Circadian Disruption and Fatal Ovarian Cancer

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Background: The International Agency for Research on Cancer determination that shift work is a "probable" human carcinogen was based primarily on studies of breast cancer but it was also noted that additional aspects of circadian disruption and other cancer sites deserved further research.

Purpose: To examine possible associations of three measures of circadian disruption: nontypical work schedules, nightly sleep duration, and monthly frequency of insomnia with risk of fatal ovarian cancer in a sample of American women.

Methods: Several measures of circadian disruption and other information were assessed in 1982 from 161,004 employed women in the American Cancer Society's Cancer Prevention Study–II, a cohort that has been followed for mortality through 2010. In 2013, Cox proportional hazards regression was used to model the relative risks (RRs) and 95% CIs of death from ovarian cancer for categories of each indicator of circadian disruption.

Results: Over 28 years of follow-up, 1289 deaths from ovarian cancer occurred in the at-risk cohort. Compared to fixed daytime work, a rotating schedule was associated with an elevated risk of fatal ovarian cancer (RR=1.27, 95% CI=1.03, 1.56). No significant associations were observed for sleep duration (p trend=0.24) or insomnia (p trend=0.44).

Conclusions: In this large prospective study, there was a higher risk of fatal ovarian cancer in women who reported a rotating work schedule. These findings and the high prevalence of rotating shift schedules underscore the need for further research examining the role of work schedule and risk of ovarian cancer.

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Introduction

In 2004, the Bureau of Labor Statistics (BLS) reported that 83.9% of employed women worked typical daytime schedules, defined by the BLS as between the hours of 6:00AM and 6:00PM. Fewer women, 11.5%, worked schedules that took them into the evening (between 2:00PM and 12MN); night (between 9:00PM and 8:00AM); or that rotated periodically.[1] Accumulated evidence suggests that working during the night has important physiological consequences and in 2007 the International Agency for Research on Cancer (IARC) concluded that shift work involving circadian disruption was "probably carcinogenic."[2] IARC based this report on animal studies and limited evidence from occupational cohorts. The association is most convincing for breast cancer[3–8] but also was observed for prostate,[9] colorectal,[10] and endometrial[11] cancers. The working group discussed the need to explore these associations with additional cancer sites as well as other aspects of circadian disruption such as other nontraditional work schedules or sleep duration and quality.[12]

Retinal exposure to light stimulates the pineal gland to modulate levels of melatonin,[13] and the response to the 24-hour day–night cycle is a powerful physiological synchronizer.[14,15] In the late 1970s, Cohen et al.[16] hypothesized that pineal gland dysfunction was linked to breast cancer after they observed that melatonin inhibits pituitary gonadotropins. Later studies found that women working night shifts were more likely to report irregular menstrual cycles, fertility problems, and negative birth outcomes due to disrupted sex hormone levels[17,18]; these hormones are important in the etiology of reproductive cancers.[19] Moreover, animal experiments have shown that nocturnal physiological levels of melatonin have direct anti-proliferative and anti-metastatic effects on cancer cells.[20,21]

There is limited evidence demonstrating an association between circadian rhythm disruption and risk of ovarian

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cancer. A case–control study of 1101 borderline and invasive ovarian cancer cases found significantly increased odds of ever working night shifts in women with cancer compared to the controls[22]; however, there was no dose–response with longer duration. In contrast, an earlier analysis of Nurses' Health Studies (NHS)–I and –II found no association between duration of rotating shift schedules and incident ovarian cancer.[23] Only one study has examined sleep duration as a measure of circadian disruption. A small Japanese cohort reported an inverse association between sleep duration and incident ovarian cancer[24]; however, that analysis included only 86 total cases and did not examine work schedule. None of the studies of circadian disruption–related factors and ovarian cancer have investigated sleep and work schedule concurrently.

The Cancer Prevention Study–II (CPS–II) is a large nationwide prospective mortality cohort of men and women followed for 28 years. The primary aims of this analysis were to examine whether three indicators of circadian disruption (i.e., work schedule, average sleep duration, and frequency of insomnia) were associated with risk of dying from ovarian cancer in this cohort. Secondary aims were to evaluate whether the association between sleep duration and ovarian cancer mortality are modified by BMI or work schedule, and whether results differed by follow-up period.

Methods

The Cancer Prevention Study–II Cohort

In 1982, the American Cancer Society initiated the CPS–II mortality cohort to identify risk factors for and opportunities to prevent cancer. Volunteers enrolled 1.2 million men and women in all 50 states, the District of Columbia, and Puerto Rico. Each returned a mailed four-page questionnaire that provided information on demographic factors, reproductive health, diet and nutrition, height and weight, current and past use of tobacco products, as well as personal and family medical histories. More detailed discussions of the Cancer Prevention Studies are available elsewhere.[25,26] Every aspect of CPS–II is approved and monitored by the Emory University School of Medicine IRB.

Women were excluded from this analysis if they reported any of the following at baseline: prevalent cancer other than nonmelanoma skin cancer (n=57,094); history of ovarian surgeries or hysterectomies (n=172,892); women who did not indicate their menopausal status or reported it as "artificially" induced (n=45,541); did not respond to questions of current rotating work schedule (n=171,366); fixed-schedule workers who did not disclose the time of day they began working (n=22,508); or who were not currently employed (n=45,755). The final analytic cohort included 161,004 employed women with a mean age of 50.3 years.

Assessment of Circadian Disruption

Three indicators of circadian disruption were considered in this analysis: work schedule, average sleep duration, and frequency of insomnia. The CPS–II questionnaire asked participants to answer *Do you work rotating shifts?* and *What time of day do you start working?* Their responses were combined to create a single variable for work schedule based on BLS definitions[1] and assuming an 8-hour workday. Rotating schedule workers were those who self-identified as so; all others were considered to work fixed schedules. Fixed daytime workers started work between 6:00AM and 10:00AM; fixed afternoon/evening workers began 2:00PM to 4:00PM; fixed night workers began 9:00PM to 12MN. Very few women began their workday outside of these hours and were not well defined within BLS descriptions; they were classified as "other."

To evaluate sleep quality and duration, participants were asked: *On the average, how many hours do you sleep each night?* and responses were categorized as 3–5, 6, 7, 8, and 9–12 hours; outliers or missing responses were combined as a separate category. Statistical models compared each group to participants who sleep 7 hours, similar to previous studies of sleep in this cohort.[27,28] Insomnia was assessed by asking: *On the average, how many times per month do you have insomnia?* and categorized as $\leq$1, 2, 3–9, and $\geq$10 nights per month; each was compared to participants reporting no insomnia.

Mortality Follow-Up

Prior to 1988, American Cancer Society volunteers made personal inquiries to determine the vital status of each CPS–II participant. Death certificates were obtained and the underlying cause of death was recorded. Subsequently, automatic linkages with the National Death Index have been completed biennially and mortality follow-up is current through December 31, 2010. Underlying cause of death is established for 99.4% of all known deaths. Ovarian cancer was coded according to ICD-9[29] codes 183.0–183.9, and ICD-10[30] codes C56, and C57.0–C57.4. There were a total of 1289 ovarian cancer deaths identified in the at-risk cohort.

Statistical Analysis

All statistical analyses were conducted in SAS v9.3. Follow-up time in years was computed for each individual as the time since enrollment in 1982 until the date of death or December 31, 2010, whichever was earliest. Age- and multivariable-adjusted Cox proportional hazards regression modeling was used to evaluate possible associations between each of the indicators of circadian disruption (i.e., work schedule, duration of sleep, and frequency of insomnia) and death from ovarian cancer. Trend variables for sleep duration and frequency of insomnia were derived by using the median value from each category and then modeling this as a continuous variable. All models stratified on single year of age at enrollment. Multivariable models adjusted for covariates found to be significant risk factors for ovarian cancer in this cohort[31]; these included categorical variables for race, family history of breast or ovarian cancer, age at menarche, menopausal status, age at menopause, age at first birth, parity, duration of oral contraceptive use, postmenopausal estrogen use, and previous tubal ligation. Continuous measures were used for BMI and height. Education, alcohol use, smoking status, and use of sleeping pills were not significantly associated with the primary exposure variables or fatal ovarian cancer; consequently, they were not included in the final model.

Two sensitivity analyses were conducted. Effect modification of the association between sleep and fatal ovarian cancer by BMI or work schedule was assessed by creating cross-product interaction terms for categories of sleep and WHO BMI categories[32] and sleep and work schedule; the results were compared to the base model using likelihood ratio tests. To evaluate the degree to which misclassification would bias the results as the cohort aged and left the workforce, follow-up time was divided in half, from 1982 to 1995 and 1996 to 2010.

Results

The distribution of baseline characteristics according to work schedule for the analytic cohort is shown in Table 1. The mean age in 1982 was 50.3 years. The majority of the women were white (92%); educated beyond high school (64.4%); not menopausal at baseline (53.4%); reported never taking oral contraceptives (57.6%); got moderate exercise (61.7%); and had a BMI <25.0 (65.2%). Only 6.6% of the cohort reported working a rotating schedule in 1982 and much smaller proportions worked fixed afternoon/evening or night shifts. Nearly all (90.9%) women reported that they slept between 6 and 8 hours a night and more than half (56.1%) did not report insomnia. Between 1982 and 2010, there were 1289 deaths from ovarian cancer over 4,146,706 person-years of follow-up.

Women working each schedule did not differ remarkably in age, BMI, height, or frequency of insomnia. A greater proportion of black women, those who did not complete high school, and heavy exercisers reported rotating schedules than did other women. The same groups were more likely to indicate either extreme of sleep duration (Appendix A, available online at www.ajpmonline.org). White women and ever postmenopausal estrogen users reported more frequent insomnia; otherwise, there were no differences (Appendix B, available online at www.ajpmonline.org).

A significant elevated risk of fatal ovarian cancer was observed with women reporting rotating work schedules in 1982 compared to fixed day workers after adjusting for reproductive, anthropometric, and other risk factors (RR=1.27, 95% CI=1.03, 1.56; Table 2), an association that was robust throughout the entire follow-up (Figure 1). Fixed afternoon/evening or night shifts were not associated with fatal ovarian cancer. There were no associations observed with sleep duration (p trend=0.2416) or insomnia (p trend=0.4438).

In sensitivity analyses, the association between sleep duration and ovarian cancer was not modified by BMI categories (p interaction=0.513), or by rotating work schedule (p interaction=0.483). When the analyses were stratified by follow-up time, results of sleep duration and insomnia remained unremarkable. The general pattern observed with rotating shift schedules persisted in both time periods: it did not reach significance in the first half, although it did in the second: RR=1.14 (95% CI=0.79, 1.63) and RR=1.34 (95% CI=1.05, 1.72).

Discussion

In this large prospective study of employed women, working rotating shifts was significantly associated with a moderately elevated risk of fatal ovarian cancer compared to a fixed day schedule beginning between 6:00AM and 10:00AM. No associations were observed for sleep duration or insomnia. Although the RR associated with working a rotating schedule is modest (1.27), it is of similar magnitude to other ovarian cancer risk factors observed in this cohort.[31,33–38]

These findings and those from other studies do not provide clear evidence of the relationship between circadian disruption and ovarian cancer. Differences in study design, exposure definitions, and outcomes might explain, in part, inconsistencies across studies. In this analysis of CPS–II, there was no association of current night shift work with fatal ovarian cancer and a positive association of rotating shifts with fatal ovarian cancer. However, a large case–control study found a significant positive association for night work but did not specifically collect information on rotating schedules.[22] Importantly, very few women in CPS–II reported fixed night work and therefore power was limited for the exposure. In CPS–II and in the NHS,[23] self-reported work schedule information was collected prospectively; however, in the NHS, detailed information on work schedule was collected in repeated follow-ups whereas in CPS–II, information was collected only at baseline. Therefore, the definitions of rotating shift work differed between the two studies. More specifically, in the NHS, rotating shift was defined as at least 3 nights per month working at night in addition to day or evening shifts; in contrast, CPS–II participants were asked to simply report if they were currently working rotating shift schedules.

Given the repeated measures over time in the NHS, there is likely to be less misclassification over time, whereas in CPS–II this misclassification is likely to attenuate any associations. This nondifferential misclassification in CPS–II over time does not explain the observed association between rotating shift work and risk of ovarian cancer. Further, the case–control and NHS studies evaluated association between shift work and ovarian cancer incidence, whereas the outcome for the CPS–II was mortality. Although most risk factors are observed consistently across most subtypes of ovarian cancer,[39] it is possible that rotating shift work might be differentially associated with highly fatal disease

Table 1. Baseline characteristics, CPS–II 1982 mortality cohort, % unless otherwise noted

		Work schedule				
	N/*n* (%)	Fixed day (*n*=141,637)	Rotating shifts (*n*=10,552)	Fixed afternoon/ evening (*n*=2288)	Fixed night (*n*=1754)	Other shifts (*n*=4773)
Age (M [SD])	161,004	50.3 (8.6)	49.7 (9.4)	50.6 (6.5)	49.9 (9.1)	51.1 (9.5)
BMI (M [SD])		24.4 (4.5)	24.8 (4.7)	25.2 (5.0)	26.3 (5.7)	25.0 (4.9)
Height (cm; M [SD])		163.9 (6.6)	163.7 (6.7)	163.8 (6.9)	163.8 (6.9)	163.5 (6.6)
Hours of sleep (M [SD])		7.2 (0.9)	7.2 (1)	7.2 (1)	6.8 (1.2)	7.2 (1.1)
Monthly frequency of insomnia (M [SD])		1.5 (3.1)	1.7 (3.5)	1.6 (3.3)	1.4 (3.0)	1.6 (3.3)
Race						
White	148,436 (92.2)	88.2	6.4	1.4	1.1	2.9
Black	8,085 (5.0)	84.5	8.6	1.7	1.7	3.6
Other	4,483 (2.8)	86.1	8.1	1.5	0.9	3.4
Family history of breast/ovarian cancers						
No	149,274 (92.7)	87.9	6.6	1.4	1.1	2.9
Yes	11,730 (7.3)	88.4	6.3	1.5	1.0	2.9
Age at menarche						
≤12	71,990 (44.7)	88.3	6.3	1.4	1.2	2.9
13	46,113 (28.6)	88.2	6.4	1.4	1.0	2.9
≥13	40,017 (24.9)	87.2	7.2	1.4	1.0	3.1
Age at menopause						
Pre-/peri-menopausal	85,903 (53.4)	88.0	6.8	1.3	1.1	2.8
<50 years	30,471 (18.9)	87.9	6.3	1.5	1.1	3.1
≥50 years	39,232 (24.4)	88.2	5.9	1.6	1.1	3.2
Parity/age of first birth						
Nulliparous	21,937 (13.6)	90.4	5.7	1.2	0.8	2.0
1–2 births, <25 years old	30,011 (18.6)	89.1	5.9	1.3	0.9	2.8
1–2 births, ≥25 years old	29,465 (18.3)	90.1	5.3	1.1	0.9	2.6
≥3 births, <25 years old	52,710 (32.7)	85.8	7.6	1.8	1.3	3.5
≥3 births, ≥25 years old	20,683 (12.8)	87.2	6.5	1.6	1.5	3.2
Duration of oral contraceptive use						
Never	92,771 (57.6)	87.9	6.3	1.5	1.2	3.1
<5 years	32,763 (20.3)	87.8	7.0	1.4	1.1	2.8
≥5 years	29,926 (18.6)	89.1	6.4	1.2	0.9	2.5

(continued on next page)

Table 1. Baseline characteristics, CPS–II 1982 mortality cohort, % unless otherwise noted *(continued)*

		Work schedule				
	N/*n* (%)	Fixed day (*n*=141,637)	Rotating shifts (*n*=10,552)	Fixed afternoon/ evening (*n*=2288)	Fixed night (*n*=1754)	Other shifts (*n*=4773)
Postmenopausal ERT use						
Pre-/peri-menopausal	85,903 (53.4)	88.0	6.8	1.3	1.1	2.8
Never	47,294 (29.4)	88.4	5.9	1.5	1.1	3.1
Ever	21,183 (13.2)	88.2	6.2	1.5	1.0	3.0
Tubal ligation						
No	143,937 (89.4)	88.1	6.5	1.4	1.1	3.0
Yes	17,067 (10.6)	87.1	7.0	1.6	1.4	2.9
Education						
<High school degree	9,691 (6.0)	79.1	10.6	2.1	1.5	6.6
High school graduate	46,423 (28.8)	87.7	6.5	1.3	0.8	3.8
Vocational/some college	51,224 (31.8)	87.3	7.0	1.7	1.4	2.7
College graduate	52,418 (32.6)	90.8	5.3	1.2	0.9	1.8
Exercise						
None/slight	50,285 (31.2)	91.8	4.6	0.8	0.7	2.1
Moderate	99,288 (61.7)	86.9	7.1	1.6	1.2	3.2
Heavy	9,383 (5.8)	79.7	11.2	2.6	1.4	5.2

ERT, estrogen replacement therapy

compared to less fatal ovarian cancer. Importantly, despite the differences in design among studies, the null results from NHS are compelling, because in that cohort, significant positive associations were reported of shift work with risk of other cancers including breast,[7,8] colorectal,[10] and endometrial[11] cancers. Regardless, taken together, findings from these three studies cannot rule out a possible association between work schedule and risk of ovarian cancer, and further research investigating a comprehensive history of lifetime work is warranted.

For sleep duration, the inverse association with incident ovarian cancer reported in a cohort of Japanese women,[24] was not observed in CPS–II. These two studies differed most notably in the total number of cases available for analysis. In CPS–II, there were 1289 ovarian cancer deaths over 28 years of follow-up, whereas in the Japanese study there were only 86 cases over 16 years. Therefore it is unclear whether their findings are due to chance, or due to underlying cultural and genetic differences between these populations.[40] Unfortunately, CPS–II does not have sufficient numbers of Asian Americans to explore possible racial differences. However, this issue deserves further research in other cohorts.

The biologic mechanisms underlying these associations are likely complex. There is considerable evidence that circadian disruption, through exposure to light at night, has profound effects on human health and risk of cancer. Even small periods of nighttime light exposure can significantly affect plasma melatonin levels[15] and disrupt the body's natural pacemaker.[14] Human studies show that hormone surges follow predictable circadian patterns, and that disruptions in these rhythms are strongly associated with reproductive dysfunction in women[41]; these hormones are particularly important in the development of reproductive cancers.[42] More directly, exposure to light at night can have nonhormonal effects on cancer risk. Blask et al.[20] exposed human breast cancer xenografts in nude rats to melatonin enriched or deficient blood and found that melatonin directly suppressed proliferative activity but that even short-term light exposure would eliminate this benefit.

Table 2. Results of Cox proportional hazards analyses for indicators of circadian disruption and fatal ovarian cancer

	Deaths[a]	Person-years	RR[b]	95% CI	RR[c]	95% CI
Work schedule						
Fixed day	1,126	3,655,986	1.00	—	1.00	—
Rotating shifts	101	269,742	1.27	(1.04, 1.56)	1.27	(1.03, 1.56)
Fixed afternoon/evening	11	57,506	0.62	(0.34, 1.11)	0.62	(0.34, 1.12)
Fixed night	15	44,394	1.14	(0.68, 1.89)	1.12	(0.67, 1.87)
Sleep duration (hours)						
3–5	41	135,499	0.99	(0.72, 1.37)	1.01	(0.73, 1.40)
6	230	681,793	1.13	(0.96, 1.32)	1.13	(0.97, 1.33)
7	453	1,566,880	1.00	—	1.00	—
8	493	1,526,660	1.16	(1.02, 1.31)	1.16	(1.02, 1.31)
9–12	58	203,872	1.08	(0.82, 1.42)	1.08	(0.82, 1.42)
			p trend=0.2689		*p* trend=0.2416	
Insomnia (nights/month)						
Never	700	2,329,285	1.00	—	1.00	—
≤1	115	378,778	0.98	(0.81, 1.20)	0.98	(0.8, 1.20)
2	138	432,378	0.99	(0.83, 1.19)	1.01	(0.84, 1.21)
3–9	228	662,491	1.02	(0.88, 1.19)	1.04	(0.89, 1.21)
≥10	30	129,390	0.69	(0.48, 0.99)	0.71	(0.49, 1.03)
			p trend=0.3213		*p* trend=0.4438	

[a]Number of deaths do not equal total because "missing" categories are excluded.
[b]Age-adjusted
[c]Multivariable results are adjusted for oral contraceptive use, age at menarche and menopause, tubal ligation, parity, postmenopausal estrogen use, race, family history of breast/ovarian cancers, exercise, BMI, and height.
RR, relative risk

The circadian system is modulated through at least nine "clock" genes,[43] many of which are important in cell cycle regulation. There is active research linking dysfunction in these genes to cancer risk, and polymorphisms in the *CLOCK*, *PER*, and *CRY* genes are important in the development of some breast[44] and ovarian[45] tumors.

The strengths of this study are its prospective design and long-term follow-up; it is remarkable for its large size and inclusion of multiple measures of circadian disruption examined in relation to fatal ovarian cancer. One limitation is that all of these exposures were self-reported and assessed only at baseline. As people age, sleeping patterns change and CPS–II participants would be expected to have long sleep latency and shorter duration over follow-up.[46] Additionally, as women left the workforce, rotating shift work would become increasingly misclassified. Despite this, analyses stratified by follow-up period did not suggest that misclassification was a major problem in this study. A second limitation was that follow-up included only fatal ovarian cancers. Data suggest that ovarian cancer is an aggregate of several distinct diseases[46,47]; analyses by subtype are advised where possible.

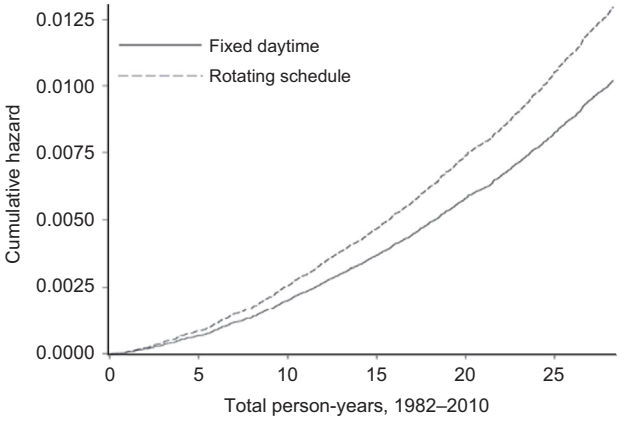

Figure 1. Cumulative hazards of fatal ovarian cancer associated with rotating shift schedules and fixed day schedules

In this study, there was a 27% higher risk of fatal ovarian cancer in women working rotating shifts compared to fixed daytime schedules, whereas sleep duration and frequency of insomnia were not associated. Further research is needed to identify subgroups of women in which circadian disruption may be more clinically meaningful, for instance, women with a family history of cancer or women who might not physiologically adapt well to frequent rotating work shifts.

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Appendix

Supplementary data

Supplementary data associated with this article can be found at, http://dx.doi.org/10.1016/j.amepre.2013.10.032.