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Benzene exposure and risk of lung cancer in the Norwegian Offshore Petroleum Worker cohort: a prospective case-cohort study

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ABSTRACT

Objective The objective of our study was to examine whether occupational exposure to benzene is associated with lung cancer among males in the Norwegian Offshore Petroleum Workers cohort.

Methods Among 25 347 male offshore workers employed during 1965–1998, we conducted a case-cohort study with 399 lung cancer cases diagnosed between 1999 and 2021, and 2035 non-cases sampled randomly by 5-year birth cohorts. Individual work histories were coupled to study-specific job-exposure matrices for benzene and other known lung carcinogens. Weighted Cox regression was used to estimate HRs and 95% CIs for the associations between benzene exposure and lung cancer, by major histological subtypes, adjusted for age, smoking and occupational exposure to welding fumes, asbestos and crystalline silica. Missing data were imputed.

Results For lung cancer (all subtypes combined), HRs (95% CIs) for the highest quartiles of benzene exposure versus unexposed were 1.15 (0.61 to 2.35) for cumulative exposure, 1.43 (0.76 to 2.69) for duration, and 1.22 (0.68 to 2.18) for average intensity ($0.280 \leq P\text{-trend} \leq 0.741$). For 152 adenocarcinoma cases, a positive trend was observed for exposure duration ($P\text{-trend}=0.044$).

Conclusions In this cohort of offshore petroleum workers generally exposed to low average levels of benzene, we did not find an overall clear support for an association with lung cancer (all subtypes combined), although an association was suggested for duration of benzene exposure and adenocarcinoma. The limited evidence might be due to restricted statistical power.

INTRODUCTION

Offshore crude oil and natural gas production has been carried out in the North Sea since the early 1970s. Benzene is a natural component of the petroleum stream and exposure in the offshore work environment may occur during drilling, production, control and maintenance of the process systems that separate crude oil, natural gas, condensate and produced water.^{1,2}

In its 2017 evaluation of benzene, the International Agency for Research on Cancer (IARC) reaffirmed the classification of benzene as a group

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Benzene is a known human carcinogen; however, the evidence for an association between benzene and lung cancer risk remained unclear in the latest evaluation of benzene by the International Agency for Research on Cancer.

WHAT THIS STUDY ADDS

⇒ This study investigated the association between occupational benzene exposure and the risk of lung cancer. Only limited evidence was found of an association between low-level benzene exposure and risk of lung cancer, suggested for adenocarcinoma and duration of benzene exposure.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Risk estimates were generally non-significantly above unity, so it is important to continue monitoring benzene levels in the workplace. Our findings for adenocarcinoma motivate future prospective analyses in large datasets with adequate confounder control to better understand a possible association between benzene and lung cancer.

1 carcinogen, primarily based on observational studies showing dose–response associations with lymphohaematopoietic cancers, strongly supported by mechanistic data.^{3,4} The IARC noted a dissension in the Working Group about whether a positive association between benzene and lung cancer was observed, as confounding could not be ruled out.³

The IARC evaluation was based on conflicting results where excesses in lung cancer incidence had been reported with varying quality of benzene exposure assessment. For lung cancer mortality, excesses have been reported among benzene-exposed workers in the UK, China and USA.^{5–7} We have reported an 8% overall excess of lung cancer incidence among Norwegian Offshore Petroleum Workers (NOPW) compared with the general



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population,⁸ while similar studies in British, Canadian and Australian petroleum workers have not.^{9–11} IARC highlighted the need for adequate control for potential confounding by smoking or other occupational lung carcinogens, lacking in most previous studies.³

After the IARC benzene evaluation, Warden *et al* reported a positive association between occupational exposure to benzene, toluene, and xylene (BTX) and lung cancer in a population-based case-control study with an expert-based retrospective exposure assessment.¹² Recently, the SYNERGY project reported results with consistently increased risks of lung cancer according to various metrics of benzene exposure based on a large pooled population-based case-control study.¹³

In the present study, we prospectively examined the association between benzene exposure and lung cancer among males in the NOPW cohort. We used incidence data from a nationwide cancer registry, exposure information from expert-developed study-specific job-exposure matrices (JEMs) of benzene and lung carcinogens, and data on smoking history for each worker.

METHODS

The NOPW cohort

The NOPW cohort comprises 27917 workers engaged in offshore work for at least 20 days between 1965 and 1998. The cohort was recruited in 1998 (baseline) using a questionnaire sent to current and former offshore workers (estimated response rate 69%).¹⁴ The questionnaire covered work history, sociodemographic factors and lifestyle habits and has been described in detail previously.⁸

All workers in the NOPW cohort gave informed consent for a prospective follow-up.

Study design

Each worker reported work histories for up to eight positions offshore, but work histories other than the first and last positions had to be manually extracted. The 2570 female workers were excluded as few were engaged in work with a potential for benzene exposure. Among the 25347 male workers, we randomly drew a subcohort (n=2268 before exclusions) within strata of 5-year birth cohorts. A stratified case-cohort design allowed us to obtain complete work histories for all lung cancer cases and the subcohort with a close to negligible loss of statistical efficiency.¹⁵

Follow-up and lung cancer

The cohort was linked to the Cancer Registry of Norway (CRN) and the National Population Registry using Norwegian residents' unique 11-digit personal identification number for cancer incidence, emigration and death. Reporting of incident cancer cases to the CRN has been mandatory by law since 1952, securing national data from 1953 onwards.¹⁶ CRN cancer data are accurate, virtually complete and timely, with verified morphology for 90.4% of the lung cancer cases.¹⁷ Cases were defined as first primary lung cancer (International Classification of Diseases 10th revision (ICD-10) code C34) diagnosed between 1 July 1999 and 31 December 2021 (end of follow-up). Histological subtypes of lung cancer were defined according to the ICD-Oncology 3rd revision (ICD-O-3) codes and the major subtypes were grouped into adenocarcinoma, squamous cell carcinoma and small cell carcinoma (ICD-O-3 codes in online supplemental table S1).

Study samples

From the case-cohort dataset of 538 lung cancer cases and 2268 subcohort members, we excluded workers according

to the criteria shown in figure 1. Lung cancer cases occurring among workers randomly drawn to the subcohort were removed from the subcohort (exclusion i) and analysed as cases only as described in Borgan *et al*.¹⁵ The final study sample included 399 male lung cancer cases and 2035 male subcohort non-cases. We applied the same set of exclusions for analyses of the major histological subtypes of lung cancer, restricting the cases to the subtype under study (online supplemental figures S1a–S1c).

Exposure assessment

Job-exposure matrices

In 2005, a group of industrial hygienists developed expert-based JEMs using a probability-oriented approach owing to the paucity of measurement data.¹⁸ JEM-ratings for benzene, asbestos, crystalline silica and welding fumes were developed for 27 job categories (defined by job positions reported in the 1998 survey) and 10-year time periods (1970–1999). For each combination of agent, job category and time period, experts assessed the likelihood of exposure as unlikely=0; possible=1; probable=2 (ie, $\geq 50\%$ of the job category were exposed); and probable=3 (those with the highest relative exposure among jobs with probable exposure). The assessments were based on individual and plenary interpretations of summary documents by industrial hygienists (eg, company visits/interviews, risk assessment reports, sampling reports, product data sheets). Details on the development of the probability-oriented JEMs have been published previously.^{2 19–21}

In 2011, the benzene and asbestos JEMs were refined using a task-oriented approach.^{18 22} By including information from measurement data and exposure determinants on the task level rather than the job-category level, exposure estimates with greater contrasts between job categories and time periods were obtained. Benzene measurement data were used to assist in scoring determinants for the exposure intensity of the relevant tasks. Subsequently, task duration and frequency were combined to create a semiquantitative benzene exposure burden score specific to job category and time period. The relative contribution from dermal absorption and inhalation was not taken into account in the refined benzene JEM. The semiquantitative ratings of benzene exposure were translated into proportional corresponding estimates of parts per million (ppm) on the basis of the full shift mean benzene exposure for process operators offshore estimated from 204 personal benzene measurements collected in the period 1994 to 2003.^{18 23} Individual work-history data (start, stop, job category) for up to eight employments per worker between 1965 and 1998 were linked to the JEMs. Overlapping employment records were handled by collapsing jobs within the same category and splitting jobs of different categories into proportionally equal parts, according to a previously described method.²⁴

Exposure duration was defined as years exposed to each agent. For all agents, cumulative exposure estimates were derived by multiplying the JEM ratings by days of duration within each year and then by summing the products from start of first employment until either the end of last employment, or 31 December 1998. Average exposure intensities were derived by dividing cumulative exposure by exposure duration. For benzene exposure metrics cumulative, duration and average intensity, the workers were divided into quartiles among exposed workers, and yielding five categories (unexposed and quartiles 1–4). For sensitivity analyses, we extrapolated benzene exposure data for those still employed and exposed in 1998. We assigned the last reported benzene exposure intensity to each year during

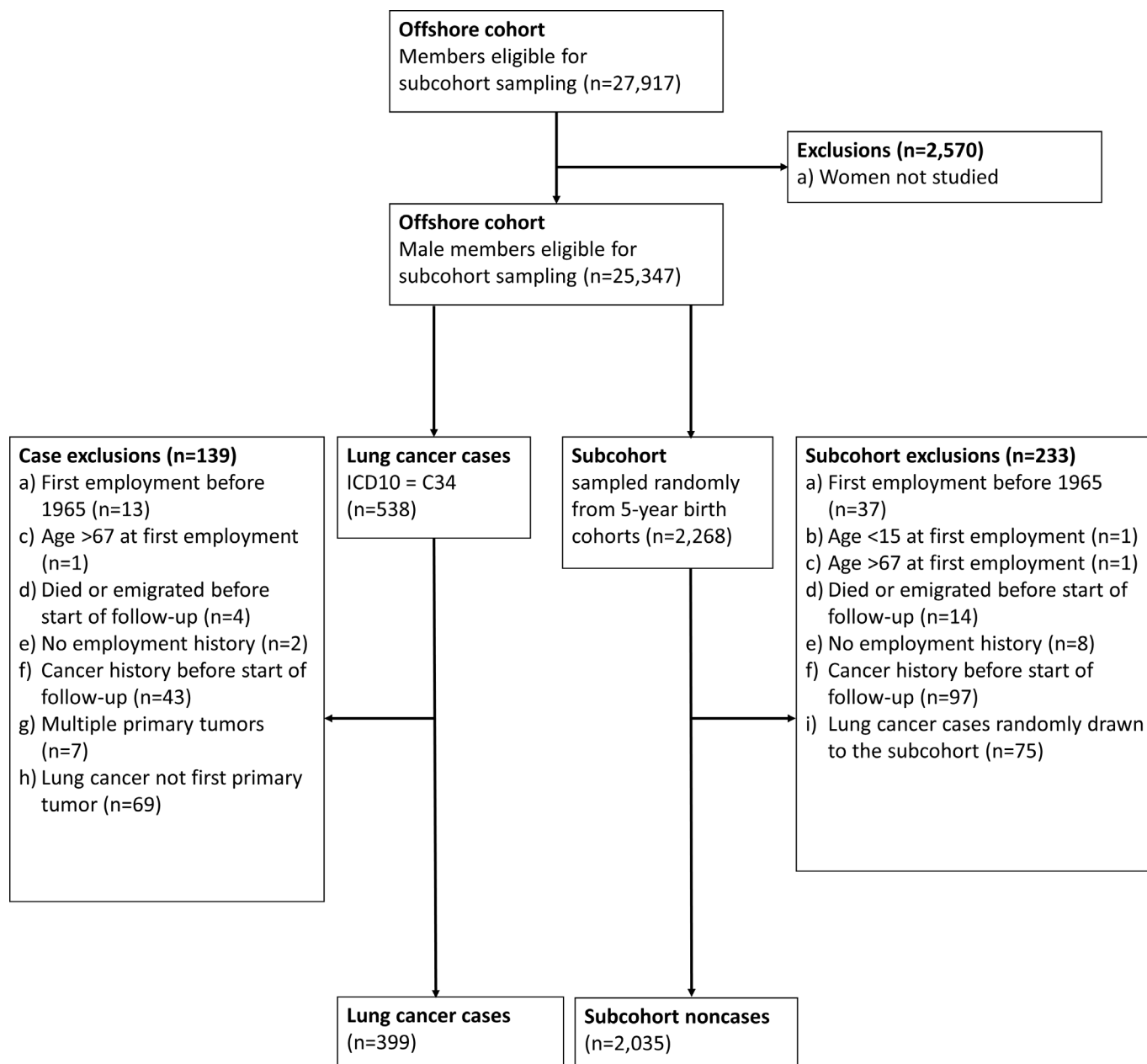


Figure 1 Overview of study design and exclusions. ICD-10, International Classification of Diseases 10th revision.

follow-up, that is, from 1998 until the retirement year (age 67 years), death, emigration, or end of follow-up (2021), whichever came first.

Covariates

The study participants reported daily smoking (yes, no) and the daily number of cigarettes or pipes of tobacco (0, 1–4, 5–9, 10–14, 15–19, 20–24, 25–29, ≥ 30) for each age span (15–19, 20–29, 30–39, 40–49, 50–59, ≥ 60). From these data, we derived individual smoking status at baseline (never, former, current), duration of smoking (years), smoking pack years (years*packs per day (1 pack=20 cigarettes)), and average intensity (defined as pack years/duration for all current smokers at baseline). From status and pack years at baseline, we computed a four-category smoking variable: never/former <15 years duration, former with ≥ 15 years duration, current low (<median of average intensity) and current high (\geq median of average intensity). Education was

recorded in the questionnaire as compulsory, vocational, folk high school and upper secondary (the latter two collapsed into upper secondary), and university/college. We did not address potential confounding from benzene exposures outside offshore work as we previously have found that such occupations had no effect on lymphohematopoietic cancers.²³

Data analysis

Missing data patterns were examined, and we used multiple imputation by chained equations to impute missing observations for smoking (duration and pack years) and education, assuming missing at random. The imputation model included all covariates and case status. The covariates had up to 4% missing; hence, we imputed eight datasets. Weighted Cox proportional hazards regression, adapted to the case-cohort design,¹⁵ was used to estimate HRs and 95% CIs for the associations between lung cancer and smoking metrics and benzene exposure (unexposed,

cumulative, duration, intensity, lagged exposure) on each of the imputed datasets. These results were then combined using Rubin's combination rules.²⁵

We used directed acyclic graphs (DAGs)²⁶ to arrive at three models. In model 1, we adjusted for age only (as the time scale). In model 2, we additionally adjusted for smoking (online supplemental figure S2). In model 3, we further adjusted for exposure to welding fumes, asbestos and crystalline silica (online supplemental figure S3). Although diesel exhaust exposure levels in the Norwegian offshore working environment have been reported to be relatively low,^{27,28} we performed additional analysis with adjustment also for diesel exhaust exposure (online supplemental model 4, figure S4). We also examined the diesel exhaust–lung cancer association for cumulative, duration and average intensity metrics of diesel exhaust, adjusted for age and smoking, and estimated Spearman rank correlation coefficients, r_{sp} , between continuous variables of benzene, crystalline silica, diesel exhaust, welding fumes and asbestos exposure.

We conducted analyses stratified by start of first employment (<1980, ≥1980) to explore whether technical and safety improvements on the Norwegian continental shelf during the 1980s altered the results.²

To explore potential latency of a benzene–lung cancer association, we conducted analyses with time-varying benzene exposure.²⁹ To assess the impact of early exposure, we modelled lagged benzene exposure (10, 15, or 20 years). We also analysed the most recent exposure within 5-year, 10-year or 15-year windows from the start to the end of follow-up, using extrapolated data during follow-up. Finally, we conducted a traditional time-dependent exposure analysis based on extrapolated data during follow-up.

We examined the association between employment duration and lung cancer risk to explore the potential role of a healthy worker survivor effect (HWSE), defined as a continuing selection process where those who remain employed tend to be healthier than those who left employment.³⁰

We tested for trend across exposure categories using the median exposure within each level of the exposure metric. The proportionality assumption was checked using Schoenfeld residuals, log–log plots and Kaplan–Meier survival curves and found satisfactory. Data analyses were performed using Stata V.17.1.³¹

RESULTS

Nearly half of the 399 cases and 2035 non-cases were born in 1940–1949, and mean age at start of follow-up was 51.5 and 53.9 years, respectively (table 1). Non-cases had a higher prevalence of university/college education (19.0%) than the cases (9.5%). There were more current smokers, and fewer never and former smokers among the cases compared with the non-cases. Cases had higher means of pack years and of smoking duration. There were minor differences between cases and non-cases in the year of first employment, and a higher proportion of cases than non-cases worked in maintenance and catering/administration.

The smoking–lung cancer analysis (table 2), yielded age-adjusted HRs (95% CIs) of 12 (6.81 to 20) for current smokers with average intensity < median (13 g/day), and 20 (12 to 34) for current smokers with average intensity ≥ median, compared with those with 0–15 year duration. The estimated HRs were consistently elevated among smokers with a strong and monotonic dose response for the major histological subtypes of lung cancer.

Models 1, 2 and 3 showed similar results in the analyses of benzene exposure and lung cancer risk (table 3), and model 3 results are presented. The HR estimates for all exposure metrics

Table 1 Baseline characteristics of the case-cohort study sample in the Norwegian Offshore Petroleum Workers cohort

Variables	Cases (n=399)	Non-cases (n=2035)
Sociodemographic		
Birth cohort, n (%)		
1910–1919	0 (0.0)	2 (0.1)
1920–1929	6 (1.5)	146 (7.2)
1930–1939	70 (17.5)	475 (23.3)
1940–1949	194 (48.6)	933 (45.8)
1950–1959	103 (25.8)	345 (17.0)
1960–1969	24 (6.0)	117 (5.7)
1970–1979	2 (0.5)	17 (0.8)
Age at start of follow-up (years), mean (SD)	51.5 (8.4)	53.9 (9.7)
Education, n (%)		
Compulsory	102 (25.6)	319 (15.7)
Vocational	192 (48.1)	1031 (50.7)
Upper secondary	65 (16.3)	280 (13.8)
University/college	38 (9.5)	386 (19.0)
Missing	2 (0.5)	19 (0.9)
Smoking status, n (%)		
Never	4 (1.0)	453 (22.3)
Former	107 (26.8)	845 (41.5)
Current	277 (69.4)	667 (32.8)
Missing	11 (2.8)	70 (3.4)
Smoking pack years, mean (SD)*	26.4 (13.8)	15.4 (14.7)
Smoking duration, mean (SD)*	33.5 (12.3)	22.1 (16.9)
Occupational		
Employment duration (years), mean (SD)†	12.2 (7.5)	12.1 (7.4)
Year of first employment, n (%)		
1965–1969	18 (4.5)	58 (2.9)
1970–1974	40 (10.0)	233 (11.4)
1975–1979	150 (37.6)	772 (37.9)
1980–1984	88 (22.1)	432 (21.2)
1985–1989	62 (15.5)	336 (16.5)
1990–1994	28 (7.0)	136 (6.7)
1995–1998	13 (3.3)	68 (3.3)
Main activity last position, n (%)		
Production	29 (7.3)	178 (8.7)
Drilling	29 (7.3)	181 (8.9)
Maintenance	226 (56.6)	1037 (51.0)
Catering/office/administration	64 (16.0)	288 (14.2)
Miscellaneous	46 (11.5)	326 (16.0)
Missing	5 (1.3)	25 (1.2)
*Missing in continuous variables: smoking pack years (n=81), smoking duration (n=81).		
†Duration calculated using complete work history data.		

and lung cancer were non-significantly close to or above unity with no indication of a trend (P-trend=0.631, 0.280 and 0.741 for cumulative, duration and intensity, respectively).

No significant trends were found for benzene exposure and squamous cell carcinoma or small cell carcinoma ($0.156 \leq P\text{-trend} \leq 0.914$) (table 4). A significant positive trend was found for duration of benzene exposure and adenocarcinoma (P-trend=0.044), the histological subgroup with the highest number of cases. The highest HR was found in the upmost quartile (HR=2.02, 95% CI 0.80 to 5.11).

The results of the analyses with additional adjustment for diesel exhaust exposure (online supplemental table S2) were

Table 2 HRs with 95% CIs for lung cancer and major subtypes according to smoking variables among males in the Norwegian Offshore Petroleum Workers (NOPW) cohort, 1999–2021

	All lung cancers (n=399)	Adenocarcinoma (n=152)	Squamous cell carcinoma (n=88)	Small cell carcinoma (n=62)
	HR* (95% CI)	HR* (95% CI)	HR* (95% CI)	HR* (95% CI)
Smoking†				
Never/Former (0–15 years duration)	1.00 (reference)	1.00 (reference)	1.00 (reference)	NA‡
Former (≥15 years duration)	6.25 (3.64 to 11)	7.51 (3.15 to 18)	4.02 (1.33 to 12)	1.00 (reference)
Current (avg. int.<median avg. int.)§	12 (6.81 to 20)	13 (5.60 to 31)	9.91 (3.40 to 29)	4.24 (2.09 to 8.60)
Current (avg. int.≥median avg. int.)§	20 (12 to 34)	18 (7.83 to 43)	23 (8.00 to 63)	8.58 (4.46 to 17)
*Adjusted for age (as the time scale).				
†Variable constructed by splitting former smokers into </≥15 years duration and current smokers into </≥median average intensity (0.65). Missing values (n=81) were imputed.				
‡Not applicable (no cases).				
§Median=13 g of tobacco per day.				
avg. int., average intensity; yrs, years.				

similar to the model 3 results. Moderate correlation was found between benzene and diesel exhaust exposure metrics (online supplemental figure S5 and table S9): $r_{sp}=0.41$ for (cumulative), $r_{sp}=0.51$ for (duration) and $r_{sp}=0.33$ (average intensity). No association was found between diesel exhaust and lung cancer for any of the diesel exhaust metrics ($0.416 \leq P\text{-trend} \leq 0.427$, model 2, online supplemental table S3), supporting the above analyses with model 3 as the main model.

Analysis stratified by year of first employment before or after 1980 (online supplemental tables S4a and S4b, Model 3) showed similar results, although HRs for Q3 and Q4 were elevated among those starting before 1980.

Estimates generally decreased with increasing lag period for lung cancer overall according to cumulative and duration exposure of benzene (online supplemental table S5a, Model 3) with no statistically significant trends ($0.121 \leq P\text{-trend} \leq 0.953$). Lagged analyses by histological subtype did not reveal any clear patterns (online supplemental table S5b). For adenocarcinoma, estimates were largest in the 10-year lag while for squamous cell carcinoma, estimates were mostly below unity.

We examined the effect of recent benzene exposure in 5-year, 10-year and 15-year windows before observation (online supplemental table S6, Model 3). In all windows, Q1 were consistently higher than Q4, but with some fluctuations in the middle

Table 3 HRs with 95% CIs of lung cancer according to benzene exposure among males in the Norwegian Offshore Petroleum Workers cohort, 1999–2021

Benzene metric	Cases/non-cases	Model 1*	Model 2†	Model 3‡
		HR§ (95% CI)	HR§ (95% CI)	HR§ (95% CI)
Cumulative (ppm years)				
Unexposed	112/655	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q1 (0.000–<0.019)	85/332	1.36 (1.00 to 1.85)	1.34 (0.96 to 1.86)	1.47 (0.90 to 2.40)
Q2 (0.019–<0.071)	72/345	1.26 (0.92 to 1.75)	1.27 (0.90 to 1.79)	1.30 (0.75 to 2.26)
Q3 (0.071–<0.175)	63/354	1.09 (0.78 to 1.52)	1.07 (0.75 to 1.51)	1.18 (0.64 to 2.15)
Q4 (0.176–0.879)	67/349	1.19 (0.86 to 1.64)	1.17 (0.84 to 1.65)	1.15 (0.61 to 2.16)
<i>P-trend</i>		0.815	0.859	0.631
Duration (years)				
Unexposed	112/655	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q1 (1–4)	69/382	0.99 (0.72 to 1.37)	1.01 (0.72 to 1.43)	1.14 (0.67 to 1.95)
Q2 (5–10)	85/366	1.41 (1.04 to 1.92)	1.36 (0.99 to 1.89)	1.55 (0.93 to 2.61)
Q3 (11–16)	64/301	1.24 (0.89 to 1.74)	1.26 (0.88 to 1.79)	1.56 (0.90 to 2.70)
Q4 (17–34)	69/331	1.33 (0.96 to 1.84)	1.26 (0.89 to 1.77)	1.43 (0.76 to 2.69)
<i>P-trend</i>		0.035	0.095	0.280
Average intensity (ppm)				
Unexposed	112/655	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q1 (0.000–<0.004)	90/327	1.47 (1.08 to 2.00)	1.36 (0.98 to 1.88)	1.42 (0.87 to 2.30)
Q2 (0.004–<0.007)	66/351	1.13 (0.82 to 1.57)	1.21 (0.86 to 1.71)	1.41 (0.80 to 2.49)
Q3 (0.007–<0.014)	73/344	1.31 (0.95 to 1.80)	1.19 (0.85 to 1.67)	1.37 (0.77 to 2.46)
Q4 (0.014–0.046)	58/358	1.00 (0.71 to 1.40)	1.07 (0.75 to 1.52)	1.22 (0.68 to 2.18)
<i>P-trend</i>		0.485	0.871	0.741
*Adjusted for age (as the time scale).				
†Adjusted for age (as the time scale), smoking.				
‡Adjusted for age (as the time scale), smoking, welding fumes, asbestos and crystalline silica				
§Missing values in covariates were imputed				
Q, quartile.				

Table 4 HRs with 95% CIs of the major histological subtypes of lung cancer according to benzene exposure among males in the Norwegian Offshore Petroleum Workers (NOPW) cohort, 1999–2021

Benzene metric	Adenocarcinoma (n=152)		Squamous cell carcinoma (n=88)		Small cell carcinoma (n=62)	
	C/NC	Model 3* HR† (95% CI)	C/NC	Model 3* HR† (95% CI)	C/NC	Model 3* HR† (95% CI)
Cumulative (ppm years)						
Unexposed	45/665	1.00 (reference)	27/671	1.00 (reference)	14/676	1.00 (reference)
Q1 (0.000–<0.019)	30/341	1.25 (0.60 to 2.61)	19/343	1.03 (0.40 to 2.69)	13/346	1.11 (0.35 to 3.49)
Q2 (0.019–<0.071)	20/355	1.01 (0.44 to 2.29)	21/353	0.73 (0.25 to 2.08)	13/357	1.07 (0.32 to 3.56)
Q3 (0.071–<0.175)	35/359	2.20 (0.98 to 4.90)	5/364	0.19 (0.05 to 0.74)	11/363	0.83 (0.19 to 3.57)
Q4 (0.176–0.879)	22/363	1.27 (0.50 to 3.28)	16/358	0.39 (0.10 to 1.56)	11/362	1.19 (0.32 to 4.33)
<i>P-trend</i>		0.986		0.283		0.642
Duration (years)						
Unexposed	45/665	1.00 (reference)	27/671	1.00 (reference)	14/676	1.00 (reference)
Q1 (1–4)	24/389	0.93 (0.43 to 2.03)	12/392	0.66 (0.20 to 2.17)	12/391	1.11 (0.32 to 3.79)
Q2 (5–10)	28/375	1.39 (0.62 to 3.11)	21/374	1.11 (0.42 to 2.94)	14/379	1.04 (0.33 to 3.27)
Q3 (11–16)	26/313	1.82 (0.80 to 4.17)	11/313	0.83 (0.30 to 2.35)	10/314	1.23 (0.36 to 4.21)
Q4 (17–34)	29/341	2.02 (0.80 to 5.11)	17/339	0.97 (0.24 to 3.90)	12/344	1.32 (0.32 to 5.40)
<i>P-trend</i>		0.044		0.914		0.639
Average intensity (ppm)						
Unexposed	45/665	1.00 (reference)	27/671	1.00 (reference)	14/676	1.00 (reference)
Q1 (0.000–<0.004)	28/337	1.15 (0.56 to 2.38)	22/338	1.00 (0.40 to 2.51)	15/344	1.18 (0.40 to 3.50)
Q2 (0.004–<0.007)	30/362	1.84 (0.81 to 4.17)	13/360	0.73 (0.23 to 2.31)	12/362	1.27 (0.35 to 4.54)
Q3 (0.007–<0.014)	27/353	1.65 (0.70 to 3.91)	17/354	0.66 (0.21 to 2.02)	15/355	1.68 (0.49 to 5.78)
Q4 (0.014–0.046)	22/366	1.34 (0.55 to 3.27)	9/366	0.50 (0.16 to 1.61)	6/367	0.72 (0.19 to 2.79)
<i>P-trend</i>		0.883		0.156		0.323

*Adjusted for age (as the time scale), smoking, welding fumes, asbestos and crystalline silica
†Missing values were imputed
C, cases; NC, non cases; Q, quartile.

categories. For the 15-year windows, Q1 were elevated for both cumulative (HR=1.60, 95% CI 1.10 to 2.33) and average intensity (HR=1.21, 95% CI 0.79 to 1.87) of exposure.

We analysed benzene exposure as a time-varying covariate with no lags or windows, using extrapolated data during follow-up for workers still active in 1998 (online supplemental table S7, Model 3). The overall results showed slightly increased estimates in Q1, Q2 and Q3, but with a drop in Q4 for cumulative exposure and exposure duration.

Lung cancer risk according to employment duration (online supplemental table S8), showed no clear pattern with lung overall or small cell carcinoma, but showed a suggestive upward trend for adenocarcinoma and a downward trend for small cell carcinoma.

There were moderate correlations between benzene and other occupational coexposures cumulative ($0.0376 \leq r_{sp} \leq 0.6608$), duration ($0.2420 \leq r_{sp} \leq 0.8026$) and average intensity ($-0.0504 \leq r_{sp} \leq 0.6175$) (online supplemental table S9).

DISCUSSION

In this large prospective cohort study, with cancer incidence data, industry-specific expert-derived JEMs, and detailed smoking history, we only found limited evidence for an association between low-level exposure to benzene (<0.050 avg. ppm and <1 ppm yrs) and lung cancer (all subtypes combined), although the estimates in the preferred DAG-based model with no lagged exposure or exposure windows, were generally above unity. Exposure duration seemed to yield a more dose–response like pattern than cumulative and average intensity of exposure, and an association was suggested for adenocarcinoma with

exposure duration, although no clear pattern was seen for the other histological subtypes. Sensitivity analyses of time of first employment, lagged exposure, most recent exposure and time-varying exposure did not add much to the main findings.

A key component of the IARC 2017 evaluation was the studies conducted in the large historical cohort of benzene-exposed workers in China.^{6,32} In the first follow-up (1972–1987), a 70% increase in lung cancer mortality was reported among those exposed to ≥ 400 ppm years compared with the unexposed.⁶ In the second follow-up (1972–1999), this persisted, where Linet *et al* reported a 50% significantly increased lung cancer mortality among benzene-exposed workers.³² However, in the latest follow-up, participants were classified as either ‘ever exposed’ or ‘never exposed’ based on whether the factory they worked in used benzene.³² Further, smoking data were lacking, which may have contributed to the increased lung cancer mortality. These limitations and the higher benzene exposure levels in the Chinese cohort, which covered a wide range of industries across over 600 factories, may explain the differences between these results and the present study.

In a population-based case-control study of lung cancer in Montreal, lung cancer was associated with exposure to benzene after adjustment for smoking.¹² The authors noted that their results suggested that exposure to benzene, toluene or xylene (each agent assessed separately) were associated with modest increases in lung cancer risk and that smoking did not clearly modify the effects of BTX exposures.¹²

Results from the SYNERGY project¹³ showed that risks of lung cancer increased consistently for all histological subtypes and for different metrics of occupational benzene exposure. Their

analyses were adjusted for age, sex, smoking and other known occupational lung carcinogens. Wan *et al* reported a decline in risk with increasing time since last exposure,¹³ while we were not able to confirm this pattern by looking only at the most recent exposure. Similar to our results, adenocarcinoma increased with increasing exposure duration. Compared with 0.879 ppm years for quartile 4 seen in our data, Wan *et al* reported >5 ppm years in their top category. The lower exposure levels in the NOPW cohort, compared with SYNERGY, and the substantially lower number of cases may explain the lack of a more consistent exposure–risk pattern seen in our data.

The studies conducted in China, Montreal and by the SYNERGY project all reported elevated risks of lung cancer associated with occupational benzene exposure.^{12 13 32} However, these studies had higher exposure levels and/or more lung cancer cases/deaths than we observed in our cohort. The effect size of the association between benzene and lung cancer is suggested to be moderate, which may hamper the possibility to observe risk patterns consistent with those seen in the large studies.

Benzene is an established leukemogen and known to have toxic effects on blood and bone marrow found at lower levels than earlier expected.³³ Accordingly, we have previously observed an association between benzene and lymphohaematopoietic cancers in the NOPW cohort.²³ Further, benzene has been shown to be genotoxic,³⁴ and to be associated with alterations to telomere length.³⁵ Also, increased telomerase activity has been shown in fibroblast-like human LL24 lung cell lines exposed to benzene, but not in human alveolar epithelial adenocarcinoma.³⁶ A biological explanation for the increased risk estimates of adenocarcinoma observed in our study is therefore difficult to find, but the systemic effect of benzene may be more important than direct epithelial contact through inhalation, as it seems to be when intraperitoneal injection of benzene in male rodents has been found to induce lung adenomas.³⁷

Strengths of the NOPW cohort include extensive information on work history and potential confounding factors; industry-specific JEMs developed for the NOPW cohort, which have proven useful in detecting an association between benzene and lymphohaematopoietic cancers; the prospective case-cohort study design that precludes differential recall bias between cases and non-cases; and linkage to a nationwide cancer registry with high validity. In addition, socioeconomic status (SES) is relatively homogenous within the cohort, which reduces the potential for confounding by SES as opposed to population-based studies where several countries, industries and occupational groups contribute. We conducted a rigorous set of sensitivity analyses, but they did not materially differ from our main results.

Limitations include exposure misclassification resulting from self-reporting of work histories, some of which started 30 years before baseline in 1998, although reporting of work histories has been found to be robust.³⁸ The stronger association seen for the duration metric, compared with the cumulative metric, may also be due to misclassifications in the JEM-ratings. Also, the lack of exposure data during follow-up, may have resulted in exposure misclassification, as partly seen in our sensitivity analysis with extrapolated data during follow-up where estimates for Q4 slightly dropped compared with the main analysis. As the NOPW cohort was relatively young in 1998 and included only those who were alive, lung cancer occurring during the first three decades of petroleum activity was not covered, and we cannot rule out bias from the HWSE due to left truncation (delayed entry). However, our analyses of lagged exposure duration showed that estimates in Q4 increased slightly with increasing lag time, supporting a weak HWSE. Furthermore, estimates for

overall lung cancer dropped slightly with employment duration, suggesting a weak HWSE.

In this cohort of offshore petroleum workers with low average exposure levels to benzene, we found generally non-significantly increased risks of lung cancer, except for duration of benzene exposure and adenocarcinoma, the largest histological subgroup. The moderate risk levels seen in other studies suggest that our study has limitations linked to statistical power.

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Contributors JSS and TKG conceived the study. All authors contributed to the project design. RB performed the data management and data analyses. MB and JK contributed to chemical exposure assessment. RB drafted the manuscript and all authors reviewed and revised it critically for important intellectual content and approved the final version for submission. RB and JSS are the guarantors.

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Competing interests None declared. However, coauthors JSS (PI) and TKG (co-PI), were awarded an industry-collaborative grant by the Research Council of Norway (RCN, a governmental agency) in 2019 to establish an updated cohort of offshore petroleum workers. The petroleum industry and RCN provided 20% (US\$175 000) and 80% (US\$700 000), respectively. The RCN governed the application process independently. The grant covers the PhD position for coauthor RB.

Patient consent for publication Not applicable.

Ethics approval This study was performed at the CRN after legal and ethical approvals were obtained from the Norwegian Data Inspectorate, the Regional Committee for Medical Research Ethics (no. 136984), and the Norwegian Directorate of Health. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data may be obtained from a third party and are not publicly available. The data that support the findings of this study are available from the CRN (cohort data and cancer data) and the National Population Register (death and emigration data) but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Requests for data sharing/case pooling for projects with necessary approvals and legal basis according to the EU General Data Protection Regulation (GDPR) may be directed to principal investigator Dr Jo S Stenehjøm; email: jo.stenehjøm@krefregisteret.no.

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REFERENCES

- Bråtveit M, Kirkeleit J, Hollund BE, et al. Biological monitoring of benzene exposure for process operators during ordinary activity in the upstream Petroleum industry. *Ann Occup Hyg* 2007;51:487–94.
- 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;64:250–8.
- IARC. *Benzene iarc monographs on the evaluation of carcinogenic risks to humans*. Lyon, France: IARC, 2018.
- Smith MT, Guyton KZ, Gibbons CF, et al. Key characteristics of Carcinogens as a basis for organizing data on mechanisms of carcinogenesis. *Environ Health Perspect* 2016;124:713–21.
- Collins JJ, Ireland B, Buckley CF, et al. Lymphohaematopoietic cancer mortality among workers with benzene exposure. *Occup Environ Med* 2003;60:676–9.
- Hayes RB, Yin SN, Dosemeci M, et al. Mortality among benzene-exposed workers in China. *Environ Health Perspect* 1996;104 Suppl 6(Suppl 6):1349–52.
- Sorahan T, Kinlen LJ, Doll R. Cancer risks in a historical UK cohort of benzene exposed workers. *Occup Environ Med* 2005;62:231–6.
- Stenehjem JS, Babigumira R, Hosgood HD, et al. Cohort profile: Norwegian offshore Petroleum workers (Nopw) cohort. *Int J Epidemiol* 2021;50:398–9.
- Gun RT, Pratt N, Ryan P, et al. Update of mortality and cancer incidence in the Australian Petroleum industry cohort. *Occup Environ Med* 2006;63:476–81.
- Lewis RJ, Schnatter AR, Drummond I, et al. Mortality and cancer morbidity in a cohort of Canadian Petroleum workers. *Occup Environ Med* 2003;60:918–28.
- Sorahan T, Nichols L, Harrington JM. Mortality of United Kingdom oil refinery and Petroleum distribution workers, 1951–1998. *Occup Med (Chic Ill)* 2002;52:333–9.
- Warden H, Richardson H, Richardson L, et al. Associations between occupational exposure to benzene, toluene and xylene and risk of lung cancer in Montréal. *Occup Environ Med* 2018;75:696–702.
- Wan W, Peters S, Portengen L, et al. Occupational benzene exposure and lung cancer risk: A pooled analysis of 14 case-control studies. *Am J Respir Crit Care Med* October 9, 2023.
- Stenehjem JS, Kjaerheim K, Rabanal KS, et al. Cancer incidence among 41,000 offshore oil industry workers. *Occupational Medicine* 2014;64:539–45.
- Borgan O, Langholz B, Samuelsen SO, et al. Exposure stratified case-cohort designs. *Lifetime Data Anal* 2000;6:39–58.
- Cancer Registry of Norway. Cancer in Norway 2021 - cancer incidence, mortality, survival and prevalence in Norway. Norway, Oslo, 2022.
- Larsen IK, Småstuen M, Johannesen TB, et al. Data quality at the cancer Registry of Norway: an overview of comparability, completeness, validity and timeliness. *European Journal of Cancer* 2009;45:1218–31.
- Bråtveit M, Hollund BE, Kirkeleit J, et al. *Supplementary information to the job exposure matrix for benzene, asbestos and oil mist/oil vapour among norwegian offshore workers*. Bergen, Norway: University of Bergen, 2011. Available: <https://w2.uib.no/filearchive/supplementary-information-to-the-jem-.pdf>
- Steinsvåg K, Bråtveit M, Moen B, et al. Expert assessment of exposure to Carcinogens in Norway's offshore Petroleum industry. *J Expo Sci Environ Epidemiol* 2008;18:175–82.
- Steinsvåg K, Bråtveit M, Moen BE, et al. Inter-Rater agreement in the assessment of exposure to Carcinogens in the offshore Petroleum industry. *Occup Environ Med* 2007;64:582–8.
- Steinsvåg K, Bråtveit M, Moen BE. Eksponering for Kreftfremkallende Faktorer I Norsk offshore Petroleumsvirksomhet, 1970–2005 [exposure to carcinogenic agents in the Norwegian offshore Petroleum industry 1970–2005]. report in Norwegian. 2005.
- Hopf NB, Waters MA, Ruder AM, et al. Development of a retrospective job exposure matrix for Pcb-exposed workers in capacitor manufacturing. *J Occup Health* 2010;52:199–208.
- Stenehjem JS, Kjaerheim K, Bråtveit M, et al. Benzene exposure and risk of Lymphohaematopoietic cancers in 25 000 offshore oil industry workers. *Br J Cancer* 2015;113:1641:1603–12..
- Stenehjem JS, Babigumira R, Friesen MC, et al. Harmonizing work history data in epidemiologic studies with overlapping employment records. *Am J Ind Med* 2019;62:422–9.
- Rubin DB. *Multiple imputation for nonresponse in surveys*. John Wiley & Sons, 2004.
- Textor J, van der Zander B, Gilthorpe MS, et al. Robust causal inference using directed Acyclic graphs: the R package 'Dagitty' *Int J Epidemiol* 2016;45:1887–94.
- Solbu K, Bakke B, Friisk G, et al. Deseleksos I Arbeidsatmosfæren I Norsk Olje- Og Gassindustri – Dagens Eksponeringsbilde. 2012.
- Simensen V, Skaugset NP, Nilsen H, et al. Deseleksoseksponering I Petroleumsnæringen – en Kunnskapsoppsummering. 2023.
- Checkoway H, Pearce N, Hickey JLS, et al. Latency analysis in occupational epidemiology. *Archives of Environmental Health: An International Journal* 1990;45:95–100.
- Arrighi HM, Hertz-Picciotto I. The evolving concept of the healthy worker survivor effect. *Epidemiology* 1994;5:189–96.
- StataCorp. *Stata statistical software: Release 1*. College Station, TX: StataCorp LLC, 2021.
- Linnet MS, Yin S-N, Gilbert ES, et al. A retrospective cohort study of cause-specific mortality and incidence of hematopoietic malignancies in Chinese benzene-exposed workers. *Int J Cancer* 2015;137:2184–97.
- Vermeulen R, Lan Q, Qu Q, et al. Nonlinear low dose Hematototoxicity of benzene; a pooled analyses of two studies among Chinese exposed workers. *Environ Int* 2023;177:108007.
- Rothman N, Haas R, Hayes RB, et al. Benzene induces gene-duplicating but not gene-inactivating mutations at the glycophorin a locus in exposed humans. *Proc Natl Acad Sci USA* 1995;92:4069–73.
- Bassig BA, Zhang L, Cawthon RM, et al. Alterations in Leukocyte Telomere length in workers Occupationally exposed to benzene. *Environ Mol Mutagen* 2014;55:673–8.
- Giuliano M, Stellavato A, Cammarota M, et al. Effects of low concentrations of benzene on human lung cells in vitro. *Toxicol Lett* 2009;188:130–6.
- Huff JE, Eastin W, Roycroft J, et al. Carcinogenesis studies of benzene, methyl benzene, and dimethyl Benzenes. *Ann N Y Acad Sci* 1988;534:427–40.
- Wärnerud 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.

SUPPLEMENTAL MATERIAL

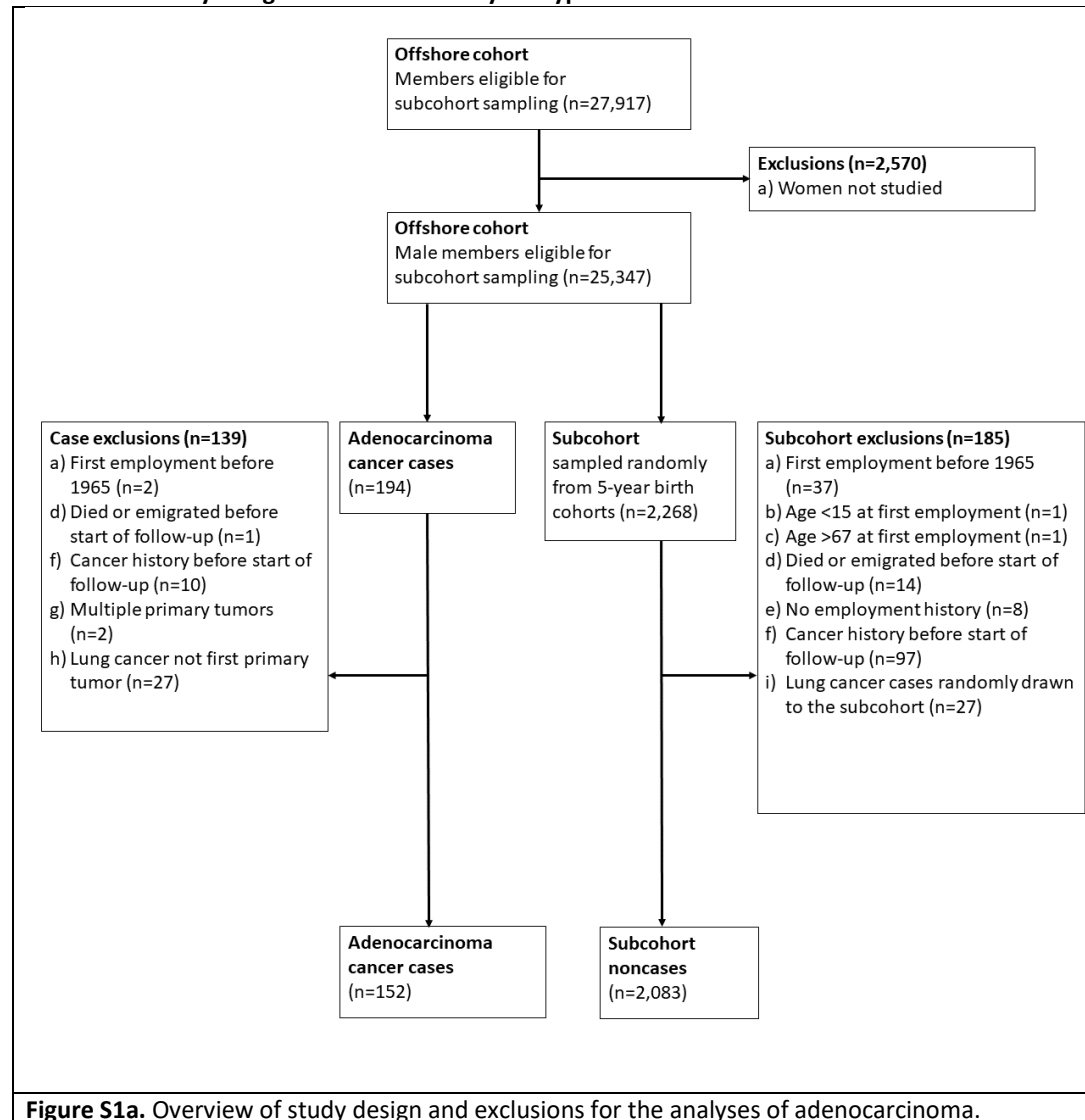
Content

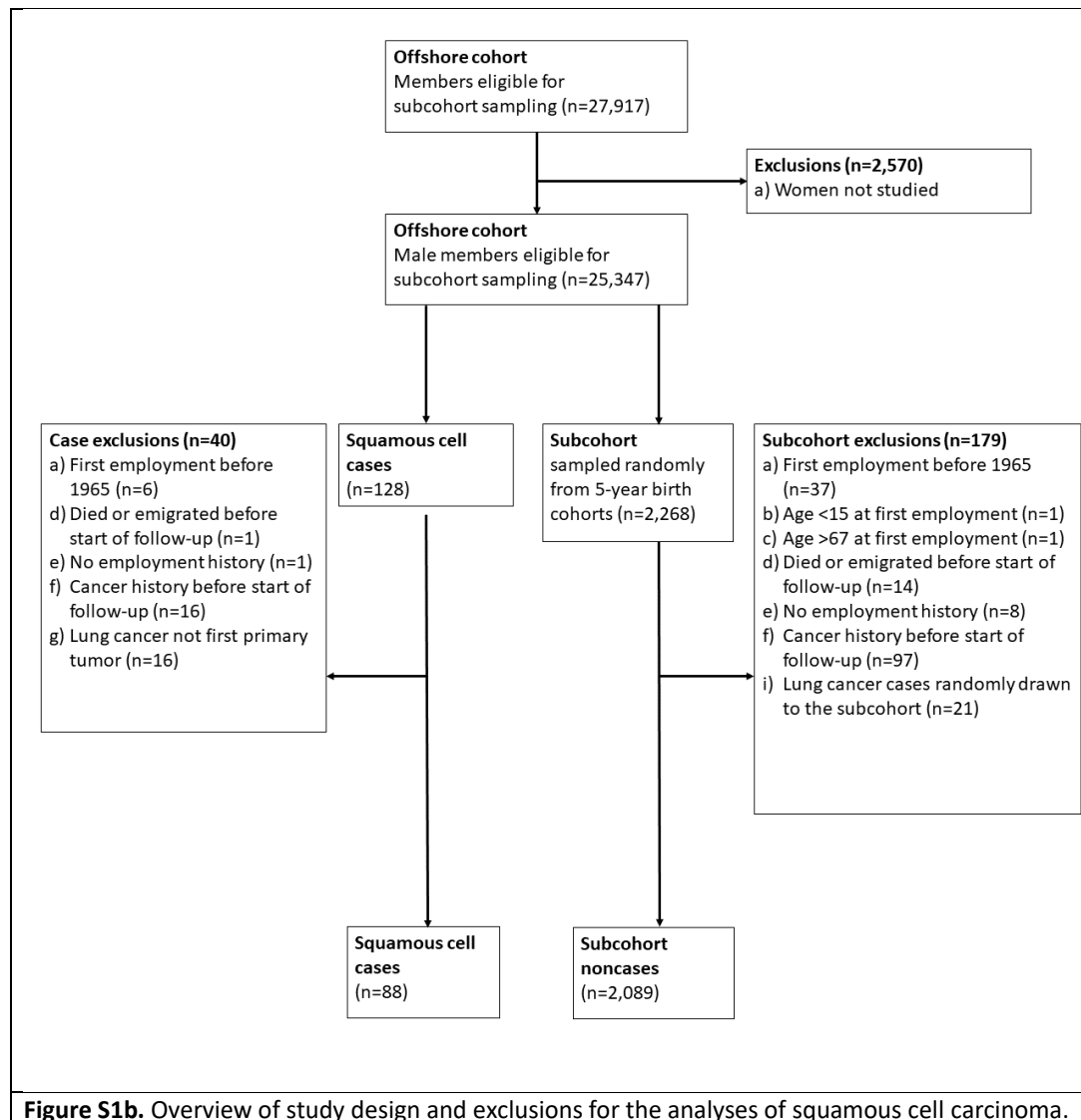
- Table S1: Number of lung cancer cases by histological subtype
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- Diesel exhaust exposure as a potential confounder – Model 4
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 - Tables S3: Diesel exhaust exposure and lung cancer risk
 - Discussion of diesel exhaust as a potential confounder
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 - Table S4b: ≥1980
- Latency analyses with time-varying benzene exposure
 - Table S5a: Lagged analysis
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 - Table S6: Most recent benzene exposure
 - Table S7: Time-varying benzene exposure during follow-up
- Table S8: Lung cancer risk according to employment duration
- Table S9. Spearman rank correlation coefficients (r_{sp}) for occupational co-exposures

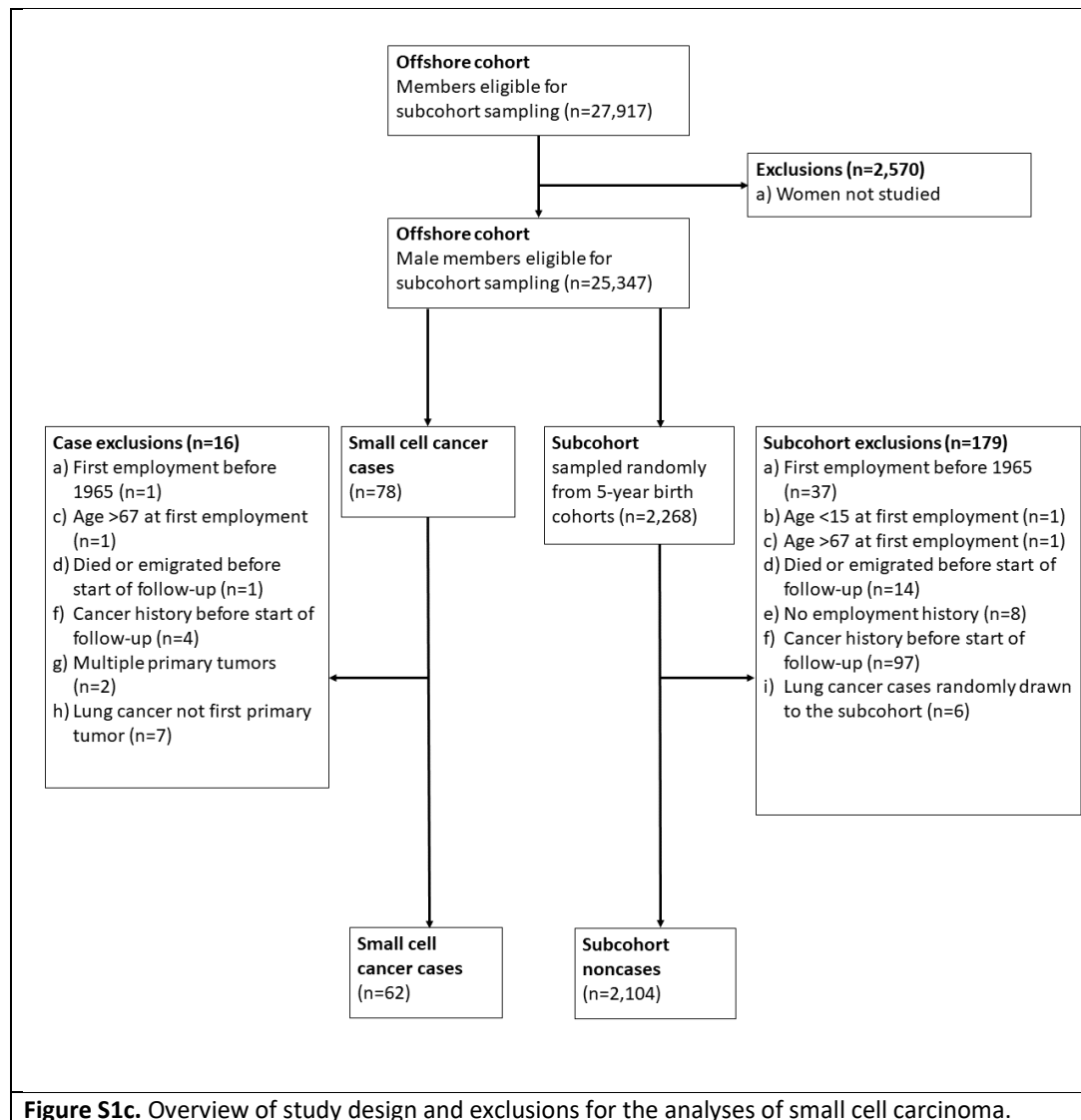
Number of lung cancer cases by histological subtype

Table S1. Number of lung cancer cases by histological subtype among 25,347 males in the Norwegian Offshore Petroleum Workers (NOPW) cohort followed 1999–2021.	
Cancer type	Number of cases
Lung (all cases)	399
Non-small cell carcinoma	337
Adenocarcinoma ¹	152
Squamous cell carcinoma ²	88
Large cell carcinoma ^{3*}	9
Large cell neuroendocrine carcinoma ^{4*}	8
Non-small cell carcinoma UNS ^{5*}	44
Carcinoid ^{6*}	6
Other ^{7*}	9
Unknown ^{8*}	21
Small cell carcinoma ⁹	62
¹⁻⁹ Codes from the International Classification of Diseases Oncology 3 rd revision (ICD-O-3) used to classify histological subtypes of lung cancer.	
¹ 7032, 7033, 7039, 7508, 8140, 8148, 8211, 8230, 8250, 8251, 8252, 8253, 8254, 8255, 8256, 8257, 8260, 8263, 8265, 8310, 8323, 8333, 8410, 8460, 8470, 8480, 8481, 8490, 8550, 8551, 8570, 8574, 8576, 8940	
² 8052, 8070, 8071, 8072, 8073, 8074, 8075, 8076, 8077, 8082	
³ 8012	
⁴ 8013	
⁵ 7160, 7161, 8010, 8020, 8046;	
⁶ 8240, 8241, 8243, 8245, 8249 ;	
⁷ 8022, 8030, 8031, 8032, 8033, 8040, 8083, 8123, 8140, 8200, 8244, 8246, 8250, 8430, 8560, 8562, 8973, 8980,	
⁸ 8000, 8001	
⁹ 8041	
*Not analysed separately	

Overview of study designs and exclusions by subtype







Directed acyclic graphs (DAGs)

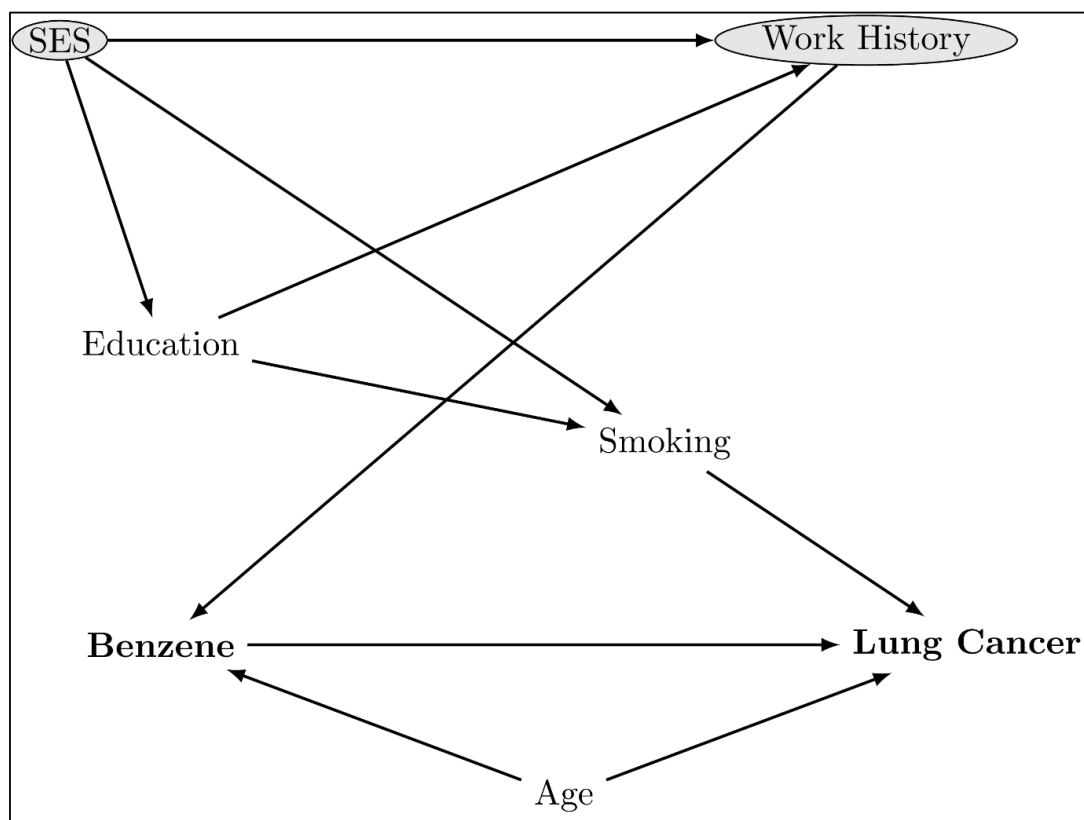


Figure S2. Directed acyclic graph showing our assumptions about causal pathways between occupational benzene (exposure of interest, limited to offshore-related activities), other factors, and lung cancer (endpoint). Socio-economic status (SES) and lifetime work history (work history) are unobserved/latent variables. All nodes represent baseline covariate levels. We assumed the following paths:

- benzene \rightarrow lung cancer
- benzene \leftarrow age¹ \rightarrow lung cancer
- work history \rightarrow benzene \rightarrow lung cancer
- SES^{2,3} \rightarrow work history⁴ \rightarrow benzene \rightarrow lung cancer
- work history \leftarrow education² \rightarrow smoking^{1,5} \rightarrow lung cancer
- SES \rightarrow education \rightarrow smoking \rightarrow lung cancer

Based on these assumptions, we need to adjust for smoking and age to obtain the total effect of occupational benzene exposure on lung cancer.

¹Bade BC, Dela Cruz CS. Lung Cancer 2020: Epidemiology, Etiology, and Prevention. Clinics in Chest Medicine. 2020;41(1):1-24.

²Larsen IK, Myklebust TÅ, Babigumira R, Vinberg E, Møller B, Ursin G. Education, income and risk of cancer: results from a Norwegian registry-based study. Acta Oncologica. 2020;59(11):1300-7

³Hovanec J, Siemiatycki J, Conway DI, Olsson A, Stücker I, Guida F, et al. Lung cancer and socioeconomic status in a pooled analysis of case-control studies. PLOS ONE. 2018;13(2):e0192999.

⁴Weissman DN, Howard J. Work-Related Lung Cancer: The Practitioner's Perspective. Am J Public Health. 2018;108(10):1290-2.

⁵Wild CP, Weiderpass E, Stewart BW, editors (2020). World Cancer Report: Cancer Research for Cancer Prevention. Lyon, France: International Agency for Research on Cancer. Available from: <http://publications.iarc.fr/586>. Licence: CC BY-NC-ND 3.0 IGO.

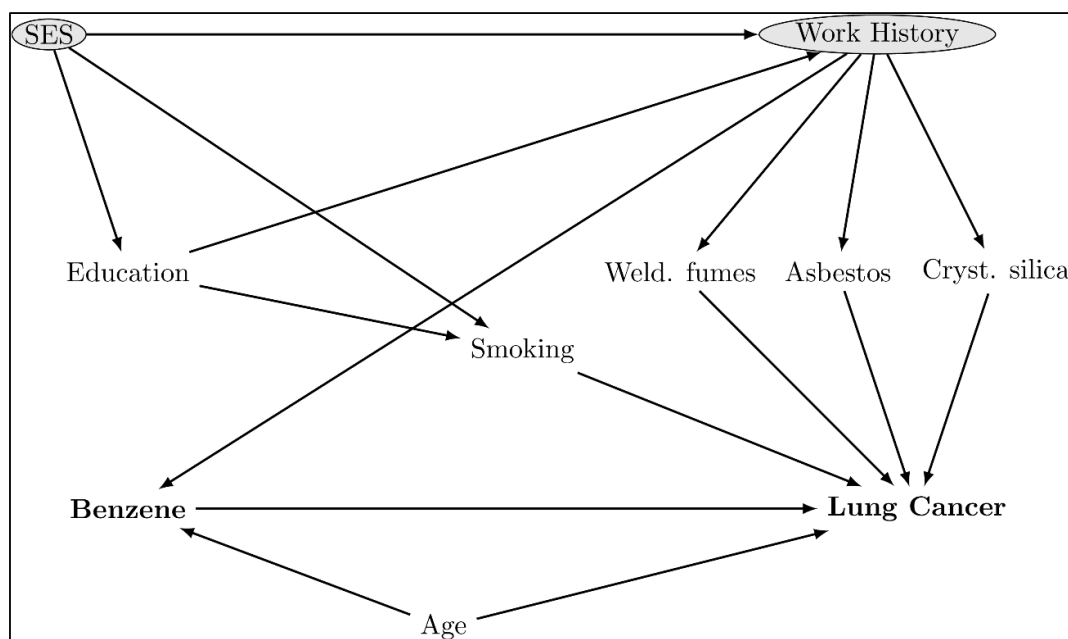


Figure S3. Directed acyclic graph showing our assumptions about causal pathways between occupational benzene (exposure of interest, limited to offshore-related activities), other factors and lung cancer (endpoint). Socio-economic status (SES) and lifetime work history (work history) are unobserved/latent variables. All nodes represent baseline covariate levels. We assumed the following paths;

- benzene \rightarrow lung cancer
- benzene \leftarrow age¹ \rightarrow lung cancer
- work history \rightarrow benzene \rightarrow lung cancer
- SES^{2,3} \rightarrow work history⁴ \rightarrow benzene \rightarrow lung cancer
- work history \leftarrow education² \rightarrow smoking^{1,5} \rightarrow lung cancer
- SES \rightarrow education \rightarrow smoking \rightarrow lung cancer
- work history \rightarrow welding fumes⁶ \rightarrow lung cancer
- work history \rightarrow asbestos^{5,6} \rightarrow lung cancer
- work history \rightarrow crystalline silica^{5,6} \rightarrow lung cancer

Based on these assumptions, we need to adjust for smoking, age, welding fumes, asbestos, and crystalline silica to obtain the total effect of occupational benzene exposure on lung cancer.

¹Bade BC, Dela Cruz CS. Lung Cancer 2020: Epidemiology, Etiology, and Prevention. Clinics in Chest Medicine. 2020;41(1):1-24.

²Larsen IK, Myklebust TÅ, Babigumira R, Vinberg E, Møller B, Ursin G. Education, income and risk of cancer: results from a Norwegian registry-based study. Acta Oncologica. 2020;59(11):1300-7

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⁶IARC. List of classifications by cancer sites with sufficient or limited evidence in humans, IARC Monographs Volumes 1–1332023 26.06.2023. Available from: https://monographs.iarc.who.int/wp-content/uploads/2019/07/Classifications_by_cancer_site.pdf.

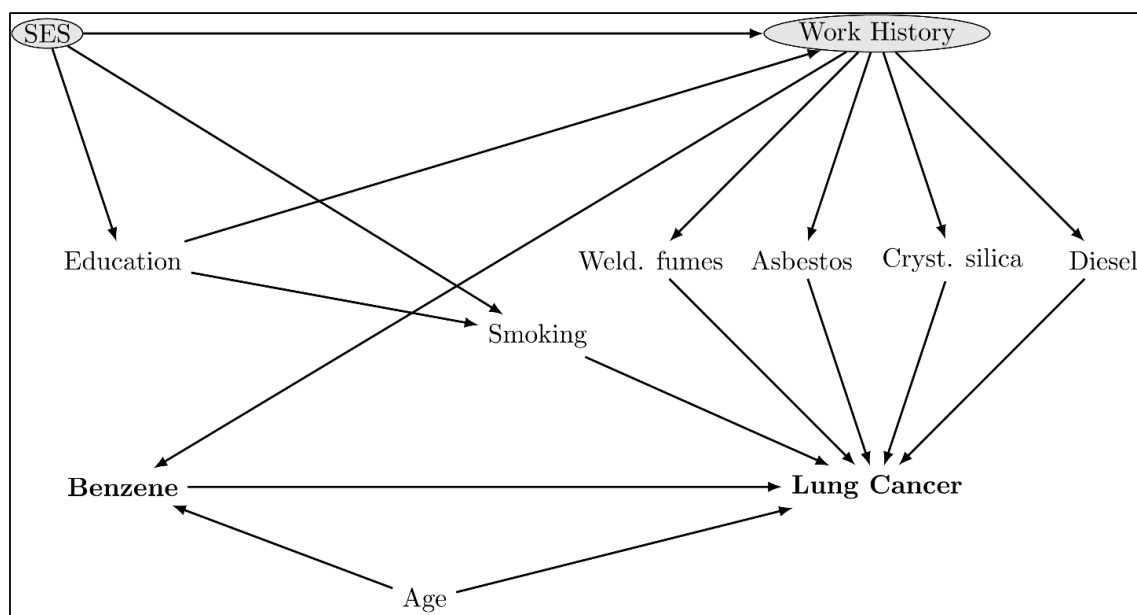


Figure S4. Directed acyclic graph showing our assumptions about causal pathways between occupational benzene (exposure of interest, limited to offshore-related activities), other factors and lung cancer (endpoint). Socio-economic status (SES) and lifetime work history (work history) are unobserved/latent variables. All nodes represent baseline covariate levels. We assumed the following paths;

- benzene → lung cancer
- benzene ← age¹ → lung cancer
- work history → benzene → lung cancer
- SES^{2,3} → work history⁴ → benzene → lung cancer
- work history ← education² → smoking^{1,5} → lung cancer
- SES → education → smoking → lung cancer
- work history → welding fumes⁶ → lung cancer
- work history → asbestos^{5,6} → lung cancer
- work history → crystalline silica^{5,6} → lung cancer
- work history → diesel exhaust^{5,6} → lung cancer

Based on these assumptions, we need to adjust for smoking, age, welding fumes, asbestos, crystalline silica and diesel exhaust to obtain the total effect of occupational benzene exposure on lung cancer.

¹Bade BC, Dela Cruz CS. Lung Cancer 2020: Epidemiology, Etiology, and Prevention. Clinics in Chest Medicine. 2020;41(1):1-24.

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⁴Weissman DN, Howard J. Work-Related Lung Cancer: The Practitioner's Perspective. Am J Public Health. 2018;108(10):1290-2.

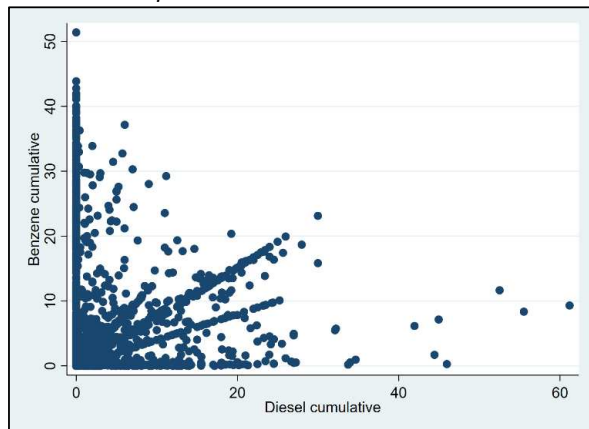
⁵Wild CP, Weiderpass E, Stewart BW, editors (2020). World Cancer Report: Cancer Research for Cancer Prevention. Lyon, France: International Agency for Research on Cancer. Available from: <http://publications.iarc.fr/586>. Licence: CC BY-NC-ND 3.0 IGO.

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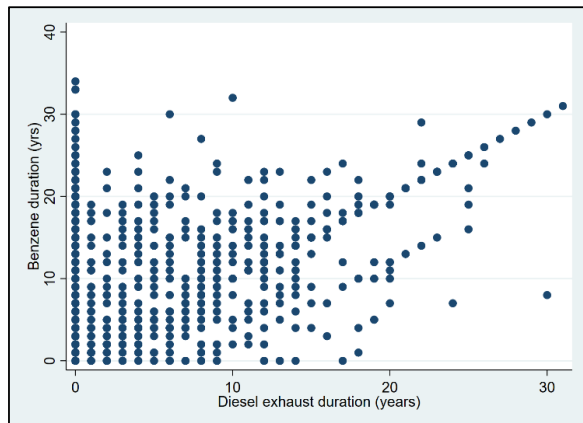
Diesel exhaust exposure as a potential confounder

Table S2, Figure S5, and Table S3 are presented below. Table S2 shows the results of analyses using Model 4, in which diesel exhaust was added to Model 3 as a potential confounder (DAG in Figure S4). Scatter plots and correlation coefficients between diesel exhaust and benzene exposure metrics are presented in Figure S5. Table S3 presents the results of diesel exhaust and lung cancer risk analyses.

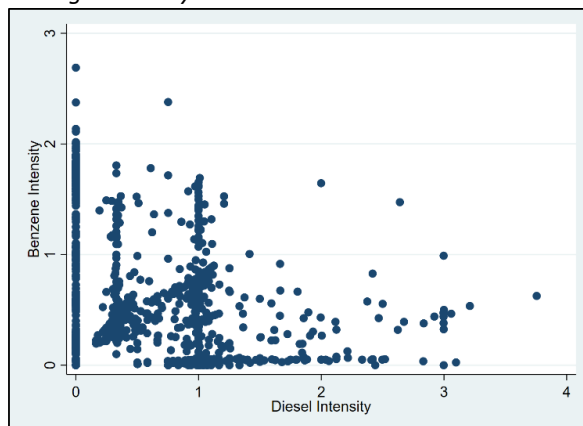
Table S2, Model 4. Hazard ratios (HR) with 95% confidence intervals (CIs) of all lung and the major histological subtypes of lung cancer according to benzene exposure among males in the Norwegian Offshore Petroleum Workers (NOPW) cohort, 1999–2021.					
		All lung^a (n=399)	Adenocarcinoma^a (n=152)	Squamous cell carcinoma^a (n=88)	Small cell carcinoma^a (n=62)
Benzene metric	C/NC	HR^b (95% CI)	HR^b (95% CI)	HR^b (95% CI)	HR^b (95% CI)
Cumulative (ppm-years)					
Unexposed	112/655	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q1 (0.000 - <0.019)	85/332	1.65 (0.98, 2.77)	1.46 (0.66, 3.23)	1.05 (0.39, 2.83)	1.27 (0.36, 4.42)
Q2 (0.019 - <0.071)	72/345	1.39 (0.79, 2.44)	1.08 (0.45, 2.56)	0.68 (0.23, 1.99)	1.29 (0.36, 4.62)
Q3 (0.071 - <0.175)	63/354	1.28 (0.69, 2.40)	2.49 (1.04, 5.95)	0.17 (0.04, 0.66)	0.99 (0.22, 4.45)
Q4 (0.176-0.879)	67/349	1.27 (0.67, 2.38)	1.46 (0.56, 3.80)	0.39 (0.10, 1.56)	1.31 (0.35, 4.90)
<i>P-Trend</i>		0.693	0.904	0.299	0.726
Duration (years)					
Unexposed	112/655	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q1 (1 - 4)	69/382	1.24 (0.71, 2.17)	0.99 (0.44, 2.24)	0.62 (0.19, 1.98)	1.35 (0.37, 4.97)
Q2 (5 - 10)	85/366	1.67 (0.98, 2.87)	1.50 (0.64, 3.50)	1.11 (0.41, 3.02)	1.17 (0.34, 4.08)
Q3 (11 - 16)	64/301	1.73 (0.98, 3.05)	2.12 (0.88, 5.09)	0.85 (0.29, 2.47)	1.32 (0.35, 4.96)
Q4 (17 - 34)	69/331	1.57 (0.83, 2.97)	2.28 (0.88, 5.90)	1.01 (0.26, 3.91)	1.50 (0.36, 6.26)
<i>P-Trend</i>		0.202	0.026	0.818	0.653
Average intensity (ppm)					
Unexposed	112/655	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q1 (0.000 - <0.004)	90/327	1.57 (0.95, 2.59)	1.36 (0.63, 2.94)	1.00 (0.39, 2.56)	1.36 (0.43, 4.37)
Q2 (0.004 - <0.007)	66/351	1.66 (0.90, 3.06)	2.22 (0.92, 5.35)	0.69 (0.21, 2.23)	1.92 (0.46, 7.94)
Q3 (0.007 - <0.014)	73/344	1.67 (0.90, 3.10)	2.15 (0.87, 5.28)	0.70 (0.22, 2.22)	2.22 (0.58, 8.47)
Q4 (0.014 - 0.046)	58/358	1.30 (0.72, 2.34)	1.43 (0.57, 3.57)	0.47 (0.15, 1.47)	0.87 (0.22, 3.38)
<i>P-Trend</i>		0.648	0.988	0.103	0.385
Abbreviations: C=cases, NC= non cases, Q=quartile					
^a Adjusted for age (as the time scale), smoking, welding fumes, asbestos, crystalline silica, and diesel exhaust					
^b Missing values were imputed					

Cumulative exposure

Spearman correlation coefficient=0.41

Duration

Spearman correlation coefficient=0.51

Average intensity

Spearman correlation coefficient=0.33

Figure S5. Correlation between benzene and diesel exhaust metrics

Examination of the association between diesel exhaust exposure and lung cancer risk

Table S3. Hazard ratios (HR) with 95% confidence intervals (CIs) of lung cancer according to diesel exhaust exposure among males in the Norwegian Offshore Petroleum Workers cohort, 1999–2021.

		Model D1 ^a	Model D2 ^b
Diesel exhaust metric	Cases/Non-cases	HR ^c (95% CI) ^c	HR ^c (95% CI)
Cumulative			
Unexposed	219/1098	1.00 (reference)	1.00 (reference)
Q1 (0.165 - <1.895)	41/239	0.86 (0.60, 1.23)	0.96 (0.65, 1.41)
Q2 (1.977 - <4.579)	38/241	0.85 (0.59, 1.24)	0.88 (0.59, 1.30)
Q3 (4.614 - <10.489)	51/228	1.14 (0.82, 1.60)	0.99 (0.69, 1.42)
Q4 (10.493 - 61.181)	50/229	1.00 (0.72, 1.40)	0.89 (0.62, 1.26)
<i>P-trend</i>		0.722	0.422
Duration (years)			
Unexposed	219/1098	1.00 (reference)	1.00 (reference)
Q1 (1 - 3)	48/262	0.91 (0.64, 1.27)	0.98 (0.68, 1.42)
Q2 (4 - 7)	46/218	1.09 (0.77, 1.55)	0.99 (0.68, 1.43)
Q3 (8 - 13)	41/226	0.91 (0.63, 1.31)	0.86 (0.58, 1.26)
Q4 (14 - 31)	45/231	0.97 (0.68, 1.37)	0.89 (0.62, 1.29)
<i>P-trend</i>		0.842	0.427
Average intensity			
Unexposed	219/1098	1.00 (reference)	1.00 (reference)
Q1 (0.165 - <0.332)	39/241	0.85 (0.59, 1.23)	0.94 (0.63, 1.41)
Q2 (0.332 - <0.940)	44/235	0.95 (0.67, 1.35)	0.98 (0.68, 1.42)
Q3 (0.941 - <1.000)	56/223	1.25 (0.90, 1.73)	1.11 (0.78, 1.57)
Q4 (1.000 - 4.004)	41/238	0.83 (0.58, 1.18)	0.72 (0.49, 1.05)
<i>P-trend</i>		0.932	0.416
Abbreviations: D=diesel exhaust; Q=quartile			
^a Adjusted for age (as the time scale).			
^b Adjusted for age (as the time scale) and smoking.			
^c Missing values in smoking were imputed.			

Evaluation of diesel exhaust as a potential confounder of the benzene–lung cancer association

In Table S2 with Model 4, we found that HRs consistently increased by 10% compared to Model 3. This increase is likely due to negative bias or negative confounding (Szklo and Janiver-Nieto, 2000) since we (A) observed positive correlations between diesel exhaust and benzene metrics, and (B) in Table S3, Model D2, observed a null or negative association between diesel exhaust and lung cancer. The lack of an association between diesel exhaust and lung cancer in our data may be due to low concentrations in the offshore working environment. Concentrations have been reported by the Norwegian Institute of Occupational Health to be low (Solbu et al., 2012).

References

- Solbu K, Bakke B, Friisk G, Skaugset NP. Deseleksos i arbeidsatmosfæren i norsk olje- og gassindustri – Dagens eksponeringsbilde. Report in Norwegian. Oslo, Norway: STAMI. No 4 (13), 2012. URL: <https://stami.no/content/uploads/2015/03/STAMI-rapport-nr-4-2012.pdf>
- Szklo M, Javier-Nieto F. Identifying non causal associations: Confounding. In: Epidemiology: Beyond the Basics. Gaithersburg, MD: Aspen Publishers, Inc.; 2000:203.

Analysis stratified by year of first employment.**Before 1980**

Table S4a. Hazard ratios (HR) with 95% confidence intervals (CIs) of lung cancer according to benzene exposure among males in the Norwegian Offshore Petroleum Workers cohort whose first employment was before 1980, 1999–2021.				
		Model 1^a	Model 2^b	Model 3^c
Benzene metric	Cases/Non-cases	HR^d (95% CI)	HR^d (95% CI)	HR^d (95% CI)
Cumulative (ppm-years)				
Unexposed	54/317	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q1 (0.000 - <0.025)	43/182	1.22 (0.79, 1.88)	1.19 (0.75, 1.89)	1.39 (0.66, 2.91)
Q2 (0.025 - <0.091)	36/189	1.28 (0.81, 2.00)	1.35 (0.84, 2.17)	1.62 (0.74, 3.55)
Q3 (0.092 - <0.198)	36/189	1.06 (0.67, 1.66)	1.12 (0.70, 1.80)	1.49 (0.68, 3.29)
Q4 (0.199 - 0.879)	38/186	1.20 (0.77, 1.87)	1.12 (0.71, 1.78)	1.50 (0.64, 3.52)
<i>P-Trend</i>		0.705	0.925	0.823
Duration (years)				
Unexposed	54/317	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q1 (1 - 5)	36/206	0.98 (0.63, 1.54)	1.02 (0.63, 1.65)	1.10 (0.48, 2.51)
Q2 (6 - 12)	39/181	1.43 (0.91, 2.24)	1.54 (0.97, 2.46)	1.69 (0.81, 3.55)
Q3 (13 - 20)	46/212	1.25 (0.82, 1.91)	1.19 (0.77, 1.85)	1.54 (0.73, 3.26)
Q4 (21 - 34)	32/147	1.12 (0.70, 1.78)	1.08 (0.66, 1.77)	1.55 (0.63, 3.79)
<i>P-Trend</i>		0.301	0.510	0.224
Average intensity (ppm)				
Unexposed	54/317	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q1 (0.000 - <0.004)	45/180	1.23 (0.80, 1.89)	1.12 (0.71, 1.77)	1.36 (0.66, 2.79)
Q2 (0.004 - <0.008)	37/189	1.18 (0.76, 1.85)	1.31 (0.82, 2.10)	1.70 (0.78, 3.71)
Q3 (0.008 - <0.013)	40/184	1.28 (0.83, 1.97)	1.26 (0.80, 1.98)	1.73 (0.77, 3.88)
Q4 (0.013 - 0.046)	31/193	1.03 (0.65, 1.65)	1.08 (0.67, 1.76)	1.35 (0.58, 3.14)
<i>P-Trend</i>		0.943	0.760	0.992
Abbreviations: Q=quartile				
^a Adjusted for age (as the time scale).				
^b Adjusted for age (as the time scale) and smoking.				
^c Adjusted for age (as the time scale), smoking, welding fumes, asbestos and crystalline silica.				
^d Missing values in covariates were imputed.				

After or in 1980

Table S4b. Hazard ratios (HR) with 95% confidence intervals (CIs) of lung cancer according to benzene exposure among males in the Norwegian Offshore Petroleum Workers cohort whose first employment was after 1980, 1999–2021.				
		Model 1^a	Model 2^b	Model 3^c
Benzene metric	Cases/Non-cases	HR^d (95% CI)	HR^d (95% CI)	HR^d (95% CI)
Cumulative (ppm-years)				
Unexposed	58/338	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q1 (0.000 - <0.016)	42/150	1.48 (0.95, 2.29)	1.50 (0.93, 2.42)	1.93 (0.97, 3.85)
Q2 (0.017 - <0.053)	38/154	1.39 (0.89, 2.19)	1.34 (0.83, 2.17)	1.76 (0.84, 3.67)
Q3 (0.053 - <0.128)	25/167	0.97 (0.58, 1.61)	0.98 (0.57, 1.69)	0.94 (0.40, 2.23)
Q4 (0.129 - 0.555)	29/163	1.04 (0.64, 1.70)	1.03 (0.61, 1.73)	0.71 (0.28, 1.83)
<i>P-Trend</i>		0.571	0.565	0.070
Duration (years)				
Unexposed	58/338	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q1 (1 - 3)	33/163	1.09 (0.68, 1.74)	1.18 (0.71, 1.95)	1.78 (0.83, 3.83)
Q2 (4 - 7)	39/151	1.52 (0.97, 2.39)	1.33 (0.82, 2.15)	1.88 (0.91, 3.88)
Q3 (8 - 12)	36/156	1.33 (0.84, 2.11)	1.29 (0.79, 2.12)	1.40 (0.66, 3.01)
Q4 (13 - 19)	26/164	0.99 (0.60, 1.63)	1.06 (0.62, 1.80)	0.90 (0.37, 2.17)
<i>P-Trend</i>		0.612	0.613	0.648
Average intensity (ppm)				
Unexposed	58/338	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q1 (0.000 - <0.004)	45/147	1.66 (1.07, 2.56)	1.63 (1.02, 2.61)	1.84 (0.95, 3.56)
Q2 (0.004 - <0.007)	32/160	1.22 (0.76, 1.95)	1.30 (0.78, 2.16)	1.51 (0.67, 3.36)
Q3 (0.007 - <0.015)	31/161	1.13 (0.70, 1.82)	0.94 (0.56, 1.57)	1.01 (0.42, 2.42)
Q4 (0.015 - 0.041)	26/166	0.91 (0.55, 1.51)	1.05 (0.62, 1.78)	0.99 (0.42, 2.32)
<i>P-Trend</i>		0.322	0.645	0.308
Abbreviations: Q=quartile				
^a Adjusted for age (as the time scale).				
^b Adjusted for age (as the time scale) and smoking.				
^c Adjusted for age (as the time scale), smoking, welding fumes, asbestos and crystalline silica.				
^d Missing values in covariates were imputed.				

Latency analyses with time-varying benzene exposure

Lagged analysis

Table S5a. Hazard Ratios (HR) of lung cancer according to lagged benzene exposure among males in the Norwegian Offshore Petroleum Workers (NOPW) cohort, 1999–2021.					
Benzene metric	Cases	Person years	Model 1^a	Model 2^b	Model 3^c
			HR^d (95% CI)	HR^d (95% CI)	HR^d (95% CI)
Cumulative (ppm-years)					
10-year lag					
Unexposed	117	13876	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q1 (0.000 - <0.017)	81	6802	1.36 (1.00, 1.86)	1.33 (0.95, 1.85)	1.38 (0.86, 2.22)
Q2 (0.017 - <0.065)	70	6768	1.26 (0.91, 1.74)	1.28 (0.91, 1.80)	1.26 (0.74, 2.14)
Q3 (0.065 - <0.157)	65	6784	1.13 (0.82, 1.57)	1.11 (0.78, 1.56)	1.09 (0.61, 1.96)
Q4 (0.157 - 0.879)	66	6831	1.07 (0.77, 1.48)	1.05 (0.75, 1.47)	0.93 (0.50, 1.71)
<i>P-trend</i>			0.719	0.668	0.212
15-year lag					
Unexposed	126	15259	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q1 (0.000 - <0.015)	78	6456	1.33 (0.98, 1.82)	1.29 (0.93, 1.79)	1.22 (0.78, 1.91)
Q2 (0.015 - <0.057)	66	6399	1.21 (0.88, 1.67)	1.26 (0.90, 1.77)	1.13 (0.68, 1.88)
Q3 (0.057 - <0.137)	61	6450	1.04 (0.75, 1.45)	1.03 (0.73, 1.44)	0.84 (0.48, 1.47)
Q4 (0.137 - 0.879)	68	6497	1.01 (0.74, 1.39)	0.99 (0.71, 1.38)	0.77 (0.43, 1.39)
<i>P-trend</i>			0.509	0.461	0.121
20-year lag					
Unexposed	141	18146	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q1 (0.000 - <0.012)	79	5695	1.51 (1.11, 2.04)	1.48 (1.07, 2.04)	1.38 (0.92, 2.05)
Q2 (0.012 - <0.044)	50	5711	0.94 (0.67, 1.33)	0.95 (0.67, 1.36)	0.81 (0.51, 1.30)
Q3 (0.044 - <0.111)	60	5725	1.08 (0.78, 1.50)	1.09 (0.78, 1.52)	0.87 (0.53, 1.43)
Q4 (0.111 - 0.879)	69	5783	1.02 (0.75, 1.39)	1.00 (0.72, 1.38)	0.80 (0.47, 1.34)
<i>P-trend</i>			0.589	0.532	0.207
Duration (years)					
10-year lag					
Unexposed	117	13876	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q1 (1 - <4)	63	7596	0.95 (0.68, 1.32)	0.96 (0.68, 1.37)	1.05 (0.63, 1.76)
Q2 (5 - <9)	79	6531	1.52 (1.11, 2.09)	1.50 (1.08, 2.09)	1.66 (0.99, 2.77)
Q3 (10 - <15)	68	6994	1.15 (0.83, 1.59)	1.16 (0.83, 1.63)	1.32 (0.78, 2.23)
Q4 (16 - 34)	72	6064	1.28 (0.93, 1.76)	1.19 (0.85, 1.66)	1.25 (0.68, 2.30)
<i>P-trend</i>			0.068	0.194	0.574
15-year lag					
Unexposed	126	15259	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q1 (1 - <4)	68	8025	0.96 (0.70, 1.32)	0.98 (0.70, 1.37)	1.00 (0.62, 1.61)
Q2 (5 - <8)	72	5878	1.53 (1.12, 2.10)	1.49 (1.07, 2.07)	1.47 (0.90, 2.42)
Q3 (9 - <13)	55	6045	1.03 (0.73, 1.44)	1.03 (0.72, 1.46)	0.98 (0.58, 1.67)
Q4 (14 - 34)	78	5854	1.17 (0.86, 1.59)	1.13 (0.82, 1.56)	1.03 (0.58, 1.81)
<i>P-trend</i>			0.237	0.378	0.953
20-year lag					
Unexposed	141	18146	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q1 (1 - <3)	62	6787	1.05 (0.76, 1.44)	1.08 (0.77, 1.51)	1.08 (0.70, 1.66)
Q2 (4 - <6)	50	5032	1.16 (0.82, 1.63)	1.16 (0.81, 1.66)	1.12 (0.71, 1.76)
Q3 (7 - <11)	67	5830	1.18 (0.86, 1.62)	1.15 (0.83, 1.59)	1.05 (0.66, 1.65)
Q4 (12 - 34)	79	5265	1.16 (0.85, 1.56)	1.12 (0.82, 1.53)	0.98 (0.59, 1.62)
<i>P-trend</i>			0.271	0.441	0.803
Abbreviations: Q=quartile					
^a Adjusted for age (as the time scale).					
^b Adjusted for age (as the time scale) and smoking.					
^c Adjusted for age (as the time scale), smoking, welding fumes, asbestos and crystalline silica					
^d Missing values were imputed					

Lagged analysis by histological subtype

Table S5b. Hazard Ratios (HR) of major histological subtypes according to lagged benzene exposure among males in the Norwegian Offshore Petroleum Workers (NOPW) cohort, 1999–2021.									
Benzene metric	Adenocarcinoma ^a			Squamous cell carcinoma ^a			Small cell carcinoma ^a		
	C	PYs	HR ^b (95% CI)	C	PYs	HR ^b (95% CI)	C	PYs	HR ^b (95% CI)
Cumulative (ppm-years)									
10-year lag									
Unexposed	48	13010	1.00 (reference)	28	12882	1.00 (reference)	15	12739	1.00 (reference)
Q1 (0.000 - <0.018)	28	6361	1.09 (0.53, 2.24)	18	6211	0.96 (0.38, 2.45)	13	6199	1.01 (0.33, 3.10)
Q2 (0.018 - <0.067)	21	6328	1.00 (0.45, 2.24)	21	6191	0.77 (0.28, 2.10)	12	6169	0.94 (0.29, 3.08)
Q3 (0.067 - <0.159)	33	6354	1.69 (0.75, 3.80)	5	6203	0.18 (0.05, 0.68)	10	6193	0.62 (0.16, 2.46)
Q4 (0.159 - 0.879)	22	6387	0.98 (0.38, 2.52)	16	6232	0.36 (0.09, 1.38)	12	6215	0.99 (0.28, 3.57)
<i>P-trend</i>			0.621			0.205			0.730
15-year lag									
Unexposed	50	14258	1.00 (reference)	30	14095	1.00 (reference)	17	13944	1.00 (reference)
Q1 (0.000 - <0.016)	28	6052	1.13 (0.58, 2.23)	17	5919	0.89 (0.37, 2.14)	11	5889	0.76 (0.26, 2.23)
Q2 (0.016 - <0.058)	19	5996	0.95 (0.43, 2.10)	19	5857	0.72 (0.27, 1.94)	10	5854	0.77 (0.25, 2.36)
Q3 (0.058 - <0.138)	33	6037	1.52 (0.69, 3.31)	6	5894	0.19 (0.05, 0.76)	11	5889	0.67 (0.19, 2.32)
Q4 (0.138 - 0.879)	22	6097	0.88 (0.36, 2.18)	16	5955	0.35 (0.10, 1.30)	13	5938	0.95 (0.30, 2.99)
<i>P-trend</i>			0.445			0.183			0.582
20-year lag									
Unexposed	56	16903	1.00 (reference)	32	16671	1.00 (reference)	18	16514	1.00 (reference)
Q1 (0.000 - <0.013)	28	5351	1.25 (0.67, 2.33)	16	5241	1.08 (0.49, 2.36)	11	5216	0.99 (0.38, 2.60)
Q2 (0.013 - <0.046)	17	5349	0.78 (0.36, 1.67)	15	5211	0.77 (0.31, 1.88)	10	5232	1.04 (0.35, 3.06)
Q3 (0.046 - <0.113)	28	5403	1.23 (0.59, 2.56)	10	5297	0.47 (0.17, 1.34)	8	5344	0.69 (0.22, 2.15)
Q4 (0.113 - 0.879)	23	5433	0.87 (0.37, 2.03)	15	5298	0.51 (0.16, 1.55)	15	5208	1.42 (0.55, 3.70)
<i>P-trend</i>			0.563			0.256			0.233
Duration (years)									
10-year lag									
Unexposed	48	13010	1.00 (reference)	28	12882	1.00 (reference)	15	12739	1.00 (reference)
Q1 (1 - <4)	18	7050	0.64 (0.29, 1.41)	12	6981	0.73 (0.24, 2.16)	12	6957	1.06 (0.31, 3.60)
Q2 (5 - <9)	28	6003	1.60 (0.71, 3.57)	18	5849	1.06 (0.40, 2.82)	12	5807	0.99 (0.33, 3.00)
Q3 (10 - <15)	26	6670	1.49 (0.66, 3.38)	13	6481	0.76 (0.27, 2.09)	10	6451	0.83 (0.26, 2.62)
Q4 (16 - 34)	32	5708	1.93 (0.78, 4.79)	17	5526	0.84 (0.22, 3.16)	13	5560	1.00 (0.26, 3.87)
<i>P-trend</i>			0.042			0.842			0.896
15-year lag									
Unexposed	50	14258	1.00 (reference)	30	14095	1.00 (reference)	17	13944	1.00 (reference)
Q1 (1 - <4)	21	7459	0.76 (0.37, 1.56)	13	7374	0.70 (0.26, 1.90)	10	7353	0.71 (0.22, 2.28)
Q2 (5 - <8)	25	5404	1.51 (0.70, 3.29)	15	5261	0.87 (0.32, 2.37)	13	5206	1.11 (0.40, 3.08)
Q3 (9 - <13)	25	5765	1.42 (0.64, 3.13)	11	5585	0.61 (0.22, 1.74)	7	5560	0.52 (0.17, 1.64)
Q4 (14 - 34)	31	5553	1.41 (0.60, 3.29)	19	5404	0.76 (0.23, 2.46)	15	5450	0.98 (0.29, 3.30)
<i>P-trend</i>			0.223			0.702			0.901
20-year lag									
Unexposed	56	16903	1.00 (reference)	32	16671	1.00 (reference)	18	16514	1.00 (reference)
Q1 (1 - <3)	20	6323	0.90 (0.46, 1.76)	13	6250	0.97 (0.41, 2.26)	7	6173	0.71 (0.22, 2.31)
Q2 (4 - <6)	17	4679	1.06 (0.52, 2.19)	9	4525	0.72 (0.27, 1.91)	12	4530	1.52 (0.58, 4.00)
Q3 (7 - <11)	26	5511	1.22 (0.60, 2.50)	14	5379	0.74 (0.30, 1.83)	11	5372	0.94 (0.36, 2.46)
Q4 (12 - 34)	33	5023	1.38 (0.62, 3.06)	20	4894	0.86 (0.32, 2.30)	14	4924	1.11 (0.38, 3.27)
<i>P-trend</i>			0.313			0.737			0.785
Abbreviations: C=Cases, PYs = Person years									
^a Adjusted for age (as the time scale), smoking, welding fumes, asbestos and crystalline silica.									
^b Missing values in covariates were imputed.									

Most recent benzene exposure

Table S6. Hazard Ratios (HR) of lung cancer according to most recent benzene exposure among males in the Norwegian Offshore Petroleum Workers (NOPW) cohort, 1999–2021. Based on extrapolated benzene exposure data during follow up among those employed in 1998.					
			Model 1^a	Model 2^b	Model 3^c
Benzene metric	Cases	Person yrs.	HR^d(95% CI)	HR^d(95% CI)	HR^d(95% CI)
Cumulative (ppm-years)					
Unexposed	312	30378	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q1 (0.001 - <0.026)	23	2646	0.90 (0.56, 1.45)	0.94 (0.57, 1.55)	0.77 (0.45, 1.31)
Q2 (0.026 - <0.034)	20	2756	0.69 (0.42, 1.13)	0.73 (0.44, 1.23)	0.66 (0.38, 1.15)
Q3 (0.034 - <0.109)	26	2618	1.07 (0.68, 1.67)	0.86 (0.53, 1.39)	0.75 (0.44, 1.27)
Q4 (0.109 - 0.138)	18	2663	0.68 (0.40, 1.15)	0.77 (0.45, 1.34)	0.71 (0.39, 1.26)
<i>P-Trend</i>			0.167	0.251	0.160
Most recent 10 years					
Unexposed	290	27932	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q1 (0.000 - <0.034)	31	3234	1.24 (0.82, 1.88)	1.33 (0.87, 2.04)	1.12 (0.71, 1.76)
Q2 (0.034 - <0.067)	30	3468	0.86 (0.57, 1.30)	0.93 (0.60, 1.44)	0.81 (0.51, 1.30)
Q3 (0.067 - <0.149)	25	3162	0.80 (0.51, 1.25)	0.66 (0.41, 1.05)	0.56 (0.34, 0.92)
Q4 (0.149 - 0.279)	23	3265	0.70 (0.44, 1.11)	0.78 (0.48, 1.26)	0.69 (0.41, 1.18)
<i>P-trend</i>			0.078	0.125	0.060
Most recent 15 years					
Unexposed	261	24834	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q1 (0.000 - <0.043)	39	3961	1.77 (1.24, 2.53)	1.83 (1.28, 2.60)	1.60 (1.10, 2.33)
Q2 (0.043 - <0.097)	31	4091	0.88 (0.59, 1.32)	0.88 (0.58, 1.33)	0.73 (0.46, 1.14)
Q3 (0.097 - <0.180)	41	4093	0.95 (0.66, 1.37)	0.87 (0.59, 1.28)	0.76 (0.49, 1.18)
Q4 (0.180 - 0.441)	27	4080	0.68 (0.44, 1.04)	0.73 (0.47, 1.14)	0.64 (0.39, 1.06)
<i>P-trend</i>			0.050	0.097	0.045
Intensity (ppm/years)					
Most recent 5 years					
Unexposed	312	30378	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q1 (0.001 - <0.007)	29	3268	0.88 (0.57, 1.35)	0.93 (0.59, 1.47)	0.78 (0.48, 1.28)
Q2 (0.007 - <0.010)	18	2080	0.87 (0.51, 1.47)	0.85 (0.49, 1.50)	0.73 (0.40, 1.31)
Q3 (0.010 - <0.027)	20	2634	0.89 (0.54, 1.48)	0.73 (0.43, 1.25)	0.66 (0.38, 1.17)
Q4 (0.027 - 0.041)	20	2700	0.68 (0.42, 1.12)	0.78 (0.47, 1.30)	0.70 (0.41, 1.22)
<i>P-trend</i>			0.118	0.203	0.131
Most recent 10 years					
Unexposed	290	27932	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q1 (0.000 - <0.007)	34	3291	1.22 (0.82, 1.82)	1.32 (0.86, 2.02)	1.10 (0.69, 1.74)
Q2 (0.007 - <0.009)	23	3255	0.67 (0.42, 1.06)	0.68 (0.42, 1.11)	0.58 (0.35, 0.98)
Q3 (0.009 - <0.026)	28	3277	1.04 (0.68, 1.60)	0.85 (0.54, 1.34)	0.76 (0.47, 1.24)
Q4 (0.026 - 0.046)	24	3305	0.69 (0.44, 1.09)	0.79 (0.49, 1.26)	0.72 (0.43, 1.20)
			0.104	0.188	0.095
Most recent 15 years					
Unexposed	261	24834	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q1 (0.000 - <0.007)	42	4037	1.41 (0.98, 2.03)	1.46 (0.99, 2.15)	1.21 (0.79, 1.87)
Q2 (0.007 - <0.008)	33	4055	0.88 (0.60, 1.31)	0.97 (0.64, 1.45)	0.89 (0.57, 1.38)
Q3 (0.008 - <0.021)	33	4045	1.01 (0.69, 1.50)	0.81 (0.53, 1.23)	0.69 (0.43, 1.11)
Q4 (0.021 - 0.049)	30	4089	0.76 (0.51, 1.14)	0.84 (0.55, 1.28)	0.75 (0.47, 1.22)
<i>P-trend</i>			0.184	0.250	0.110
^a Adjusted for age (as the time scale).					
^b Adjusted for age (as the time scale), smoking					
^c Adjusted for age (as the time scale), smoking, welding fumes, asbestos and crystalline silica (not extrapolated)					
^d Missing values in covariates were imputed					

Time-varying benzene exposure during follow-up

Table S7. Hazard Ratios (HR) of lung cancer according to time-varying benzene exposure among 25,347 males in the Norwegian Offshore Petroleum Workers (NOPW) cohort, 1999–2021. Based on extrapolated data during follow up among those employed in 1998.

			Model 1 ^a	Model 2 ^b	Model 3 ^c
Benzene metric	Cases	Person years	HR ^d (95% CI)	HR ^d (95% CI)	HR ^d (95% CI)
Cumulative (ppm-years)					
Unexposed	112	13034	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q1 (0.000 - <0.021)	82	7012	1.40 (1.02, 1.91)	1.34 (0.96, 1.87)	1.48 (0.91, 2.42)
Q2 (0.021 - <0.091)	65	6952	1.32 (0.94, 1.83)	1.34 (0.94, 1.90)	1.40 (0.78, 2.53)
Q3 (0.091 - <0.234)	67	7018	1.13 (0.81, 1.56)	1.14 (0.81, 1.60)	1.20 (0.68, 2.12)
Q4 (0.234-1.289)	73	7045	1.10 (0.80, 1.51)	1.05 (0.75, 1.46)	1.03 (0.57, 1.86)
<i>P-Trend</i>			0.727	0.551	0.196
Duration (years)					
Unexposed	112	13034	1.00 (reference)	1.00 (reference)	1.00 (reference)
Q1 (1 - <5)	74	8166	1.10 (0.80, 1.51)	1.13 (0.81, 1.59)	1.33 (0.79, 2.25)
Q2 (6 - <12)	77	6365	1.71 (1.25, 2.36)	1.58 (1.12, 2.21)	1.66 (0.97, 2.83)
Q3 (13 - <22)	60	6647	1.33 (0.95, 1.85)	1.25 (0.89, 1.77)	1.32 (0.77, 2.28)
Q4 (23-50)	76	6848	0.99 (0.72, 1.35)	0.99 (0.71, 1.37)	0.98 (0.56, 1.73)
<i>P-trend</i>			0.984	0.909	0.169
^a Adjusted for age (as the time scale).					
^b Adjusted for age (as the time scale), smoking					
^c Adjusted for age (as the time scale), smoking, welding fumes, asbestos and crystalline silica					
^d Missing values in covariates were imputed					

Lung cancer risk according to employment duration

Table S8. Hazard ratios (HR) with 95% confidence intervals (CIs) of lung cancer according to employment duration among males in the Norwegian Offshore Petroleum Workers cohort, 1999–2021			
Cancer site	Employment duration	Cases/Non Cases	HR^a (95% CI)
All lung (n= 399)	Q1 (0 - 4)	81/435	1.00 (reference)
	Q2 (5 - 10)	90/456	1.03 (0.72, 1.47)
	Q3 (11 - 14)	65/338	1.09 (0.74, 1.60)
	Q4 (15 - 19)	84/402	0.97 (0.67, 1.40)
	Q5 (20 - 34)	79/404	0.95 (0.66, 1.37)
	<i>P-Trend</i>		0.72
Adenocarcinoma (n= 152)	Q1 (0 - 4)	30/441	1.00 (reference)
	Q2 (5 - 10)	27/467	0.85 (0.49, 1.49)
	Q3 (11 - 15)	30/424	1.17 (0.68, 2.03)
	Q4 (16 - 20)	41/440	1.29 (0.76, 2.18)
	Q5 (21 - 34)	24/311	1.26 (0.69, 2.29)
	<i>P-Trend</i>		0.183
Squamous cell carcinoma (n=88)	Q1 (0 - 4)	19/443	1.00 (reference)
	Q2 (5 - 10)	24/465	1.19 (0.61, 2.30)
	Q3 (11 - 14)	13/351	0.91 (0.43, 1.94)
	Q4 (15 - 19)	19/414	0.89 (0.44, 1.76)
	Q5 (20 - 34)	13/416	0.61 (0.28, 1.31)
	<i>P-Trend</i>		0.127
Small cell carcinoma (n=62)	Q1 (0 - 4)	13/445	1.00 (reference)
	Q2 (5 - 10)	11/469	0.78 (0.34, 1.84)
	Q3 (11 - 14)	13/351	1.32 (0.57, 3.02)
	Q4 (15 - 20)	13/524	0.71 (0.32, 1.62)
	Q5 (21 - 34)	12/315	1.13 (0.51, 2.52)
	<i>P-Trend</i>		0.972
Abbreviations: Q = Quartile			
^a adjusted for age, smoking, and education.			

Table S9. Spearman rank correlation Coefficients (r_{sp}) for occupational co-exposures

Metric	Exposure	<i>Benzene</i>	<i>Crystalline silica</i>	<i>Diesel exhaust</i>	<i>Welding fumes</i>	<i>Asbestos</i>
Cumulative (ppm-years)	<i>Benzene</i>	1				
	<i>Crystalline silica</i>	0.0376	1			
	<i>Diesel exhaust</i>	0.4059	0.3451	1		
	<i>Welding fumes</i>	0.6608	0.1256	0.4020	1	
	<i>Asbestos</i>	0.6324	0.5119	0.5211	0.3949	1
Duration (years)	<i>Benzene</i>	1				
	<i>Crystalline silica</i>	0.2420	1			
	<i>Diesel exhaust</i>	0.5135	0.4430	1		
	<i>Welding fumes</i>	0.6360	0.2649	0.5268	1	
	<i>Asbestos</i>	0.8026	0.4758	0.4285	0.4745	1
Average intensity (ppm)	<i>Benzene</i>	1				
	<i>Crystalline silica</i>	-0.0504	1			
	<i>Diesel exhaust</i>	0.3318	0.3246	1		
	<i>Welding fumes</i>	0.6175	0.0283	0.3134	1	
	<i>Asbestos</i>	0.4356	0.5037	0.5499	0.3110	1