Night Shift Work and the Risk of Endometrial Cancer

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Abstract

Melatonin has several oncostatic properties, including possible anti-estrogenic and anti-aromatase activity, and seems to be linked with fat metabolism. Night workers have lower levels of melatonin, which may predispose them to develop cancer. Endometrial cancer risk is influenced significantly by hormonal and metabolic factors; therefore, we hypothesize that night workers may have an increased risk of endometrial cancer. Of the 121,701 women enrolled in a prospective cohort study, 53,487 women provided data on rotating night shift work in 1988 and were followed through on June 1, 2004. A total of 515 women developed medical record–confirmed invasive endometrial cancer. We used Cox regression models to calculate multivariate relative risks (MVRRs), controlling for endometrial cancer risk factors. Women who worked 20+ years of rotating night shifts had a significantly increased risk of endometrial cancer [MVRR, 1.47; 95% confidence interval (95% CI), 1.03–1.14]. In stratified analyses, obese women working rotating night shifts doubled their baseline risk of endometrial cancer (MVRR, 2.09; 95% CI, 1.24–3.52) compared with obese women who did no night work, whereas a nonsignificant increase was seen among non-obese women (MVRR, 1.07; 95% CI, 0.60–1.92). Women working rotating night shifts for a long duration have a significantly increased risk of endometrial cancer, particularly if they are obese. We speculate that this increased risk is attributable to the effects of melatonin on hormonal and metabolic factors. Our results add to growing literature that suggests women who work at night may benefit from cancer prevention strategies. [Cancer Res 2007;67(21):10618–22]

Introduction

In the United States, endometrial cancer causes ~7,000 deaths annually, with an estimated 40,684 new cases in 2007 (1), making uterine cancer the most common gynecologic malignancy nationally. Known risk factors include an increase in unopposed estrogen exposure due to obesity or postmenopausal hormone use (2). Parity, age at first birth, oral contraceptive use, smoking, age at menarche, and menopause have also been related to endometrial cancer through their hormone-modulating effects. Nulliparity, older age at first birth, early menarche, and late menopause increase the risk of endometrial cancer, whereas smoking and oral contraceptive use decrease its risk (2). However, endometrial carcinogenesis is likely a complex interplay of unopposed estrogen exposure, progesterone levels, and other factors regulating endometrial remodeling.

Observational studies report a higher risk of breast (3), colorectal (4), and prostate cancer (5) among night workers. Night shift work decreases serum melatonin levels, which in turn may enhance tumor development, as consistently suggested by animal and *in vitro* studies (6). In addition to its potential anti-estrogenic activities (7), melatonin seems to modulate aromatase activity in mammary tumors (8). Melatonin further seems to play an important role in fat metabolism, and increased adiposity is associated with an increased risk of endometrial cancer (9–12).

Cross-sectional studies have shown lower melatonin levels in women with endometrial cancer (13, 14). An MT2 melatonin receptor subtype that may mediate the cancer-protective effect of melatonin has been described in a human endometrial cancer cell line (15, 16). This report presents the first evaluation of the relationship between night work and endometrial cancer risk in a large prospective cohort of pre- and postmenopausal women.

Materials and Methods

The Nurses' Health Study began in 1976, when 121,701 female registered nurses 30 to 55 years of age and living in 11 large U.S. states were enrolled. Since 1976, biennial mailed questionnaires have queried their health status, medical history, and known or suspected risk factors for cancer and heart disease. Follow-up data are available for more than 90% of the ongoing cohort. Further details of the Nurses' Health Study are described elsewhere (17). This study was approved by the Human Subjects Research Committee.

Ascertainment of night shift working status. In 1988, nurses were asked how many years in total they had worked rotating night shifts. Rotating night shifts are defined as working at least three nights per month, in addition to daytime or evening shifts in that month. Information on lifetime years worked on rotating night shift was gathered in eight prespecified categories of total years summed: never, 1 to 2, 3 to 5, 6 to 9, 10 to 14, 15 to 19, 20 to 29, and 30+ years.

Documentation of endometrial cancer and deaths. Invasive endometrial cancer cases were defined as having occurred between June 1988 and May 2004. Nurses who reported having endometrial cancer were asked for permission to review their medical records; diagnosis was confirmed by a physician unaware of exposure status. Deaths among cohort members were identified through report by nurses' next of kin and the National Death Index; data on mortality were more than 98% complete.

Study population. A total of 103,613 of the women returned the 1988 questionnaire, of whom 85,197 responded to a question on lifetime night work history. We excluded women who reported endometrial cancer or any other cancer other than non–melanoma skin cancer on the 1988 questionnaire or any previous questionnaire. Furthermore, women who did not have an intact uterus were excluded at the beginning of each questionnaire cycle because they would not have been at risk for endometrial cancer. After all exclusions, a total of 53,487 women remained to form the baseline population for this analysis, and 720,698 person-years of follow-up were accrued from June 1988 through May 2004.

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Table 1. Age and age-standardized baseline characteristics according to rotating shift work status in 1988 among 53,487 women participating in the Nurses' Health Study

Characteristics	Value of indicated characteristic by years worked on rotating night shifts			
	Never (n = 22,045)	1–9 (n = 25,455)	10–19 (n = 3,725)	≥20 (n = 2,262)
Age (y), mean (SD)	53.1 (7.2)	53.4 (7.2)	54.5 (7.3)	57.0 (6.5)
Height, in. (SD)	64.4 (3.1)	64.5 (3.4)	64.4 (2.7)	64.2 (3.7)
BMI (kg/m^2), mean (SD)	23.5 (8.0)	23.8 (8.0)	24.4 (8.7)	25.0 (9.0)
PMH use (ever, %)*	44.9	44.0	42.1	31.9
Age at menarche (y), mean (SD)	12.4 (1.8)	12.5 (1.7)	12.5 (1.9)	12.6 (1.9)
Ever used oral contraceptive (%)	51.0	50.6	47.9	44.7
Nulliparous (%)	4.6	6.0	6.5	5.9
Postmenopausal (%)	58.3	58.6	60.4	64.2
Age at menopause (y), mean (SD)	50.2 (6.0)	50.1 (5.5)	49.9 (5.9)	50.3 (5.7)
Ever smokers (%)	55.0	57.1	60.3	57.4
Current smoker (%)	18.4	18.9	26.4	23.6
History of diabetes (%)	3.6	3.5	5.5	6.2
History of high blood pressure (%)	23.9	24.8	29.2	31.6
Total energy intake (kcal) in 1986 (SD)	1,759 (519)	1,791 (524)	1,794 (537)	1,773 (561)

NOTE: Age standardized according to five categories of age (<35, 35–39, 40–44, 45–49, 50+ y) as of the 2-y period when participants first entered follow-up.
*Among postmenopausal women only.

Covariate data. Information on most potential confounders, including age, menopausal status, postmenopausal hormone (PMH) use, weight, diabetes, smoking, and hypertension, was collected on the baseline questionnaire and in 2-year updates. Updated covariate information was used in multivariate analyses. Information on oral contraceptive use was collected through 1982, when fewer than 500 women reported current use of oral contraceptives. Menarche and height were only recorded at baseline. For smoking use, information from consecutive questionnaires was used to update prior ones and to derive years of use.

Body mass index (BMI; weight in kilograms/height in square meters) was calculated from height at baseline and from the updated report of current weight. Weight from the prior questionnaire cycle was brought forward if it was missing. Because BMI is such a strong predictor of endometrial cancer risk, if weight was not reported for two consecutive time periods, these women were defined as missing and were excluded from follow-up until an updated weight was reported. Measurements of waist and hip were queried in 1986 and used to calculate a waist-hip ratio variable. A nurse was classified as postmenopausal from the time she returned a questionnaire reporting natural menopause (women reporting a hysterectomy were excluded from subsequent follow-up).

Statistical analysis. Women were categorized according to their night work status with groupings of never, 1 to 9, 10 to 19, and 20+ years. For each participant, person-months were allocated to categories of years having worked on rotating night shifts, according to the 1988 data. The

Table 2. Relative risk (RR) of endometrial cancer by rotating night shift work in four categories among 53,487 women in the Nurses' Health Study, with prospective follow-up from 1988 to 2004 and with a total of 515 endometrial cancer case subjects

Years on rotating night shift	Person-years	Number of case subjects	Age-adjusted RR (95% CI)	Multivariate RR* (95% CI)
Never †	298,283	210	1.0	1.0
1–9	343,742	224	0.91 (0.75–1.10)	0.89 (0.74–1.08)
10–19	49,099	43	1.16 (0.83–1.60)	1.06 (0.76–1.49)
20+	29,574	38	1.48 (1.05–2.10)	1.47 (1.03–2.10)
P for trend ‡			0.07	0.04

*Relative risk adjusted for age, age at menarche (<12, 12†, >12 y), age at menopause (premenopausal†, <45, 45–50, >50–53, >53 to <65 y old), parity (nulliparous†, 1–2, 3–4, 5+), BMI (weight in kilograms divided by the square of the height in meters) in 13 categories (<20†, 20 to <21, 21 to <22, 22 to <23, 23 to <24, 24 to <25, 25 to <27, 27 to <29, 29 to <30, 30 to <32, 32 to <35, 35 to < 40, 40+ kg/m^2), duration of oral contraceptive use (never†, past duration, <3, 3–5, >5 y), use and duration of postmenopausal hormones (never/premenopausal†, past use <5 y, past use >5 y, current use <5 y, current use >5 y), hypertension (reported no†, yes), diabetes (reported no†, yes), pack-years of smoking (0†, 1–20, >20–40, >40 y).
† Reference category.
‡ P value (Wald test) for continuous linear term (number of years having worked rotating night shifts).

Table 3. Relative risk of endometrial cancer by BMI and night work status among 53,487 women with prospective follow-up from 1988 to 2004 in the Nurses' Health Study

Years on rotating night shift	Person-years	Number of case subjects	Age-adjusted RR (95% CI)	Multivariate RR* (95% CI)
BMI < 30				
Never †	240,497	140	1.0	1.0
1–9	273,017	138	0.85 (0.67–1.08)	0.82 (0.64–1.05)
10–19	36,433	21	0.92 (0.58–1.45)	1.04 (0.65–1.67)
20+	20,934	15	0.99 (0.58–1.70)	1.07 (0.60–1.92)
P for trend ‡			0.59	0.81
BMI ≥ 30				
Never †	52,218	67	1.0	1.0
1–9	64,292	85	1.02 (0.74–1.41)	1.09 (0.78–1.52)
10–19	11,807	22	1.36 (0.84–2.20)	1.42 (0.86–2.37)
20+	7,852	23	1.92 (1.18–3.12)	2.09 (1.24–3.52)
P for trend ‡			0.006	0.003

*Relative risk adjusted for oral contraceptive use (never †, <3, 3–5, >5 y), postmenopausal hormone use (premenopausal †, postmenopausal never, past <5 y, past >5 y, current <5 y, current >5 y), parity (1–2 †, 3–4, 5+), age at menopause (premenopausal †, <45, 45–50, >50–53, >53 to <65 y old), aspirin use (never †, ever), age at menarche (<12, 12 †, >12), hypertension (yes, no †), diabetes (yes, no †), pack-years of smoking (never †, 1–20, >20–40, >40 y), BMI (<20 †, 20 to <21, 21 to <22, 22 to <23, 23 to <24, 24 to <25, 25 to <27, 27 to <29, 29 to <30), or BMI (30 †, >30 to <32, 32 to <35, 35 to <40, 40+ kg/m^2).

† Reference category.

‡ *P* value (Wald test) for continuous linear term (number of years having worked rotating night shifts); *P* for interaction = 0.05.

primary analysis was based on incidence rates, with person-months of follow-up as the denominator. Mantel-Haenszel summary relative risks were calculated, adjusting for age in 5-year categories. Cox hazard regression models were used to calculate multivariate relative risks with adjustment for confounding factors. For the primary analysis, the following covariates, all of which are known risk or preventive factors for endometrial cancer, were included: age, age at menarche, age at menopause, parity, BMI, duration of oral contraceptive use, use and duration of PMHs, hypertension, diabetes, and pack-years of smoking. In secondary analyses, we also adjusted for height, type of PMHs used, intrauterine device use, age at first birth, BMI at age 18, physical activity (in metabolic equivalents), socioeconomic status (as determined by husband's educational level), race, caloric consumption (in kcal/day), aspirin use, β-blocker use, geographic region, waist-hip ratio, alcohol consumption, and baseline BMI in 1988; however, we did not keep them in our main model because they only marginally influenced our RRs. Using the likelihood ratio test for interaction to determine significance, we conducted stratified analyses for factors that influence endometrial cancer risk, including smoking, parity, menopausal status, BMI, or use of oral contraceptives, PMH, or aspirin. All statistical tests were two-sided. Tests of trends across categories of exposure were calculated by treating the levels of exposure as a continuous ordinal variable in the regression model.

Results

We documented 515 incident endometrial cancer cases during 16 years of follow-up (1988–2004). Women who had never worked on rotating night shifts accounted for 41.2% of the person-years of follow-up, whereas those who worked for 20+ years accounted for 4.2% (Table 1). There was slightly less use of PMHs among those in the highest night shift work category. There were slightly fewer women with diabetes or high blood pressure among the never night shift workers, and they tended to be less likely to smoke and were somewhat leaner. By contrast, there was no difference in caloric consumption across night work categories.

Total years working on rotating night shifts was modestly associated with an increased endometrial cancer risk (*P* trend = 0.04). Women with 20 or more years on rotating night shifts had a 47% greater risk of endometrial cancer compared with women who never worked night shifts [multivariate relative risk (MVRR), 1.47; 95% confidence interval (95% CI), 1.03–2.10; Table 2]. Night shift work was not related to the risk of preinvasive endometrial cancer, although small numbers of cases limited this analysis.

In analyses stratified by aspirin use (ever/never), parity (0, 1+), menopausal status (premenopausal versus postmenopausal), or smoking (never, past, current), we observed no effect modification by any of these variables. However, in analyses stratified by PMH use (never, past, current use) and BMI (<25, 25–30, >30), we detected a nonsignificant higher risk for women who had never used postmenopausal hormones (*P* for interaction, 0.34) and a more than 2-fold increased risk of endometrial cancer among night shift workers with a BMI > 30 (*P* for interaction, 0.05; *P* for trend, 0.003; see Table 3).

Discussion

In this large and, to our knowledge, first prospective cohort study of shift work and endometrial cancer, the risk of endometrial cancer was significantly elevated among women with many years' work on rotating night shifts, particularly obese women. We detected no significant increase in endometrial cancer risk among leaner women working rotating night shifts.

The mechanism by which night shift work increases endometrial cancer risk is unknown. One possible factor may be the influence of melatonin. Melatonin secretion is abnormal in night workers, as duration of secretion decreases with their typically shorter sleep duration (18). A higher risk of breast, colon, and prostate cancer has been reported among night workers (3–5), which is likely also mediated through altered melatonin levels. The complex oncostatic

action of melatonin results from a number of complementary mechanisms, including its antioxidant activity; influence on the immune system through activation of the cytokine system; suppression of fatty acid uptake and metabolism; ability to increase the degradation of calmodulin, which is a key player in cell proliferation; and inducing apoptosis and possibly acting as a natural antiangiogenic molecule (19–22).

In addition, melatonin acts as an anti-estrogenic factor at different levels of the estrogen-signaling pathway, including the down-regulation of the hypothalamic-pituitary reproductive axis, which lowers circulating estrogen levels (7). Direct actions of melatonin at the tumor cell level include blockage of the ERα but not the ERβ receptors (23), effectively becoming a selective estrogen receptor modulator. Furthermore, melatonin interferes with the local synthesis of estrogens by inhibiting aromatases, the enzymes controlling the conversion from androgenic precursors to estrogens. Specifically, melatonin reduces the aromatase activity of MCF-7 mouse breast cancer cells both *in vitro* (8) and in animal models (24). Urinary melatonin levels have been studied in relation to human sex steroid levels; there was a significant inverse association between bioavailable estradiol and melatonin, a significant positive correlation with progesterone, but no association with total estradiol levels (25).

In our study, we saw an increased risk of endometrial cancer that was limited to women who had worked night shifts for longer than 20 years and was most pronounced in women with a BMI of more than 30. Previous studies have shown the risk of endometrial cancer to increase with BMI, with a possible threshold of a significantly increased risk over 30 kg/m^2 (2). However, women in the subgroup of 20+ years of night shift work and a BMI of more than 30 have a more than 2-fold increased risk compared not only with women with similar BMI who did not work any night shifts, but also with women whose BMI was <30. Night shift workers have similar caloric intake among night shift work categories, but have a slightly higher BMI in the highest categories, indicating that fat metabolism may be different for night shift workers. Several mechanisms may account for this fact, which indicates a role for melatonin in fat metabolism. Prior studies suggest that melatonin has a role in obesity and energy balance (26). In rodents, melatonin regulates intestinal motility, with a shorter postprandial intestinal motor response during the dark phase than in the light phase: body weight gain was greater in animals kept under short days compared with animals kept under a natural photoperiod (27). In humans, an association between night work and the metabolic syndrome has previously been noted (28). Exogenous melatonin reduces weight gain, particularly among obese women (12), and melatonin may influence appetite (29, 30). In addition, women with a BMI > 30 are thought to have an increased risk of endometrial cancer due to an increased level of unopposed estrogens, and melatonin may affect hormone receptor regulation in endometrial tissues. Whether melatonin decreases progesterone levels is unknown. Although other observational studies have indicated an increased risk of prostate, colon, and breast cancer, none of these is as clearly influenced by BMI as endometrial cancer, and none shows as clear an effect on stratification by BMI.

Our study has several limitations. We did not validate self-reported duration of rotating night shifts. However, it is likely that our results are accurate because other self-reports have been shown to be highly accurate in this cohort, and previous validations of similar questions have shown reasonable reproducibility. The prospective design of our study eliminates recall bias, but nondifferential exposure misclassification may have biased our results toward the null. Another possible limitation is the potential for uncontrolled confounding not ascertained in the database.

In conclusion, working on rotating night shifts was associated with a 2-fold increased endometrial cancer risk among obese female nurses in our cohort. These findings are novel and require confirmation. With an increasing proportion of the U.S. population working multiple jobs including night shifts and an already high volume of cancer cases, further exploration of the relationship between light exposure and cancer risk through the melatonin pathway will be important.

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