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Rotating night shift work and risk of ovarian cancer

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Abstract

Background—Night shift work has been associated with higher risks of breast and endometrial cancer, but few studies have evaluated associations with other reproductive cancers.

Methods—We examined the association between rotating night shift work and risk of ovarian cancer during 20 years of follow-up in 181,548 women participating in two large cohort studies, the Nurses' Health Study (NHS) and NHSII. Number of years of rotating night shift work was queried in 1988 for NHS and in 1989, 1991, 1993, 2001, and 2005 for NHSII. We used Cox proportional hazards regression to model hazard ratios (HRs) and 95% confidence intervals (CI) of ovarian cancer for each shift work category (1-2 years, 3-5 years, 6-9 years, 10-14 years, 15-19 years, and 20+ years).

Results—We confirmed 718 incident cases of ovarian cancer over 2,974,672 person-years of follow-up. Rotating shift work was not associated with ovarian cancer risk in either cohort individually. Combining both cohorts, compared to women without any night work, the HR for 15-19 years of rotating night shift work was 1.28 (95% CI: 0.84-1.94), and for 20+ years 0.80 (95% CI: 0.51-1.23).

Conclusions—In this large prospective study, there was no association between duration of rotating night shift work and risk of ovarian cancer.

Impact—Although associated with other cancers, night shift work does not appear to be associated with increased risk of ovarian cancer. However, further exploration of the association between melatonin and risk of ovarian cancer is warranted.

Keywords

ovarian cancer; night shift work

Introduction

Night shift work has been associated with increased risks of multiple cancer types (1-12), including hormonally-sensitive cancers such as breast (1-7) and endometrial (8) cancers, prompting the International Agency for Research on Cancer to classify night shift work as a probable carcinogen (13). Night shift work may be linked to cancer risk by the diminished ability of the pineal gland to produce melatonin among those exposed to light at night (14). There are likely several anti-cancer mechanisms for melatonin (reviewed in (15)), including

modulation of estradiol levels and aromatase activity and down-regulation of ER α expression in mammary tumors.

Animal and experimental studies suggest a chemoprotective role of melatonin specifically in ovarian carcinogenesis. Treatment of ovarian cancer cell lines with melatonin resulted in growth inhibition (16). Further, in turkey breeder hens with ovarian adenocarcinomas, short day length (i.e. short exposure to sunlight) was associated with tumor regression (17); when the same hens were exposed to longer days, the tumors re-grew. Treatment with melatonin slowed tumor growth among the hens exposed to a long day length. In healthy volunteer women, treatment with melatonin in combination with the synthetic progestin norethisterone resulted in suppression of the pituitary-ovarian axis and inhibition of ovarian function and ovulation (18). Despite this suggestive evidence, few studies of have examined the association between exposures that disrupt melatonin production, such as night shift work, and risk of ovarian cancer. In the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII), we prospectively examined potential associations between duration of rotating night shift work and risk of epithelial ovarian cancer.

Methods

The NHS cohort was established in 1976 among 121,700 US female registered nurses, ages 30 to 55 years, and NHSII was established in 1989 among 116,430 female registered nurses, ages 25 to 42 years. All women completed an initial questionnaire about their lifestyle factors, health behaviors, and medical history, and, since baseline, have been followed biennially by questionnaire to update exposure status and disease diagnoses (19, 20).

Ascertainment of night shift working status

In 1988, NHS participants were asked how many total years they had worked rotating night shifts at least three nights per month in addition to day or evening shifts. Duration of rotating night shift work was ascertained in the following pre-specified categories: never, 1-2, 3-5, 6-9, 10-14, 15-19, 20-29, and 30+ years. Of the 103,614 participants who responded to the 1988 questionnaire, 85,197 answered the shift work question. The majority (91.8%) who did not answer the shift work question received a shortened questionnaire that did not contain the shift work question. Among those who received the long version of the questionnaire, the follow-up rate through June 2008 was 86.5% of the potential person-years.

NHSII participants were first asked about their duration of rotating night shift work in 1989 in the following pre-specified categories: 1-2, 3-5, 6-9, 10-14, 15-19, and 20+ years. This information was updated in 1991, 1993, 2001, and 2005. In each cycle in which shift work was assessed, duration was obtained since the prior update and used to update the total shift work variable. Of the 116,430 women who responded to the 1989 questionnaire, 115,841 answered the shift work question. The follow-up rate of the NHSII cohort through June 2007 was 87.6% of the potential person-years. If a nurse failed to respond to one of the shift work questions, her previous duration was carried forward.

Documentation of ovarian cancer cases and deaths

We collected information about new ovarian cancer diagnoses on each questionnaire. For all reported cases and deaths due to ovarian cancer identified by family members, the National Death Index, or the US Postal Service, we obtained medical records pertaining to the ovarian cancer diagnosis. A gynecologic pathologist blinded to exposure status reviewed the medical records to confirm the diagnosis, as well as stage, histology, and invasiveness. In a subset of 215 ovarian cancer cases, concordance between the medical records and the pathologist's review was 98% for invasiveness and 83% for histologic type (21).

Statistical Analysis

The eligible population for this analysis included the 85,197 NHS participants who answered the rotating shift work question on the 1988 questionnaire and the 115,841 NHSII participants who answered the same question on the 1989 questionnaire. Women with a cancer (except non-melanoma skin cancer) diagnosis prior to the baseline year (NHS=2977; NHSII=1038), a bilateral oophorectomy (NHS=13,036; NHSII=2224), menopause due to pelvic irradiation (NHS=150; NHSII=30), or who were missing date of birth (NHS=35) were excluded. After all exclusions, a total of 68,999 NHS participants and 112,549 NHSII participants were left in the analyses. Participants accrued person-time from the time of the return of the 1988/1989 questionnaire until the date of ovarian cancer diagnosis, diagnosis of cancer (except non-melanoma skin cancer), bilateral oophorectomy, pelvic irradiation, death, or the end of follow-up (NHS: June 1, 2008; NHSII: June 1, 2007), whichever occurred first.

We used Cox proportional hazards regression, with age in months and 2-year questionnaire cycle as the time scale, to estimate the hazard ratios (HRs) and 95% confidence intervals (CIs) of ovarian cancer for each shift work duration category, compared to those who never worked rotating night shifts, adjusting for known and suspected ovarian cancer risk factors (see Tables for detail). Tests for trend were conducted by treating the shift work duration categories as an ordinal variable and calculating the Wald statistic.

Data analyses were conducted separately for both cohorts and then pooled using a random effects model to test for heterogeneity (22). To assess whether results varied by menopausal status (pre- vs. postmenopausal), age (<55 vs., 55+ years), postmenopausal hormone (PMH) use (never vs. ever; postmenopausal only), menstrual regularity (no irregularity vs. any irregularity), BMI (<25 vs. 25+), or infertility, we included multiplicative interaction terms in multivariate models and tested their significance using the Wald statistic.

We performed several sensitivity analyses. First, because duration of shift work was only collected once in NHS, we analyzed NHSII using only the reported baseline shift work duration, in addition to our primary analyses in which we updated shift work information. Additionally, because there were so few cases in the higher duration categories, we analyzed the data in categories of none, 1-5 years, 16-14 years and 15+ years. We also performed an analysis censoring all women who did not respond to the shift work questions after baseline (in NHSII). Fourth, we performed both a 2- and 4-year lag analysis to account for potential healthy worker effects.

Results

At the midpoint of follow-up, 41.0% of the NHS participants and 32.2% of NHSII participants reported never having worked rotating night shifts. Women who reported never working night shifts generally were similar to women who reported night shift work, except that those who had worked rotating night shifts for at least 20 years were older, had a higher BMI, and were more likely to smoke (Table 1).

Combining both cohorts, there was no association between duration of rotating night shift work and risk of ovarian cancer (for example, 15-19 years, HR: 1.28; 95% CI: 0.84-1.94; 20+ years, HR: 0.80; 95% CI: 0.51-1.23; p-trend=0.74), compared to women without any night work, and results were similar across cohorts (Table 2). Results did not differ when duration categories were collapsed, when a lag of 2 or 4 years was employed between exposure and ovarian cancer diagnosis, when only baseline NHSII duration was used, or when missing NHSII updated shift work duration values were censored (data not shown). The association between duration of rotating night shift work and ovarian cancer did not

vary by category of age, menopausal status, PMH use, BMI, oral contraceptive use, menstrual irregularity, or infertility.

Discussion

In this large, prospective study of rotating night shift work and risk of ovarian cancer, we observed no association between increasing duration of night shift work and risk. Few previous studies have examined potential associations between shift work and ovarian cancer. In a Norwegian study, no association with ovarian cancer incidence was observed for radio and telegraph operators (SIR: 0.8; 95% CI: 0.3-1.6) (5), many of whom worked night shifts. However, this result was based on only 7 cases. Karasek and colleagues compared serum circadian melatonin profiles between women with genital tract cancers (including ovarian, endometrial, and cervical cancers) with normal volunteers (23). They reported no differences between melatonin profiles of the ovarian cancer patients compared to the normal controls, but their sample size was limited, and melatonin was measured after ovarian cancer diagnosis.

This study has several potential limitations. First, duration of rotating night shift work was only assessed once in NHS (in 1998). It is possible that the true duration of shift work was underestimated for NHS participants. However, in 1996, only 3% of nurses reported any shift work in the past 6 months, indicating that the extent of the misclassification of duration is limited. Also, duration of shift work was only updated every four years in NHSII; however, sensitivity analyses using only baseline shift work duration in NHSII showed similar results, suggesting that the effects of potential misclassification were minimal. Nevertheless, the possibility remains that a small proportion of nurses may have been misclassified as to their true duration of rotating night shift work.

Second, rotating night shift work was assessed through self-report and was not confirmed with personnel or hospital records. However, women in this cohort have been shown to accurately report their exposures to many lifestyle and occupational exposures (e.g., (24, 25)). Third, we did not collect data on permanent or infrequent rotating (less than 3 nights per month) night shift work. Although the disruption of melatonin production likely is less severe from these exposures, we cannot rule out the possibility that the observed lack of association in our study could be due to misclassification among a subset of women with different forms of night shift work. However, as breast, colorectal, and endometrial cancers were associated with rotating night shift work in these cohorts (3, 4, 8, 9), the likely degree of misclassification is low.

The strengths of this analysis include the large number of ovarian cancer cases and prospective data collection. Because women were asked about their rotating shift work exposure prior to the diagnosis of ovarian cancer, the likelihood of recall bias is low. Further, we have collected detailed information on many of the potential confounders of the association between rotating night shift work and ovarian cancer risk, such as reproductive history and hormonal therapy, thus reducing the likelihood of uncontrolled confounding in our analysis.

In conclusion, increasing duration of rotating night shift work was not associated with ovarian cancer risk in the NHS and NHSII cohorts. However, further exploration of the association between melatonin and risk of ovarian cancer is warranted.

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Table 1

Age-standardized characteristics of participant in the Nurses' Health Study (NHS) in 1998 and NHSII in 1999, the mid-point of the follow-up period (1988-2008 for NHS and 1989-2007 for NHSII)

	NHS			NHSII		
	none	6-10	20+	none	6-10	20+
Years of shift work						
Sample size	22,376	3,686	2,303	32,993	9,657	282
Means						
Age in years	63.8 (7.1)	64.8 (7.1)	67.3 (6.5)	44.6 (4.6)	44.4 (4.3)	49.4 (2.8)
Age at menarche	12.5 (1.4)	12.6 (1.5)	12.6 (1.6)	12.4 (1.4)	12.4 (1.5)	12.3 (1.6)
Duration of oral contraceptive use (years)	2.1 (3.5)	2.1 (3.5)	1.9 (3.4)	3.8 (4.7)	3.8 (4.7)	3.3 (4.3)
BMI (kg/m ²)	26.3 (5.1)	27.1 (5.4)	27.9 (5.7)	25.9 (5.5)	27.0 (6.2)	29.1 (9.5)
Percentage						
Parous	95	93	95	86	81	80
Premenopausal	4	4	3	74	73	62
Postmenopausal	93	92	93	8	8	14
Family history of ovarian cancer	3	3	4	2	2	4
Tubal ligation	21	22	22	26	26	30
Ever breastfed (among parous women)	63	64	58	66	65	45
Current postmenopausal hormone user (among postmenopausal women)	43	40	34	54	51	57
Current smoker	10	12	14	8	10	15

Values are means (SD) or percentages and are standardized to the age distribution of the study population. All factors except age and age at menarche were age-standardized in 5-year intervals for each cohort.

Table 2

Multivariate hazard ratios (HR) and 95% confidence intervals (CI) for risk of epithelial ovarian cancer by years of rotating night shift work in NHS and NHSII

	NHS			NHSII			NHS and NHSII						
	Cases	Person-years	Age-adjusted HR	Multivariate ^d HR (95% CI)	Cases	Person-years	Age-adjusted HR	Multivariate ^d HR (95% CI)	Cases	Person-years	Age-adjusted HR	Multivariate ^d HR (95% CI)	p-het ^b
Years of rotating shift work													
none	202	454,004	1.00	1.00 (ref.)	68	602,593	1.00	1.00 (ref.)	270	1,056,596	1.00	1.00 (ref.)	
1-2	143	270,522	1.20	1.20 (0.97-1.49)	54	591,716	0.82	0.80 (0.56-1.14)	197	862,237	1.08	1.07 (0.89-1.29)	0.06
3-5	80	183,352	0.96	0.95 (0.73-1.23)	35	386,364	0.82	0.79 (0.52-1.18)	115	569,716	0.93	0.90 (0.72-1.13)	0.46
6-9	33	74,671	0.98	0.96 (0.67-1.40)	18	178,426	0.89	0.80 (0.47-1.35)	51	253,098	0.96	0.92 (0.68-1.25)	0.55
10-14	25	48,771	1.12	1.06 (0.70-1.62)	14	76,496	1.42	1.25 (0.70-2.24)	39	125,268	1.22	1.14 (0.81-1.60)	0.65
15-19	19	29,849	1.33	1.30 (0.81-2.10)	5	24,001	1.41	1.21 (0.48-3.02)	24	53,850	1.34	1.28 (0.84-1.94)	0.90
20+	22	47,034	0.90	0.88 (0.56-1.37)	0	6,873	NA	NA	22	53,907	0.84	0.80 (0.51-1.23)	NA
p-trend ^c			0.97	0.84			0.77	0.78			0.88	0.74	0.87

^aMultivariate analyses adjusted for age (continuous), duration of oral contraceptive use (continuous), parity (continuous), BMI (continuous), smoking status (current/past/never/missing), tubal ligation history (yes/no), menopausal status (postmenopausal/premenopausal or unknown), family history of ovarian cancer (yes/no), duration of breastfeeding (none/≤6 months/7-11 months/12-17 months/18+ months/missing), and cohort (combined analyses only).

^bP-heterogeneity by cohort was assessed using the DerSimonian and Laird random effects model.

^cP-value for multivariate model including duration of shift work as a continuous variable.