National Toxicology Program
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Draft Report on Carcinogens Monograph on Light at Night

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

Appendix D: Shiftwork and Prostate Cancer

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List of Tables

Appendix D: Prostate Cancer Studies Tables

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

Table D-1a. Evaluation of selection bias in human prostate cancer studies.

Reference	Selection Bias rating
Åkerstedt *et al.* 2017	++ ? The cohort is clearly defined, and no evidence suggests follow-up differed by exposure status. The study did not account for HWE due to lack of information on work history on this older population.
Behrens *et al.* 2017	++ ? The cohort is clearly defined for a specific time period and geographic location. No evidence that follow-up differed by exposure status. Higher prostate cancer risk in individuals lost to follow-up may be due to shift work and may be biasing results toward the null. To account for HWE, shift work information was censored after baseline questionnaires.
Dickerman *et al.* 2016	+++ ? The prospective cohort is clearly defined as to its source and population, and given it is not an occupational cohort is not susceptible to HWSE. The authors were interested in the influence of midlife circadian-related exposures on prostate cancer risk and mortality later in life; thus, the mean age of the cohort at baseline questionnaire (mean age 40) ignores any effect from early life exposures and early prostate cancer.
Gapstur *et al.* 2014	+++ ? The cohort is clearly defined with a relevant exposed, non-exposed and referent group, and no evidence that follow-up differed between the groups. General population cohort so less concern with HWSE, however, this is still a survival cohort.
Hammer *et al.* 2015	++ ? The cohort is clearly defined and includes the relevant exposed and unexposed populations for a specific time period and location. HWE may be induced through ongoing selection based on health-related criteria into, or out of, shift or day work. To correct a potential on-going selection due to differentially declining health status, the authors included a term for employment duration in regression models as a proxy for work-related health effects.
Kubo *et al.* 2006	++ ? The cohort is clearly defined with no evidence that follow-up differed between exposed and non-exposed subjects. There is no discussion of healthy worker effect (HWE) or healthy worker survivor effect (HWSE) in this cohort of survivors.
Kubo *et al.* 2011	+ ↔ Cohort is selected from a larger cohort to avoid selection bias by potential for prostate cancer screening (recent prostate-specific antigen [PSA] screening in health checkups). Follow-up significantly differed between unexposed and exposed subjects because shift workers entered the database earlier. HWSE is also possible if previous shift workers with prostate cancer symptoms were more likely to become day workers, die, or be excluded.

Reference	Selection Bias rating
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.
Conlon *et al.* 2007	++ ↔ Cases and controls were selected from same population; however, low response rates, especially in controls, may have produced a non-representative control group; unrealistically high proportion of controls and cases who normally worked rotating shifts (44% and 49% respectively); and insufficient information to evaluate impact of differential screening of cases and controls.
Papantoniou *et al.* 2015	++ ↔ Cases and controls were selected from the same general population with controls being randomly selected. Lower response rate by controls may be related to ongoing shift work at night, which may impact the directionality of selection bias in either direction.
Parent *et al.* 2012	+++ ↔ Cases and controls selected from the same population using similar criteria; 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.
Tse *et al.* 2017	++ ↔ Cases and controls were selected from the same population using similar methods and criteria. There is no evidence that selection was related to both exposure and disease. Cases ages were similarly distributed to the Hong Kong Cancer Registry. Hospital controls (i.e. colorectal and pancreatic diseases) may not have been an appropriate comparator group and may have biased results toward the null.
Wendeu-Foyet *et al.* 2018	+++ ↔ Differences in controls was minimized by socioeconomic status (SES) matching, and expected and realized recruitment of cases were similar. Proportion of night shift workers in study population was similar to general French population.

Table D-1b. Evaluation of exposure assessment methods in human prostate cancer studies

Reference	Exposure Assessment rating
Åkerstedt *et al.* 2017	+ ? Exposure assessment methods were less than ideal; the singular question used to determine exposure status is subject to exposure misclassification. For those considered unexposed, it is unknown what type of work patterns they engaged in (day/shift/evening). Night work was not clearly defined. If the unexposed were actually exposed, this will bias results toward the null.
Behrens *et al.* 2017	+++ ? The exposure assessment methods have good sensitivity and specificity, leading to reliable classification with respect to ever/never exposure, shift and night work, exposure duration, and time-to-event. Although 18% of participants had less-detailed shift-work information, results from sensitivity analysis excluding these participants did not see a change in risk estimates.

Reference	Exposure Assessment rating
Dickerman *et al.* 2016	0 ? Critical concern for exposure assessment methods, as current night work exposure is captured without additional information on prior work history.
Gapstur *et al.* 2014	0 ? Critical concern for exposure assessment methods, as current night work exposure is captured without additional information on prior work history.
Hammer *et al.* 2015	+ ? Detailed information on shift work schedule and intensity were used. Years of shift work were 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.
Kubo *et al.* 2006	+ ? Exposure methods are not able to discriminate well between exposed and unexposed. Restricting the question about shift work to the longest held type of schedule with no information on duration or intensity or timing of this longest schedule, the length and timing of other schedules is unknown both for the exposed and unexposed, thus rendering overall exposure incomplete.
Kubo *et al.* 2011	++ ↔ Exposure assessment methods have good sensitivity and specificity for discriminating ever-exposure and exposure level within this highly selected group. No measure of duration was included. Work schedules were recorded at the time of annual health checkups, so any short-term rearrangements were missed.
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.
Conlon *et al.* 2007	++ ? Exposure assessment methods are clearly defined and reflect information about rotating shift work, duration and timing (age started and years since stopped). Given the large difference in response rates, there is some likelihood of recall bias.
Papantoniou *et al.* 2015	++ ? Exposure assessment methods were sufficient to differentiate exposed and unexposed with respect to ever-exposure, duration, and frequency. However, there was a higher percentage of cases with missing information on cumulative frequency.
Parent *et al.* 2012	++ ? Exposure methods reliably discriminate between ever and never exposed. However, no information was gathered on frequency or types of shifts, 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.
Tse *et al.* 2017	+ ? The exposure methods reliably distinguish between ever and never exposure to shift work. No information was given on exposure level, timing, intensity, or types of shift work schedules. Potential for recall bias.

Reference	Exposure Assessment rating
Wendeu-Foyet *et al.* 2018	+++ ↔ Exposure assessment methods were sufficient to differentiate between exposed and unexposed.

Table D-1c. Evaluation of outcome assessment in human prostate cancer studies.

Reference	Outcome Assessment rating
Åkerstedt *et al.* 2017	+++ ↔ Outcome methods distinguish between diseased and non-diseased using either a physician-diagnosed registry or a cause of death standardized register. Prostate specific antigen (PSA), staging, or other specific outcome data were not reported.
Behrens *et al.* 2017	++ ↔ Outcome methods distinguish between diseased and non-diseased in the cohort. Follow-up and diagnoses were conducted independent of exposure status. Self-reported prostate cancer data were used in this study, which is subject to misclassification. No information was provided on tumor stage or grade.
Dickerman *et al.* 2016	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects; follow-up and diagnosis conducted independent of exposure status.
Gapstur *et al.* 2014	++ ↔ Outcome methods distinguish between subjects with and without prostate cancer deaths; follow up and diagnoses appear to be conducted independent of exposure. no information on screening differences.
Hammer *et al.* 2015	++ ? 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 (only 80% complete), some cases may have been missed, although it is likely that this is non-differential, leading to a bias towards the null.
Kubo *et al.* 2006	++ ↔ Cancer registry linkage should provide adequate data to distinguish diseased and non-diseased; however, for prostate cancer, there is variability in diagnosis, thus more information regarding the classification of malignant tumors, would have been desirable. Follow-up and diagnosis were conducted independent of exposure status.
Kubo *et al.* 2011	+ ? Information about outcome methods are not sufficient to determine how the disease classification was made, only that disease classification was noted in health insurance records. If this was incomplete, a bias towards the null would be likely; outcome methods only explored company records, not national or regional death records.
Schwartzbaum *et al.* 2007	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Follow-up and diagnoses are conducted independent of exposure status.
Conlon *et al.* 2007	++ ↔ Outcome methods distinguish overall diseased and non-diseased subjects, but lack of information on stage and screening limit the usefulness of this prostate cancer study; diagnoses conducted independent of exposure.

Reference	Outcome Assessment rating
Papantoniou *et al.* 2015	+++ ↔ Histopathological confirmation of prostate cancer with accompanying clinical information (i.e., PSA, Gleason scores) for cases distinguishes between diseased and non-diseased subjects. Diagnosis was conducted prior to the determination of exposure status.
Parent *et al.* 2012	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects. Diagnosis conducted independent of exposure status.
Tse *et al.* 2017	+++ ? Outcome methods distinguish between prostate and non-prostate cancers. Tumor grade, stage, and PSA scores were also collected.
Wendeu-Foyet *et al.* 2018	+++ ↔ Outcome methods clearly distinguish between diseased and non-diseased subjects.

Table D-1d. Evaluation of study sensitivity in human prostate cancer studies.

Reference	Sensitivity rating
Åkerstedt *et al.* 2017	+ ? The study has an intermediate size of exposed cases and a small number with a long duration. Apart from ever- and duration of exposure, no information was provided further characterizing type and timing exposure. Follow-up on this older cohort was short.
Behrens *et al.* 2017	++ ? Small number of exposed cases. Study had good sensitivity regarding ever- exposure, shift vs. night work, duration of exposure, time-to-event, stratification by preferred midpoint of sleep, and vitamin D status. No information on shift schedules.
Dickerman *et al.* 2016	+ ? Exposure level limited to current job at prospective period in order to look at night work exposure in midlife. The study has an adequate number of incident cases exposed to rotating work. No information on level, duration, or intensity. Follow-up is adequate to detect prostate cancer, particularly in this older population (mean age at entry was 40).
Gapstur *et al.* 2014	+ ? The study has an adequate number of deaths but with unknown exposure level, duration, or timing; and follow-up was adequate (up to 28 years). Insensitive to any relationship of early exposure and prostate cancer, or to duration or frequency of shift work.
Hammer *et al.* 2015	+ ↔ Adequate number of exposed subjects; workers were an average ~50 years of age at end of follow-up, so relatively young for a study of prostate cancer. Elevated SIRs for both shift and day workers compared to the population may indicate detection bias in this population. No information level, duration, or range.
Kubo *et al.* 2006	+ ? The study has a very small number of exposed subjects with unknown exposure level (e.g., level, duration, or timing); duration of follow-up is inadequate. Young cohort followed for only 8 years.

Reference	Sensitivity rating
Kubo *et al.* 2011	+ ? The study has a very small number of exposed cases with substantial duration, and cancer was not assessed in a window when prostate cancer is common.
Schwartzbaum *et al.* 2007	+ ↔ Adequately long follow-up period for incident prostate cancer. Large number of exposed cases for men. However, poor categorization of level, duration, and range of exposure to shift work due to the nature of non-specific registries.
Conlon *et al.* 2007	++ ↔ The study has an adequate number of exposed subjects with substantial exposure (30+ years), but little information on frequency or type of rotation.
Papantoniou *et al.* 2015	++ ? The study has an adequate number of exposed subjects with substantial frequency, duration, and variability of shift work. Additionally, the study was able to examine chronotype and severity of disease. There is potential for inadequate latency duration for the development of prostate cancer given the range in age (27-85 years old) of cases and controls.
Parent *et al.* 2012	++ ? The study has a moderate number of exposed prostate cancer cases, but no information on intensity/frequency or pattern of exposure (e.g., type of shifts); or screening information.
Tse *et al.* 2017	+ ↔ The study has a small number of ever-exposed prostate cancer cases. Apart from ever vs. never exposure, no information was given on level, type, duration, frequency, or other metrics associated with shift work.
Wendeu-Foyet *et al.* 2018	+++ ↔ Moderate-to-large number of exposed prostate cancer cases. Study was highly sensitive and examined shift work exposure and prostate cancer aggressiveness via numerous metrics.

Table D-1e. Evaluation of potential for confounding bias for human prostate cancer studies.

Reference	Confounding rating
Åkerstedt et al. 2017	Prostate: +++ ↔ The study measured relevant potential confounders and used appropriate analysis to address them.
Behrens et al. 2017	Prostate: +++ ↔ The study measured relevant potential confounders and used appropriate analysis to address them. Study presented multiple models to allow for parsimonious and full models.
Dickerman et al. 2016	Prostate: +++ ↔ The study measured all relevant potential confounders and used appropriate analyses to address them.
Gapstur et al. 2014	Prostate: ++ ? Potential confounders were measured and presented either as age or multivariate adjustments. Employment status (present in the cohort or left) is a potential confounder in this study, but not measurable.
Hammer et al. 2015	Prostate: +++ ↔ The study measured relevant potential confounders (age and job level which

Reference	Confounding rating
	varied between exposed and non-exposed) and used appropriate analyses to address them.
Kubo et al. 2006	Prostate: +++ ↔ The study measured all relevant potential confounders and also ran models with dietary variables including meat consumption (not shown in paper). For rotating shift work, the model with just age yielded equivalent results to the full model.
Kubo et al. 2011	Prostate: +++ ↔ The study measured all relevant potential confounders (e.g., age).
Schwartzbaum *et al.* 2007	Prostate: +++ ↔ The study measured all relevant potential confounders and appropriate analyses to address them.
Conlon *et al.* 2007	Prostate: +++ ↔ The study measured all relevant potential confounders and used appropriate analyses to address them
Papantoniou *et al.* 2015	Prostate: +++ ↔ The study measured all releveant potential confounders and used appropriate analyses to address them.
Parent *et al.* 2012	Prostate: ++ ? The study measured all relevant potential confounders and used appropriate analyses to address them; however, model possibly over-controlled for variables not related to prostate cancer (e.g., smoking, physical activity, education, farming, alcohol, body mass index [BMI] that may bias estimates toward the null.
Tse *et al.* 2017	Prostate: +++ ↔ The study measured relevant potential confounders and used appropriate analysis to address them. Study used a parsimonious "base" model to increase statistical power.
Wendeu-Foyet *et al.* 2018	Prostate: +++ ↔ The study measured all releveant potential confounders and used appropriate analyses to address them.

Table D-1f. Evaluation of analysis and selective reporting for human prostate cancer studies.

Reference	Analysis rating	Selective Reporting rating
Åkerstedt *et al.* 2017	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ No evidence that reporting of the data or analyses were limited to a subset of the data collected.
Behrens *et al.* 2017	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ No evidence that reporting of the data or analyses were limited to a subset of data collected.
Dickerman *et al.* 2016	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ No evidence that reporting of data or analyses were limited to only a subset of the data collected.
Gapstur *et al.* 2014	+++ ?	+++ ↔

Reference	Analysis rating	Selective Reporting rating
	The study used relevant data and appropriate assumptions and methods of analysis	No evidence that reporting of the data were limited to a subset of the data collected.
Hammer *et al.* 2015	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ No evidence that reporting of the data or analyses were limited to a subset of data collected.
Kubo *et al.* 2006	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ No evidence that selective reporting of data or analyses were limited to subsets of the data collected.
Kubo *et al.* 2011	+ ? The study used relevant data but choice of model may not have been ideal, as the hazard ratio (HR) and odds ratio (OR) are equal for short follow-up periods, but the ORs increases in magnitude compared with the HR when the follow-up is extended as in this study. The use of logistic regression in studies with long follow-up time instead of the Cox proportional hazards models tends to bias results away from the null.	++ ↔ Reporting of data were limited to a subset of the data that were collected. While this may have been to test a 3-shift system against no shifts, no data on 2-shift systems were shown.
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.
Conlon *et al.* 2007	++ ↔ The study used relevant data; however, assumptions and methods of analysis unclear.	+++ ↔ No evidence that reporting of the data were limited to a subset of the data collected.
Papantoniou *et al.* 2015	+++ ↔ The study used relevant data, appropriate assumptions and methods for analysis.	+++ ↔ No evidence that reporting of the data or analyses were limited to a subset of the data collected.
Parent *et al.* 2012	+++ ↔ Study used relevant data, and appropriate assumptions and methods of analysis.	+++ ↔ No evidence that reporting of the data or analyses were limited to a subset of data collected.
Tse *et al.* 2017	+++ ↔ The study used relevant data and appropriate assumptions and methods of analysis.	+++ ↔ No evidence that reporting of the data or analyses were limited to a subset of data collected.
Wendeu-Foyet *et al.* 2018	+++ ↔ The study used relevant data and appropriate assumptions and methods	+++ ↔ No evidence that reporting of the data or analyses were limited to a

Reference	Analysis rating	Selective Reporting rating
	of analysis.	subset of data collected.

Table D-2. Evidence from epidemiological cohort and case-control studies on prostate 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
Åkerstedt *et al.* 2017 Cohort Sweden **Enrollment or follow-up:** 1998–2003; follow-up until 12/31/2010	**Population:** Swedish Twin Registry (STR) Cohort 12 ,322 men **Exposure assessment method:** questionnaire	**HR Ever and duration of night work: complete follow-up**		Age, education, tobacco consumption, BMI, having children, coffee consumption, previous cancer	**Exposure information:** Night shift work 1–45 years; night not defined. **Strengths:** Data linkage study from a unique twin cohort of men. **Limitations:** Poor exposure characterization can lead to substantial misclassification. No information on timing of exposure. Moderate number of exposed cases. Longer duration of follow-up after baseline is desired considering mortality data was used. **Additional results:** Results from unadjusted models and models restricting follow-up to 60 years old were similar to adjusted models. **Confidence in evidence:** Null
		0 yr (Reference)	-		
		Ever	0.91 (0.74–1.12); 160		
		1–5 yr	0.86 (0.63–1.17); 55		
		6–10 yr	1.09 (0.74–1.61); 31		
		11–20 yr	1.12 (0.78–1.63); 38		
		21–45 yr	0.72 (0.5–1.05); 36		
Behrens *et al.* 2017 Cohort Ruhr area, Germany **Enrollment or follow-up:** 2000–2003	**Population:** Heinz-Noxdorf Recall (HNR) Cohort Study 1,757 men **Exposure assessment method:** questionnaire	**HR Ever and duration of shift work**		Age at event, smoking status, family history of prostate cancer, education, income	**Exposure information:** Ever exposure and duration, stratified by night and shift work, preferred midpoint of sleep, and vitamin D status **Strengths:** Good sensitivity regarding duration of exposure. Examined night and shift work separately. Unique consideration of sleep preferences and vitamin D status as modifying factors. Had both baseline and follow-up information. Exposure categorized by time of day.
		Never/<1 yr (Reference)	-		
		Ever: 1+ yr	2.29 (1.43–3.67); 38		
		1–<10 yr	1.87 (0.99–3.55); 13		
		10–<20 yr	2.18 (1.01–4.72); 8		
		20+ yr	3.08 (1.67–5.69); 17		

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: 0.0001			**Limitations:** Small number of exposed cases. Potential for recall bias given retrospective analysis. Higher prostate cancer risk not included in the cohort. **Additional results:** - **Confidence in evidence:** Evidence
		HR Ever and duration of night work		Same as above	
		0-<1 yr (Reference)	-		
		Ever: 1+ yr	2.27 (1.42–3.64); 32		
		1–<10 yr	1.72 (0.88–3.35); 11		
		10–<20 yr	1.68 (0.66–4.26); 5		
		20+ yr	3.76 (2.04–6.93); 16		
		Trend-test *p*-value: <0.0001			
		HR Ever exposure to night shift work among early sleepers		Same as above	
		0-<1 yr (Reference)	-		
		Ever night work (1+ years)	6.43 (1.81–22.8); 7		
		HR Ever exposure to night shift work among intermediate sleepers		Same as above	
		0-<1 yr (Reference)	-		
		Ever night work (1+ years)	2.3 (1.22–4.35); 18		
		HR Ever exposure to night shift work among late sleepers		Same as above	
		0-<1 yr (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
		Ever night work (1+ years)	1.42 (0.33–6.2); 3		
Dickerman *et al.* 2016 Cohort Finland **Enrollment or follow-up:** 1981-2012	**Population:** Older Finnish Twin Cohort study 11,370 male twins **Exposure assessment method:** questionnaire	**Incidence: HR Type of shift work**		Age, education, BMI, physical activity, social status, smoking status, alcohol consumption, snoring, zygosity	**Exposure information:** Rotating shift pattern of morning, evening or night in 2- or 3-shift patterns; fixed nights **Strengths:** Prospective population-based design, long duration of follow-up, complete outcome data from registry linkage, high initial question response rate, use of within-family analysis with a twin-co-twin design. Information on chronotype incorporated. **Limitations:** Definition of shift work is limited to current job and metrics limited in order to restrict study to exposures during midlife. **Additional results:** Age-adjusted results are similar in models examining prostate cancer incidence and mortality **Confidence in evidence:** No confidence, not included in the assessment.
		Day (Reference)	-		
		Night	0.5 (0.1–1.9); 2		
		Rotating	1 (0.7–1.2); 80		
		Mortality: HR Type of shift work		Same as above	
		Day (Reference)	-		
		Rotating	0.8 (0.3–1.5); 11		
		Incidence: HR Shift type and chronotype			
		Day, definite morning chronotype (Reference)	-		
		Rotating, definite morning chronotype	1 (0.7–1.5); 26		
		Rotating, somewhat morning chronotype	0.5 (0.3–1); 12		
		Rotating, somewhat evening chronotype	1.5 (1–2.2); 29		
		Rotating, definite evening chronotype	1.5 (0.8–2.9); 10		
Gapstur *et al.* 2014	**Population:** American Cancer Society	**HR Ever rotating and permanent night shift work**		Age, race, education, BMI,	**Exposure information:** Fixed nights (started work 9 PM-12 AM),

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
Cohort 50 states in the U.S. **Enrollment or follow-up:** 1982-2010	II (ACS-II) Study 305,057 men **Exposure assessment method:** questionnaire	Fixed day (Reference)	-	smoking status, family history of prostate cancer, painful/frequent urination	fixed day (started working 6AM- 10AM), fixed afternoon/evening (started work 2pm - 4pm); rotating (not clearly defined) **Strengths:** Prospective design, large, nationwide sample of employed men, ability to adjust for potential confounders. **Limitations:** Exposure information limited to current employment at baseline thus adds information only for midlife exposures on later prostate cancer. **Additional results:** Age-adjusted estimates are similar **Confidence in evidence:** No confidence, not included in the assessment.
		Rotating	1.08 (0.95–1.22); 268		
		Fixed night	0.72 (0.44–1.18); 16		
Hammer *et al.* 2015 Cohort Germany **Enrollment or follow-up:** 1995–2005; follow-up: 2000–2009	**Population:** Male chemical production workers in Rhineland-Palatinate Germany 27,828 employed men **Exposure assessment method:** company records	**Internal analysis: HR (RR)**		Age	**Exposure information:** Ever worked forward rotating shift work pattern: either 3 x 12 hours (day, off, night) or 4 x 12 (day, off, off, night) **Strengths:** Large retrospective cohort with adequate number of cases based on personnel records, with balanced numbers of daytime and shift workers from the same parts of the company and with the same working conditions, thus comparable in terms of risk profile, age, and SES. **Limitations:** Limited follow-up due to availability of data at cancer registry; exposure assessment does not include lifetime exposure to shift work; cancer case reporting is somewhat
		Daytime (Reference)	-		
		Rotating (all stages)	0.93 (0.73–1.18); 146		
		Stage T1	1.26 (0.44–3.86); 10		
		Stage T2	0.84 (0.62–1.15); 84		
		Stage T3	0.9 (0.53–1.52); 32		
		Stage T4	1.36 (0.25–6.18); 3		
		Stage T Unknown	1.42 (0.64–3.19); 17		

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
					less than complete; and stage was incomplete for 25%–30% of subjects. This was a young cohort to detect prostate cancer; potential detection bias for external analysis. **Additional results:** Sensitivity analyses controlled for smoking, type of job (manual or professional), and/or duration of employment (<20 vs. >20 years) in models; risk estimates did not greatly differ. **Confidence in evidence:** Null
Kubo *et al.* 2006 Cohort Japan **Enrollment or follow-up:** 1988–1990	**Population:** Japan Collaborative Cohort (JACC) Study for Evaluation of Cancer Risk 14,052 men **Exposure assessment method:** questionnaire	**RR (Hazard ratio) Ever rotating and permanent night shift work** Daytime (Reference) Rotating Fixed night	 - 3 (1.2–7.7); 7 2.3 (0.6–9.2); 3	Age, study area, BMI, smoking, alcohol consumption, job type, physical activity at work, workplace, perceived stress, education, marital status, family history of prostate cancer	**Exposure information:** Rotating and fixed night work, not defined **Strengths:** Nationwide sample of workers, complete collection of potential confounders. **Limitations:** Incomplete exposure histories leading to likely misclassification; short follow-up time for prostate cancer; no discussion of the impact of healthy worker survivor effect (HWSE) on this restricted set of current workers; low statistical power. **Additional results:** Authors states similar findings found in additional analysis using data for an additional 15,906 working men aged 40–79 years with 55 total cases of prostate cancer; although the number of exposed cases were not reported. Author could not provide additional information upon follow-up. **Confidence in evidence:**

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
					Some evidence
Kubo *et al.* 2011 Cohort Japan **Enrollment or follow-up:** Records from 2006–2008	**Population:** Industry-based retrospective manufacturing cohort 4,995 male workers **Exposure assessment method:** company records	**RR Ever worked rotating shifts**		Age, BMI, alcohol consumption, exercise, marital status, smoking status	**Exposure information:** Ever exposure (counterclockwise 3-shift system for 80%+ of career, vs. day workers) **Strengths:** High-quality long-term work schedule information from industry records; annual health records from the same health plan and annual prostate-specific antigen (PSA) exams. Homogeneity in socioeconomic status (SES) and healthcare access. **Limitations:** Small number of exposed cases; follow-up did not extend past the age of 65 years when prostate cancer is common; analytic method may not have been appropriate; highly selected group of survivors with no information on HWSE. **Additional results:** Estimates from age-adjusted model are similar **Confidence in evidence:** Inconclusive
		Daytime (Reference)	-		
		Rotating	1.79 (0.57–5.68); 4		
Schwartzbaum *et al.* 2007 Cohort Sweden **Enrollment or follow-up:** enrollment: 1977-1981; follow-up:	**Population:** Swedish working men registered in 1960 and 1970 census data. 2,101,126 men **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:** Large number of exposed cases in a nationwide cohort of men in diverse industries followed for 19 years. **Limitations:**
		1970	1.04 (0.99–1.1); 1319		

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
1971-1989					Aggregate exposure data, lack of data on potential confounders or co-exposures. **Additional results:** Similar results seen when restricted to participants in 1960 and 1970 census **Confidence in evidence:** No confidence, not included in the assessment.
Conlon *et al*. 2007 Case-Control Northeastern Ontario, Canada **Enrollment or follow-up:** 1995–1998	**Population:** Population based case-control study Cases: 760; Controls: 1,632 **Exposure assessment method:** questionnaire	**OR Ever and duration of full-time rotating shift work**		Age, family history of prostate cancer	**Exposure information:** Ever rotating shift work; duration of full-time rotating work; age first began working full time rotating shift; age working fulll-time rotating shift; years since full-time rotating shift **Strengths:** Large population-based case-control study with adequate numbers of cases working rotating shifts. **Limitations:** Poor response rates especially in the controls, suggesting some attrition bias, lack of information on grade of prostate cancer or screening information, potential recall bias; and little information on stage or grade of cancer. **Additional results:** - **Confidence in evidence:** Some evidence
		No (Reference)	-		
		Yes (Ever)	1.19 (1–1.42); 369		
		≤ 7 yr	1.44 (1.1–1.87); 115		
		> 7–22 yr	1.14 (0.86–1.52); 87		
		> 22–34 yr	0.93 (0.7–1.23); 81		
		>34 yr	1.3 (0.97–1.74); 86		
		Trend-test *p*-value: 0.42			
		OR Age at first full-time rotating shift work		Same as above	
		No (Reference)	-		
		11–19 yr	1.04 (0.79–1.36); 98		
		20–22 yr	1.11 (0.81–1.52); 67		
		23–29 yr	1.38 (1.05–1.8); 107		
		≥ 30 yr	1.13 (0.94–1.65); 97		

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: 0.05			
		OR Years since working full-time rotating shift work (latency)		Same as above	
		No (Reference)	-		
		1–36 yr	1.17 (0.88–1.56); 93		
		21–30 yr	1.34 (1.01–1.76); 100		
		31–40 yr	1.13 (0.85–1.5); 86		
		41–50 yr	1.11 (0.82–1.49); 89		
		Trend-test *p*-value: 0.16			
Papantoniou *et al.* 2015 Case-Control Spain **Enrollment or follow-up:** 2008–2013	**Population:** MCC-Spain Cases: 1,095; Controls: 1,388 **Exposure assessment method:** questionnaire	**OR Ever exposure to night shift work by shift work type**		Age, study center, education, physical activity over the past decade, past sun exposure, daily meat consumption, smoking status, family history of prostate cancer	**Exposure information:** Partly or entirely working midnight-6:00 AM, 3+ nights/month **Strengths:** Large population-based case-control study; detailed exposure assessment including differentiation of rotating and permanent night work; duration and frequency of night shifts. Investigated effect modification by chronotype and cancer severity. **Limitations:** Low response rate in controls, potential for recall bias; large proportion of missing data for shiftwork frequency. **Additional results:** When examining cumulative frequency of night shifts in morning chronotype individuals, risk of prostate cancer increased by tertile of cumulative
		Never (Reference)	-		
		Permanent and rotating	1.14 (0.94–1.37); 362		
		Permanent only	1.1 (0.85–1.43); 158		
		Rotating only	1.16 (0.92–1.46); 206		
		OR Lifetime cumulative duration of night work: Permanent and rotating		Same as above	
		Never (Reference)	-		
		≤ 10 yr	1.1 (0.83–1.45); 128		
		11–27 yr	0.94 (0.69–1.27); 92		

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
		≥ 28 yr	1.38 (1.05–1.81); 138		frequency, but no significant trend was seen (P = 0.11). Results were similar when examining cumulative frequency for evening chronotype Results generally similar when examining cumulative frequency for high risk cancer. Also similar results seen when Gleason score was used to categorize severity (high risk = Gleason score >7). **Confidence in evidence:** Evidence
		Trend-test *p*-value: 0.047			
		OR Cumulative duration of night work: Permanent only		Same as above	
		Never (Reference)	-		
		≤ 10 yr	1.07 (0.75–1.51); 75		
		11–27 yr	1.01 (0.65–1.56); 41		
		≥ 28 yr	1.4 (0.83–2.37); 36		
		Trend-test *p*-value: 0.251			
		OR Cumulative duration of night work: Rotating only		Same as above	
		Never (Reference)	-		
		≤ 10 yr	1.21 (0.85–1.74); 73		
		11–27 yr	0.84 (0.56–1.26); 47		
		≥ 28 yr	1.37 (0.97–1.94); 85		
		Trend-test *p*-value: 0.158			
		OR Cumulative frequency of night shifts: Permanent and rotating		Same as above	
		Never (Reference)	-		
		≤ 1,152 nights	1.03 (0.75–1.42); 85		
		1,153–2,856 nights	1.09 (0.78–1.52);		

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
			71		
		≥ 2,857 nights	1.3 (0.97–1.74); 100		
		Trend-test *p*-value: 0.084			
		OR Type and cumulative duration of night work: Morning chronotype		Same as above	
		Never (Reference)	-		
		Permanent and rotating	1.14 (0.87–1.51); 152		
		Permanent only	1.19 (0.8–1.76); 67		
		Rotating only	1.12 (0.8–1.56); 85		
		1-10 yr	0.95 (0.63–1.43); 51		
		11-27 yr	0.9 (0.57–1.4); 39		
		≥ 28 yr	1.79 (1.16–2.76); 61		
		Trend-test *p*-value: 0.017			
		OR Type and cumulative duration of night work: Evening chronotype		Same as above	
		Never (Reference)	-		
		Permanent and rotating	1.5 (0.85–2.66); 49		
		Permanent only	1.57 (0.76–3.27); 24		
		Rotating only	1.44 (0.7–2.93); 25		
		≤ 10 yr	1.92 (0.8–4.54); 19		
		11-27 yr	1.3 (0.55–3.07); 14		

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
		≥ 28 yr	1.33 (0.56–3.16); 16		
		Trend-test *p*-value: 0.619			
		OR Type and cumulative duration of night work: High risk cancer		Same as above	
		Never (Reference)	-		
		Permanent and rotating	1.4 (1.05–1.86); 106		
		Permanent only	1.35 (0.91–1.99); 44		
		Rotating only	1.44 (1.02–2.03); 62		
		≤ 10 yr	1.32 (0.86–2.02); 35		
		11-27 yr	1.26 (0.8–1.98); 30		
		≥ 28 yr	1.63 (1.08–2.45); 40		
		Trend-test *p*-value: 0.027			
Parent *et al.* 2012 Case-Control Montreal, Canada **Enrollment or follow-up:** 1979–1985	**Population:** Population based occupational case-control study Cases: 400; Controls: 512 **Exposure assessment method:** questionnaire	**OR Ever and duration of night work**		Age, ancestry, education, family income, respondent status, smoking, alcohol, BMI, occupational physical activity, farming	**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; nighttime definition likely to encompass a period pertinent to the hypothetical mechanism of carcinogenesis.
		Never (Reference)	-		
		Ever	2.77 (1.96–3.92); 132		
		<5 yr	3.13 (1.98–4.95); 68		
		5–10 yr	2.11 (1.11–3.99); 27		
		≥ 10 yr	2.68 (1.45–4.95); 36		

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
		OR Timing of night work		Same as above	**Limitations:** No screening, grade or severity information about prostate cancer; approximately 18% of cases contributed information through proxies. **Additional results:** - **Confidence in evidence:** Evidence
		Never (Reference)	-		
		Recent: ≤ 20 yr ago	3.17 (1.89–5.31); 55		
		Distant: > 20 yr ago	3.01 (1.83–4.93); 57		
Tse *et al*. 2017 Case-Control Hong Kong, China **Enrollment or follow-up:** 2011–2016	**Population:** Hospital-based case-control study from Prince of Wales Hospital Cases: 431; Controls: 402 **Exposure assessment method:** questionnaire	**OR Ever exposure to night shift work**		Age, marital status, unemployment status, family history of prostate cancer, consumption of deep fried food, consumption of pickled vegetables, green tea drinking habits, cumulative BPA index	**Exposure information:** Ever worked nights (at least 1 hour from 1:00 AM–5:00 AM for more than 1x/month for >1 year) **Strengths:** Moderate-sized case-control study from the same population. Explicit definition of night work exposure. **Limitations:** Low number of exposed cases. Only categorized shift work as ever exposure, limited sensitivity. **Additional results:** Base model had similar results. **Confidence in evidence:** Some evidence
		Never (Reference)	-		
		Ever	1.76 (1.07–2.89); 58		
Wendeu-Foyet *et al.* 2018 Case-Control France **Enrollment or follow-up:** 2012–2013	**Population:** Epidemiology of Prostate Cancer (EPICAP) study Cases: 818; Controls: 875 **Exposure assessment method:** interview	**OR Ever night work: permanent and rotating**		Age, family history of prostate cancer, race, education level	**Exposure information:** Ever worked, shift type (permanent or rotating), duration, number of consecutive nights worked, night shift length, cumulative frequency, shift timing, rotation type, shift rotation speed, sleep duration, chronotype. **Strengths:**
		Never (Reference)	-		
		Ever	0.97 (0.79–1.19); 286		
		Ever permanent night work	1.04 (0.82–1.32); 210		
		Ever rotating night	0.81 (0.59–1.16);		

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
		work	84		Large-size case-control study from the same population. Highly sensitive study with numerous metrics to capture shift work exposure. **Limitations:** Potential for recall bias. **Additional results:** Rotating shifts did not see a significant increased risk or trend with duration. Frequency of rotating shifts were not associated with a significant increased risk or trend. Shift length >10 hours was associated with elevated prostate cancer for permanent or rotating night shift (OR = 1.57, 95% CI = 0.79 to 1.19). Duration of 20+ years and either 6+ nights or 10+ hour shift length increased the risk of prostate cancer for permanent night work. 10+ hour shift length and either 1314 cumulative nights worked or 6+ nights consecutively worked increased the risk of prostate cancer, particularly for permanent night shift workers. For permanent shift workers, working 6+ consecutive permanent night shifts, >10 hours shift length, and a combination of longest duration, consecutive nights, shift length, and frequency of night work was associated was associated with increased risk of aggressive prostate cancer (Gleason score 7+). Results did not hold for non-aggressive prostate cancer or for rotating shift work.
		OR Total duration of permanent night work		Same as above	
		Never (Reference)	-		
		<10 yr	0.91 (0.62–1.38); 54		
		10-19 yr	1.17 (0.76–1.83); 48		
		20-29 yr	0.87 (0.56–1.37); 39		
		30+ yr	1.22 (0.83–1.79); 69		
		Trend-test *p*-value: 0.26			
		OR Lifetime frequency of permanent night work		Same as above	
		Never (Reference)	-		
		< 1,314 nights	1.05 (0.76–1.46); 90		
		1,314+ nights	1.03 (0.77–1.38); 120		
		Trend-test *p*-value: 0.89			
		OR Number of consecutive permanent nights worked		Same as above	
		Never (Reference)	-		
		< 6 nights	1.01 (0.74–1.39); 95		
		6+ nights	1.33 (0.95–1.87); 93		
		Trend-test *p*-value: 0.25			

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
		OR Permanent night shift length (hours)		Same as above	**Confidence in evidence:** Some evidence
		Never (Reference)	-		
		< 8 hr	0.32 (0.16–0.64); 11		
		8–10 hr	0.86 (0.48–1.53); 23		
		> 10 hr	1.88 (1.08–3.26); 38		
		Trend-test *p*-value: 0.29			
		OR Duration (years) and number of consecutive permanent nights		Same as above	
		Never (Reference)	-		
		<20 yr & <6 nights	1.06 (0.71–1.58); 57		
		<20 yr & 6+ nights	1.21 (0.74–2); 35		
		20+ yr & <6 nights	0.91 (0.57–1.46); 38		
		20+ yr & 6+ nights	1.42 (0.92–2.18); 58		
		OR Ever and duration of permanent night work: Gleason score 7+		Same as above	
		Never (Reference)	-		
		Ever	1.41 (0.98–2.04); 58		
		< 20 yr	1.09 (0.66–1.81); 23		
		20+ yr	1.76 (1.13–2.75); 35		

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: 0.003			

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