International Journal of Epidemiology, 2022, 1–12
https://doi.org/10.1093/ije/dyac235
Original article

Original article

Night shift work and risk of aggressive prostate cancer in the Norwegian Offshore Petroleum Workers (NOPW) cohort

Leon AM Berge ,[1,2]* Fei-Chih Liu,[1,2] Tom K Grimsrud,[2] Ronnie Babigumira,[2] Nathalie C Støer,[2,3] Kristina Kjærheim,[2] Trude E Robsahm,[2] Reza Ghiasvand ,[2,4] H Dean Hosgood,[5] Sven Ove Samuelsen,[6] Debra T Silverman,[7] Melissa C Friesen ,[7] Nita K Shala,[2] Marit B Veierød [1] and Jo S Stenehjem[2]

[1]Oslo Centre for Biostatistics and Epidemiology, Department of Biostatistics, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway, [2]Department of Research, Cancer Registry of Norway, Oslo, Norway, [3]Norwegian Research Centre for Women's Health, Women's Clinic, Oslo University Hospital, Oslo, Norway, [4]Oslo Centre for Biostatistics and Epidemiology, Oslo University Hospital, Oslo, Norway, [5]Department of Epidemiology and Population Health, Albert Einstein College of Medicine, The Bronx, NY, USA, [6]Department of Mathematics, University of Oslo, Oslo, Norway and [7]Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, MD, USA

*Corresponding author. Oslo Centre for Biostatistics and Epidemiology, Department of Biostatistics, Institute of Basic Medical Sciences,University of Oslo, P.O. Box 1110 Blindern, 0317 Oslo, Norway. E-mail: l.a.m.berge@medisin.uio.no

Received 22 March 2022; Editorial decision 28 November 2022; Accepted 13 December 2022

Abstract

Background: Night shift work may acutely disrupt the circadian rhythm, with possible carcinogenic effects. Prostate cancer has few established risk factors though night shift work, a probable human carcinogen, may increase the risk. We aimed to study the association between night shift work and chlorinated degreasing agents (CDAs) as possible endocrine disrupters in relation to aggressive prostate cancer as verified malignancies.

Methods: We conducted a case-cohort study on 299 aggressive prostate cancer cases and 2056 randomly drawn non-cases in the Norwegian Offshore Petroleum Workers cohort (1965–98) with linkage to the Cancer Registry of Norway (1953–2019). Work history was recorded as years with day, night, and rollover (rotating) shift work, and CDA exposure was assessed with expert-made job-exposure matrices. Weighted Cox regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for aggressive prostate cancer, adjusted for education and year of first employment, stratified by 10-year birth cohorts, and with 10, 15, and 20 years of exposure lag periods.

Results: Compared with day work only, an increased hazard of aggressive prostate cancer (HR = 1.86, 95% CI 1.18–2.91; *P*-trend = 0.046) was found in workers exposed to $\geq$19.5 years of rollover shift work. This persisted with longer lag periods (HR = 1.90, 95% CI 0.92–3.95; *P*-

trend = 0.007). The exposure-hazard curve for a non-linear model increased linearly (HRs ≥ 1.00) for 18–26 years of rollover shift work. No association was found with CDA exposure.

Conclusions: Long-term exposure to rollover shift work may increase the hazard of aggressive prostate cancer in offshore petroleum workers.

Key words: Night shift work, prostate cancer, case-cohort, cancer incidence, offshore workers, petroleum industry

Key Messages

- Exposure to night shift work, and particularly long-term exposure to rollover shift work (day and night shift rotation) was associated with an increased hazard of aggressive prostate cancer in offshore petroleum workers.
- Exposure to chlorinated degreasing agents, as endocrine disrupting agents, was not associated with aggressive prostate cancer hazard.
- Our data support that long-term rotating shift work should be considered when evaluating night shift work as a risk factor for prostate cancer.

Introduction

Prostate cancer has few established risk factors apart from advanced age, family history of prostate cancer and genetic susceptibility.[1] There is limited evidence for other exposures like smoking, body mass index (BMI), dietary intakes and chemical agents such as certain organophosphate insecticides[2] and chlorinated hydrocarbons with potential endocrine disrupting properties.[3–5] Prostate cancer incidence is three times higher in developed than in developing countries,[1] and despite differences in life expectancy and diagnostic practices, occupational or environmental exposures may still constitute risk factors. This includes night shift work, which can cause circadian rhythm disruptions, sleep deprivation, increased stress, vitamin D deficiency and prolonged exposure to artificial light sources at night.[6]

The International Agency for Research on Cancer (IARC) recently reconfirmed its classification of night shift work as a probable human carcinogen (group 2A), with limited positive evidence for prostate cancer.[6] Individual studies[7–13] as well as systematic reviews and meta-analyses[14,15] have shown inconsistent results, although positive associations have been found for aggressive prostate cancer and longer durations of night shift work exposure.[10,11] A positive association with prostate cancer has also been found in relation to rotating shift work (day and night shift rotation).[16,17] However, no meta-analysis has differentiated between the risk of total and aggressive prostate cancer in relation to night shift work. Heterogeneity in the observational evidence may stem from differential exposure classifications and a lack of differentiation between aggressive and non-aggressive (indolent) prostate cancer. Aggressive prostate cancer cases have increased validity through reduced sensitivity to variations in diagnostic practices (i.e. the prostate-specific antigen test)[18,19] and its definition has been suggested for aetiological studies.[19]

The Norwegian Offshore Petroleum Workers (NOPW) cohort contains detailed work histories for over 25 000 male offshore workers employed on the Norwegian continental shelf during 1965–98. An excess risk of total prostate cancer was found in the NOPW cohort, compared with the general population,[20] but to our knowledge, this is the first study to prospectively investigate the association between the night shift work patterns of offshore petroleum workers and the hazard of aggressive prostate cancer. We conducted a case-cohort study within the NOPW cohort, examining this association. To assess the impact of delayed effects of exposure, we conducted lagged exposure-effect analyses and examined the exposure-hazard curve by applying a non-linear model. Finally, to address potential chemical co-exposures, we examined if the hazard was associated with exposure to chlorinated degreasing agents (CDA), as potential endocrine disrupters.

Methods

Study population and study design

The NOPW cohort was established by the Cancer Registry of Norway (CRN) in 1998 for prospective follow-up of cancer incidence.[20] The cohort ($n = 27\ 917$) comprises male ($n = 25\,347$) and female ($n = 2570$) workers with current or former employment (minimum 20 days) in the offshore petroleum industry on the Norwegian continental shelf during 1965–98, who completed a questionnaire.[20] The final cohort has an estimated participation rate of 69%, and includes 25 347 male workers with information on work history as well as sociodemographic and lifestyle factors relevant to cancer.[20]

Workers reported up to eight offshore employments (27 categories) within the petroleum industry in 1965–98 (less than 2% reported eight jobs).[20] Employments one and eight were recorded electronically, information regarding employments two to seven was not. Because of this a stratified case-cohort design was chosen, which required manual extraction of work history data for a random sample of the cohort (i.e. subcohort) and all aggressive prostate cancer cases.[21]

Cancer cases

The NOPW cohort was linked to the CRN and the National Population Registry for information on cancer diagnoses, death and emigration from the start of the registries to 31 December 2019, through unique personal identification numbers assigned to residents in Norway since 1960. The CRN collects data from pathology laboratories, physicians, the Norwegian Patient Register and the Cause of Death Registry, providing a high degree of completeness and validity,[22] with 92.7% and 95.1% of all prostate cancer cases morphologically verified in 2000–05 and 2016–2020, respectively.[23,24]

For the period 1 July 1999 to 31 December 2003, aggressive prostate cancer cases were defined as any worker diagnosed with prostate cancer (International Classification of Disease 10th revision: C61) with any regional or distant lymph node or organ metastasis. From 1 January 2004 to 31 December 2019, the diagnostic criteria for aggressive prostate cancer were a primary tumour (T) category = 4 or regional lymph node (N) category = 1 or distant metastasis (M) category = 1 or a Gleason score ≥8, as the Norwegian Prostate Cancer Registry (a clinical registry nested within the CRN) was established.[19] Any other prostate cancer diagnosis was classified as non-aggressive.

Study sample

Using stratified random sampling by 5-year birth cohorts, a random subcohort ($n = 2268$) was drawn from the 25 347 male NOPW cohort members. From the aggressive prostate cancer cases ($n = 310$) and subcohort ($n = 2268$) we excluded workers based on the following criteria: (i) offshore employment before 1965; (ii) <15 years at first employment; (iii) >67 years at first employment; (iv) death or emigration prior to start of follow-up; (v) missing work history; and (vi) any cancer diagnosis prior to start of follow-up. Aggressive prostate cancer cases randomly drawn to the subcohort were reassigned to cases according to the method (Estimator II) described by Borgan *et al.*[21] This resulted in a final study sample of 2355 workers, consisting of 299 aggressive prostate cancer cases and 2056 non-cases (Figure 1). Person-time was generated for cases and non-cases from the start of follow-up (1 July 1999) to the date of the first prostate cancer diagnosis (aggressive or non-aggressive), emigration, death or end of follow-up (31 December 2019), whichever occurred first.

Exposure assessment

Work schedule

Each employment period consists of standard work tours lasting 14 days, with 12-hour shifts. The work schedule for each employment period was categorized as either day work (14 days of day work each work tour, 07:00–19:00), night shift work (14 night shifts each work tour, 19:00–07:00) or rollover shift work (7 days of day work and 7 days of night shifts, or vice versa, each work tour).[25] Overlapping employment records were harmonized by collapsing jobs of the same category and by splitting jobs of different categories into equal periods, according to a previous method.[26]

Work schedules were categorized as day work only (only day work employment periods), night shift work only (only night shift work employment periods), rollover shift work only (only rollover shift work employment periods), and mixed work (any combination of employment periods with day, night shift or rollover shift work schedules). Day work, night shift work and rollover shift work exposure was calculated by summing the duration (in years) of day work, night shift or rollover shift work for each worker, respectively. Total employment duration was categorized as quartiles (based on all cases and non-cases) and rollover shift work duration was categorized into five categories: non-exposed and quartiles among exposed. To capture the tail of the distribution, the upper quartile was divided by its median (six categories in total).

Assessment of exposure to chlorinated degreasers

In 2005, industrial hygienists with expertise on the offshore industry developed job-exposure matrices (JEMs) to measure exposure to agents and situations with known or suspected carcinogenicity for the present cohort.[27,28] The CDA JEM (i.e. tri- and tetrachloroethylene) was probability-based due to a lack of quantitative exposure data. CDA exposure ratings were defined as likelihoods of exposure (unlikely = 0, possible = 1, probable = 2 and probable highest relative ranking = 3) by each combination

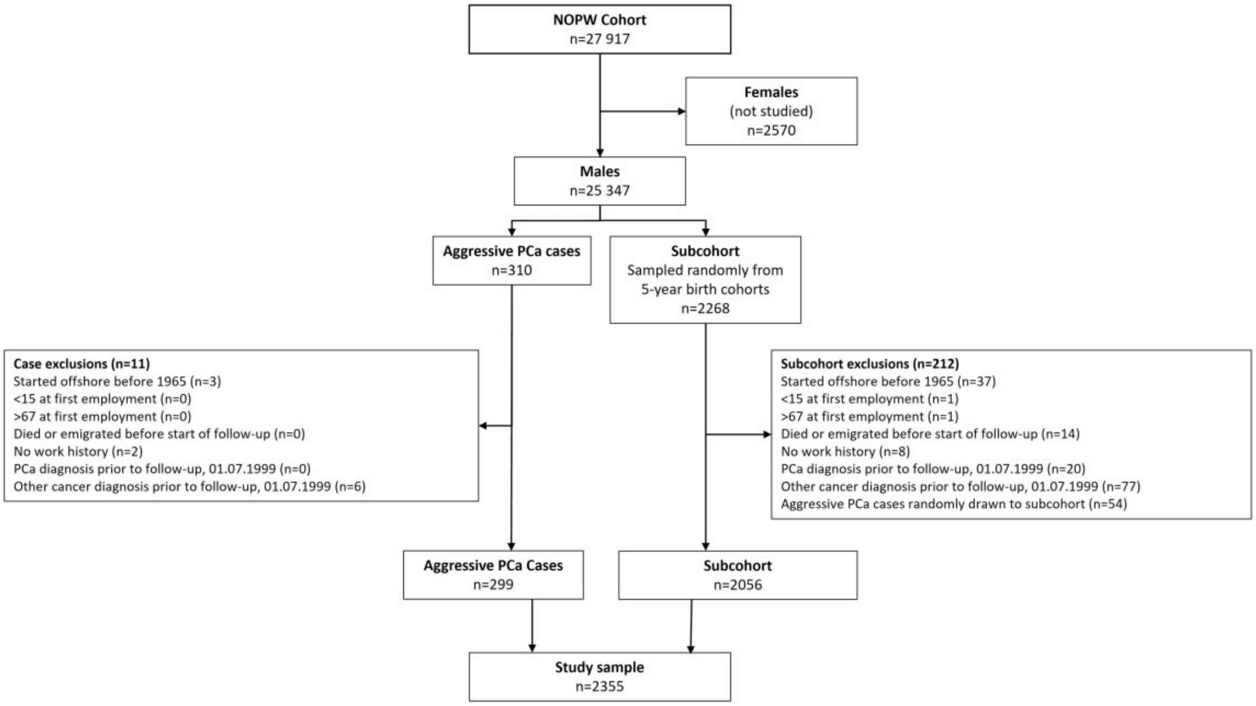

Figure 1 Overview of study design and study sample. PCa, prostate cancer. NOPW, Norwegian Offshore Petroleum Worker

of 27 job categories and time periods (1970–79, 1980–89 and 1990–99). Ratings were based on summary documents, including descriptions of exposure sources, sampling data and job-specific work processes.[27] For our study, the CDA JEM ratings were linked to work histories and exposure duration was defined as years of exposure to CDA (exposure likelihood 1–3). For cumulative CDA exposure, JEM ratings were multiplied by duration (in years) for each employment period and summarized for each worker from the start of employment until 31 December 1998. Both CDA exposure duration and cumulative exposure metrics were categorized into three categories: non-exposed and by the median among exposed.

Other variables

Education was recorded as compulsory, vocational, upper secondary and university/college. Year of first employment was recorded as the year of first employment in the offshore petroleum sector. BMI (kg/m^2) was calculated based on self-reported height (cm) and weight (kg). Smoking status in 1998 was defined as never, current or former. Type of company was defined as operating or contractor.

Data analysis

Cox regression, stratified by 10-year birth cohorts and with age as the time scale, was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the night shift work and CDA-prostate cancer associations.[21] Aggressive prostate cancer cases were weighted 1 and non-cases were weighted based on the inverse sampling fraction in 5-year birth cohort strata. In the analysis of rollover shift work duration, we also excluded 60 workers with only night shift work or with a combination of only day work and night shift work employment periods, ensuring that the reference category (0 years of rollover shift work) only consisted of workers with day work exposure only. Restricted cubic splines (RCS) with five knots (0.58, 3.82, 8.99, 14.98 and 21.5 years), based on 0.05, 0.275, 0.5, 0.725, 0.95 percentiles, were incorporated to assess the form of the rollover shift work-prostate cancer association. Lagged analyses were also conducted, modelling rollover shift work duration as a time-dependent variable, discounting exposure 10, 15 or 20 years prior to diagnosis/end of follow-up.[29]

The choice of covariates was based upon estimating the total effect in directed acyclic graphs, drawn to model the relationship between night shift work and CDA exposure among offshore petroleum workers, and aggressive prostate cancer hazard (Supplementary Figures S1 and S2, available as Supplementary data at *IJE* online). We adjusted for year of first employment, incorporating RCS with five knots (1972, 1977, 1979, 1984, 1992), and education. We also included BMI, smoking status and company type as additional covariates for interaction analyses.

A Wald test was used to test for interactions between rollover shift work exposure and year of first employment (continuous; indicating increased use of closed systems, technical improvements and personal protective equipment),[30] BMI (continuous), smoking status and company type. Stratified analyses were performed by education and year of first employment before and after 1980, following systematic implementations of improved safety measures (not shown).[30] To investigate the effect of BMI and smoking[31] on the rollover shift work-aggressive prostate cancer association, we also adjusted for BMI (continuous) or smoking status (not shown).

Up to 6% of the covariates were missing in the multivariable model. Assuming missing at random, multiple imputation by chained equations was used to impute 10 datasets, with job category, shift work type, type of platform, education, year of first employment, 5-year birth cohort and case status as predictors.[32] Each dataset was analysed with the respective model and the results pooled into a final point estimate and standard error using Rubin's rule.[33] Results are reported with and without imputed data.

The statistical software package R (version 3.6.1) was used to conduct all statistical analyses.[34]

Results

Median age at start of follow-up was 52 for cases and 54 for non-cases (Table 1), and median age at aggressive prostate cancer diagnosis was 67. The most frequent main occupational activity in last position was maintenance/inspection/deck construction for both cases (48%) and non-cases (51%). Compared with non-cases, the median rollover shift work duration in cases was 1.2 years (12%) higher, whereas median day work duration was 2 years (20%) lower. When stratified by work schedule, the proportion of workers with a vocational education was 9% lower and a university/college education was 13% higher among day shift workers only, compared with rollover shift workers only (Supplementary Table S1, available as Supplementary data at *IJE* online).

Results from the complete study sample (without missing) and multiple imputation analyses were similar and estimates from the multiple imputation are reported here. Compared with day work only, an increased hazard was suggested for ever exposure to night and/or rollover shift work (HR = 1.26, 95% CI 0.99–1.61), and rollover shift work only (HR = 1.27, 95% CI 0.97–1.66). An additional analysis of work schedule categories, with mixed workers divided into mostly day work, mostly night shift work and mostly rollover shift work, were in line with the main analysis (Supplementary Table S3, available as Supplementary data at *IJE* online). Increased hazard of aggressive prostate cancer was found in workers exposed to ≥19.5 years of rollover shift work, compared with day work only (HR = 1.86, 95% CI 1.18–2.91; *P*-trend = 0.046) (Table 2). Using RCS, the exposure-hazard curve increased linearly with 95% CIs ≥1.00 for 18–26 years of rollover shift work (Figure 2). No association with aggressive prostate cancer hazard was found for total employment duration (not shown).

Compared with day work only, increased hazard was also found for workers exposed to ≥19.5 years of rollover shift work with lag periods of 10 (HR = 1.92, 95% CI 1.21–3.05; *P*-trend = 0.046), 15 (HR = 1.92, 95% CI 1.15–3.21; *P*-trend = 0.015), and 20 years (HR = 1.90, 95% CI 0.92–3.95; *P*-trend = 0.007) (Table 3). No interactions were found between rollover shift work and year of first employment (*P*-interaction = 0.250), BMI (*P*-interaction = 0.370), smoking status (*P*-interaction = 0.380) or type of company (*P*-interaction = 0.150) in relation to aggressive prostate cancer. Additionally, no interaction was found between work schedule category and cumulative CDA exposure (not shown). Adjusting for smoking status or BMI did not alter the rollover shift work-prostate cancer association. Additionally, we found no association between duration or cumulative exposure of CDA and aggressive prostate cancer (Supplementary Table S2, available as Supplementary data at *IJE* online).

Discussion

In this prospective case-cohort analysis of offshore workers in the NOPW cohort, results indicated an increased hazard of aggressive prostate cancer in workers ever exposed to night shift work and to rollover shift work only, compared with day work only. The hazard increased with increasing years of rollover shift work compared with day work only, and persisted with 10-, 15-, and 20-year periods of lag time. The exposure-hazard curve of the non-linear model further illustrated a hazard increase and a linear association for most of the exposure range.

The work schedules of offshore petroleum workers make the NOPW cohort an interesting setting in which to study night shift work and cancer associations. Our results are in line with recent systematic reviews and meta-analyses on night shift work and prostate cancer for longer durations of night shift work[17,35] and rotating shift work.[16,17] However, this stands in contrast with the most recent systematic reviews and meta-analyses, in which no associations were found between night shift work and prostate cancer.[14,15] Based on autopsy findings, prostate cancers may have latency times of up to 15–20 years, the estimated time period from the first malignant transformation of cells to clinical diagnosis.[36] The effect estimates in our analysis indicated that the hazard of aggressive prostate cancer is not affected by 10, 15 and 20 years of

Table 1 Characteristics of the study sample ($n = 2355$) in the Norwegian Offshore Petroleum Workers Cohort

Variables[a]	Cases ($n = 299$)	Non-cases ($n = 2056$)
Age at start of follow-up (years), median (range)	52 (32–73)	54 (20–80)
10-year birth cohort, *n* (%)		
1915–24	0 (0.0)	25 (1.2)
1925–34	(NA)	325 (15.8)
1935–44	99 (33.1)	748 (36.4)
1945–54	143 (47.8)	676 (32.9)
1955–64	37 (12.4)	236 (11.5)
1965–79	<5 (NA)	46 (2.2)
Education, *n* (%)		
Compulsory	44 (14.7)	327 (15.9)
Vocational	144 (48.2)	1046 (50.9)
Upper secondary	51 (17.0)	278 (13.5)
University/college	57 (19.1)	387 (18.8)
Missing	3 (1.00)	18 (0.9)
Anthropometric factors		
Height (cm), median (range)[b]	180 (160–199)	179 (156–200)
Weight (kg), median (range)[b]	82 (54–130)	82 (48–184)
BMI (kg/m^2) *n* (%), median (range)[b]	25.8 (18–36)	25.6 (13.7–60.8)
Work history		
Year of first employment (years), median (range)	1980 (1965, 1997)	1979 (1965, 1998)
Year of first employment, *n* (%)		
1965–74	36 (12.0)	293 (14.3)
1975–84	185 (61.9)	1220 (59.3)
1985–94	72 (24.1)	472 (22.9)
1995–98	6 (2.0)	70 (3.4)
Missing	0 (0.0)	1 (0.1)
Main occupational activity in last position, *n* (%)		
Production and process	26 (8.7)	184 (8.9)
Drilling and well maintenance	27 (9.0)	175 (8.5)
Maintenance/inspection/deck construction	143 (47.8)	1055 (51.3)
Catering/office/administration	51 (17.1)	293 (14.3)
Miscellaneous	50 (16.7)	324 (15.8)
Missing	2 (0.7)	25 (1.2)
Total employment duration (years), median (range)	12.3 (0.09–30.9)	12.2 (0.09–33.5)
Total employment duration (years) in quartiles, *n* (%)[b]		
<6 years	77 (25.8)	530 (25.8)
6–<12 years	70 (23.4)	488 (23.7)
12–<18 years	74 (24.7)	511 (24.9)
≥18 years	78 (26.1)	526 (25.6)
Work schedule, *n* (%)[b]		
Day work only	112 (37.5)	857 (41.7)
Night work only	<5 (NA)	32 (1.6)
Rollover work only	112 (37.5)	745 (36.2)
Mixed work	<100 (NA)	320 (15.6)
Missing	17 (5.6)	102 (4.9)
Duration by work schedule[c]		
Day work (years), median (range)	8.0 (0.09–28.5)	10.0 (0.08–32.5)
Night work (years), median (range)	2.0 (0.2–8.0)	4.2 (0.08–23.2)
Rollover shift (years), median (range)	10 (0.3–30.9)	8.8 (0.04–33.5)
Rollover shift work duration (years), *n* (%)[d,e]		
0	118 (39.5)	912 (44.4)
>0–<3	38 (12.7)	267 (13.0)
3–<9	39 (13.0)	275 (13.4)

(Continued)

Table 1 Continued

Variables[a]	Cases ($n = 299$)	Non-cases ($n = 2056$)
9–<16	39 (13.0)	266 (12.9)
16–<19.5	20 (6.7)	118 (5.7)
>19.5	28 (9.4)	116 (5.6)
Missing work schedule	17 (5.7)	102 (5.0)
Duration (years) of chlorinated degreaser exposure, *n* (%)		
0	49 (16.4)	325 (15.8)
<Median	123 (41.1)	881 (42.9)
≥Median	127 (42.5)	850 (41.3)
Cumulative chlorinated degreaser exposure, *n* (%)[f]		
0	49 (16.4)	325 (15.8)
<Median	121 (40.5)	869 (42.3)
≥Median	129 (43.1)	862 (41.9)

BMI, body mass index; NA, not available.

[a]All numbers up to five are listed as <5 due to European Union (EU) General Data Protection Regulations (GDPR), unless this only concerns missing. If only one cell per variable lists a number <5, the next smallest number is listed as <25, <50 or <100.

[b]Missing: Height ($n = 35$); weight ($n = 38$); body mass index (BMI) ($n = 41$); employment duration ($n = 1$); work schedule ($n = 119$).

[c]Workers with completely missing information on day, night and rollover shift work ($n = 119$) were excluded when calculating the median.

[d]Categorized into non-exposed (0) and quartiles among exposed. To capture the tail of the distribution, the upper quartile was divided into two by its median.

[e]Any workers with rollover shift work were included in the exposure categories.

[f]Cumulative exposure: job-exposure matrix (JEM) rating multiplied by duration (in years) for each employment period and summarized for each individual from the start of employment until 31 December 1998.

Table 2 Hazard ratios (HR) and 95% confidence intervals (95% CI) of aggressive prostate cancer in the Norwegian Offshore Petroleum Workers cohort

	Complete study sample ($n = 2219$)[a]		**Multiple imputation ($n = 2355$)[a]**
Work schedule variable[b]	No. cases/non-cases	**HR (95% CI)[f]**	**HR (95% CI)[f]**
Ever exposure[c,d,e]			
Day shifts only	112/853	1.00 (reference)	1.00 (reference)
Ever night/rollover shift work	168/1086	1.23 (0.95–1.61)	1.26 (0.99–1.61)
Work schedule exposure category[c,d,e]			
Day work only	112/853	1.00 (reference)	1.00 (reference)
Night shift work only	<5/32	1.19 (0.40–3.50)	1.50 (0.61–3.72)
Rollover shift work only	111/736	1.26 (0.94–1.69)	1.27 (0.97–1.66)
Mixed work	<100/318	1.18 (0.82–1.69)	1.23 (0.90–1.69)
Rollover shift work duration (years)[a,c,d,e,g]			
0	112/853	1.00 (reference)	1.00 (reference)
>0–<3	38/261	1.24 (0.83–1.85)	1.27 (0.88–1.83)
3–<9	39/273	1.15 (0.78–1.72)	1.19 (0.84–1.70)
9–<16	39/264	1.15 (0.76–1.75)	1.15 (0.80–1.67)
16–<19.5	19/117	1.18 (0.68–2.03)	1.22 (0.74–2.00)
19.5–33.5	28/116	1.90 (1.15–3.13)	1.86 (1.18–2.91)
P-trend[h]		0.064	0.046

[a]An additional $n = 60$ workers without pure day work (the number varied for imputed data) were excluded to ensure the reference category (0 years) contained workers with day work only.

[b]All numbers up to five are listed as <5 due to European Union (EU) General Data Protection Regulations (GDPR), unless this only concerns missing. If only one cell per variable lists a number <5, the next smallest number is listed as <25, <50 or <100.

[c]Adjusted for year of first employment and education, and stratified by 10-year birth cohorts.

[d]Complete work history i.e. up to eight employments as an offshore worker.

[e]Missing: ever exposure ($n = 119$), work schedule exposure category ($n = 119$), rollover shift work duration ($n = 119$), year of first employment ($n = 1$), education ($n = 21$).

[f]Cox regression adapted to a case cohort design with age as the time scale.

[g]Categorized into non-exposed (0) and quartiles among exposed. To capture the tail of the distribution, the upper quartile was divided into two by its median.

[h]Modelled as a continuous variable to test for linear trend.

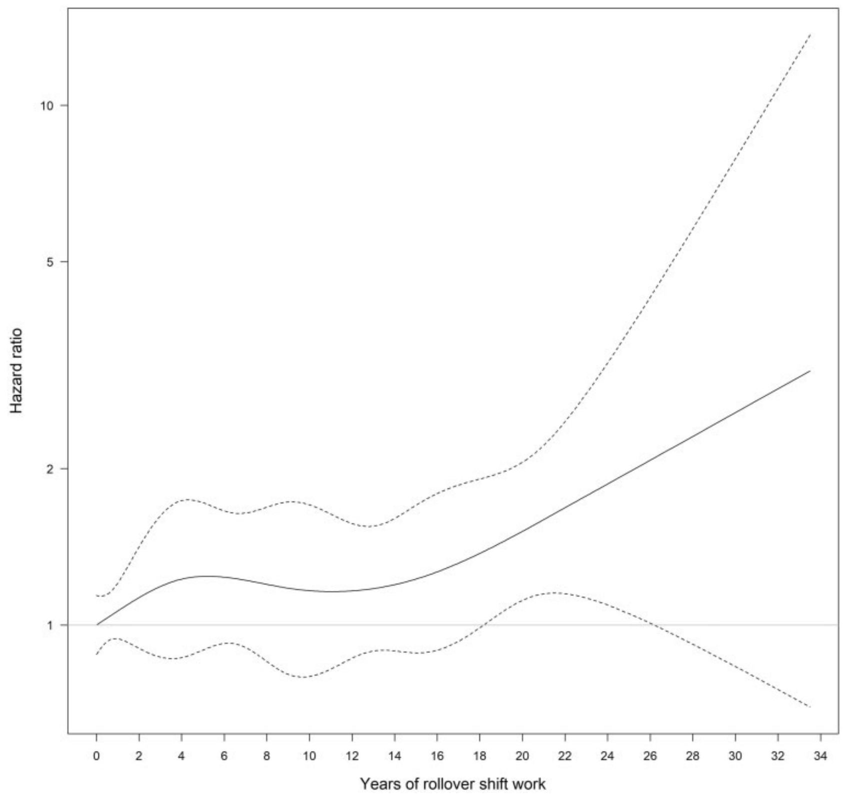

Figure 2 Exposure-risk curve for a non-linear model of rollover shift work exposure, generated using restricted cubic splines with five knots (0.58, 3.82, 8.99, 14.98 and 21.5 years)

exposure lag time. This supports a latency time of up to 20 years for more aggressive, high-risk forms of prostate cancer, which was previously considered uncertain.[36]

Few studies make distinctions between aggressive and non-aggressive prostate cancer,[7,10,11,13] however, our results are in line with two case-control studies that found an association between night shift work and aggressive forms of prostate cancer.[10,11] Another recent case-control study, however, found that whereas night shift work increased prostate cancer risk, disease aggressiveness did not modify the association with night shift work.[13]

There are several biological mechanisms through which the association between rollover shift work and aggressive prostate cancer in our study may be explained. The hormone melatonin is an important regulator and biomarker of circadian rhythm and has several anti-tumorigenic effects.[37] The increased hazard of aggressive prostate cancer among rollover shift workers found in our study aligns with the possible mechanistic role of melatonin on human prostate cancer cells[38] and is consistent with findings that melatonin is suppressed in humans with irregular sleep patterns.[39,40]

Studies have found a higher risk of prostate cancer for rotating shift work than for night shift work only.[13,16] It is hypothesized that workers may have less time to adapt to a rotating shift work schedule and thus experience more circadian disruption, compared with night shift work only.[13,16] Compared with day work, day/night rotating shift work among offshore petroleum workers is associated with sleep problems and gastric problems.[41] Moreover, circadian disruption has been linked to several other oncogenic changes with long-term implications, including increased oxidative stress,[42] epigenetic changes,[43] telomere shortening[44] and chronic inflammation.[45] This may be compounded further during work tours by the rollover shift work pattern among workers on Norwegian offshore installations.[25]

Suppression of melatonin has also been linked to irregular production of sex hormones, which may lead to the development of hormone-sensitive cancers such as breast and prostate cancer.[37,46] We estimated the association between cumulative exposure and duration of exposure to CDA to investigate the possible impact of endocrine disrupting agents,[4,5,47] though no association was found in the present study.

According to the IARC, there is sufficient mechanistic evidence from experimental systems to show that alterations in the light-dark schedule promote carcinogenic effects.[6] An important consideration highlighted in their evaluation of the observational evidence was the varying

Table 3 Hazard ratios (HR) and 95% confidence intervals (95% CI) of aggressive prostate cancer in the Norwegian Offshore Petroleum Workers cohort

10-year lag	Complete study sample ($n = 2159$)[a]			Multiple imputation ($n = 2355$)[a]
Rollover shift work duration (years)[b,c,d,e]	No. of cases	Person-years	HR (95% CI)[f]	HR (95% CI)[f]
0	112	16 957.55	1.00 (reference)	1.00 (reference)
>0–<3	38	5304.36	1.23 (0.84–1.78)	1.26 (0.88–1.81)
3–<9	41	5571.12	1.20 (0.83–1.72)	1.23 (0.87–1.74)
9–<16	40	5550.14	1.14 (0.78–1.68)	1.15 (0.80–1.65)
16–<19.5	18	1765.68	1.17 (0.69–1.95)	1.22 (0.74–2.02)
19.5–33.3	26	1477.74	1.97 (1.23–3.14)	1.92 (1.21–3.05)
P–trend[g]			0.047	0.046
15–year lag				
Rollover shift work duration (years)[b,c,d,e]				
0	113	18 138.75	1.00 (reference)	1.00 (reference)
>0–<3	37	5477.71	1.16 (0.80–1.70)	1.20 (0.83–1.73)
3–<9	45	6182.65	1.24 (0.87–1.76)	1.25 (0.89–1.75)
9–<16	38	4810.03	1.05 (0.72–1.55)	1.06 (0.73–1.54)
16–<19.5	22	1149.64	1.72 (1.06–2.78)	1.79 (1.12–2.86)
19.5–33.3	20	867.82	1.97 (1.16–3.34)	1.92 (1.15–3.21)
P–trend[g]			0.018	0.015
20–year lag				
Rollover shift work duration (years)[b,c,d,e]				
0	117	20 410.65	1.00 (reference)	1.00 (reference)
>0–<3	41	5950.03	1.21 (0.84–1.74)	1.18 (0.83–1.69)
3–<9	48	5958.95	1.20 (0.85–1.69)	1.19 (0.86–1.66)
9–<16	46	3397.82	1.34 (0.94–1.93)	1.38 (0.97–1.95)
16–<19.5	15	578.60	1.98 (1.12–3.51)	1.92 (1.09–3.37)
19.5–33.3	9	343.46	1.99 (0.95–4.16)	1.90 (0.92–3.95)
P-trend[g]			0.009	0.007

[a]Any workers without pure day work (for complete and multiple imputed data) were excluded to ensure the reference category (0 years) contained workers with day work only, *n* varied with lag period as shift type exposure changed among workers.

[b]Adjusted for year of first employment and education, and stratified by 10-year birth cohorts.

[c]Complete work history i.e. up to eight employments as an offshore worker.

[d]Missing: rollover shift work duration ($n = 119$), year of first employment ($n = 1$), education ($n = 21$).

[e]Categorized into non-exposed (0) and quartiles among exposed. To capture the tail of the distribution, the upper quartile was divided into two by its median.

[f]Cox regression adapted to a case cohort design with age as the time scale.

[g]Modelled as a continuous variable to test for linear trend.

definitions of night shift work. Some studies define night shift work as including night shift work only or rotating shift work, or both. Despite being subject to specific national and occupational regulations, the strengths of our study include the analysis of all types of shift work, although the abundance of rollover shift workers excluded an analysis of night shift work only.

Important strengths of our study also include a prospective case-cohort design, JEMs developed specifically for the NOPW cohort by experts in industrial hygiene, and linkage to the nationwide CRN, giving complete and high-quality cancer information. Moreover, linkage to the National Population Registry ensured control of loss to follow-up. Most studies of night shift work exposure are based on industry-specific occupational cohorts and occupations such as airline staff, nurses and oil rig workers. Such workers may be subject to regular health checks and thereby increased diagnostic intensity. However, our focus on aggressive prostate cancer mitigated the potential impact of diagnostic bias. It is also important to note that non-aggressive prostate cancer may be associated with different risk factors than aggressive subtypes.[7,10,11,13] This makes it important to differentiate between aggressive and non-aggressive prostate cancer in studies of aetiology.

Work history information in our study was based on a prospectively collected self-report questionnaire. The validity and robustness of self-reported work history is supported by its correspondence to occupational census data and employer records.[48,49] The probabilistic nature of the CDA JEM means that CDA exposure was based on likelihood of exposure rather than on quantifiable data sources. This type of exposure assessment could have led to exposure misclassifications that may have weakened a potential exposure-response pattern. A major limitation of our study is also the lack of work history and CDA exposure data in the NOPW cohort during follow-up. This lack of exposure information may be a source of misclassification that could have masked a potential dose-response association.

Conclusion

To our knowledge, this is the first prospective study examining the association between the night and rotating shift work patterns of offshore petroleum workers and aggressive prostate cancer hazard. We found that exposure to rollover shift work was associated with an increased hazard compared with day work only, and that the hazard estimates were highest for long-term exposure. Additionally, we found no association between CDA exposure and aggressive prostate cancer hazard. Our findings are supported by recent discussions regarding recommendations for fewer consecutive night shifts and longer shift intervals as measures to reduce cancer risk among shift workers.[50]

Ethics approval

All cohort members provided informed consent for participation in the study. Necessary legal and ethical approvals were obtained from the Regional Committee for Medical Research Ethics (2018/1162), the Norwegian Data Inspectorate and the Norwegian Directorate of Health. The linkage key for the 11-digit PINs was stored and governed by a third party unavailable to the research team. All data management and analyses were conducted on data with no individual person identified. All results are distributed on a group level, without any possibilities for individual identification.

Data availability

The data are available as presented in the paper. According to Norwegian legislation, our approvals to use the data for the current study do not allow us to distribute or make the data directly available to other parties.

Supplementary data

Supplementary data are available at *IJE* online.

Author contributions

J.S.S. and T.K.G conceived of the study. J.S.S., T.K.G. and M.B.V. designed the study and directed its implementation. L.A.M.B., F.C.L. and R.B. conducted all data management and constructed the shift work exposure variables. L.A.M.B., F.C.L., J.S.S., T.K.G., M.B.V., N.C.S. and N.K.S. designed the analytical strategy. All authors helped interpret the findings. L.A.M.B. conducted all statistical analyses and the literature review. L.A.M.B., F.C.L., J.S.S., T.K.G., M.B.V. and N.C.S. drafted the Introduction, Methods, Results and Discussion sections. R.B., K.K.,T.E.R., R.G., H.D.H., S.O.S., D.T.S., M.C.F. and N.K.S. reviewed and critically revised the manuscript. All authors gave final approval of the version to be published and agreed to be accountable for all aspects of the work. L.A.M.B. is the guarantor.

Funding

This work was supported by the Research Council of Norway [grant number 280537].

Acknowledgements

We wish to thank Professor Magne Bråtveit and Researcher Jorunn Kirkeleit at the University of Bergen, Norway, for their expertise and advice.

Conflict of interest

None declared.

References

1. Sung H, Ferlay J, Siegel RL *et al.* Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;**71**:209–49.
2. Koutros S, Beane Freeman LE, Lubin JH *et al.* Risk of total and aggressive prostate cancer and pesticide use in the agricultural health study. *Am J Epidemiol* 2013;**177**:59–74.
3. Patel AR, Klein EA. Risk factors for prostate cancer. *Nat Clin Pract Urol* 2009;**6**:87–95.
4. Radican L, Blair A, Stewart P, Wartenberg D. Mortality of aircraft maintenance workers exposed to trichloroethylene and other hydrocarbons and chemicals: extended follow-up. *J Occup Environ Med* 2008;**50**:1306–19.
5. Tachachartvanich P, Sangsuwan R, Ruiz HS *et al.* Assessment of the endocrine-disrupting effects of trichloroethylene and its metabolites using in vitro and in silico approaches. *Environ Sci Technol* 2018;**52**:1542–50.
6. IARC. Night shift work. *IARC Monogr Identif Carcinog Hazards Hum* 2020;**124**:1–371.
7. Barul C, Richard H, Parent ME. Night-shift work and risk of prostate cancer: results from a Canadian case-control study, the prostate cancer and environment study. *Am J Epidemiol* 2019;**188**:1801–11.
8. Behrens T, Rabstein S, Wichert K *et al.* Shift work and the incidence of prostate cancer: a 10-year follow-up of a German population-based cohort study. *Scand J Work Environ Health* 2017;560–68.

9. Dickerman BA, Markt SC, Koskenvuo M *et al.* Sleep disruption, chronotype, shift work, and prostate cancer risk and mortality: a 30-year prospective cohort study of Finnish twins. *Cancer Causes Control* 2016;**27**:1361–70.
10. Papantoniou K, Castaño-Vinyals G, Espinosa A *et al.* Night shift work, chronotype and prostate cancer risk in the MCC-Spain case-control study. *Int J Cancer* 2015;**137**:1147–57.
11. Wendeu-Foyet MG, Bayon V, Cénée S *et al.* Night work and prostate cancer risk: results from the EPICAP Study. *Occup Environ Med* 2018;**75**:573–81.
12. Åkerstedt T, Narusyte J, Svedberg P, Kecklund G, Alexanderson K. Night work and prostate cancer in men: a Swedish prospective cohort study. *BMJ Open* 2017;**7**:e015751.
13. Lozano-Lorca M, Olmedo-Requena R, Vega-Galindo M-V *et al.* Night shift work, chronotype, sleep duration, and prostate cancer risk: CAPLIFE Study. *Int J Environ Res Public Health* 2020; **17**:6300.
14. Dun A, Zhao X, Jin X *et al.* Association between night-shift work and cancer risk: updated systematic review and meta-analysis. *Front Oncol* 2020;**10**:1006.
15. Rivera-Izquierdo M, Martínez-Ruiz V, Castillo-Ruiz EM, Manzaneda-Navío M, Pérez-Gómez B, Jiménez-Moleón JJ. Shift work and prostate cancer: an updated systematic review and meta-analysis. *Int J Environ Res Public Health* 2020;**17**:1345.
16. Mancio J, Leal C, Ferreira M, Norton P, Lunet N. Does the association of prostate cancer with night-shift work differ according to rotating vs. fixed schedule? A systematic review and meta-analysis. *Prostate Cancer Prostatic Dis* 2018;**21**:337–44.
17. Gan Y, Li L, Zhang L *et al.* Association between shift work and risk of prostate cancer: a systematic review and meta-analysis of observational studies. *Carcinogenesis* 2018;**39**:87–97.
18. Jahn JL, Giovannucci EL, Stampfer MJ. The high prevalence of undiagnosed prostate cancer at autopsy: implications for epidemiology and treatment of prostate cancer in the prostate-specific antigen-era. *Int J Cancer* 2015;**137**:2795–802.
19. Hurwitz LM, Agalliu I, Albanes D *et al.*; Prostate Cancer Cohort Consortium (PC3) Working Group. Recommended definitions of aggressive prostate cancer for etiologic epidemiologic research. *J Natl Cancer Inst* 2021;**113**:727–34.
20. Stenehjem JS, Babigumira R, Hosgood HD *et al.* Cohort Profile: Norwegian Offshore Petroleum Workers (NOPW) cohort. *Int J Epidemiol* 2021;**50**:398–99.
21. Borgan O, Langholz B, Samuelsen SO, Goldstein L, Pogoda J. Exposure stratified case-cohort designs. *Lifetime Data Anal* 2000;**6**:39–58.
22. Larsen IK, Småstuen M, Johannesen TB *et al.* Data quality at the Cancer Registry of Norway: an overview of comparability, completeness, validity and timeliness. *Eur J Cancer* 2009;**45**: 1218–31.
23. Cancer Registry of Norway. *Cancer in Norway 2020: Cancer Incidence, Mortality, Survival and Prevalence in Norway*. Oslo: Cancer Registry of Norway, 2021.
24. Cancer Registry of Norway. *Cancer in Norway 2006: Cancer Incidence, Mortality, Survival and Prevalence in Norway*. Oslo: Cancer Registry of Norway, 2007.
25. Mikkelsen A, Ringstad AJ, Steineke JM. Working time arrangements and safety for offshore workers in the North Sea. *Saf Sci* 2004;**42**:167–84.
26. Stenehjem JS, Babigumira R, Friesen MC, Grimsrud TK. Harmonizing work history data in epidemiologic studies with overlapping employment records. *Am J Ind Med* 2019;**62**: 422–29.
27. Steinsvåg K, Bråtveit M, Moen BE, Kromhout H. Inter-rater agreement in the assessment of exposure to carcinogens in the offshore petroleum industry. *Occup Environ Med* 2007;**64**: 582–88.
28. Steinsvåg K, Bråtveit M, Moen BE. Exposure to carcinogens for defined job categories in Norway's offshore petroleum industry, 1970 to 2005. *Occup Environ Med* 2007;**64**:250–58.
29. Checkoway H, Pearce N, Hickey JLS, Dement JM. Latency analysis in occupational epidemiology. *Arch Environ Health* 1990;**45**:95–100.
30. Stenehjem JS, Friesen MC, Eggen T, Kjærheim K, Bråtveit M, Grimsrud TK. Self-reported occupational exposures relevant for cancer among 28,000 offshore oil industry workers employed between 1965 and 1999. *J Occup Environ Hyg* 2015;**12**: 458–68.
31. Hickey K, Do K-A, Green A. Smoking and prostate cancer. *Epidemiol Rev* 2001;**23**:115–25.
32. Harel O, Mitchell EM, Perkins NJ *et al.* Multiple imputation for incomplete data in epidemiologic studies. *Am J Epidemiol* 2018; **187**:576–84.
33. Rubin DB. *Multiple Imputation for Nonresponse in Surveys*. Vol. **81**. Chichester, UK: John Wiley & Sons, 2004.
34. R Core Team. *R: A Language and Environment for Statistical Computing*. (Computer program.) Vienna: R Foundation for Statistical Computing, 2020.
35. Rao D, Yu H, Bai Y, Zheng X, Xie L. Does night-shift work increase the risk of prostate cancer? A systematic review and meta-analysis. *Onco Targets Ther* 2015;**8**:2817–26.
36. Haas GP, Delongchamps N, Brawley OW, Wang CY, de la Roza G. The worldwide epidemiology of prostate cancer: perspectives from autopsy studies. *Can J Urol* 2008;**15**:3866–71.
37. Schernhammer ES, Schulmeister K. Melatonin and cancer risk: does light at night compromise physiologic cancer protection by lowering serum melatonin levels? *Br J Cancer* 2004;**90**:941–43.
38. Shen D, Ju L, Zhou F *et al.* The inhibitory effect of melatonin on human prostate cancer. *Cell Commun Signal* 2021;**19**:34.
39. Barnes RG, Deacon SJ, Forbes MJ, Arendt J. Adaptation of the 6-sulphatoxymelatonin rhythm in shiftworkers on offshore oil installations during a 2-week 12-h night shift. *Neurosci Lett* 1998;**241**:9–12.
40. Wei T, Li C, Heng Y *et al.* Association between night-shift work and level of melatonin: systematic review and meta-analysis. *Sleep Med* 2020;**75**:502–09.
41. Parkes KR. Shiftwork, job type, and the work environment as joint predictors of health-related outcomes. *J Occup Health Psychol* 1999;**4**:256–68.
42. Bhatti P, Mirick DK, Randolph TW *et al.* Oxidative DNA damage during night shift work. *Occup Environ Med* 2017;**74**:680–83.
43. Bhatti P, Zhang Y, Song X *et al.* Nightshift work and genome-wide DNA methylation. *Chronobiol Int* 2015;**32**:103–12.
44. Samulin Erdem J, Notø HØ, Skare Ø *et al.* Mechanisms of breast cancer risk in shift workers: association of telomere shortening with the duration and intensity of night work. *Cancer Med* 2017;**6**:1988–97.

45. Herrero L, Valcarcel L, da Silva CA *et al.* Altered circadian rhythm and metabolic gene profile in rats subjected to advanced light phase shifts. *PLoS One* 2015;**10**:e0122570-e0122570.
46. Papantoniou K, Pozo OJ, Espinosa A *et al.* Increased and mistimed sex hormone production in night shift workers. *Cancer Epidemiol Biomarkers Prev* 2015;**24**:854–63.
47. Sweeney MF, Hasan N, Soto AM, Sonnenschein C. Environmental endocrine disruptors: Effects on the human male reproductive system. *Rev Endocr Metab Disord* 2015;**16**: 341–57.
48. Wärneryd B, Thorslund M, Ostlin P. The quality of retrospective questions about occupational history: a comparison between survey and census data. *Scand J Soc Med* 1991;**19**: 7–13.
49. Hobson AJ, Sterling DA, Emo B *et al.* Validity and reliability of an occupational exposure questionnaire for parkinsonism in welders. *J Occup Environ Hyg* 2009;**6**:324–31.
50. Garde AH, Begtrup L, Bjorvatn B *et al.* How to schedule night shift work in order to reduce health and safety risks. *Scand J Work Environ Health* 2020;**46**:557–69.