BRIEF COMMUNICATION

Night-Shift Work and Risk of Colorectal Cancer in the Nurses' Health Study

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Exposure to light at night suppresses the physiologic production of melatonin, a hormone that has antiproliferative effects on intestinal cancers. Although observational studies have associated night-shift work with an increased risk of breast cancer, the effect of night-shift work on the risk of other cancers is not known. We prospectively examined the relationship between working rotating night shifts and the risk of colorectal cancers among female participants in the Nurses' Health Study. We documented 602 incident cases of colorectal cancer among 78 586 women who were followed up from 1988 through 1998. Compared with women who never worked rotating night shifts, women who worked 1–14 years or 15 years or more on rotating night shifts had multivariate relative risks of colorectal cancer of 1.00 (95% confidence interval [CI] = 0.84 to 1.19) and 1.35 (95% CI = 1.03 to 1.77), respectively (P_{trend} = .04). These data suggest that working a rotating night shift at least three nights per month for 15 or more years may increase the risk of colorectal cancer in women. [J Natl Cancer Inst 2003;95:825–8]

Environmental lighting alters the physiologic release of the hormone melatonin that typically peaks in the middle of the night *(1):* in humans, a profound reduction in melatonin production was observed after 2 weeks of intermittent nightly exposure to light *(2,3).* This decreased melatonin production has been hypothesized to induce an increase in the levels of reproductive hormones such as estrogens, thereby stimulating the growth of hormone-sensitive tumors in the breast *(4).* Results from observational studies *(5–10)* have associated night-shift work (a surrogate for exposure to light at night) with an increased risk of breast cancer. Other groups have proposed that the increase in light exposure decreases the amount of time available for melatonin production, which reduces the possible nonspecific oncostatic effect of the pineal gland, thus increasing the risk of breast cancer as well as of other cancers *(11).* Results from *in vitro* and animal studies suggest that the antiproliferative effect of melatonin is not limited to breast cancer *(12–17)* but may also affect other cancers, especially intestinal cancers. For example, melatonin substantially inhibited the growth of cell lines derived from hormone-independent colon carcinomas, and the anticarcinogenic properties of melatonin have repeatedly been demonstrated in chemically induced colon cancers in rodents *(18–21).* Furthermore, the finding that colorectal cancer patients had lower plasma levels of melatonin than healthy control subjects suggests a possible link between low melatonin levels and the enhanced development of colorectal cancer in humans *(22,23).*

To date, no observational studies have been published that examine possible associations between night-shift work and the risk of colorectal cancer. We assessed this association among women enrolled in the Nurses' Health Study (NHS), a cohort unique in its prospective assessment of the participants' night-work status. Details of the study design and population have been reported elsewhere *(10, 24–27).*

In 1988, participants in the NHS were asked how many years in total they had worked rotating night shifts at least three nights per month in addition to working days or evenings in that month. Information on lifetime years worked on rotating night shifts was gathered into eight prespecified categories: never, 1–2, 3–5, 6–9, 10–14, 15–19, 20–29, and 30 years or more. Incident cases of colorectal cancer were identified through self-reports and confirmed through a blinded review of the nurses' medical records. In addition, we used the National Death Index, a highly sensitive method of identifying deaths among nonrespondents *(28).*

Of the 103 614 women who returned the 1988 questionnaire, 85 162 (82.2%) answered the question on night-shift work. After excluding women who reported having a previous cancer (except non-melanoma skin cancer), ulcerative colitis, Crohn's disease, or familial polyposis syndrome, 78 586 women remained to form the baseline population for this analysis. Mantel–Haenszel summary relative risks (RRs) [adjusting for age in 5-year categories *(29)*], 95% confidence intervals (CIs), and tests for trends across categories of exposure (based on the midpoints of the original exposure categories) were calculated using Cox proportional hazards models. The data conformed to proportional haz-

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Journal of the National Cancer Institute, Vol. 95, No. 11,

ards assumptions, and all statistical tests were two-sided.

We documented 602 incident cases of colorectal cancer during 758 903 person-years of follow-up. Most of the baseline characteristics of women who had worked on rotating night shifts were similar to those of women who had never worked night shifts (Table 1). The relationships between the total numbers of years worked on rotating night shifts and the risk of colorectal cancer, both overall and by subsites, are shown in Table 2. A longer extent of night-shift work was modestly associated with an increased risk of colorectal cancer (P_{trend} = .04). Compared with women who never worked rotating night shifts, women who worked such shifts for 1–14 years had a multivariate RR of colorectal cancer of 1.00 (95% CI = 0.84 to 1.19), whereas women who worked 15 years or more on rotating night shifts had a multivariate RR of 1.35 (95% CI = 1.03 to 1.77) (P_{trend} = .04). Compared with women who never worked night shifts, women who worked rotating night shifts for 15 or more years also had increased risks of cancers in the right colon (RR = 1.41, 95% CI = 0.88 to 2.27), in the left colon (RR = 1.22, 95% CI = 0.72 to 2.09), and in the rectum (RR = 1.51, 95% CI = 0.82 to 2.81), when those cancers were considered individually (Table 2).

To address potential confounding by other lifestyle and dietary factors, we included past oral contraceptive use; parity; dietary variables, such as total intake of calcium or vitamin D; daily hours of sleep; and the educational levels of the nurses and their husbands (as markers of socioeconomic status) in our proportional hazards models. However, we did not keep these variables in the final model because they did not substantially alter our risk estimates (data not shown). We found only slight variations in the association between the duration of night-shift work and risk of colorectal cancer across levels of physical activity, body mass index, family history of colorectal cancer, ethnicity, and sigmoidoscopy (data not shown).

Results from two mortality studies *(30,31)* among male shift workers provided the first suggestions that an increased cancer risk was associated with night-shift work. Subsequent studies *(5–10)* consistently showed that night-shift work is associated with an elevated risk of breast cancer. The results from our study are compatible with a possible oncogenic effect of nighttime light exposure on colorectal cancer through decreased melatonin levels. Melatonin has well-established anticarcinogenic properties *(32),* and a link between light exposure at night and cancer risk through the melatonin pathway could offer one plausible explanation for the increased risk we observed. Although other etiologic mechanisms may be involved in the influence of night work on cancer risk, such as the loss of normal diurnal variation in cortisol *(33),* the melatonin hypothesis remains the primary etiologic mechanism under consideration to date.

Our study has several potential limitations. Although we did not validate the self-reported duration of rotating night shifts by the study participants, it is likely that these reports were reliable because other self-reports by members of this cohort have been highly accurate *(34)* and previous validations of similar questions (e.g., the use of electric blankets) *(35)* have shown reasonable reproducibility. Moreover, the prospective

Table 1. Age and age-standardized characteristics according to rotating night-shift work status in 1988 among 78 586 women in the Nurses' Health Study*

Characteristic	No. of years worked on rotating night shifts		
	Never (N = 31 777)	1–14 (N = 40 990)	⩾15 (N = 5819)
Median age, y (range)	54.3 (41–68)	54.7 (41–68)	57.1 (41–68)
Former or current smokers, %	17.4	18.7	24.6
Mean No. of pack-years (SD)†	2.9 (5.1)	3.0 (5.2)	3.1 (5.3)
Body mass index ⩾30, %‡	13.5	15.1	22.4
Mean physical activity, METs/wk (SD)§	14.6 (20.7)	16.0 (21.9)	16.7 (23.8)
Regular aspirin use, %‖	16.5	16.9	19.3
Parent or sibling with colorectal cancer, %	10.1	10.3	10.6
Screening endoscopy, %	11.1	11.1	10.2
Intake of beef, pork, or lamb as a main dish (>2 servings/wk), %	17.7	18.2	18.2
Mean alcohol intake, g/day (SD)	6.1 (10.6)	6.3 (10.7)	5.4 (10.7)
Mean height, in (SD)	64.4 (3.2)	64.5 (3.3)	64.3 (3.1)
Regular multivitamin use, %	37.9	39.0	38.2
Mean total caloric intake, kcal (SD)	1748 (519)	1782 (526)	1781 (554)
Postmenopausal in 1988, %	62.4	62.6	64.0
Ever use of postmenopausal hormones, %	13.8	14.3	15.0
Mean vitamin D intake, IU/day (SD)	339.7 (253)	347.2 (258)	345.6 (257)
Mean calcium intake, mg/day (SD)	1140 (549)	1155 (550)	1137 (570)
Mean sleep, h/day (SD)	7.0 (1.2)	6.9 (1.3)	6.5 (1.6)
Husband's educational level beyond high school, %	41.7	42.2	30.1
Nurses's educational level beyond a bachelor's degree, %	9.2	9.2	5.2
Oral contraceptive use, %	48.3	48.3	44.6
Nulliparous, %	5.7	7.3	6.8

*Age-standardized according to eight categories of age (<44, 45–49, 50–54, 55–59, 60–64, 65–69, 70–74, and ⩾75 years) as of the 2-year period when participants first entered follow-up. SD = standardized deviation; METs = metabolic equivalents (caloric need per kilogram of body weight per hour of activity divided by caloric need per kilogram of body weight per hour at rest); IU = international units.

†Pack-years were calculated for former and current smokers only.

‡Body mass index is weight in kilograms divided by the square of the height in meters.

§Sum of the average time per week spent in each activity by its typical energy expenditure requirements expressed in METs.

‖Regular aspirin use is defined as intake of two or more aspirin tablets per week.

Table 2. Adjusted relative risk (RR) and 95% confidence intervals (CIs) of colon and rectal cancers associated with night-shift work among 78 586 women in the Nurses' Health Study with prospective follow-up from 1988 through 1998 with 602 cases of colorectal cancer

Cancer site and years on rotating night shift	No. of cases	Age-adjusted RR (95% CI)	Multivariate RR* (95% CI)
Colon and rectum combined†			
Never	229	1.0 (referent)	1.0 (referent)
1–14	303	1.00 (0.84 to 1.18)	1.00 (0.84 to 1.19)
⩾15	70	1.44 (1.10 to 1.89)	1.35 (1.03 to 1.77)
P_{trend}‡		.01	.04
Right colon			
Never	73	1.0 (referent)	1.0 (referent)
1–14	93	0.95 (0.70 to 1.30)	0.97 (0.71 to 1.32)
⩾15	23	1.47 (0.91 to 2.37)	1.41 (0.88 to 2.27)
P_{trend}‡		.38	.31
Left colon			
Never	64	1.0 (referent)	1.0 (referent)
1–14	76	0.90 (0.64 to 1.25)	0.89 (0.63 to 1.24)
⩾15	18	1.27 (0.75 to 2.14)	1.22 (0.72 to 2.09)
P_{trend}‡		.50	.44
Combined colon			
Never	137	1.0 (referent)	1.0 (referent)
1–14	169	0.93 (0.74 to 1.16)	0.93 (0.74 to 1.17)
⩾15	41	1.37 (0.97 to 1.95)	1.32 (0.93 to 1.87)
P_{trend}‡		.26	.20
Rectum			
Never	41	1.0 (referent)	1.0 (referent)
1–14	48	0.87 (0.57 to 1.33)	0.86 (0.56 to 1.30)
⩾15	14	1.54 (0.75 to 3.16)	1.51 (0.82 to 2.81)
P_{trend}‡		.15	.15

*Multivariate RRs have been adjusted for age in years; pack-years of smoking before age 30 in quintiles; body mass index in five categories (<21, 21–22.9, 23–24.9, 25–28.9, or 29–40 or higher); physical activity (sum of the average time per week spent in each activity by its typical energy expenditure requirements expressed in metabolic equivalents [caloric need per kilogram of body weight per hour of activity divided by caloric need per kilogram of body weight per hour at rest] per week) in quintiles; regular aspirin use (⩾2 versus <2 times per week); colorectal cancer in parent or sibling (yes or no); screening endoscopy during the study period (yes or no); consumption of beef, pork, or lamb as a main dish (<1 serving/month, 1–3 servings/month, 1 serving/week, 2–4 servings/week, or ⩾5 servings/week); alcohol consumption status (abstainer, 0.1–4.9 g/day, 5–14.9 g/day, or ⩾15 g/day); total caloric intake in quintiles; use of postmenopausal hormones (never, past user for <5 years, past user for >5 years, current user for <5 years, current user for >5 years); menopausal status (yes or no); and height in seven categories (⩽150 cm, 151–155 cm, 156–160 cm, 161–165 cm, 166–170 cm, 171–175 cm, 176–180 cm, or >180 cm).

†Right colon denotes the segment from the cecum to the splenic flexure, and left colon denotes the segment from the splenic flexure to the rectosigmoid junction. The numbers of colon and rectal cancers may not be equal to the total number of colorectal cancers because, in some cases, the specific site of the cancer was unknown.

‡Two-sided *P* value (Wald test) for continuous linear term.

design of our study eliminates potential recall bias. On the other hand, misclassification of exposure status is likely because our assessments of exposure status with regard to working on rotating night shifts are only rough estimates. Because there were more than two comparison groups in our study, even random misclassification could have biased the study results in any direction *(36).* Our major concern, however, is that we potentially underestimated the number of actual shift workers in our study because nurses who worked on permanent night shifts may have classified themselves as non-rotating night-workers *(10).* However, because permanent night-shift workers are more likely to adopt a new circadian rhythm than women who permanently rotate between day and night shifts, melatonin would be less strongly suppressed among women working on permanent night shifts than among women who work on rotating night shifts. Thus, such misclassification would have likely biased our results only toward the null.

Another potential bias that might have influenced our results is what could be referred to as an "unhealthy shift-worker effect" *(37):* persons with a less healthy lifestyle (such as workers of a lower socioeconomic status) may tend to choose to do shift work, resulting in a bias that could lead to an overestimation of the true association between shift work and cancer risk. However, we found that the excess cancer risk associated with night-shift work persisted after we controlled for lifestyle factors known to be associated with breast cancer risk and adjusted for the educational level of the nurse-participants and their spouses.

Another possible explanation for our results is that women who had ever worked night shifts may have been more likely to undergo screening endoscopy than women who had not. However, in this cohort, women who worked night shifts were of lower socioeconomic status and may have been less concerned about their health (for example, they tended to be heavier and to have smoked more) than women who did not work night shifts (Table 1). In addition, in this cohort, colorectal cancer screening rates at baseline of women who worked rotating night shifts were similar to those of women who never worked rotating shifts and continued to be similar throughout follow-up.

Another potential limitation of our study is that the nurses who worked night shifts may have differed from those who did not in an unknown manner that influenced their risk of colon cancer. Although we controlled for known potential confounding factors, there may still be residual confounding by factors, such as hormone levels, or other differences in lifestyle that we did not control for. Because the risk we identified was modest and the potential for unexplained confounding cannot be excluded, it will be important to replicate these observations in additional cohorts and to assess the physiologic impact of this form of night-shift work to explore potential mechanisms for the increase in risk. Finally, we were limited by our data in drawing inferences about the latency period with respect to when rotating night-shift work was performed and incidence of colorectal cancer (i.e., whether past night-work exposure accounts more accurately for a change in colorectal cancer risk than does current night-work exposure) because we did not ascertain current shift-work status.

In conclusion, working on rotating night shifts was associated with an increased risk of colorectal cancer among the female nurses in our cohort. These findings are novel and require confirmation in other cohorts. Because night-shift

work has become very common in developed countries, future studies should assess the relationship of light exposure to the risk of other cancers and consider the risks in men.

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NOTES

Supported by Public Health Service grants CA/ES62984 and CA87969 from the National Cancer Institute, National Institutes of Health, Department of Health and Human Services. E. S. Schernhammer was supported in part by a research grant from Austrian Research Centers (ARC) Seibersdorf Research, Health Physics Division.

We are indebted to the participants of the Nurses' Health Study for their continuing outstanding dedication to the study and to Karen Corsano for technical assistance.

Manuscript received October 17, 2002; revised March 21, 2003; accepted March 31, 2003.