National Toxicology Program
U.S. Department of Health and Human Services

Draft Report on Carcinogens Monograph on Light at Night

Peer Review Draft

Running title: Draft RoC Monograph on Night Shift Work and Light at Night

Appendix E: Shiftwork and Colorectal Cancer

August 24, 2018

Office of the Report on Carcinogens
Division of the National Toxicology Program
National Institute of Environmental Health Sciences
U.S. Department of Health and Human Services

List of Tables

Appendix E: Colorectal Cancer Studies Tables

Appendix E encompasses tables related to human studies on shift work exposure and risk of colorectal cancer. Tables E-1a to E-1f provide ratings and the rationales for the domains of study quality and study sensitivity. Table E-2 gives detailed results for each evaluated epidemiological study.

Table E-1a. Evaluation of selection bias in human colorectal cancer studies.

Reference	Selection Bias rating
Jørgensen *et al.* 2017	+ ? The cohort was clearly defined by exposure status for a specific time period and location. Follow-up did not differ by exposure status. Left truncation is an issue in this older survivor cohort. Authors indicated most nurses have to participate in rotating shift work early in their careers, and this is a >44 year old cohort, so selection of exposure status may not be appropriate. Mortality analysis is likely to miss about 1/3 of cases having longer survival and later death, likely resulting in non-differential (not related to exposure status) misclassification, loss of power, and an underestimation of the risk estimate.
Papantoniou *et al.* 2018	++ ? The cohort is clearly defined with no evidence that follow-up differed between exposed and non-exposed subjects. Together, the two cohorts cover broad windows of exposure for women of different ages; however, analysis was done separately for each cohort. For NHS2, women are less likely to be selected out due to inability to adapt to shift work. For NHS, there is a higher likelihood of HWE given it is an older population.
Schwartzbaum *et al.* 2007	++ ↔ Only an external analysis was conducted. No evidence of HWE, as the overall SIR for all cancers was approaching unity. HWSE is still possible and may bias results toward the null.
Yong *et al.* 2014	++ ? The cohort is clearly defined and includes the relevant exposed and unexposed populations for a specific time period and location. Healthy worker effect (HWE) is possible, as cancer incidence was higher among shift workers and lower among day workers, compared to the general population. There was also no consideration of HWSE in this occupational cohort. In Hammer *et al.* (2015), a validation analysis of the same cohort reported no change in day to shift work for 893 (97%) of the employees, and there was little movement between shifts in this company suggesting HWSE was minimized.
Papantoniou *et al.* 2017	++ ↔ Cases and controls were selected from the same population by similar criteria. No evidence that the selection of the subjects was related to both exposure and disease. However, the very low response rates for controls raises the question of potential selection bias with unknown direction of effect. Subjects working at night, especially permanent night workers, might have been more likely to be at home during the day when phone calls were performed and, if so, they might have been overrepresented among controls.
Parent *et al.* 2012	+++ ↔ Cases and controls selected from the same population using similar criteria;

Reference	Selection Bias rating
	no evidence that selection of subjects was related to both exposure and disease. Distribution of occupations of controls was comparable to distribution in the Canadian censuses, and percentage of those who were shift workers (14.5%) was similar to the general male population.
Walasa *et al.* 2018	++ ↔ Cases and controls were selected from the same population using similar criteria. There was no evidence that selection of subjects was related to both exposure and disease. Poor response rates in both cases and controls may lead to selection bias, although rates are comparably low in both groups. The prevalence of ever graveyard shift in the study (20%) was similar to current shift work in Australia (16% of employed persons, Australian Bureau of Statistics 2015).

Table E-1b. Evaluation of exposure assessment methods in human colorectal cancer studies.

Reference	Exposure Assessment rating
Jørgensen *et al.* 2017	0 ? Current information on work status at baseline only. No information on past employment status casting doubt on those classified as unexposed. No data on duration of shift schedule and shift work intensity lead to a less sensitive exposure categorization. Furthermore, authors mention the high likelihood of exposure misclassification for nurses whose training involves shift work early in their career.
Papantoniou *et al.* 2018	++ ? The exposure assessment methods have moderate to good sensitivity and specificity for NHS-2, but poorer sensitivity and specificity for NHS. No information on frequency or intensity was provided. NHS: the shift work question was asked at baseline. No data on permanent or less frequent rotating night shift work was collected.
Schwartzbaum *et al.* 2007	0 ? Night shift work was determined according to percentage of those in each job category reporting shift work in a survey independent of the study cohort. Given the lack of individual-level data on exposure, participants categorized as unexposed are more likely to have been misclassified.
Yong *et al.* 2014	+ ? Detailed information on shift work schedule and intensity was examined. Years of shift work was also captured, but not prior to 1995. Exposure status prior to 1995 was estimated to be misclassified for both unexposed (1.2%–3.1%) and exposed (9.8%–13.4%) participants based on a sensitivity analysis of 300 participants. Validation study revealed the likelihood of misclassification impacting results was low; however, potential differential misclassification for exposed subjects will bias results toward the null.
Papantoniou *et al.* 2017	++ ? Exposure assessment methods have good sensitivity and specificity leading to reliable classification of exposure. Recall bias may have been introduced into assessment of exposure frequency which had a high degree of missing values (35% of shift workers) compared to duration (< 1% missing), perhaps explaining the differential risk observed across groups with increasing rotating night shift work intensity.
Parent *et al.* 2012	++ ? Exposure methods reliably discriminate between ever and never exposed. However, no information was gathered on frequency (exposure-level) or types of shifts (fixed or rotating), direction or rate of shift rotation. Timing of shift work was collected but crudely divided as recent (within past 20 years), or distant past (20+ years ago) exposure.
Walasa *et al.* 2018	+ ↔ Characterization of graveyard, early-morning, and phase shift exposures were conducted via a group-level job exposure matrix (JEM), and therefore, is subject to exposure misclassification.

Table E-1c. Evaluation of outcome assessment in human colorectal cancer studies.

Reference	Outcome Assessment rating
Jørgensen *et al.* 2017	++ ? Reported causes of death were not histologically-confirmed, rather only based on physician report from death records.
Papantoniou *et al.* 2018	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnoses are conducted independent of exposure status. Pathology confirmation of cause of death in 98% of cases, although all cases were included in analysis. No subtypes ascertained.
Schwartzbaum *et al.* 2007	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnoses are conducted independent of exposure status.
Yong *et al.* 2014	++ ? Outcome methods distinguish between diseased and non-diseased subjects, and follow-up was conducted independent of exposure classification; however, given the development of the registry, some cases may have been missed, although it is likely that this is non-differential, leading to a bias towards the null.
Papantoniou *et al.* 2017	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Diagnosis was conducted independent of exposure.
Parent *et al.* 2012	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Diagnosis conducted independent of exposure status.
Walasa *et al.* 2018	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Diagnosis was conducted independent of exposure status.

Table E-1d. Evaluation of study sensitivity for human colorectal cancer studies.

Reference	Sensitivity rating
Jørgensen *et al.* 2017	+ ? Small number of CRC mortality cases. Poor sensitivity of exposure status due to lack of level, duration, or range of exposure. Adequately long follow-up duration.
Papantoniou *et al.* 2018	+++ ↔ The study has an adequate number of exposed subjects, and adequate (N=98) to small (N=15) number of women with 15+ years of exposure in NHS and NHS-2, respectively. Both cohorts only measure ever and duration of exposure. NHS examined CRC subsite.
Schwartzbaum *et al.* 2007	+ ↔ Adequate number of exposed cases for males but not females, and no information about intensity or duration. Adequate duration of follow-up.
Yong *et al.* 2014	+ ↔ The study has a small-to-moderate number of exposed colorectal subjects, but no information on level, duration, or range, and exposure variation is essentially flat across the exposed. Latency follow-up was adequate.
Papantoniou *et al.* 2017	++ ↔ The study has an adequate number of exposed subjects with substantial exposure (duration and timing of exposure). However, no information on type of schedule or intensity of exposure.
Parent *et al.* 2012	++ ? The study has a moderate-to-large number of exposed colon and rectal cancer cases, but no information on intensity/frequency or pattern of exposure (e.g., type of shifts); or screening information.
Walasa *et al.* 2018	++ ↔ There was a small-to-moderate number of exposed cases for graveyard shift workers. Numerous shift work variables were appropriately examined, although not on shift work intensity due to reliance on JEM.

Table E-1e. Evaluation of potential for confounding bias in human colorectal cancer studies.

Reference	Confounding rating
Jørgensen *et al.* 2017	+++ ? The study measured all relevant confounders and used appropriate analyses to address them. The addition of all possible confounders may attenuate results and widen confidence in the estimates.
Papantoniou *et al.* 2018	+++ ↔ The study measured all relevant confounders and used appropriate analyses to address them. The addition of all possible confounders may attenuate results and widen confidence in the estimates.
Schwartzbaum *et al.* 2007	+ ? The study did not measure potential confounders such as alcohol, red meat consumption and BMI.
Yong *et al.* 2014	+ ? The study did not measure potential confounders such as alcohol consumption, red meat consumption; job level can stand as a proxy for physical exercise, although there is no dietary or body mass index (BMI) information.
Papantoniou *et al.* 2017	++ ? The study measured all relevant potential confounders and used appropriate analyses to address them. The addition of all possible confounders may have attenuated results and widened confidence in the estimates.
Parent *et al.* 2012	++ ? The study measured all relevant potential confounders with the exception of red meat. Additional factors such as smoking and beta carotene may have reduced effect estimates.
Walasa *et al.* 2018	++ ↔ The study measured most of the relevant potential confounders and used appropriate analyses to address them, but did not account for BMI and red meat consumption in the main analyses.

Table E-1f. Evaluation of analysis and selective reporting for human colorectal cancer studies.

Reference	Analysis rating	Selective Reporting rating
Jørgensen *et al.* 2017	++ ? Inclusion of multiple covariates not related to the exposure and outcome of interest may have attenuated results and widened confidence intervals.	+++ ↔ No evidence that data or analysis was limited to a subset of data.
Papantoniou *et al.* 2018	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ No evidence suggests analysis was limited to only a subset of the data that were collected.
Schwartzbaum *et al.* 2007	++ ↔ Study used relevant data, had appropriate assumptions and used adequate methods for an external analysis (SIR).	+++ ↔ No evidence that reporting of the data or analyses were limited to only a subset of the data collected.
Yong *et al.* 2014	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ No evidence that reporting of the data or analyses were limited to only a subset of the collected data.
Papantoniou *et al.* 2017	+++ ↔ Study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ No evidence that reporting of the data or analyses were limited to only a subset of the data collected.
Parent *et al.* 2012	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ No evidence that reporting of the data or analyses were limited to only a subset of data collected.
Walasa *et al.* 2018	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ No evidence that reporting of the data or analyses were limited to only a subset of the data collected.

Table E-2. Evidence from epidemiological cohort and case-control studies on colorectal cancer and exposure to night shift work.

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
Jørgensen *et al.* 2017 Cohort Denmark **Enrollment or follow-up:** 1993-2013	**Population:** Danish Nurses Cohort (DNC) 28,731 women **Exposure assessment method:** questionnaire	**HR Ever evening, night, and rotating shift work**		Age, smoking status, pack years, physical activity, BMI, alcohol consumption, diet (veggies, fruit, meat), pre-existing disease (hypertension, diabetes, MI), self-reported health, stressful work environment, marital status, use of HRT, OC use	**Exposure information:** Ever evening, night, rotating shifts **Strengths:** Nationwide prospective cohort of female nurses with detailed information on work schedules at baseline, and potential confounders. **Limitations:** Small numbers of colorectal cancer deaths, no information on duration or intensity, type of rotations, or past information on night work. No cancer validation. **Additional results:** Unadjusted estimates are similar to adjusted estimates (night shifts have a higher magnitude of effect but still non-significant). **Confidence in evidence:** No confidence; not included in assessment.
		Day	-		
		Night	1.02 (0.5–2.11); 9		
		Rotating	0.83 (0.5–1.36); 20		
Papantoniou *et al.* 2018 Cohort 11 U.S. states	**Population:** Nurses in Nurses Health Study NHS and NHS-2 NHS: 77,349 women; NHS-2:	**HR (RR) NHS: Duration (years) of rotating shift work, baseline**		Age, height, BMI, education level, menopausal status, menopausal hormone therapy, family history of	**Exposure information:** Ever and duration of rotating shift work **Strengths:** Utilization of two cohorts with long follow up
		Never (Reference)	-		
		1–14 yrs	1.04 (0.94–1.16); 800		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
Enrollment or follow-up: NHS: 1976 (enrolled), 1988-2012 (follow-up); NHS-2: 1989 (enrolled), 1989-2013 (follow-up)	113,371 women **Exposure assessment method:** questionnaire	≥ 15 yrs	1.15 (0.95–1.39); 143	colorectal cancer, alcohol consumption, physical activity, Smoking status, colonoscopy/sigmoidoscopy in previous 2 years, current regular aspirin/NSAIDS use, daily energy intake, red or processed meat intake, folate consumption	time; complete information on potential confounders; ability to analyze by subtype; ability to compare two similar, but age differentiated cohorts. **Limitations:** Potential misclassification of unexposed potentially including permanent night workers and non-shift workers as most women exposed to some light at night. Small number of NHS2 women exposed for 15+years; no information on intensity or pattern of nightshift work most disruptive to circadian rhythms. **Additional results:** For NHS, a base model adjusted for age and follow-up cycle only had a significant RR of 1.34 (95%CI = 1.02 to 1.76) for nurses working 20-29 years rotating night shift work. For NHS2, baseline rotating night shift work history showed generally similar nonsignificant risk estimates by duration of exposure. **Confidence in evidence:** Some evidence (Will delete this, but my call for some evidence is that you see significant RR for 15+ years for baseline NHS cohort (1.60, 95%CI: 1.09, 2.34). Thoughts? Should this be considered null?)
		HR (RR) NHS: Duration (years) of rotating shift work, baseline		Same as above	
		Never (Reference)	-		
		1–2 yr	1.04 (0.91–1.19); 346		
		3–4 yr	1.05 (0.91–1.22); 269		
		5–9 yr	1.06 (0.87–1.3); 112		
		10–14 yr	1.01 (0.79–1.29); 73		
		15–19 yr	1.02 (0.75–1.39); 45		
		20–29 yr	1.26 (0.96–1.65); 59		
		≥ 30 yr	1.17 (0.84–1.63); 39		
		Trend-test *p*-value: 0.14			
		HR (RR) NHS2: Duration (years) of rotating shift work, updated		Same as above	
		Never (Reference)	-		
		1–4 yr	0.77 (0.62–0.95); 187		
		5–9 yr	0.9 (0.66–1.21); 60		
		10–14 yr	1 (0.66–1.51); 27		
		≥ 15 yr	0.96 (0.56–1.64); 15		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		Trend-test *p*-value: 0.88			
		HR (RR) NHS2: Duration (years) of rotating shift work, updated		Same as above	
		Never (Reference)	-		
		1-14	0.81 (0.66–0.99); 274		
		15+	0.96 (0.56–1.64); 15		
		Combined proximal and distal colon: HR (RR) NHS: Duration (years) of rotating shift work, baseline		Same as above	
		Never (Reference)	-		
		1–14 yr	1.02 (0.9–1.16); 542		
		≥ 15 yr	1.09 (0.87–1.37); 93		
		Trend-test *p*-value: 0.62			
		Proximal colon: HR (RR) NHS: Duration (years) of rotating shift work, baseline		Same as above	
		Never (Reference)	-		
		1–14 yr	0.98 (0.83–1.14); 347		
		≥ 15 yr	1 (0.75–1.34); 57		
		Trend-test *p*-value: 0.90			
		Distal colon: HR (RR) NHS: Duration (years) of rotating shift work, baseline		Same as above	
		Never (Reference)	-		
		1–14 yr	1.12 (0.9–1.4); 195		
		≥ 15 yr	1.27 (0.87–1.85); 36		
		Trend-test *p*-value: 0.32			

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		Rectum only: HR (RR) NHS: Duration of rotating shift work			
		Never (Reference)	-		
		1–14 yr	1.05 (0.82–1.34); 156		
		≥ 15 yr	1.6 (1.09–2.34); 36		
		Trend-test p-value: 0.02			
Schwartzbaum *et al.* 2007 Cohort Sweden **Enrollment or follow-up:** 1977-1981 (enrollment); 1971-1989 (follow-up)	**Population:** Swedish working women registered in 1960 and 1970 census data. 1,148,661 female workers and 2,102,126 male workers **Exposure assessment method:** JEM	**Colon only; Females: SIR Ever worked night shift by census period**		Age, socioeconomic status, occupational position, county of residence	**Exposure information:** Workplace (aggregate-level) either had a rotating schedule or had work hours between 1-4 AM **Strengths:** Nationwide cohort of men and women in diverse industries followed for 19 years. **Limitations:** In men, adequate number of exposed cases of colon and rectal cancer; in women, very small number of colon cancer cases. Aggregate exposure data, lack of data on potential confounders or co-exposures such as diet and alcohol use. **Additional results:** Risk estimates for female colon cancer using the 1960 and 1970 census were on 3 cases, with a low risk and imprecise confidence estimates (SIR: 0.42, 95% CI 0.09-1.23). Other risk estimates reported had similar results when restricted to participants in 1960 & 1970 censuses. **Confidence in evidence:** No confidence, not included in the assessment.
		1970	0.94 (0.54–1.52); 16		
		Colon only; Males: SIR Ever worked night shift by census period		Same as above	
		1970	1.03 (0.94–1.13); 449		
		Rectum only; Females: SIR Ever worked night shift by census period		Same as above	
		1970	0.46 (0.12–1.17); 4		
		Rectum only; Males: SIR Ever worked night shift by census period		Same as above	
		1970	1.02 (0.91–1.13); 326		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
Yong *et al.* 2014 Cohort Germany **Enrollment or follow-up:** 2000–2009	**Population:** Male chemical production workers in Rhineland-Palatinate Germany 27,828 men **Exposure assessment method:** company records	**HR (RR) Internal analysis: rotating shift work**		Age, job level, smoking, employment duration	**Exposure information:** Ever worked forward rotating shift work pattern: either 3 x 12 hours (day, off, night) or 4 x 12 hours (day, off, off, night) **Strengths:** Large retrospective cohort with adequate number of cases. Attempts to estimate bias from lack of exposure data. **Limitations:** Exposure data did not encompass all employment history. No variation in exposure metrics beyond ever exposure; duration crudely estimated and not used in analysis; only 80% estimated completeness of cancer case reporting; potential confounders not controlled; HWE is evident. **Additional results:** - **Confidence in evidence:** Some evidence
		Rotating	1.33 (0.86–2.06); NR		
		SIR External analysis: ever rotating shift work		Age, calendar year	
		Rotating	1.08 (0.84–1.36); 68		
		Ratio of rotating vs. day	1.24 (0.88–1.77); NR		
Papantoniou *et al.* 2017 Case-Control Spain **Enrollment or follow-up:** 2008–2013	**Population:** MCC-Spain Cases: 1626 men and women; Controls: 3378 men and women **Exposure assessment method:** questionnaire	**OR Ever rotating and night shift work**		Age, center, education, BMI, smoking status, physical activity, leisure, alcohol consumption, past, total energy intake gms/day, red meat consumption gms/day, sleep duration hrs/day, NSAIDs, family history of colorectal cancer, sex	**Exposure information:** Ever shift work, lifetime cumulative duration, age of first shift work exposure, years since last exposure. **Strengths:** Large, representative population based case-control study of histologically confirmed tumors, large number of exposed cases with long duration of rotating shift work; and control for potential confounders. **Limitations:** Low response rate in controls, potential for
		Never (Reference)	-		
		Rotating	1.22 (1.04–1.43); 426		
		Permanent night	0.79 (0.62–1); 129		
		OR Cumulative duration of rotating shift work: quartiles and fixed categories		Same as above	

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		Never (Reference)	-		recall bias. Large proportion of missing data for shift work frequency. **Additional results:** When restricted to permanent night shift work for cumulative duration, there was no increased risk of colorectal cancer incidence by quartile or fixed category, both in base and full models. For age at first permanent shift work, results were reaching unity and non-significant when stratifying by age at first permanent shift work. **Confidence in evidence:** Evidence
		<8 years	1.14 (0.85–1.51); 89		
		8-19 years	1.12 (0.84–1.49); 87		
		20-34 years	1.38 (1.06–1.81); 119		
		35+ years	1.36 (1.02–1.79); 127		
		<15 years	1.19 (0.95–1.49); 147		
		15+ years	1.28 (1.06–1.56); 274		
		Trend-test *p*-value: 0.005 (quartiles)			
		OR Age at first rotating shift work		Same as above	
		Never (Reference)	-		
		<25 years	1.24 (0.99–1.56); 166		
		25+ years	0.95 (0.72–1.25); 99		
		OR Years since stopped rotating night shift work		Same as above	
		Never (Reference)	-		
		<15 years	1.12 (0.83–1.52); 89		
		15+ years	0.97 (0.76–1.24); 136		
		Colon only: OR Ever rotating and permanent night shift work		Same as above	
		Never (Reference)	-		
		Rotating	1.22 (1.02–1.46); 282		
		Permanent night	0.79 (0.6–1.11); 83		
		Rectum only: OR Ever rotating and permanent night shift work		Same as above	
		Never (Reference)	-		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
		Rotating	1.26 (0.99–1.58); 143		
		Permanent night	0.76 (0.53–1.11); 42		
Parent *et al.* 2012 Case-Control Montreal, Canada **Enrollment or follow-up:** 1979–1985	**Population:** Montreal population based occupational case-control study of cancer in men 35-70 years of age. Cases: 439; Controls: 512 **Exposure assessment method:** questionnaire	**Colon only: OR Ever, duration, and timing of night shift work**		Age, ancestry, education, family income, respondent status, smoking, BMI, alcohol, beta carotene, occupational exposure to aromatic amines	**Exposure information:** Ever, cumulative duration, and timing of night work (worked from 1:00 AM – 2:00 AM for 6+ months) **Strengths:** Possible to compare risks across cancer sites; complete population-based case-ascertainment system; histologic confirmation of primary cancers; large number of cases; detailed lifetime occupational histories; information on potential covariates; night definition likely to encompass a period pertinent to the hypothetical mechanism of carcinogenesis. **Limitations:** No screening, grade or severity information about colorectal cancer; approximately 18% of cases contributed information through proxies. **Additional results:** - **Confidence in evidence:** Evidence
		Never (Reference)	-		
		Ever (6+ months)	2.03 (1.43–2.89); 110		
		6 months - < 5 years	2.32 (1.47–3.68); 61		
		5-10 years	1.43 (0.73–2.8); 20		
		10+ years	2.11 (1.13–3.94); 29		
		≤ 20 years ago	2.5 (1.51–4.14); 53		
		< 20 years ago	2.08 (1.24–3.47); 45		
		Rectum only: OR Ever, duration, and timing of night shift work		Same as above	
		Never (Reference)	-		
		Ever (6+ months)	2.09 (1.4–3.14); 58		
		6 months - < 5 years	2.58 (1.53–4.33); 35		
		5-10 years	1.42 (0.64–3.18); 10		
		10+ years	1.67 (0.77–3.61); 12		
		≤ 20 years ago worked nights	2.27 (1.27–4.05); 25		
		20+ years ago worked nights	2.35 (1.32–4.02); 26		
Walasa *et al.* 2018 Case-Control Australia	**Population:** Western Australia Bowel Health Study (WABOHS). Cases: 350; Controls: 410	**Colorectal (Female): OR Ever and duration of graveyard shift work**		Age group, education level, socioeconomic status, lifetime cigarette smoking, alcohol intake 10 years ago	**Exposure information:** Ever and duration of graveyard and early shifts, LAN, phase shift, poor diet, physical inactivity, sleep disturbance, vitamin D status; CRC,
		Never (Reference)	-		
		Ever (0.1+ years)	1.06 (0.73–1.54); 73		

Reference, study-design, location, and year	Population description & exposure assessment method	Exposure category or level	Risk estimate (95% CI); exposed cases	Co-variates controlled	Comments, strengths, and weaknesses
Enrollment or follow-up: 2005–2007	**Exposure assessment method:** JEM	> 0 - <7.5 yeras	1.17 (0.73–1.88); 40		colon, and rectal cancers **Strengths:** Good sensitivity in regard to shift work characterization. Use of JEM allowed for standardized exposure definitions. **Limitations:** Poor response rates in cases and controls. Poor exposure characterization based on group-level information. In women, there was a small-to-moderate number of exposed cases. **Additional results:** Age-adjusted only model results and results when examining graveyard shift work and colon cancer only were similar. Graveyard shift exposure and rectal cancer was elevated but n.s. [OR: 1.38 (95% CI 0.81 - 2.33)]. Similar elevated risks were seen in shorter and longer durations. Ever exposure to shift work involving LAN and rectal cancer had an elevated but n.s. OR: 1.40 (95% CI: 0.83 - 2.38). Ever exposure to phase shift work and rectal cancer was elevated but n.s. [OR: 1.40 (95% CI: 0.82-2.38)]. **Confidence in evidence:** Null
		7.5+ years	0.95 (0.57–1.58); 33		
		Colorectal (Female): OR Ever and duration of shift work involving light at night (LAN)		Same as above	
		0 (Reference)	-		
		Ever (0.1+ years)	1.02 (0.7–1.48); 70		
		> 0 - <7.5 years	1.12 (0.69–1.81); 38		
		7.5+ years	0.91 (0.55–1.53); 32		
		Colorectal (Female): OR Ever and duration of phase shift work		Same as above	
		Never (Reference)	-		
		Ever (0.1+ years)	1 (0.69–1.45); 69		
		> 0 - <7.5 yeras	1.09 (0.68–1.76); 38		
		7.5+ years	0.89 (0.53–1.51); 31		

References

1. Jørgensen JT, Karlsen S, Stayner L, Andersen J, Andersen ZJ. 2017. Shift work and overall and cause-specific mortality in the Danish nurse cohort. *Scand J Work Environ Health* 43(2): 117-126. (Support not reported. Authors affiliated with University of Copenhagen, Denmark; University of Illinois at Chicago School of Public Health, IL; Danish Cancer Society, Denmark.)

2. Papantoniou K, Castaño-Vinyals G, Espinosa A, Turner MC, Alonso-Aguado MH, Martin V, Aragonés N, Pérez-Gómez B, Pozo BM, Gómez-Acebo I, Ardanaz E, Altzibar JM, Peiro R, Tardon A, Lorca JA, Chirlaque MD, García-Palomo A, Jimenez-Moleon JJ, Ierssen T, Ederra M, Amiano P, Pollan M, Moreno V, Kogevinas M. 2017. Shift work and colorectal cancer risk in the MCC-Spain case-control study. *Scand J Work Environ Health* 43(3): 250-259. (Supported by the "Accion Transversal del Cancer", approved on the Spanish Ministry Council on 11 October 2007, by the Instituto de Salud Carlos III-FEDER, by the Fundación Marqués de Valdecilla, by the ICGC International Cancer Genome Consortium CLL (The ICGC CLL-Genome Project is funded by Spanish Ministerio de Economía y Competitividad (MINECO) through the Instituto de Salud Carlos III (ISCIII) and Red Temática de Investigación del Cáncer (RTICC) del ISCIII), by the Junta de Castilla y León, by the Consejería de Salud of the Junta de Andalucía, by the Conselleria de Sanitat of the Generalitat Valenciana, by the Recercaixa, by the European Commission grants, by the Spanish Association Against Cancer (AECC) Scientific Foundation, by the Catalan Government DURSI grant, by a predoctoral grant PFIS, by FEDER, by the European Commission, by the the Catalan Government DURSI, and by the Canadian Institutes of Health Research. Authors affiliated with CREAL, Spain; Medical University of Vienna, Austria; IMIM, Spain; Universitat Pompeu Fabra, Spain; University of Ottawa, Canada; IDIBELL, Spain; Hospitalet de Llobregat, Spain; Universidad de León, Spain; Carlos III Health Institute, Spain; IIS Puerta de Hierro, Spain; Complejo Hospitales Universitarios de Granada, Spain; University of Cantabria, Spain; Instituto de Salud Publica de Navarra, Spain; Navarra Institute for Health Research, Spain; Public Health Division of Gipuzkoa, Spain; Biodonostia Research Institute, Spain; FISABIO, Spain; Universidad de Oviedo, Spain; CYSMA, Spain; Universidad de Huelva, Spain; IMIB-Arrixaca, Spain; Universidad Murcia, Spain; Universidad de Granada, Spain; University of Barcelona, Spain; CIBERESP, Spain.)

3. Papantoniou K, Devore EE, Massa J, Strohmaier S, Vetter C, Yang L, Shi Y, Giovannucci E, Speizer F, Schernhammer ES. 2018. Rotating night shift work and colorectal cancer risk in the nurses' health studies. *Int J Cancer*(ePub ahead of print). (Supported by CDC/NIOSH and NIH. Authors affiliated with Medical University of Vienna, Austria; Brigham and Women's Hospital, MA: Harvard Medical School, MA; Harvard T. H. Chan School of Public Health, MA; University of Colorado, CO; Chinese PLA General Hospital, China.)

4. Parent ME, El-Zein M, Rousseau MC, Pintos J, Siemiatycki J. 2012. Night work and the risk of cancer among men. *Am J Epidemiol* 176(9): 751-759. (Supported by the Health Canada, the National Cancer Institute of Canada, the Institut de recherche en santé et

sécurité au travail du Québec, the Fonds de la recherche en santé du Québec, and the Canadian Institutes of Health Research. Authors affiliated with INRS, Canada.)

5. Schwartzbaum J, Ahlbom A, Feychting M. 2007. Cohort study of cancer risk among male and female shift workers. *Scand J Work Environ Health* 33(5): 336-343. (Supported by the Swedish Council for Working Life. Authors affiliated with Ohio State University, OH; Karolinska Institutet, Sweden.)

6. Walasa WM, Carey RN, Si S, Fritschi L, Heyworth JS, Fernandez RC, Boyle T. 2018. Association between shiftwork and the risk of colorectal cancer in females: a population-based case-control study. *Occup Environ Med* 75: 344-350. (Supported by the Australian National Health and Medical Research Council, the University of Adelaide, NHMRC, and the Cancer Council Western Australia. Authors affiliated with Curtin University, Australia; University of Western Australia. Australia; University of Adelaide, Australia; University of South Australia, Australia.)

7. Yong M, Blettner M, Emrich K, Nasterlack M, Oberlinner C, Hammer GP. 2014. A retrospective cohort study of shift work and risk of incident cancer among German male chemical workers. *Scand J Work Environ Health* 40(5): 502-510. (Supported by the Deutsche Gesetzliche Unfallversicherung. Authors affiliated with BASF SE, Germany; Johannes Gutenberg University Mainz, Germany; Laboratoire National de Santé, Luxembourg.)