IJC
International Journal of Cancer

Rotating night shift work and colorectal cancer risk in the nurses' health studies

Kyriaki Papantoniou[1], Elizabeth E. Devore[2], Jennifer Massa[3], Susanne Strohmaier[2], Céline Vetter[2,4], Lin Yang[1], Yan Shi[5], Edward Giovannucci[3,6], Frank Speizer[2] and Eva S. Schernhammer[1,2,6]

[1]Department of Epidemiology, Center of Public Health, Medical University of Vienna, Vienna, Austria
[2]Channing Division of Network Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA
[3]Department of Nutrition, Harvard T. H. Chan School of Public Health, Boston, MA
[4]Department of Integrative Physiology, University of Colorado, Boulder, CO
[5]Department of Medical Oncology, Chinese PLA General Hospital, Beijing, China
[6]Department of Epidemiology, Harvard T. H. Chan School of Public Health, Boston, MA

Animal and human data have suggested that shift work involving circadian disruption may be carcinogenic for humans, but epidemiological evidence for colorectal cancer remains limited. We investigated the association of rotating night shift work and colorectal cancer risk in two prospective female cohorts, the Nurses´ Health Study (NHS) and NHS2, with 24 years of follow-up. In total, 190,810 women (NHS = 77,439; NHS2 = 113,371) were included in this analysis, and 1,965 incident colorectal cancer cases (NHS = 1,527; NHS2 = 438) were reported during followup (NHS: 1988–2012, NHS2: 1989–2013). We used Cox proportional hazards models adjusted for a wide range of potential confounders. We did not observe an association between rotating night work duration and colorectal cancer risk in these cohorts (NHS: 1–14 years: Hazard Ratio (HR) 1.04, 95% CI: 0.94, 1.16; 15+ years: HR 1.15, 95% CI: 0.95, 1.39; P_{trend} = 0.14 and NHS2: 1–14 years: HR 0.81, 95% CI: 0.66, 0.99; 15+ years: HR 0.96, 95% CI: 0.56, 1.64 and P_{trend} = 0.88). In subsite analysis in NHS, rectal cancer risk increased after long-term (15+ years) rotating night shift work (proximal colon cancer: HR 1.00, 95% CI: 0.75, 1.34, P_{trend} = 0.90; distal colon cancer: HR 1.27, 95% CI: 0.87, 1.85, P_{trend} = 0.32; rectal cancer: HR 1.60, 95% CI: 1.09, 2.34, P_{trend} = 0.02). We found no overall evidence of an association between rotating night shift work and colorectal cancer risk in these two large cohorts of nurses. Risk for rectal cancer significantly increased with shift work duration, suggesting that long-term circadian disruption may play a role in rectal cancer development.

Introduction

In 2007, shift work that involves circadian disruption was classified as a probable human carcinogen based on sufficient experimental data and limited evidence from observational studies that had largely focused on breast cancer.[1–5] Today, 10 years later, evidence on the effect of shift work on other common tumors, such as colorectal cancer, remains very limited.

A few epidemiologic studies have examined the association of shift work with colorectal cancer risk, and evidence is inconclusive.[6–12] However, the association between shift work and colorectal cancer is biologically plausible. Circadian disruption, sleep deprivation, light induced suppression of melatonin, and lifestyle changes are important mechanisms that have been suggested to explain the possible link between shift work and colorectal cancer risk.[13,14] Disruption of the circadian clock may lead to deregulation of cell proliferation and mistiming of basic cell functions, such as DNA damage repair.[14–16] In addition, melatonin—which is often suppressed in night workers—exhibits direct and indirect oncostatic properties specific to colorectal cancer, for example, melatonin can cause growth inhibition of cell lines derived from colon carcinomas *in vitro* and animal studies.[17–19] Short sleep duration (a common consequence of night shift work) and a length polymorphism in the PER3 clock gene (a genotype associated with morning chronotype and sleep disorders) have been associated with a higher risk for formation of colorectal

Key words: rotating night work, shift work, colorectal cancer, colon cancer, rectum cancer
Conflict of interest: The authors report no conflicts of interest.
Grant sponsor: National Institutes of Health; **Grant numbers:** UM1CA186107, UM1CA176726; **Grant sponsor:** The National Institutes of Health; **Grant sponsor:** Center for Disease Control and Prevention/The National Institute for Occupational Safety and Health; **Grant numbers:** R01OH009803
DOI: 10.1002/ijc.31655

History: Received 28 Feb 2018; Accepted 1 Jun 2018; Online 6 July 2018
Correspondence to: Kyriaki Papantoniou, Department of Epidemiology, Centre for Public Health, Medical University of Vienna, Kinderspitalgasse 15/1, 1090, Vienna, Austria, E-mail: kyriaki.papantoniou@meduniwien.ac.at

What's new?

Night shift work is associated with circadian rhythm disruption, sleep deprivation, and lifestyle changes. Circadian disruption in particular can lead to the deregulation of basic cellular functions, including DNA damage repair, and thus is potentially carcinogenic in humans. In the present study, involving two large prospective cohorts of nurses, no overall evidence of an association was detected between rotating night shift work and colorectal cancer risk. Risk for rectal cancer increased significantly, however, with long-term rotating night shift work, lasting 15 or more years, suggesting that long-term circadian disruption may play a role in rectal cancer development.

adenoma, the precursor lesion to colorectal cancer.[20,21] However, in a recent report, we found no evidence for an association between night shift work and risk for colorectal adenomas among female nurses.[22] It is unclear if night work that involves circadian disruption plays a role in colorectal carcinogenesis, and if so, which stage of cancer development it influences (i.e., initiation or promotion). It is also possible that similar to other environmental risk factors, the effect of night work might vary depending on the anatomical location of colorectal tumors, although the potential for differential effects of circadian disruption has not been explored in this regard.[23,24]

We have previously reported an increased colorectal cancer risk with long term night shift work (15+ years) in the Nurses' Health study (NHS) with 10 years of follow-up.[8] In the present analysis, we update the previous NHS analysis with twice as much follow-up time and twice as many cases of colorectal cancer; in addition, we evaluate the association between night shift work and colorectal cancer risk in the Nurses' Health Study 2 (NHS2) for the first time. We hypothesized that longer duration of rotating night shift work might be associated with a higher risk of colorectal cancer.

Methods

Study population

The NHS cohort was established in 1976 among 121,701 female US registered nurses, aged 30–55 years, and NHS2 in 1989 among 116,430 female US registered nurses, aged 25–42 years. Since baseline, cohort members have completed biennial mailed questionnaires to update information on potential risk factors for chronic diseases and to identify newly diagnosed cancer cases and other major disease outcomes. Response rates have been ≥90% for every follow-up questionnaire cycle to date. We excluded women with missing birth date, women who died before baseline or were diagnosed with cancer (except nonmelanoma skin cancer), inflammatory bowel disease, ulcerative colitis, Crohn's disease, or familial polyposis syndrome before baseline (NHS: 13,899; NHS2: 2,484) and women with missing shift work information at baseline (NHS: 30,363; NHS2: 575). Therefore, the present analyses included 77,439 women in NHS and 113,371 women in NHS2. Our study was approved by the Institutional Review Boards of the Brigham and Women's Hospital and the Harvard T. H. Chan School of Public Health.

Ascertainment of colorectal cancer

Colorectal cancer cases were defined as having occurred between June 1, 1988 and May 31, 2012 in NHS and between June 1, 1989 and May 31, 2013 in NHS2. In both cohorts, self-reported diagnoses of colorectal cancer were obtained on biennial questionnaires, and participants who reported a diagnosis of colorectal cancer were asked for permission to acquire their medical records and pathological reports. We identified deaths through the National Death Index and next of kin. For all colorectal cancer deaths, we requested permission from next of kin to review medical records. A study physician, blinded to shift work information, reviewed records to confirm the colorectal cancer diagnosis and to extract relevant information, including anatomical location, stage, and histological type of the cancer. In the main analyses, all histological types of colorectal cancer were included (epithelial, carcinoids, nonepithelial, e.g., leiomyosarcoma) to preserve power. Sensitivity analyses were restricted to nonsquamous epithelial malignancies and results were unchanged (data not shown). Colorectal cancer and subsites (e.g., proximal colon, distal colon, or rectum) were defined according to the International Classification of Diseases, Ninth Revision (ICD-9). Right or proximal colon cancers were defined as those from the cecum to and including the splenic flexure. Distal colon cancers were defined as those in the descending and sigmoid colon. Rectal cancers were defined as those in the rectosigmoid or rectum. In NHS, 675 right/proximal colon cases, 363 left/distal colon cases, and 303 rectum cases were reported. The specific cancer subsite was unknown or missing in 186 cases.

Shift work assessment

In 1988, NHS participants were asked how many years in total they had worked rotating night shifts, which was defined as "at least 3 nights per month in addition to days or evenings in that month," Women responded in eight prespecified categories, which largely reflected life-time history of rotating night shift work (the majority was close to retirement age): never, 1–2 years, 3–5 years, 6–9 years, 10–14 years, 15–19 years, 20–29 years, and 30+ years. NHS2 participants were asked about their rotating shift work history in 1989 (when they were much younger) in the same categories, except the top category was 20+ years. In contrast to the NHS cohort, in NHS2 shift work information was updated (question about the total number of months having worked rotating night

shifts in the prior years) in 1991, 1993, 1997, 2001, 2005, and 2007 (in this last year, information was updated only for a subset of women with email addresses who received an online questionnaire). Because the 1995, 1999, and 2003 questionnaires did not include this question, retrospective assessments of rotating night shift work performed in 1993–1995, 1997–1999, and 2001–2003 were included on the 2001 and 2005 questionnaires. To estimate the total duration of shift work, the midpoint of the chosen response category was assigned to each participant, except for the highest category of exposure where the lower bound of duration was conservatively assigned. These values were summed up to estimate the total duration of shift work through disease diagnosis, death, or end of follow-up. If a participant did not respond to one of the shift work questions, her previous cumulative duration was carried forward once (zero years were assigned for that particular cycle). Of those asked about current shift-work exposure in 2007, only 8% were still working rotating night shifts. Therefore, for 2009 and subsequent cycles in which shift-work duration was not assessed, zero shift work was assumed.

Statistical analysis

Participants contributed person-time from the year of the return of the baseline questionnaire (NHS: 1988; NHS2: 1989) until the date of colorectal cancer diagnosis, diagnosis of any other cancer (except melanoma skin cancer), death, or end of followup (NHS: June 1 2012; NHS2: June 2013), whichever came first. In total, 1,551,827 person years of follow-up were accrued from 1988 to 2012 in NHS, and 2,549,000 person years were accrued from 1989 to 2013 in NHS2.

We assessed total shift work duration across the following groups: never, 1–2 years, 3–4 years, 5–9 years, 10–14 years, 15–19 years, 20–29 years, and 30 or more years in NHS; never, 1–2 years, 3–4 years, 5–9 years, 10–14 years, and 15 or more years in NHS2. In NHS2 for the category of 15 or more years of rotating night-shift work, we conservatively used 20 years because this category was the combination of 15–19, 20–29, and 30 or more years. We additionally collapsed years spent working on rotating night shifts into three categories (never, 1–14 years, and 15 or more years) to compare these results with our previously published report.[8] We used Cox proportional hazard models, with age in months and 2 year questionnaire cycles as the time-scale, to estimate the hazard ratios (HRs) and 95% confidence intervals of colorectal cancer for each shift work duration category, compared to those who never worked night shift work. We calculated p values for trend (Wald statistic) based on the median of the original categories of shift work duration (NHS: 1–2 years, 3–4 years, 5–9 years, 10–14 years, 15–19 years, 20–29 years, and 30 or more years, NHS2: never, 1–2 years, 3–4 years, 5–9 years, 10–14 years, and 15 or more years. Models were adjusted for known and suspected risk factors for colorectal cancer. We considered a wide range of known or suspected risk factors for colorectal cancer in our multivariable models that are summarized in Table 1. Because assessments of shift-work exposure differed by cohort (i.e., not updated in NHS; updated in NHS2), models are presented separately for each cohort. The proportional hazards assumption was tested by adding the interaction terms of shift work with follow-up time in both cohorts.

In NHS only, secondary analyses were performed where power was sufficient; they were not performed in NHS2 given very limited power in that cohort. First, we estimated relative risks separately for each anatomical subsite of colorectal cancer (proximal colon, distal colon, and rectum). Second, in stratified analysis, we assessed whether results varied by BMI (<25, 25–29, ≥30) and smoking status (never, current, and past smokers). To test for statistical interaction by categories of BMI and smoking status, we included multiplicative interaction terms in multivariate models. The p value for interaction was calculated using the log-likelihood ratio test, which compares the models with and without the interaction term of interest. All statistical analyses were performed using SAS software, version 9.1.3 (SAS Institute, Inc., Cary, North NC), and all statistical tests were two-sided.

Results

We documented 1,965 new colorectal cancer cases (1,527 in NHS and 438 in NHS II) during 24 years of follow-up. In both cohorts, women with longer duration of shift work were older, had a greater BMI, and were more likely to smoke (with more pack-years of smoking), but they reported lower alcohol consumption and higher levels of physical activity, compared to never shift workers (Table 1). Long-term night shift workers were more likely to have a lower educational level or a husband with a lower educational level compared to day workers, while no significant differences were observed in reported dietary habits known to predict colorectal cancer risk, such as folate, fiber, and red meat consumption.

In age-adjusted analyses, colorectal cancer risk increased with increasing years of rotating night shift work in NHS (p-trend = .04), but this was no longer significant after adjusting for additional potential confounders (p-trend = .14) (Table 2). Compared to women who never worked rotating night shifts, we found an increase in colorectal cancer risk after long-term (20+ years) exposure to night shift work in the age-adjusted models (20–29 years: HR 1.34 95%, CI: 1.02, 1.76; 30+ years: 1.21 95%, CI: 0.87, 1.68), which was attenuated and no longer statistically significant in the fully adjusted models (20–29 years: HR 1.26 95%, CI: 0.96, 1.65; 30+ years: 1.17 95%, CI: 0.84, 1.63). In NHS2, we observed no association between rotating night shift work and colorectal cancer risk, with both shift work history at baseline (1–14 years: HR 0.86 95%, CI: 0.71, 1.04; 15+ years: HR 0.97 95%, CI: 0.45, 2.09; p-trend = .49), and shift work information updated through follow-up (1–14 years: HR 0.81 95%, CI: 0.66, 0.99;

Table 1. Age-standardized characteristics of the study population by rotating night shift work duration at baseline in the Nurses' Health Study (NHS) and NHS2 (NHS: 1988, NHS2: 1989)

	NHS (*N* = 77,439)				NHS2 (*N* = 113,371)			
	No. of years worked on rotating night shifts				No. of years worked on rotating night shifts			
	Never	1–14	15–29	30+	Never	1–5	6–14	15+
Characteristic	*N* = 31,369	*N* = 40,342	*N* = 4,373	*N* = 1,355	*N* = 43,071	*N* = 55,377	*N* = 13,701	*N* = 1,222
Age, y; mean (SD)	54.3 (7.2)	54.7 (7.1)	56.1 (6.9)	60.4 (4.6)	34.8 (4.7)	34.5 (4.8)	35.5 (4.0)	39.2 (2.5)
Height, inches; mean (SD)	64.5 (2.4)	64.5 (2.4)	64.5 (2.5)	64.5 (2.5)	64.9 (2.6)	64.9 (2.6)	64.9 (2.7)	64.8 (2.7)
BMI, kg/m^2; mean (SD)	25.3 (4.8)	25.6 (4.9)	26.9 (5.5)	26.6 (5.2)	23.9 (4.9)	24.0 (5.0)	24.9 (5.6)	26.2 (6.9)
Obese (BMI › 30) (%)	14	16	24	24	11	11	15	20
Nurse's education level bachelor's or higher (%)[1]	31	30	24	22	–	–	–	–
Husband's education level college or higher (%)[2]	54	56	41	49	80	83	80	82
Nulliparous (%)	5	6	6	6	26	29	34	39
Postmenopausal (%)	67	68	70	86	2	2	3	3
Current menopausal hormone therapy use (%)[3]	35	35	29	29	82	79	80	74
First-degree family history of colorectal cancer (%)	12	12	12	16	4	4	5	4
Current smoker (%)	17	19	25	25	12	13	17	24
Pack-years smoked; mean (SD)[4]	23.0 (19.5)	23.2 (19.4)	26.1 (20.0)	26.3 (20.1)	11.3 (8.2)	11.2 (8.2)	11.7 (8.1)	13.1 (8.0)
Physical activity, MET-hours/week; mean (SD)	14.7 (20.8)	16.0 (22.0)	16.1 (21.7)	19.3 (28.4)	22.8 (34.2)	25.8 (37.6)	27.7 (40.1)	40.8 (61.9)
Alcohol consumption, grams/day; mean (SD)	6.2 (10.7)	6.3 (10.7)	5.3 (10.4)	5.5 (9.7)	3.0 (6.0)	3.2 (6.2)	3.1 (5.9)	3.3 (8.2)
Total energy intake (kcal/day); mean (SD)	1747 (519)	1782 (525)	1790 (556)	1780 (560)	1771 (540)	1799 (549)	1810 (568)	1855 (534)
Red or processed meat, servings/day; mean (SD)	0.5 (0.3)	0.5 (0.3)	0.5 (0.3)	0.5 (0.3)	0.8 (0.6)	0.8 (0.6)	0.8 (0.6)	0.8 (0.7)
Folate, ug/day; mean (SD)	402.9 (221.2)	406.6 (223.7)	392.5 (211.4)	412.9 (269.0)	475.2 (293.8)	480.6 (292.0)	478.1 (288.0)	515.9 (268.5)
Fiber, g/day; mean (SD)	17.6 (5.3)	17.8 (5.4)	17.5 (5.1)	18.5 (6.4)	4.8 (1.6)	4.9 (1.6)	4.9 (1.6)	5.1 (1.7)
Current aspirin use (›2 tablets/week) (%)	33	33	35	35	11	11	12	10
Current NSAIDS use (›2 tablets/week) (%)	18	19	21	21	18	20	23	19
Colonoscopy/ sigmoidoscopy in the last 2 years (%)	6	6	5	5	2	2	2	1

[1]Nurse's education level.
[2]Among married or widowed women.
[3]Among postmenopausal women.
[4]Among smokers.

15+ years: HR 0.96 95%, CI: 0.56, 1.64; *p*-trend = .88) (Table 3). The interaction of shift work with follow-up time period was not statistically significant for either cohort group (data not shown).

In subsite analysis in the NHS, we observed that risks associated with long-term night shift work (15+ years) tended to increase toward the distal parts of the colon and were highest for rectum cancer (proximal colon: HR 1.00; 95% CI: 0.75–1.34,

Table 2. Rotating night shift work duration and colorectal cancer risk in the Nurses' Health Study, 1988–2012 (N = 77,439)

	No. of cases	Person-yrs	RR (95% CI)[1]	p-trend[1,3]	RR (95% CI)[2]	p-trend[2,3]
NHS *baseline* rotating night shift work history in years						
Never	584	634,953	1.0 (ref)		1.0 (ref)	
1–2	346	376,925	1.02 (0.90, 1.17)		1.04 (0.91, 1.19)	
3–4	269	257,258	1.05 (0.91, 1.22)		1.05 (0.91, 1.22)	
5–9	112	104,179	1.08 (0.88, 1.32)		1.06 (0.87, 1.30)	
10–14	73	69,547	1.04 (0.82, 1.33)		1.01 (0.79, 1.29)	
15–19	45	42,259	1.05 (0.78, 1.43)		1.02 (0.75, 1.39)	
20–29	59	41,964	1.34 (1.02, 1.76)		1.26 (0.96, 1.65)	
30+	39	24,740	1.21 (0.87, 1.68)	*0.04*	1.17 (0.84, 1.63)	*0.14*
	1,527	1,551,827				
NHS *baseline* rotating night shift work history in years[4]						
Never	584	634,953	1.0 (ref)		1.0 (ref)	
1–14	800	807,909	1.04 (0.94, 1.16)		1.04 (0.94, 1.16)	
15+	143	108,964	1.20 (1.00, 1.45)		1.15 (0.95, 1.39)	
	1,527	1,551,827				

[1]Adjusted for age (months) and follow-up cycle.
[2]Adjusted for age (months), height (continuous in inches), BMI (‹18.5, 18.5–24.9, 25.0–29.9, 30 kg/m^2), educational level (RN license, bachelor's degree, masters or doctoral degree), menopausal status (premenopausal, postmenopausal), menopausal hormone therapy (never, past, current), first-degree family history of colorectal cancer (yes, no), alcohol consumption (0, 0.1–4.9, 5–14.9, 15 g/day), physical activity (8, 8.1–16, 16.1–24, ›24 MET-hr/week), smoking status (never smoker, current smoker, past smoker), colonoscopy/sigmoidoscopy in the previous 2 years (yes, no), current regular aspirin or NSAIDS use (›2 tablets/week), daily energy intake (kcal/day), red or processed meat (servings/day) and folate consumption (ug/day) in quintiles.
[3]p-trend was calculated using the midpoint of each category of rotating shift work duration in years (1–2, 3–4, 5–9, 10–14, 15–19, 20–29, 30+).
[4]Categories of shift work duration (Never, 1–14 years, 15+ years) were used to compare with our previously published results.

p-trend = .90; distal colon: HR 1.27; 95% CI: 0.87, 1.85, p-trend = .32; rectum: HR 1.60; 95% CI: 1.09, 2.34; p-trend = .02) after adjusting for potential confounders (Table 4).

In secondary analysis, we did not observe effect modification of the associations between rotating night-shift work history and colorectal cancer by BMI or smoking status (results not shown).

Discussion

We found no evidence of an overall association between rotating night shift work and colorectal cancer risk in these two large cohorts of nurses. However, there was a suggestion that longer durations of shift work (15+ years) were associated with a higher risk of rectal cancer specifically. These findings suggest that long-term circadian disruption may play a role in colorectal cancer development at specific subsites.

Results of the updated analysis of the NHS cohort, although mostly positive in direction, were attenuated and no longer statistically significant, compared to our previous report suggesting a positive association between long durations (15+ years) of night work and colorectal cancer risk.[8] Potential explanations for this attenuated risk include: *(i)* the older age of women in the NHS at baseline and the addition of 14 years of follow-up, where we may have captured mostly postretirement time, and probably only a few more years of rotating night shift work; *(ii)* the influence of the healthy worker effect, as subjects that are more susceptible to the symptoms caused by circadian disruption may have dropped out of shift work; and *(iii)* the possibility that women recover from the negative effects of circadian disruption after retirement especially after longer periods off of shift work. A similar pattern of increased risk during the first half of follow-up and decreased risk over the second half was also observed for breast cancer and coronary heart disease in this cohort.[25,26] In the younger and mostly premenopausal, NHS2 cohort no overall association was observed with shift work history. Exposure assessment in this cohort captured earlier career stages of the nurses and was updated throughout follow-up, therefore was improved compared to NHS. However, due to the participants younger age, less than 20 cases had experienced 15+ years of rotating night shift work in our analyses of the NHS2 cohort, and therefore power was limited in the analysis of longer shift work durations.

Our results are in line with some, but not all, previous studies of shift work and colorectal cancer. In a recent population-based case-control study in Spain (including 1,626 colorectal cancer cases), long-term rotating night-shift work was associated with an increased colorectal cancer risk among men, but not women.[6] In a another case-control study in Canada only including men (439 colon cancer cases,

Table 3. Rotating night shift work duration and incident colorectal cancer risk in the Nurses' Health Study 2 (N = 113,371) 1989–2013

	No. of cases	Person-yrs	RR (95%CI)[1]	p-trend[1,3]	RR (95% CI)[2]	p-trend[2,3]
NHS2 *baseline* rotating night shift work history in years						
Never	183	970,255	1.0 (ref)		1.0 (ref)	
1–2	102	741,924	0.74 (0.58, 0.95)		0.75 (0.59, 0.95)	
3–4	83	503,839	0.90 (0.69, 1.17)		0.90 (0.70, 1.17)	
5–9	42	218,082	1.02 (0.73, 1.43)		1.02 (0.72, 1.43)	
10–14	21	88,147	1.15 (0.73, 1.81)		1.15 (0.73, 1.81)	
15+	7	26,753	1.02 (0.47, 2.17)	*0.44*	0.97 (0.45, 2.09)	*0.49*
	438	2,549,000				
NHS2 *baseline* rotating night shift work history in years[4]						
Never	183	970,255	1.0 (ref)		1.0 (ref)	
1–14	248	1,551,992	0.86 (0.71, 1.04)		0.86 (0.71, 1.04)	
15+	7	26,753	1.01 (0.47, 2.17)		0.97 (0.45, 2.09)	
	438	2,549,000				
NHS2 *updated* rotating night shift work history in years						
Never	149	780,176	1.0 (ref)		1.0 (ref)	
1–4	187	1,262,145	0.77 (0.62, 0.96)		0.77 (0.62, 0.95)	
5–9	60	329,260	0.92 (0.68, 1.24)		0.90 (0.66, 1.21)	
10–14	27	120,745	1.03 (0.68, 1.55)		1.00 (0.66, 1.51)	
15+	15	56,674	1.02 (0.60, 1.75)	*0.69*	0.96 (0.56, 1.64)	*0.88*
	438	2,549,000				
NHS2 *updated* rotating night shift work history in years[4]						
Never	149	780,176	1.0 (ref)		1.0 (ref)	
1–14	274	1,712,149	0.82 (0.67, 1.00)		0.81 (0.66, 0.99)	
15+	15	56,674	1.02 (0.60, 1.74)		0.96 (0.56, 1.64)	
	438	2,549,000				

[1]Adjusted for age (months) and follow-up cycle.
[2]See footnote Table 2.
[3]p-trend was calculated using the midpoint of each category of rotating shift work duration in years (1–4, 5–9, 10–14, 15+).
[4]Categories of shift work duration (Never, 1–14 years, 15+ years) were used to compare with our previously published results.

236 rectum cancer cases) a higher risk for colon and rectum cancer was reported after permanent night shift work,[7] whereas in a recent case-control study among Australian women (350 colorectal cancer cases) no association was described.[11] A population based record-linkage study showed no association between shift work and colorectal cancer in both sexes, although the potential for exposure misclassification was high.[9] Finally, an earlier female cohort of radio and telegraph operators had shown a nonsignificant increase in risk for colon cancer after evening or night shifts.[10] Our study included only women and results from previous studies seem to be more suggestive for a positive association between night work and colorectal cancer among men. Reproductive and hormonal differences may explain some of the sex differences since exogenous estrogens seem to protect women against colorectal cancer.[27,28] Alternatively, women might have better coping mechanisms and sleep hygiene, or may adhere more frequently to screening programs compared to men. It is likely that job types are different for the two sexes, and thus shift patterns and other job-specific exposures may vary. In addition, night shift work definitions (e.g., permanent *vs.* rotating) and metrics (e.g., ever/never, duration, frequency of night shift work) used to quantify circadian disruption vary largely across studies.[29] Our exposure definition included rotating night shift work schedules with at least 3 nights per month and we assessed cumulative night shift work duration in years. However, recent evidence suggests that other exposure metrics such as shift work frequency (nights/month or number of consecutive nights) and length (hours/day) may also predict breast cancer risk in addition to cumulative lifetime duration (years).[30] Our study lacked information on shift work frequency and length but these metrics should be considered in future studies.

In subsite analyses in the NHS, we found evidence that risk increased toward the distal parts of the colon, and was highest

Table 4. Rotating night shift work duration and incident colorectal cancer by tumor anatomical site (NHS: 1988–2012)

	No. of cases ($N = 1{,}341$)[5]	RR (95% CI)[1]	*p*-trend[1,3]	RR (95% CI)[2]	*p*-trend[2,3]
NHS *baseline* rotating night shift work history in years[4]					
Colon combined					
Never	403	1.0 (ref)		1.0 (ref)	
1–14	542	1.02 (0.90, 1.16)		1.02 (0.90, 1.16)	
15+	93	1.11 (0.89, 1.40)	*0.45*	1.09 (0.87, 1.37)	*0.62*
	1038				
Proximal colon					
Never	271	1.0 (ref)		1.0 (ref)	
1–14	347	0.98 (0.83, 1.14)		0.98 (0.83, 1.14)	
15+	57	1.02 (0.76, 1.36)	*0.98*	1.00 (0.75, 1.34)	*0.90*
	675				
Distal colon					
Never	132	1.0 (ref)		1.0 (ref)	
1–14	195	1.12 (0.89, 1.39)		1.12 (0.90, 1.40)	
15+	36	1.32 (0.91, 1.92)	*0.21*	1.27 (0.87, 1.85)	*0.32*
	363				
Rectum					
Never	111	1.0 (ref)		1.0 (ref)	
1–14	156	1.07 (0.83, 1.36)		1.05 (0.82, 1.34)	
15+	36	1.68 (1.15, 2.46)	*0.01*	1.60 (1.09, 2.34)	*0.02*
	303				

[1]Adjusted for age and follow-up cycle.
[2]See footnote Table 2.
[3]*p*-trend was calculated using the midpoint of each category of rotating shift work duration in years (1–2, 3–4, 5–9, 10–14, 15–19, 20–29, 30+).
[4]Categories of shift work duration (Never, 1–14 years, 15+ years) were used to compare with our previously published results.
[5]The numbers of colon and rectal cancers may not be equal to total number of colorectal cancers because, in some cases, the specific cancer site was unknown.

(60% increase) for rectal cancer. This is a novel finding, which is partly in line with prior evidence supporting a differential etiology between colon and rectum cancer.[23,24] Increasing evidence supports variation in pathological characteristics of colorectal cancers along the colorectal segments due to different embryonic origins, but also due to exposure to bowel contents (including microbiota) and host immune response.[31–34] Further, the colon and rectum serve different functions, and are exposed to fecal matter for different durations and at different times of the day; thus, circadian disruption and mistimed meals (e.g., nighttime snacks) in night workers could shift the timing of bowel movements, impacting the distal bowel the most as more undigested matter travels through the distal parts of the colon and rectum. In addition, it has been suggested that cancers arising in the distal colon and rectum begin as adenomatous polyps, whereas a *de novo* pathway is more important in lesions that arise in the proximal colon.[35] However, we recently found no association between night shift work and colorectal adenomas—a precursor for most colorectal cancers that can be detected by screening. Still, it is possible that shift work does not act as a cancer initiator (e.g., adenoma formation), but may have more downstream effects as a cancer promoter. Finally, the observed difference between colon and rectum cancer might be a result of differential screening. Colonoscopic polypectomy may reduce subsequent colorectal cancer incidence by at least 66%.[36–38] Flexible sigmoidoscopy, the routine screening method in the United States (recommended every 5 years in adults >50 years), examines the lower half of the colon lumen and, thus, reduces cancer incidence only in the distal colon and rectum.[39,40] If shift work status influences adherence to sigmoidoscopy (e.g., day workers are more likely to adhere to it compared to night workers), then this would influence their subsequent rectum and distal colon cancer risk.[41] However, in this cohort colorectal cancer screening practices (including sigmoidoscopy) were similar between night and day workers at baseline and during follow up.[42]

Our study has several limitations. First, night shift work was assessed by questionnaire, which might have resulted in nondifferential exposure misclassification and could have biased our results toward the null. Specifically, given our definition of night shift work (3 or more nights per month, in addition to other day/evening shifts in that month), it is possible that a nurse who worked permanent night shifts may have

classified herself not as a rotating night shift worker. Further, we were not able to compare different intensities or patterns of night-shift work since we have no information on the actual number of nights worked per month. In addition, in the NHS, cumulative (lifetime) shift work history (in years) was assessed only once at baseline (1988). Therefore, we do not know the specific work schedule of nurses after 1988 and if there were any changes (e.g., continuing, starting, or quitting rotating night shift work). Thus, we were able to assess the cumulative years of rotating night shift work exposure from the beginning to approximately the middle of the nurses' working life in NHS and may have underestimated total life exposure, which could have biased our results toward the null. In addition, women with missing information on rotating night shift work at baseline were excluded from the analysis, another potential source of bias, which likely would have led to an underestimate of the actual risk. By contrast, in NHS2, shift work history was assessed first at an earlier stage of a woman's work life and subsequently updated every 2 years throughout follow up, which allowed for a more accurate estimation of the total years of rotating night shift work history capturing all career stages. Our study included female nurses, and results may not fully apply to men. Still, the NHS and NHS2 are among the largest prospective studies available for evaluating the association between night shift work and colorectal cancer. These studies are unique, in that, they prospectively assess shift work and a wide range of well-known and suspected risk factors for colorectal cancer development, which might confound the described associations.

In conclusion, we found no evidence of an overall association between rotating night shift work and colorectal cancer risk in these two large cohorts of female nurses. Yet, risk for rectal cancer significantly increased with shift work duration. Taken together, these findings suggest that long-term circadian disruption may play a role in rectal cancer development.

Acknowledgements

This work was supported by the Center for Disease Control and Prevention/The National Institute for Occupational Safety and Health grant R01OH009803 (PI: Eva Schernhammer). The NHS and NHS2 cohorts are supported by The National Institutes of Health grants UM1CA186107 (PI: Meir Stampfer) and UM1CA176726 (PI: Walter Willett). The authors would like to thank the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, WY. The authors assume full responsibility for analyses and interpretation of these data.

References

1. Straif K, Baan R, Grosse Y, et al. Carcinogenicity of shift-work, painting, and fire-fighting. *Lancet Oncol* 2007;8:1065–6.
2. Schernhammer ES, Kroenke CH, Laden F, et al. Night work and risk of breast cancer. *Epidemiology* 2006;17:108–1.
3. Schernhammer ES, Laden F, Speizer FE, et al. Rotating night shifts and risk of breast cancer in women participating in the nurses' health study. *J Natl Cancer Inst* 2001;93:1563–8.
4. Stevens RG, Brainard GC, Blask DE, et al. Breast cancer and circadian disruption from electric lighting in the modern world. *CA Cancer J Clin* 2013;64:207–18.
5. Hansen J, Stevens RG. Case-control study of shift-work and breast cancer risk in Danish nurses: impact of shift systems. *Eur J Cancer* 2012;48:1722–9.
6. Papantoniou K, Castano-Vinyals G, Espinosa A, et al. Shift work and colorectal cancer risk in the MCC-Spain case-control study. *Scand J Work Environ Health* 2017;43:250–9.
7. Parent ME, El-Zein M, Rousseau MC, et al. Night work and the risk of cancer among men. *Am J Epidemiol* 2012;176:751–9.
8. Schernhammer ES, Laden F, Speizer FE, et al. Night-shift work and risk of colorectal cancer in the nurses' health study. *J Natl Cancer Inst* 2003; 95:825–NaN.
9. Schwartzbaum J, Ahlbom A, Feychting M. Cohort study of cancer risk among male and female shift workers. *Scand J Work Environ Health* 2007;33: 336–43.
10. Tynes T, Hannevik M, Andersen A, et al. Incidence of breast cancer in Norwegian female radio and telegraph operators. *Cancer Causes Control* 1996;7:197–204.
11. Walasa WM, Carey RN, Si S, et al. Association between shiftwork and the risk of colorectal cancer in females: a population-based case-control study. *Occup Environ Med* 2018;75:344–50.
12. Wang X, Ji A, Zhu Y, et al. A meta-analysis including dose-response relationship between night shift work and the risk of colorectal cancer. *Oncotarget* 2015;6:25046–60.
13. Fritschi L, Glass DC, Heyworth JS, et al. Hypotheses for mechanisms linking shiftwork and cancer. *Med Hypotheses* 2011;77:430–6.
14. IARC. Painting Firefighting and shiftwork. *IARC Monograph* 2010;98:9–764.
15. Sancar A, Lindsey-Boltz LA, Kang TH, et al. Circadian clock control of the cellular response to DNA damage. *FEBS Lett* 2010;584:2618–5.
16. Savvidis C, Koutsilieris M. Circadian rhythm disruption in cancer biology. *Mol Med* 2012;18:1249–60.
17. Anisimov VN, Kvetnoy IM, Chumakova NK, et al. Melatonin and colon carcinogenesis. II. Intestinal melatonin-containing cells and serum melatonin level in rats with 1,2-dimethylhydrazine-induced colon tumors. *Exp Toxicol Pathol* 1999;51: 47–52.
18. Anisimov VN, Popovich IG, Shtylik AV, et al. Melatonin and colon carcinogenesis. III. Effect of melatonin on proliferative activity and apoptosis in colon mucosa and colon tumors induced by 1,2-dimethylhydrazine in rats. *Exp Toxicol Pathol* 2000;52:71–6.
19. Farriol M, Venereo Y, Orta X, et al. In vitro effects of melatonin on cell proliferation in a colon adenocarcinoma line. *J Appl Toxicol* 2000; 20:21–4.
20. Alexander M, Burch JB, Steck SE, et al. Case-control study of the PERIOD3 clock gene length polymorphism and colorectal adenoma formation. *Oncol Rep* 2015;33:935–41.
21. Archer SN, Carpen JD, Gibson M, et al. Polymorphism in the PER3 promoter associates with diurnal preference and delayed sleep phase disorder. *Sleep* 2010;33:695–701.
22. Devore EE, Massa J, Papantoniou K, et al. Rotating night shift work, sleep, and colorectal adenoma in women. *Int J Color Dis* 2017;32: 1013–8.
23. Wei EK, Colditz GA, Giovannucci EL, et al. A comprehensive model of colorectal cancer by risk factor status and subsite using data from the Nurses' health study. *Am J Epidemiol* 2017;185: 224–37.
24. Wei EK, Giovannucci E, Wu K, et al. Comparison of risk factors for colon and rectal cancer. *Int J Cancer* 2004;108:433–2.
25. Wegrzyn LR, Tamimi RM, Rosner BA, et al. Rotating night-shift work and the risk of breast cancer in the Nurses' health studies. *Am J Epidemiol* 2017;186:532–40.
26. Vetter C, Devore EE, Wegrzyn LR, et al. Association between rotating night shift work and risk of coronary heart disease among women. *JAMA* 2016;315:1726–34.
27. Kabat GC, Miller AB, Rohan TE. Oral contraceptive use, hormone replacement therapy, reproductive history and risk of colorectal cancer in women. *Int J Cancer* 2008;122:643–NaN.

28. Rennert G. Reproductive factors, hormones and colorectal cancer-still unresolved. *Br J Cancer* 2017;116:1–3.
29. Stevens RG, Hansen J, Costa G, et al. Considerations of circadian impact for defining 'shift work' in cancer studies: IARC working group report. *Occup Environ Med* 2010;68:154–62.
30. Cordina-Duverger E, Menegaux F, Popa A, et al. Night shift work and breast cancer: a pooled analysis of population-based case-control studies with complete work history. *Eur J Epidemiol* 2018; 33:369–79.
31. Bufill JA. Colorectal cancer: evidence for distinct genetic categories based on proximal or distal tumor location. *Ann Intern Med* 1990;113:779–88.
32. Carethers JM. One colon lumen but two organs. *Gastroenterology* 2011;141:411–2.
33. Yamauchi M, Lochhead P, Morikawa T, et al. Colorectal cancer: a tale of two sides or a continuum. *Gut* 2012;61:794–NaN.
34. Yamauchi M, Morikawa T, Kuchiba A, et al. Assessment of colorectal cancer molecular features along bowel subsites challenges the conception of distinct dichotomy of proximal versus distal colorectum. *Gut* 2012;61:847–54.
35. Konishi K, Fujii T, Boku N, et al. Clinicopathological differences between colonic and rectal carcinomas: are they based on the same mechanism of carcinogenesis. *Gut* 1999;45:818–21.
36. Citarda F, Tomaselli G, Capocaccia R, et al. Efficacy in standard clinical practice of colonoscopic polypectomy in reducing colorectal cancer incidence. *Gut* 2001;48:812–5.
37. Thiis-Evensen E, Hoff GS, Sauar J, et al. Population-based surveillance by colonoscopy: effect on the incidence of colorectal cancer. Telemark polyp study I. *Scand J Gastroenterol* 1999;34:414–20.
38. Winawer SJ, Zauber AG, Fletcher RH, et al. Guidelines for colonoscopy surveillance after polypectomy: a consensus update by the US multi-society task force on colorectal cancer and the American Cancer Society. *Gastroenterology* 2006;130:1872–85.
39. Strum WB. Colorectal adenomas. *N Engl J Med* 2016;375:389–90.
40. Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US multi-society task force on colorectal cancer, and the American College of Radiology. *CA Cancer J Clin* 2008;58:130–60.
41. Tsai RJ, Luckhaupt SE, Sweeney MH, et al. Shift work and cancer screening: do females who work alternative shifts undergo recommended cancer screening. *Am J Ind Med* 2014;57:265–75.
42. Devore EE, Massa J, Papantoniou K, et al. Rotating night shift work, sleep, and colorectal adenoma in women. *Int J Color Dis* 2017;32: 1013–8.