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 F: Shiftwork and Female Hormonal Cancer

August 24, 2018

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List of Tables

Appendix F: Female Hormonal Cancer Studies Tables

Appendix F encompasses tables related to human studies on shift work exposure and risk of female hormonal cancers, which include ovarian and endometrial cancers. Tables F-1a to F-1f provide ratings and the rationales for the domains of study quality and study sensitivity. Table F-2 gives detailed results for each evaluated epidemiological study.

Table F-1a. Evaluation of selection bias in female hormonal cancer studies.

Reference	Selection Bias rating
Carter *et al.* 2014	+++ ↔ The cohort is clearly defined by exposure status for a specific time period and location. Follow-up did not differ by exposure status.
Jørgensen *et al.* 2017	+ ? The cohort was clearly defined by exposed/non-exposed 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 yr 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.
Poole *et al.* 2011	+++ ? The cohort is clearly defined with no evidence that follow-up differed between exposed and non-exposed subjects. Given that this is a combination of Nurses' Health Study (NHS) and NHS-2, women are less likely to be selected out due to inability to adapt to shift work.
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.
Bhatti *et al.* 2013	+++ ↔ Cases and controls were selected from the same population using similar criteria. No evidence that selection of subjects was related to both exposure and disease. Known predictors of ovarian cancer in evidence in this population. Response rate was relatively high.
Viswanathan *et al.* 2007	++ ? The cohort is clearly defined by exposure status for a specific time period/location, with no evidence that follow-up differed between exposed and non-exposed subjects. There is no discussion of healthy worker survivor effect (HWSE) in this occupational cohort, although this is an older survivor cohort. If early exposure for long durations is a risk factor for colorectal cancer, this cohort would likely not be able to detect it.

Table F-1b. Evaluation of exposure assessment methods in female hormonal cancer studies.

Reference	Exposure Assessment rating
Carter *et al.* 2014	0 Exposure assessment methods have poor sensitivity and specificity leading to questionable classification of the unexposed. With no information on previous lifetime job history, it cannot be certain that those not currently working night shifts, never did so. No information on exposure level/frequency was available.
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.
Poole *et al.* 2011	++ The exposure assessment methods have less than moderate sensitivity and specificity with respect to rotating shifts, and have poor sensitivity in relation to ever worked nights. For NHS nurses, the shiftwork question was only asked once and not updated; however, sensitivity analysis indicated this would lead to a small misclassification of exposure. No data on permanent or less frequent rotating night shift work was collected; however, sensitivity analyses indicated that the effects of such bias were likely to be small. These issues would have biased results towards the null. Data on exposure was collected prior to diagnosis of cancer thus avoiding recall bias.
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.
Bhatti *et al.* 2013	++ The exposure methods have moderate sensitivity and specificity for distinguishing by exposure status. Starting at age 25 may have eliminated some with shift work early in their careers, meaning that the unexposed may not have been truly unexposed.
Viswanathan *et al.* 2007	++ The exposure assessment methods have less than ideal sensitivity and specificity with respect to rotating shifts, and have poor sensitivity in relation to ever working nights. Nurses working permanent night shifts may have misinterpreted the question and not classified themselves as working rotations, but rather as non-rotation workers, or did not answer the question. This would have biased results towards the null. Data on exposure was collected prior to diagnosis of cancer thus avoiding recall bias.

Table F-1c. Evaluation of outcome assessment in female hormonal cancer studies.

Reference	Outcome Assessment rating
Carter *et al.* 2014	++ ↔ Outcome methods distinguish between diseased and non-diseased subjects. However, as ovarian cancer is typically considered a heterogenous mix of tumor types, having no information on tumor type is less than ideal. Follow-up and diagnoses are conducted independently of one another.
Jørgensen *et al.* 2017	++ ? Reported causes of death were not histologically-confirmed, rather only based on physician report from death records.
Poole *et al.* 2011	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnoses were conducted independent of exposure status.
Schwartzbaum *et al.* 2007	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnoses are conducted independent of exposure status.
Bhatti *et al.* 2013	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects; subtypes and grade of tumors are reported, and cases were histologically verified.
Viswanathan *et al.* 2007	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnoses were conducted independent of exposure status.

Table F-1d. Evaluation of study sensitivity in female hormonal cancer studies.

Reference	Sensitivity rating
Carter *et al.* 2014	+ ? Adequate number of currently exposed subjects, but total exposure is unknown for these subjects and for the unexposed. Sufficient latency to detect cases.
Jørgensen *et al.* 2017	+ ? Small number of night and rotating shift ovarian cancer cases. Poor sensitivity of exposure status due to lack of level, duration, or range of exposure. Adequately long follow-up duration.
Poole *et al.* 2011	++ ? The study had a large number of exposed cases, but inadequate number in the younger cohort to capture effect from longer durations; intensity/level of exposure not addressed.
Schwartzbaum *et al.* 2007	+ ? Study has very small number of ever exposed ovarian cancer cases. No information about intensity or duration. Adequate duration of follow-up.
Bhatti *et al.* 2013	++ ? The study has adequate number of exposed cases ever working nights, and information on cumulative work/years of night shifts (short durations), but no information on intensity or type of shift rotations was available.
Viswanathan *et al.* 2007	++ ? The study had adequate numbers of exposed endometrial cancer cases and information on duration; but intensity/level of exposure not addressed.

Table F-1e. Evaluation of the potential for confounding bias in female hormonal cancer studies.

Reference	Confounding rating
Carter *et al.* 2014	+++ ↔ The study controlled for many potential confounders as well as age alone. The multivariable control while including many variables of no consequence to Ovarian cancer, were not materially different from the model controlling for age alone.
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.
Poole *et al.* 2011	+++ ↔ The study measured all relevant potential confounders and used appropriate analyses.
Schwartzbaum *et al.* 2007	+ ? The study did not measure potential confounders such as parity, smoking, or OC use.
Bhatti *et al.* 2013	+++ ↔ The study measured all relevant potential confounders and used appropriate analyses to address them.
Viswanathan *et al.* 2007	++ ? Models may have over-controlled by including variables in the pathway in the model: age at menarche and menopause, diabetes, hypertension, and body mass index (BMI).

Table F-1f. Evaluation of analysis and selective reporting in female hormonal cancer studies.

Reference	Analysis rating	Selective Reporting rating
Carter *et al.* 2014	+++ ↔ The study used relevant data and assumptions and methods of analysis.	+++ ↔ No evidence that reporting of the data or analyses were limited only to a subset of the data collected.
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.	+++ ↔ There isn't any evidence that data or analysis was limited to a subset of data.
Poole *et al.* 2011	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ There is no evidence that reporting of the data or analyses were 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.
Bhatti *et al.* 2013	++ ? The study used relevant data and appropriate assumptions and methods of analysis; however, "never" exposed were not consistently defined throughout the analysis, as in some analyses, exposed women with fewer night shifts were included in the "unexposed" category, biasing these analyses towards the null.	+++ ↔ No evidence that reporting of the data or analyses were limited to a subset of the data.
Viswanathan *et al.* 2007	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ There is no evidence that reporting of the data or analyses were limited to only a subset of the data that were collected.

Table F-2. Evidence from epidemiological cohort and case-control studies on female hormonal 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
Ovarian Cancer					
Carter *et al.* 2014 Cohort U.S. **Enrollment or follow-up:** 1982-2010	**Population:** Cancer Prevention Study II (CPS-II) cohort 161,004 employed women **Exposure assessment method:** questionnaire	**RR Ever worked rotating, fixed evening or night shifts**		Age, OC use, age at menarche, age at menopause, tubal ligation, parity, HRT use, race, family history of breast/ovarian ca, exercise, BMI, height	**Exposure information:** Fixed day, rotating shift workers, fixed aft/evening workers, fixed night workers. **Strengths:** Large prospective population based study of fatal ovarian cancer. **Limitations:** Exposure classification based only on current job; ovarian cancer based on fatal cases with no differentiation by type. **Additional results:** Results from age-adjusted model are similar to fully-adjusted model. **Confidence in evidence:** No confidence; not included in assessment.
		Fixed day (Reference)	-		
		Rotating	1.27 (1.03–1.56); 101		
		Fixed afternoon/evening	0.62 (0.34–1.12); 11		
		Fixed night	1.12 (0.67–1.87); 15		
Jørgensen *et al.* 2017 Cohort	**Population:** Danish Nurses Cohort (DNC) 28,731 women	**HR Ever day, night, and rotating shifts**		Age, smoking status, pack years, physical activity, BMI, alcohol	**Exposure information:** Ever evening, night, rotating shifts **Strengths:**
		Day (Reference)	-		
		Night	0.63 (0.22–1.78); 4		

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
Denmark **Enrollment or follow-up:** 1993-2013	**Exposure assessment method:** questionnaire	Rotating	0.64 (0.35–1.16); 13	consumption, diet (veggies, fruit, meat), pre-existing disease (hypertension, diabetes, MI), self-reported health, stressful work enviornment, marital status, parity, age at first birth, use of HRT, OC use	Nationwide prospective cohort of female nurses with detailed information on work schedules at baseline, and potential confounders. **Limitations:** Small numbers of ovarian cancer deaths, no information on duration or intensity, type of rotations, or past information on night work. No cancer validation. **Additional results:** Age-adjusted model results are similar to adjusted model results. **Confidence in evidence:** No confidence, not included in the assessment
Poole *et al*. 2011 Cohort 11 U.S. states **Enrollment or follow-up:** NHS: 1976 (enrolled), 1988–2008 (follow-up); NHS-2 1989–2007	**Population:** Nurses' Health Study (NHS and NHS-2) 181,548 women (NHS = 68,999; NHS-2 = 112,549) **Exposure assessment method:** questionnaire	**HR NHS & NHS-2: Duration of rotating night shift work**		Age, OC duration, parity, BMI, smoking status, tubal ligation history, menopausal status, fam hx ovarian ca, breastfeeding duration, cohort	**Exposure information:** Ever and duration of rotating shift work **Strengths:** Large number of ovarian cancer cases in a large prospective study of nurses with well-documented follow-up procedures and outcome definitions, with adequate data on potential confounders. Analyses to address healthy worker survival were conducted. **Limitations:** Exposure assessment may have biased results towards the null as permanent night workers may have been classified as unexposed in NHS. **Additional results:** Multivariate adjusted: Combined NHS and NHS-2 cohorts. Hazard ratio (HR) for age-adjusted model was similar for combined. **Confidence in evidence:** Some evidence
		None (Reference)	-		
		1–2 yr	1.07 (0.89–1.29); 197		
		3–5 yr	0.9 (0.72–1.13); 115		
		6–9 yr	0.92 (0.68–1.25); 51		
		10–14 yr	1.14 (0.81–1.6); 39		
		15–19 yr	1.28 (0.84–1.94); 24		
		20+ yr	0.8 (0.51–1.23); 22		
		Trend-test *p*-value: 0.74			
		HR NHS: Duration of rotating night shift work		Same as above	
		None (Reference)	-		
		1-2 years	1.2 (0.97–1.49); 143		
		3-5 years	0.95 (0.73–1.23); 80		
		6-9 years	0.96 (0.67–1.4); 33		

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
		10-14 years	1.06 (0.7–1.62); 25		
		15-19 years	1.3 (0.81–2.1); 19		
		20+ years	0.88 (0.56–1.37); 22		
		Trend-test *p*-value: 0.84			
		HR NHS2: Duration of rotating night shift work		Same as above	
		None (Reference)	-		
		1-2 years	0.8 (0.56–1.14); 54		
		3-5 years	0.79 (0.52–1.18); 35		
		6-9 years	0.8 (0.47–1.35); 18		
		10-14 years	1.25 (0.7–2.24); 14		
		15-19 years	1.21 (0.48–3.02); 5		
		Trend-test *p*-value: 0.78			
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 **Exposure assessment method:** JEM	**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 women in diverse industries followed for 19 years. **Limitations:** Very small number of ovarian cancer cases. Aggregate exposure data, lack of data on potential confounders or co-exposures such as smoking and diet. **Additional results:** - **Confidence in evidence:** No confidence, not included in the assessment.
		1970	0.8 (0.45–1.32); 15		
		1960 and 1970	1.13 (0.49–2.23); 8		

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
Bhatti *et al.* 2013 Case-Control Western Washington State U.S. **Enrollment or follow-up:** 2002–2009	**Population:** Population-based case control study Cases: 1,490 (1,101 invasive, 389 borderline); Controls: 1,832 **Exposure assessment method:** questionnaire	**Invasive tumors: OR Ever and cumulative duration of night shift work**		Age, county, reference year, OC duration, parity, BMI at age 30	**Exposure information:** Ever and cumulative night shift work years **Strengths:** Large population-based study of ovarian cancer, and subtypes; comprehensive data on nightshift schedules, complete data on confounders, and high participation rates. **Limitations:** Exposure assessment metrics did not adequately capture features of night shift work that could could help evaluate levels or intensity of circadian disruption. **Additional results:** - **Confidence in evidence:** Evidence
		Never (Reference)	-		
		Ever	1.24 (1.04–1.49); 293		
		4 mo–1 nightshift work-years	1.03 (0.72–1.47); 55		
		>1–3 nightshift work-years	1.13 (0.82–1.54); 75		
		>3 –7 nightshift work-years	1.95 (1.41–2.68); 94		
		>7 nightshift work-years	1.02 (0.74–1.42); 68		
		Borderline tumors: OR Ever and cumulative duration of night shift work		Same as above	
		Never (Reference)	-		
		Ever	1.48 (1.15–1.9); 126		
		4 months - 1 year	1.44 (0.9–2.29); 27		
		>1 - 3 years	1.33 (0.87–2.02); 35		
		>3 - 7 years	2.37 (1.57–3.57); 44		
		>7 years	0.97 (0.58–1.61); 20		
Endometrial cancer					
Viswanathan *et al.* 2007 Cohort 11 U.S. states **Enrollment or follow-up:**	**Population:** Nurses' Health Study (NHS) 53,487 women **Exposure assessment method:** questionnaire	**RR Duration of rotating night shift work**		Age, age at menarche, age at menopause, parity, BMI, OC duration, HRT duration, hypertension,	**Exposure information:** Women who had never worked rotating shifts accounted for 40.4% of person-years of follow-up; 1–14 years = 52.2%; 15–29 years = 5.6%; 30+ years =1.8%. **Strengths:**
		Never (Reference)	-		
		1–9 yr	0.89 (0.74–1.08); 224		
		10–19 yr	1.06 (0.76–1.49); 43		
		20+ yr	1.47 (1.03–2.1); 38		

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
NHS: 1976 (enrolled); 1988–2004 (follow-up)		Trend-test *p*-value: 0.04		diabetes, park-years of smoking	Large prospective study of nurses with well documented follow-up procedures and outcome definitions, with adequate data on potential confounders. **Limitations:** Exposure assessment may have biased results towards the null as permanent night workers may have been classified as unexposed. No analyses on HWSE in this occupational cohort. **Additional results:** Results similar in age-adjusted model **Confidence in evidence:** Evidence

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