identify deaths among the nonrespondents to each 2-year questionnaire.[7] A total of 1,352 cases of breast cancer were reported in the base population during 12 years of follow up, and pathology records were obtained for 98%. We based our analyses on the total, because the accuracy of the self-reporting was extremely high in this cohort (>99%).

Study Population

The population for this study consisted of 116,087 women who returned the 1989 questionnaire and answered the question on night work (99.5% of the total). Women with a history of cancer (except nonmelanoma skin cancer) at baseline were excluded. A total of 115,022 women remained to form the baseline population for this analysis, and 1,313,203 person years of follow-up were accrued from 1989 to 2001.

Statistical Analysis

We computed person-years of follow up to the date of diagnosis of breast cancer, death from any cause, or the end

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of the study period (1 June 2001), whichever came first. Information on lifetime history of rotating night shift work obtained from the 1989 questionnaire was updated according to the biennial follow-up questionnaires. Gaps in the prospectively collected information for 1993–1995 and 1997–1999 were filled with retrospectively assessed information on months of rotating night work during these 2-year periods, as ascertained on the 2001 questionnaire. To evaluate the validity of this approach, we conducted sensitivity analyses either carrying forward night work information from the previous cycle or setting number of months worked on rotating night shifts to zero for these 2 time periods.

Women were categorized according to the total number of years they worked rotating night shifts at least 3 nights per month in addition to days or evenings in that month ("never," "1–9 years," "10–19 years," or "≥20 years"). Information about breast cancer and established risk factors for breast cancer was updated biennially. We calculated Mantel-Haenszel summary relative risks (RRs) and associated 95% confidence intervals (CIs) adjusting for age in 5-year categories.[8] Cox proportional hazards models were used to calculate RRs and 95% CIs with adjustment for age (in years) and a number of known breast cancer risk factors.

RESULTS

At baseline, in 1989, women who had never worked on rotating night shifts accounted for 38% of the person-years of follow up among all women. Women who worked rotating shifts were similar in their characteristics to those who had never done such work (Table 1). However, night shift workers were older and tended to smoke more than those who had never worked on rotating nightshifts.

Table 2 shows the relationship between total number of years on rotating night shifts and breast cancer. Higher duration of shift work was associated with an increased breast cancer risk; women who had worked for 20 or more years on rotating night shifts had a 79% greater risk of breast cancer compared with women who had never worked this schedule (multivariate-adjusted RR =1.79; 95% CI = 1.06–3.01; P for trend = 0.65). Moreover, results were similar when the same analysis was limited to rotating night shifts at baseline (2.79; 1.38–5.66). However, this analysis was based on only 8 cases exposed at baseline who reported 20 or more years of night work in 1989.

In our main analyses, we used retrospective information from 2001 to create a composite night work variable. We also conducted 2 types of sensitivity analyses. In the first, rather than using the 2001 data retrospectively, we conservatively assumed that nurses had not worked a single month on rotating night shifts during the time periods in question, which produced essentially no change in the results (2.01; 1.17–3.44). Second, we carried forward the last reported value (ie, from the previous questionnaire cycle), an approach commonly applied for missing information in updated analyses. In this analysis, we saw a slightly weaker association (1.56; 0.91–2.66) when compared with our main approach.

In stratified analyses, although limited by small case numbers, we observed no effect modification by body mass index or smoking history. The exclusion of current smokers did strengthen our estimates but only modestly (1.92; 1.10–3.35).

It is possible that women stopped working night shifts due to early symptoms associated with breast cancer. If true, such a "healthy worker effect" would have biased our results

TABLE 1. Age and Age-Standardized* Characteristics (1995) According to Rotating Shift Work Status in 1995 (halfway through the follow-up period) Among 113,216 Women in the Nurses' Health Study*

	Duration of Work on Rotating Night Shifts (years)			
Characteristics	**Never (n = 35,153)**	**1–9 (n = 70,773)**	**10–19 (n = 6759)**	**≥20 (n = 531)**
Age (years); mean ± SD	40.5 ± 4.6	40.0 ± 4.7	41.5 ± 4.0	45.0 ± 2.6
Family history of breast cancer; %	6	6	6	7
Body mass index (kg/m^2); mean ± SD	25.4 ± 5.7	25.9 ± 6.0	27.6 ± 6.7	28.9 ± 7.5
Height (inches); mean ± SD	64.9 ± 2.6	64.9 ± 2.6	64.8 ± 2.7	64.8 ± 2.7
Age at menarche ≥14 yr; %	17	18	18	14
History of benign breast disease; %	40	40	39	47
Ever used oral contraceptive; %	79	80	77	80
Age at first birth† (years); mean ± SD	26.0 ± 4.4	26.3 ± 4.5	26.0 ± 4.8	24.9 ± 4.3
Parity† (number of children); mean ± SD	1.9 ± 1.2	1.8 ± 1.2	1.7 ± 1.3	1.7 ± 1.3
Alcohol consumption (gram/d); mean ± SD	3.4 ± 6.6	3.5 ± 6.7	3.1 ± 6.3	3.1 ± 7.8
Premenopausal; %	82	83	75	62
Packyears smoked; mean ± SD	4.1 ± 8.1	4.5 ± 8.3	5.7 ± 9.5	8.4 ± 11.9
Current smokers; %	10	11	15	14

*Age-standardized according to 5 categories of age (<35, 35–39, 40–44, 45–49, 50+ y) as of 1995.
†Among parous women only.
SD indicates standard deviation.

TABLE 2. Association of Rotating Night Shift Work With Breast Cancer Among 115,022 Women in the Nurses' Health Study II, With Prospective Follow Up From 1989 Through 2001

Duration of Rotating Night Shift (years)	Person-Years	No. of Cases	Age-Adjusted RR (95% CI)	Multivariate RR* (95% CI)
Never[†]	426,119	441	1.0	1.0
1–9	809,374	816	0.97 (0.87–1.09)	0.98 (0.87–1.10)
10–19	72,829	80	0.90 (0.71–1.15)	0.91 (0.72–1.16)
20+	4,881	15	1.88 (1.12–3.15)	1.79 (1.06–3.01)
P for trend[‡]			0.96	0.65

*Relative risk adjusted for age, age at menarche(<12, 12, 13, ≥14 yr), menopausal status (premenopausal, postmenopausal, unknown), age at menopause (<48, 48, 49, ≥50 yr), age at first birth and parity combined (nulliparous; age at first birth <25, 1–2 children; age at first birth 25–29, 1–2 children; age at first birth ≥30, 1–2 children; age at first birth <25, ≥3 children; age at first birth ≥25, ≥3 children), body mass index (weight in kilograms divided by the square of height in meters; <18.5, 18.5–19.9, 20.0–22.4, 22.5–24.9, 25.0–29.0, and ≥30 kg/m^2), current alcohol consumption (nondrinkers, <5 g/d, 5–9.9 g/d, 10–19.9 g/d, and ≥20 g/d), oral contraceptive use (ever/never), postmenopausal hormone use (ever/never), smoking status (nonsmoker, current smoker <25 cigarettes/d, current smoker ≥25 cigarettes/d), benign breast disease (yes/no), family history of breast cancer (yes/no), and physical activity (in quintiles of metabolic equivalents/wk [METs, the caloric need per kilogram body weight per hour activity, divided by the caloric need per kilogram per hour at rest]).

[†]Reference category in all analyses.

[‡]*P* value(Wald test) for continuous linear term (number of years having worked rotating night shifts).

toward the null. To address this hypothesis, we repeated our analyses excluding the first 4 years of follow up after the baseline report on night work (1989–1993). We analyzed the relation between number of nights worked as assessed in 1989 and the risk of breast cancer from 1993 through 2001. This 4-year latency period was associated with an increase in breast cancer risk (1.79; 0.88–3.63), similar to the risk we observed in our main analyses.

DISCUSSION

In this large prospective cohort study with detailed and updated information on night shift work, the risk of breast cancer was found to be modestly elevated in women who worked for 20 or more years on rotating night shifts compared with those who never worked rotating night shifts. Our finding, which is consistent with previous studies suggesting a link between night work and breast cancer risk, is the first prospective report on this association in premenopausal women.

Several retrospective studies[9–15] and one prospective study[4] of night workers have found an elevated breast cancer risk associated with occupational exposure to light at night. The only prospective cohort study to date used data from the original Nurses' Health Study.[4] In that study, the RR associated with extended periods (30 or more years) of rotating night work was 1.36 (95% CI = 1.04–1.78) after controlling for known breast cancer risk factors. This risk increased with numbers of years of shift work (*P* for trend = 0.02). Studies of flight attendants also consistently find that female cabin crew members are at increased risk for breast cancer,[14] although the incomplete assessment of possible confounding factors remains an important limitation of these retrospective studies.

Although we did not validate self-reported duration of rotating night shifts, it is likely that our results are accurate, because other self-reports have been highly accurate in a similar cohort,[16] and previous validations of similar questions (eg, electric blanket use)[17] have shown reasonable reproducibility. Moreover, the prospective design of our study eliminates recall bias. We may have missed women who were on permanent nightshifts and thus perhaps did not classify themselves as working on rotating shifts; assuming that the average serum melatonin levels would likely be higher than those of rotating shift workers (because of better entrainment of their circadian rhythm), we anticipate that such misclassification would bias our results toward the null. In secondary analyses, we excluded women who had worked 6 or more months of permanent night work, with similar findings, thus providing support for our theory.

A potential limitation in our study is that women who work most frequently on night shifts may differ from women with no night shift experience in ways that influence risk of breast cancer and in ways we were not able to control. For example, there was a marked difference in smoking history among women who never had worked night shift and those with 20 or more years of night work; moreover, smoking duration rather than current smoking status was most strongly related to breast cancer risk in this cohort.[18] However, neither the additional adjustment for pack-years smoked nor the exclusion of smokers from our analyses altered our results. Nonetheless, although we controlled for known potential confounding factors, uncontrolled confounding may stem from differences in socioeconomic status or other differences in lifestyle that we were not able to consider.

Another limitation of our study is that few women had worked rotating night shifts for 20 or more years, leading to small case numbers in the longest exposure categories. Thus, although we have seen similarly increased risks of breast cancer with 30 or more years of night work based on much larger case numbers in our previous study[4] of older women (Nurses' Health Study), larger studies of premenopausal women are still needed to confirm our findings. In addition, we had no information on the actual number of nights worked per month. It is conceivable that women with the longest duration of night work are also those who work the highest number of night shifts per month. Thus, frequency of night

shifts, as well as number of years of such work, should be considered in future studies.

In conclusion, working on rotating night shifts was associated with a modestly increased breast cancer risk among the female nurses in our cohort. The findings from our study, in combination with the results of earlier work, reduce the likelihood that this association is due solely to chance. Because breast cancer constitutes an enormous disease burden in the United States, and because a significant portion of workers engage in shift work, further studies examining the relationship between light exposure at night and cancer risk through the melatonin pathway are warranted.

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