

Research Article

Night Shift Work and Hormone Levels in Women

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Abstract

Background: Night shift work may disrupt the normal nocturnal rise in melatonin, resulting in increased breast cancer risk, possibly through increased reproductive hormone levels. We investigated whether night shift work is associated with decreased levels of urinary 6-sulfatoxymelatonin, the primary metabolite of melatonin, and increased urinary reproductive hormone levels.

Methods: Participants were 172 night shift and 151 day shift–working nurses, aged 20–49 years, with regular menstrual cycles. Urine samples were collected throughout work and sleep periods and assayed for 6-sulfatoxymelatonin, luteinizing hormone (LH), follicle–stimulating hormone (FSH), and estrone conjugate (E1C).

Results: 6-Sulfatoxymelatonin levels were 62% lower and FSH and LH were 62% and 58% higher, respectively, in night shift–working women during daytime sleep than in day shift–working women during nighttime sleep ($P \leq 0.0001$). Nighttime sleep on off-nights was associated with 42% lower 6-sulfatoxymelatonin levels among the night shift workers, relative to the day shift workers ($P < 0.0001$); no significant differences in LH or FSH were observed. 6-Sulfatoxymelatonin levels during night work were approximately 69% lower and FSH and LH were 35% and 38% higher, compared with day shift workers during nighttime sleep. No differences in E1C levels between night and day shift workers were observed. Within night shift workers, 6-sulfatoxymelatonin levels were lower and reproductive hormone levels were higher during daytime sleep and nighttime work, relative to nighttime sleep ($P < 0.05$).

Conclusions: These results indicate that night shift workers have substantially reduced 6-sulfatoxymelatonin levels during night work and daytime sleep and that levels remain low even when a night shift worker sleeps at night.

Impact: Shift work could be an important risk factor for many other cancers in addition to breast cancer.

MeSH Subject Headings: breast cancer, shift work, circadian rhythm, environmental carcinogens, estrogen, melatonin, 6-sulfatoxymelatonin, pineal. *Cancer Epidemiol Biomarkers Prev*; 21(4); 609–18. ©2012 AACR.

Introduction

Previously, we reported an increased risk of breast cancer associated with night shift work (1); others have reported similar findings (2–8). Two mechanisms have been proposed that might explain such a relationship: a reduction in circulating levels of melatonin, a hormone with direct oncostatic properties, and/or increased levels of reproductive hormones important in the development of breast cancer, both as a conse-

quence of light-at-night exposure resulting from shift work.

The production and release of nearly all hormones exhibit a diurnal timing patterned on approximately a 24-hour cycle. Lifestyle factors (e.g., night shift work, sleep disruption) or exposures to particular agents (e.g., light-at-night) that disrupt circadian rhythm may therefore also alter endocrine function and possibly the regulation of reproductive hormones that are relevant to the etiology of hormone-related diseases such as breast cancer (9). This study was undertaken to determine whether night shift work is associated with a decrease in nocturnal 6-sulfatoxymelatonin levels and increases in urinary levels of luteinizing hormone (LH), follicle–stimulating hormone (FSH), and estrogens (via estrone conjugate, E1C) in healthy premenopausal women. To date, previous studies have largely focused on circulating melatonin levels at a single point in time; the current study is the first to evaluate levels of all of the hormones listed above at multiple critical time points throughout the course of a shift worker's typical "work day" and subsequent sleep.

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doi: 10.1158/1055-9965.EPI-11-1128

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Methods

Study participants

Participants were women aged 20 to 49 years employed as health care workers in the Seattle metropolitan area. Advertisement for the study included postings in local area hospitals, direct mailing to Washington State Department of Health licensed and certified health care workers, and referrals from eligible and ineligible participants. A brief screening interview was used to determine eligibility, based on the following criteria: regular menstrual periods of 25–35 days in length; body mass index (BMI) between 18 and 30 kg/m²; no hormone use (contraceptive or otherwise) at least 30 days before screening; no personal history of breast cancer, chemotherapy, or tamoxifen therapy; no pregnancy or breast feeding within the past year; no use of supplements containing melatonin, phytoestrogens, or isoflavones; and consumption of no more than 5 servings per week of soy-based foods. These criteria were intended to ensure as much as possible that participants exhibited normal ovarian function and were not under the influence of factors that may alter levels of the hormones under study. Night shift workers were required to work at least 20 hours per week exclusively during the graveyard shift (i.e., stop work no earlier than 6:00 am and work at least 8 hours per shift) and to sleep at night during off-days. Day shift workers were required to be employed for at least 20 hours per week and work exclusively during the day shift (i.e., begin work no earlier than 6:00 am and work at least 8 hours per shift) and were chosen to have a similar age distribution as the night shift workers.

Data collection

Overview. Participation spanned for approximately 2 months and began with an in-home visit to obtain informed consent and provide instructions on menstrual cycle and ovulation tracking using a daily calendar and a commercial ovulation test kit (Clearblue Easy brand, manufactured by Unipath Limited). Participants tracked their cycles and ovulation for 2 consecutive months to verify 2 normal ovulatory and menstrual cycles and to identify the early to mid-luteal phase for the sample collection period.

Upon the second month's positive ovulation reading (Ov), urine collections were scheduled for the early to mid-luteal phase (Ov + 2 days through Ov + 10 days) and coincided with days when at least 2 consecutive shifts were to be worked, followed by an off-night (for the night shift workers) or at least one day shift worked, followed by a night of sleep (for the day shift workers). Before urine collection, the interviewer met with the participant to provide supplies and instructions for the collections and to administer a brief in-person interview to collect a detailed employment history, demographic information, reproductive and menstrual history, medical history, physical activity, and current hormone and medication use.

Urine sample collection

Just prior to each urine collection period, the participant was instructed to void her bladder and discard the urine; all subsequent urine excreted throughout either the work shift or the sleep period was collected, including the first void immediately following the end of the time period. Afterward, participants completed a urine sample adherence form, which included questions about situations which could compromise the urine sample (e.g., spillage or a missed collection) and transferred the sample to a refrigerated opaque collection bottle. The sample was picked up soon after and delivered immediately to the FHCRC Specimen Processing Shared Resource. Night shift workers collected all urine excreted during the daytime sleep period (following the first night shift) and the first void upon rising. During the second night shift, the participant collected all urine excreted during the shift and the first void immediately following the shift. During the following night's sleep (the "off" night), the participants collected all urine excreted and the first void the next morning. Day shift workers collected all urine excreted during the day work shift and the first void immediately following the shift, as well as all urine excreted during the subsequent night of sleep and the first void the next morning.

Some participants did not void their bladder immediately following their work or sleep period. These were considered either as minor protocol violations for urine collection (the last urine collection occurred 30–90 minutes after ending the work or sleep period) or moderate protocol violations (last urine collection occurred 90–120 minutes after ending the work or sleep period).

Assessment of urinary 6-sulfatoxymelatonin

Each sample was assayed for creatinine concentration based on a kinetic modification of the Jaffe reaction using Diagnostic Chemicals Ltd. reagents supplied by Roche Diagnostic Systems on a Roche Cobas Mira Plus chemistry analyzer. Intra- and interassay coefficients of variation were 0.9% to 1.3% and 1.8% to 2.3%, respectively. Urinary concentrations of the primary metabolite of melatonin, 6-sulfatoxymelatonin, were determined with a radioimmunoassay kit (Stockgrand Ltd.). The assay was run in duplicate with low, medium, and high kit controls as well as an in-house control using a urine sample from a volunteer. Assay sensitivity was 0.5 ng/mL urine. Intra- and interassay coefficients of variation were 5.1% to 12.8% and 11.2% to 17.4%, respectively.

Assessment of urinary reproductive hormones

Urinary FSH concentrations were measured with a 2-site chemiluminescence (sandwich) immunoassay (10, 11), which uses constant amounts of 2 antibodies that have a specificity for the intact FSH molecule, a polyclonal sheep anti-FSH antibody labeled with acridinium ester and a monoclonal mouse anti-FSH antibody covalently coupled to paramagnetic particles.

Separation, aspiration, and deionized water wash steps separate bound from free. The intra- and interassay coefficients of variation were 3.9% and 10.9%, respectively. Urinary LH concentrations were measured with a 2-site chemiluminescent immunoassay (10), using the same technique as the FSH assay, between 2 monoclonal antibodies. One antibody is directed at the α -subunit and the other at the β -subunit [one coupled to paramagnetic particles and the other labeled with dimethyl-ethanolamine (DMAE)] with specificity for intact LH. The intra- and interassay coefficients of variation were 4.8% and 10.7%, respectively. The urinary E1C assay is a competitive immunoassay with manual steps and off-line incubation (12). Urine samples and quality, semiautomated control preparations are prediluted in potassium phosphate buffer. First antibody, rabbit anti-E1C antibody, and estrone glucuronide labeled with DMAE are added; the tubes are then incubated for several hours at room temperature and placed on Bayer Diagnostic's ACS-180 automated analyzer with a goat anti-rabbit antibody covalently coupled to 1-phenyl-3-methyl-5-pyrazolone (PMP) for analysis. The assay is standardized against a dual standard prepared with estrone glucuronide and estrone sulfate. Intra- and interassay coefficients of variation were 7.8% and 11.0%, respectively. The urinary pregnanediol 3-glucuronide (PDG) assay is a competitive semiautomated immunoassay with manual steps and off-line incubation (12). Urine samples and quality control preparations are prediluted in potassium phosphate buffer. First antibody, rabbit anti-PDG antibody, and PDG labeled with DMAE are added, followed by incubation for several hours at room temperature. Tubes are then placed on Bayer Diagnostic's ACS-180 automated analyzer with goat anti-rabbit antibody covalently coupled to PMP for analysis. The intra- and interassay coefficients of variation were 7.6% and 12.3%, respectively.

Ovulation assessment

Participants were required to have normal ovarian function, as indicated by a positive LH level surge (detected by the ovulation kit) for the 2 successive menstrual cycles immediately before sample collection. Once data collection was complete, a more definitive test of ovulation was used to determine the ovulatory status of the menstrual cycle during sample collection. This algorithm used the urinary PDG level combined with the dates of the LH surge and subsequent onset of menses to determine the length of the luteal phase. Ovulation was indicated if (i) the participant had a period subsequent to data collection, (ii) the length of the luteal phase was at least 12 days, and (iii) the urinary PDG level was at least 1.25 mg/g creatinine for one or more of the urine collections. It was recognized that a few cycles which were positive according to the commercial kit would be determined to be anovulatory according to the algorithm described above.

Statistical methods

Primary analyses used linear regression models (SAS Proc REG, SAS Institute) to evaluate differences in hormone levels between the day and night shift workers, with covariate adjustment for factors known or suspected to influence the hormones under study. These included participant age; day length, calculated for the Seattle area from U.S. Naval Observatory data; BMI [weight (kg)/height (m)²]; number of pregnancies lasting 6 months or longer; number of alcoholic beverages consumed in the previous 24 hours; and psychotherapeutic use in the previous 24 hours. These covariates were specified *a priori*, based on results from previous studies showing these factors to be associated with urinary 6-sulfatoxymelatonin and/or reproductive hormone levels (13–15).

An additional objective of this study was to investigate whether 6-sulfatoxymelatonin levels are lower and reproductive hormone levels are higher during daytime sleep relative to nighttime sleep among night shift workers. SAS Proc MIXED (SAS Institute) was used to fit linear regression models with correlated error structure, which allowed for time-dependent covariate adjustment (16–18). The models used to evaluate within-subject comparisons in the night shift workers were adjusted for the same covariates listed above.

Urinary hormone values were approximately log normally distributed. Log-transformed urinary hormone levels, normalized to creatinine concentration, were analyzed as continuous response variables. All statistical tests were two-sided. Parameter estimates from the regression models were exponentiated to display results as percentage increases or decreases in hormone levels for the comparisons of interest. Standard errors and 95% confidence intervals were constructed using the Delta Method (19).

Exploratory analyses were conducted to determine whether removal of certain participants affected the results of the primary analyses. These included removal of: participants with minor or moderate violations to the urine collection protocol (described above) and participants with anovulatory cycles as determined using the algorithm described above.

Results

Of the 471 women determined to be eligible, 447 (94.9%) agreed to participate. Of these, 124 participants did not complete data collection, primarily because they became ineligible before data collection ($n = 103$) or withdrew from the study ($n = 21$). Of the remaining 323 participants who consented and completed data collection, 172 were night shift workers and 151 were day shift workers. There were a total of 6 missed sample collections among the participants who completed the study.

Participants were 20 to 49 years old, with a mean age of 34.5 years for night shift workers and 34.9 years for day shift workers. Table 1 displays distributions of the

Table 1. Descriptive characteristics of Shift Worker Study participants according to work shift status

Covariate	Day shift N (% ^a)	Night shift N (% ^a)
Age group, ^b y		
20–25	20 (13)	25 (14)
26–30	25 (16)	31 (18)
31–35	25 (16)	34 (20)
36–40	39 (26)	37 (22)
41–45	41 (27)	42 (24)
46–50 ^c	1 (1)	3 (2)
BMI, kg/m ²		
<22	38 (25)	34 (20)
22–26	79 (52)	77 (45)
26–30	33 (22)	59 (34)
>30	1 (1)	2 (1)
Pregnancies		
None	75 (50)	89 (52)
1–2	58 (38)	55 (32)
≥3	18 (12)	28 (16)
Alcohol consumption ^d		
Any	45 (30)	52 (30)
Number of drinks		
0	108 (72)	125 (73)
1	24 (16)	17 (10)
2	12 (8)	10 (6)
≥3	7 (5)	20 (12)
Tobacco use (any) ^d		
Cigarettes	10 (7)	16 (9)
Other tobacco or nicotine products ^e	1 (1)	1 (1)
Medication use (any) ^d		
Psychotherapeutics	20 (13)	16 (9)
Sedatives	2 (1)	1 (1)
β-Blockers	2 (1)	3 (2)
Thyroid medications	11 (7)	11 (6)
Steroids	7 (5)	7 (4)
Antidiabetics	1 (1)	2 (1)
Narcotics	3 (2)	0 (0)
Ovulation		
No ^f	26 (17)	23 (13)
Yes	125 (83)	149 (87)

^aPercentage calculated from 151 day shift participants and 172 night shift participants, respectively.

^bCalculated according to date of first urine collection.

^cThree participants were aged 46 years and one participant was aged 49 years.

^dIn the 24 hours ending the nighttime sleep period.

^eSuch as a nicotine skin patch or gum.

^fAs indicated by an algorithm using the PDG assay and luteal phase length (see text).

primary covariates used in the analysis, as well as ovulation status, by day and night shift participants. Night and day shift participants were similar with respect to BMI (mean = 24.4 and 23.6 kg/m², night vs. day shift), although night shift workers were more likely to be in the highest BMI category considered for eligibility. Night and day shift participants were similar with respect to number of pregnancies, tobacco use, and alcohol consumption, with the exception that, among drinkers, night shift workers consumed slightly more alcohol than day shift workers (mean = 2.6 and 1.8 drinks, night vs. day shift). Day shift participants were slightly more likely to use medications classified as psychotherapeutics, but use was very similar for both groups in most other medication categories. Using the algorithm described above for determining anovulatory cycles, 23 night shift and 26 day shift participants had an anovulatory cycle during data collection.

Urinary 6-sulfatoxymelatonin levels were substantially reduced among the night shift workers during daytime sleep compared with day shift-working women during nighttime sleep (mean = 18.1 vs. 35.3 ng/mg creatinine, night vs. day shift), and the result was highly statistically significant (Table 2). Results of regression analyses indicate that 6-sulfatoxymelatonin levels in the night shift workers were approximately 62% lower than those in the day shift workers ($P \leq 0.0001$). Daytime sleep among the night shift workers was associated with statistically significantly increased FSH and LH levels, but not E1C levels, relative to the day shift workers (FSH, mean = 6.1 vs. 4.6 ng/mg creatinine; LH, mean = 1.8 vs. 1.2 mIU/mg creatinine; E1C, 62.4 vs. 61.3 ng/mg creatinine; night vs. day shift).

Urinary 6-sulfatoxymelatonin levels were decreased in the night shift workers during their off-night of sleep (mean = 27.7 ng/mg creatinine), relative to day shift workers during their nighttime sleep (Table 3). Nocturnal 6-sulfatoxymelatonin levels in the night shift workers were approximately 42% lower than those of day shift workers ($P < 0.0001$). Nighttime sleep on off-nights among the night shift workers was not associated with significantly increased FSH (mean = 5.2 ng/mg creatinine), LH (mean = 1.7 mIU/mg creatinine), or E1C levels (mean = 57.6 ng/mg creatinine), relative to day shift workers. 6-Sulfatoxymelatonin levels were substantially reduced among the night shift workers during nighttime work (mean = 14.9 ng/mg creatinine) compared with the day shift workers during nighttime sleep, and this result is highly statistically significant (Table 4). Nocturnal 6-sulfatoxymelatonin levels in the night shift workers were approximately 69% lower than 6-sulfatoxymelatonin levels in the day shift workers ($P < 0.0001$). Nighttime work among the night shift workers was associated with significantly increased FSH (mean = 5.8 ng/mg creatinine) and LH levels (mean = 1.7 mIU/mg creatinine), relative to the day shift workers ($P < 0.05$). There is no evidence of a difference in E1C levels between the 2 groups.

Table 2. Results from regression analyses of melatonin and reproductive hormone levels during day sleep (night shift workers), relative to night sleep (day shift workers), all participants ($n = 151$ day and 170 night shift workers)

Urinary hormone ^a	% increase (+) or decrease (–) in NSW hormone levels, relative to DSW levels ^b	95% confidence interval
6-Sulfatoxymelatonin	–62.5% ^c	(–69.8% to –55.1%)
FSH	+61.6% ^d	(+23.6% to +99.6%)
LH	+58.4% ^d	(+24.2% to +92.6%)
E1C	+4.1%	(–6.1% to +14.2%)

Abbreviations: DSW, day shift workers; NSW, night shift workers.

^aAnalyzed using the natural log transformation.

^bAdjusted for the effects of age, hours of darkness, BMI, number of pregnancies, number of alcoholic beverages consumed, and use of psychotherapeutics.

^c $P \leq 0.0001$, using 2-sided t test.

^d $P < 0.01$, using 2-sided t test.

Results regarding analyses within the night shift workers are presented in Tables 5 and 6. Daytime sleep was associated with statistically significantly decreased 6-sulfatoxymelatonin and increased reproductive hormone levels, relative to nighttime sleep on off-nights (Table 5). Urinary 6-sulfatoxymelatonin levels were approximately 38% lower, and FSH, LH, and E1C levels were approximately 51%, 46%, and 8% higher, respectively, during daytime sleep, relative to nighttime sleep on off-nights. Nighttime work was also associated with statistically significantly decreased 6-sulfatoxymelatonin levels and increased reproductive hormone levels, relative to nighttime sleep on off-nights (Table 6). Urinary 6-sulfatoxymelatonin levels were approximately 47% lower, and FSH, LH, and E1C levels were 23%, 21%, and 13% higher, respectively, during nighttime work, relative to nighttime sleep on off-nights.

As described above, exploratory analyses were conducted in which certain subgroups of participants were

removed from each of the primary hypotheses to be tested. Removal of these participants did not change the size of the effects or significance level for any of the results described in detail above (results not tabulated).

Discussion

Night shift work has long been associated with a number of health problems, including short-term effects such as headache, fatigue, and gastrointestinal disturbances (reviewed in refs. 20–22); bone fractures (23); cardiovascular morbidity (reviewed in refs. 21, 24, 25); ischemic stroke (26, 27); and some aspects of reproductive health [e.g., preterm births and low birth weight (refs. 28–35), spontaneous abortion (refs. 36–42), and reduced fecundity (refs. 40, 43, 44)]. Night shift workers get considerably less sleep, and such sleep is of lower quality and efficiency than that of day shift workers (20, 21, 24, 45, 46). The mounting evidence of an association between night shift

Table 3. Results from regression analyses of melatonin and reproductive hormone levels during nighttime sleep, night shift workers vs. day shift workers, all participants ($n = 151$ day and 172 night shift workers)

Urinary hormone ^a	% increase (+) or decrease (–) in NSW hormone levels, relative to DSW levels ^b	95% confidence interval
6-Sulfatoxymelatonin	–41.7% ^c	(–53.1% to –30.3%)
FSH	+5.1%	(–21.6% to +31.9%)
LH	+4.1%	(–22.4% to +30.6%)
E1C	–6.8%	(–15.9% to +2.4%)

Abbreviations: DSW, day shift workers; NSW, night shift workers.

^aAnalyzed using the natural log transformation.

^bAdjusted for the effects of age, hours of darkness, BMI, number of pregnancies, number of alcoholic beverages consumed, and use of psychotherapeutics.

^c $P < 0.0001$, using 2-sided t test.

Table 4. Results from regression analyses of nocturnal melatonin and reproductive hormone levels during nighttime work (night shift worker), relative to nighttime sleep (day shift worker), all participants ($n = 151$ day and 170 night shift workers)

Urinary hormone ^a	% increase (+) or decrease (–) in NSW hormone levels, relative to DSW levels ^b	95% confidence interval
6-Sulfatoxymelatonin	–68.6% ^c	(–74.8% to –62.5%)
FSH	+35.0% ^d	(+0.6% to +69.4%)
LH	+37.7% ^d	(+2.6% to +72.8%)
E1C	+7.2%	(–3.3% to +17.8%)

Abbreviations: DSW, day shift workers; NSW, night shift workers.

^aAnalyzed using the natural log transformation.

^bAdjusted for the effects of age, hours of darkness, BMI, number of pregnancies, number of alcoholic beverages consumed, and use of psychotherapeutics.

^c $P < 0.0001$, using 2-sided t test.

^d $P < 0.05$, using 2-sided t test.

work and cancer risk is increasingly of concern (47), including breast (reviewed in ref. 8), prostate (48), endometrial (49), and colon (50) cancer. The present study was undertaken to investigate 2 interrelated underlying mechanisms by which night shift work could increase breast cancer risk.

Night shift workers are at high risk for circadian disruption and the resulting effects on hormonal regulation. Melatonin is a primary output signal of the central circadian pacemaker (e.g., suprachiasmatic nucleus) that synchronizes the internal hormonal environment to the light–dark cycle of the external environment. Melatonin is primarily produced and secreted by the pineal gland, a neuroendocrine transducer that is stimulated by darkness and suppressed by light as perceived by the retina (51). Melatonin acts as a chemical code for the night: the longer the night, the longer the duration of secretion (52). Hence, during the typical

sleep–wake period of the non–night shift worker, circulating melatonin concentrations are low during the day and higher at night, exhibiting a characteristic rise in concentration after darkness and peak near the midpoint of the dark interval (53). Melatonin appears to be involved in the regulation of gonadal function by affecting the release of gonadotropins (LH and FSH) from the pituitary (54–57) and stimulating ovarian estrogen production and release. Human studies point to a possible role of melatonin in the release of LH, FSH, and estrogen (58–62), suggesting a mechanism whereby decreased concentrations of circulating melatonin (such as those brought about by circadian disruption) could result in increased release of estrogen by the ovaries. However, this mechanism has not been comprehensively evaluated previously in a population of actual shift workers, which is critical in determining whether melatonin may have an inhibitory effect on

Table 5. Results from regression analyses of nocturnal melatonin and reproductive hormone levels during daytime sleep, relative to nighttime sleep, all night shift workers ($n = 172$ night and 170 day sleep measurements)

Urinary hormone ^a	% increase (+) or decrease (–) in DS hormone levels, relative to NS levels ^b	95% confidence interval
6-Sulfatoxymelatonin	–37.5% ^c	(–47.8% to –27.2%)
FSH	+50.7% ^c	(+27.0% to +74.3%)
LH	+46.2% ^c	(+20.4% to +72.0%)
E1C	+8.3% ^d	(+2.0% to +14.7%)

Abbreviations: DS, daytime sleep; NS, nighttime sleep.

^aAnalyzed using the natural log transformation.

^bAdjusted for the effects of age, hours of darkness, BMI, number of pregnancies, number of alcoholic beverages consumed, and use of psychotherapeutics.

^c $P < 0.001$, using 2-sided t test.

^d $P < 0.01$, using 2-sided t test.

Table 6. Results from regression analyses of nocturnal melatonin and reproductive hormone levels during nighttime work, relative to nighttime sleep, all night shift workers ($n = 172$ night sleep and 170 night work measurements)

Urinary hormone ^a	% increase (+) or decrease (-) in NW hormone levels, relative to NS levels ^b	95% confidence interval
6-Sulfatoxymelatonin	-47.3% ^c	(-54.5% to -40.0%)
FSH	+23.4% ^d	(+1.6% to +45.1%)
LH	+20.9% ^d	(-0.4% to +42.2%)
E1C	+12.8% ^d	(+6.1% to +19.4%)

Abbreviations: NS, nighttime sleep; NW, nighttime work.

^aAnalyzed using the natural log transformation.

^bAdjusted for the effects of age, hours of darkness, BMI, number of pregnancies, number of alcoholic beverages consumed, and use of psychotherapeutics.

^c $P < 0.0001$, using 2-sided t test.

^d $P \leq 0.05$, using 2-sided t test.

hormone-dependent tumors such as breast cancer through its control of gonadal hormone production.

A more direct mechanism whereby night shift work could increase cancer risk lies in the well-described growth-inhibitory and oncostatic properties of melatonin: melatonin both protects the cells from DNA damage and promotes the repair of DNA damage once it has occurred (63–65). Recently, Blask and colleagues showed that both steroid receptor-positive and -negative human breast cancer xenografts in rats exhibited markedly suppressed proliferative activity when perfused with melatonin-rich blood collected from healthy premenopausal women, compared with tumors perfused with daytime-collected melatonin-deficient blood (66, 67). Furthermore, tumors perfused with melatonin-deficient blood collected following exposure to light at night exhibited the daytime pattern of high proliferative activity.

Six epidemiologic studies have reported decreased melatonin levels in patients with breast cancer (68–73), although in each of these studies, melatonin levels were measured after diagnosis, making it uncertain whether the disease itself and/or treatment might have affected melatonin levels among the cases. At least 4 studies have measured urinary melatonin levels in women before their development of breast cancer (74–77). Three of the 4 reported decreased pre- and postmenopausal breast cancer risk among women with higher nocturnal melatonin levels (74–76); the fourth study found no relationship between melatonin level and breast cancer risk (77); however, this study used a 24-hour urine sample to assess melatonin levels, which raised a number of concerns (78).

The present study found that night shift work is associated with reduced urinary 6-sulfatoxymelatonin levels during night work as well as daytime sleep and that levels remain low even during night sleep on off-nights. Within the night shift working group, 6-sulfatoxymelatonin levels were significantly lower during both daytime sleep and nighttime work, relative to nighttime sleep on off-

nights. Sensitivity analyses were undertaken to investigate whether removing certain subgroups of participants would affect the observed associations (described above). In no instance did removal of any of these groups of participants affect either the size or significance of the effect of night shift work on the hormones under study. Our results are similar to those from several other studies. Hansen and colleagues (79) found decreased 24-hour 6-sulfatoxymelatonin levels in nurses working the night shift compared with day shift on a workday and an off-day. Schernhammer and colleagues reported significantly decreased urinary 6-sulfatoxymelatonin levels in nurses with increasing number of nights worked before urine collection (80). Miyauchi and colleagues (81) reported significantly decreased plasma melatonin levels at 2:00 am among nurses working at night. In a study of postmenopausal Japanese women with a history of graveyard shift work, Nagata and colleagues (82) reported lower urinary 6-sulfatoxymelatonin levels in women who were not asleep by 1:00 am. Burch and colleagues (83) reported significantly lower urinary melatonin levels during daytime sleep among men and women who work the night shift; they also reported an altered sleep:work urinary melatonin ratio among the night shift workers, indicating a lack of a robust diurnal melatonin rhythm typically seen in the non-night shift-working population. Although a recent study of rotating night shift nurses (two 12-hour days, two 12-hour nights, 5 days off) reported an inverse association between light exposure and urinary melatonin levels, they did not find altered salivary melatonin levels during night work and concluded that 2 nights of rotating shift work may not be sufficient to alter the timing of melatonin production (84).

This study also found that night shift work is associated with higher levels of FSH and LH during night work and daytime sleep but not during night sleep on off-nights. We found no evidence that shift work status is associated with changes in urinary estrogen levels, regardless of the

measurement period. Within the night shift working group, reproductive hormone levels (including estrogen) were significantly higher during both daytime sleep and nighttime work, relative to nighttime sleep on off-nights. Because we did not observe differences in urinary estrogen levels between the night and day shift groups but did observe such differences *within* the night shift workers, it is possible that the effect of night shift work on estrogen levels is too small (or, conversely, the variability in estrogen levels is too great) to detect differences between the 2 groups. At least 4 other studies have investigated the effect of night shift work and/or exposure to light-at-night on levels of reproductive hormones (80–82, 85). Two studies reported increased serum estradiol levels associated with either not being asleep by 1:00 am (82) or longer durations of night shift work (80); however, neither study analyzed FSH or LH levels. In contrast, another study found no effect on plasma estradiol levels in premenopausal women after 2 nights of exposure to bright light (85). We are aware of only one other study that has investigated levels of LH and FSH with night shift work, but the investigators found no effect on plasma concentrations of these hormones in nurses during the night shift (81).

This study has a number of strengths. Reproductive hormone levels have not been widely studied with respect to night shift work; the studies that have evaluated these hormones have not done so comprehensively. The present study evaluated 6-sulfatoxymelatonin and reproductive hormone levels simultaneously at multiple critical time points throughout the course of a shift worker's typical "work day" and subsequent sleep; unlike blood, saliva, or "spot" urine samples typically collected, urine samples were collected throughout each time period, allowing for an integrated measure of the hormones under study. The study design allowed for comparisons between night and day shift working groups, as well as within the night shift workers. Study participation entailed multiple tasks in which the precise timing was essential for complete and accurate data collection. Interviewers kept in close contact with participants to guide them through the data collection protocol; this was extremely useful in helping the participants adhere to the stringent data collection procedures and resulted in a data set of high quality. A primary limitation of this study is the inability to analyze melatonin secretion over a 24-hour period. We did not

collect urine during the time between the day sleep/work sample and the night work/sleep sample. It is possible that night shift workers secrete a nonnegligible amount of melatonin during the evening hours leading up to the beginning of their night shift. However, whether any melatonin secreted during this time is biologically important, particularly in the absence of a strong diurnal rhythm, is unknown (78). An additional limitation of this study is the inability to measure light levels either in the home or at work. If light levels did, in fact, have an effect on any of the hormones under study, then our inability to adjust for such exposure would most likely attenuate the actual effect of night shift work on hormone levels, and we would observe even greater differences between the day and night shift working groups.

This study investigated 2 potentially interrelated mechanisms by which night shift work could increase breast cancer risk. Although LH and FSH levels were modestly increased among night shift workers, estrogen levels were not increased. These findings do not support the proposed mechanism by which night shift work could increase breast cancer risk through increased levels of reproductive hormones. In contrast, the substantial reductions we observed in 6-sulfatoxymelatonin levels among night shift workers during both sleep and work periods, relative to day shift workers, may indicate that shift work, via the direct oncostatic properties of melatonin, could be an important risk factor not just for breast cancer, but for many other cancers as well.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

The authors thank the following individuals for their valuable contributions to this work: Laurie Shields, project management; Christy Callahan, field operations management; Catherine Kirkwood, data management; Kim Glorieux, Marjorie Laws, Denise Sagmoen, and Ramey Fair, field technicians; Dr. Dan McConnell, reproductive hormone measurement consultation; Dr. Bill Lasley, ovulation assessment consultation; and Dr. Parveen Bhatti, manuscript consultation.

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Received December 1, 2011; revised January 29, 2012; accepted February 2, 2012; published OnlineFirst February 7, 2012.

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Scott Davis, Dana K. Mirick, Chu Chen, et al.

Cancer Epidemiol Biomarkers Prev 2012;21:609-618. Published OnlineFirst February 7, 2012.

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