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Increased risk of acute myelogenous leukemia and multiple myeloma in a historical cohort of upstream petroleum workers exposed to crude oil

Jorunn Kirkeleit · Trond Riise · Magne Bråtveit · Bente E. Moen

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Abstract Benzene exposure has been shown to be related to acute myelogenous leukemia, while the association with multiple myeloma and non-Hodgkin lymphoma has been a much-debated issue. We performed a historical cohort study to investigate whether workers employed in Norway's upstream petroleum industry exposed to crude oil and other products containing benzene have an increased risk of developing various subtypes of hematologic neoplasms. Using the Norwegian Registry of Employers and Employees we included all 27,919 offshore workers registered from 1981 to 2003 and 366,114 referents from the general working population matched by gender, age, and community of residence. The cohort was linked to the Cancer Registry of Norway. Workers in the job category "upstream operator offshore", having the most extensive contact with crude oil, had an excess risk of hematologic neoplasms (blood and bone marrow) (rate ratio (RR) 1.90, 95% confidence interval (95% CI): 1.19–3.02). This was ascribed to an increased risk of acute myelogenous leukemia (RR 2.89, 95% CI: 1.25–6.67) and multiple myeloma (RR 2.49, 95% CI: 1.21–5.13). There were no statistical differences between the groups in respect to non-Hodgkin lymphoma. The results suggest that benzene exposure, which most probably caused the increased risk of acute myelogenous leukemia, also resulted in an increased risk of multiple myeloma.

Keywords Benzene · Cohort studies · Hematologic neoplasms · Leukemia · Multiple myeloma

J. Kirkeleit (✉) · T. Riise · M. Bråtveit · B. E. Moen
Section for Occupational Medicine, Department of Public Health and Primary Health Care, University of Bergen, PO Box 7804, Bergen 5020, Norway
e-mail: Jorunn.Kirkeleit@isf.uib.no

Introduction

Benzene is known to cause leukemia [1, 2]. The association is strongest for acute myelogenous leukemia, but unclear for the other subtypes of leukemia [2]. Further, the association of benzene exposure with multiple myeloma [3, 4] and non-Hodgkin lymphoma [5–8] has been much debated.

Benzene is a natural component of crude oil and natural gas, and is a potential hazard in the petroleum industry. Studies of petroleum workers have shown an association between benzene exposure and leukemia [9–12]. Some studies of petroleum workers have found an elevated risk of multiple myeloma [13–15], while others have not [9, 12, 16]. Further, although a relation between non-Hodgkin lymphoma and benzene exposure has been suggested [7, 8], most studies in the petroleum industry have not found any increased risk [5, 17]. The majority of these studies comprised of workers employed in oil refinery operations and the distribution and consumption of refined oil products and include only to a limited degree upstream operations such as drilling and production of crude oil, natural gas, and natural gas liquids. Upstream workers are exposed to benzene through contact with crude oil and natural gas, and some of these workers experience high levels of benzene exposure over shorter periods of time [18, 19]. In addition, benzene has been reported to be found as a laboratory chemical (solvent), as a component or a degradation product in drilling mud, as a minor component in diesel exhaust, and possibly as a degreasing agent [20, 21].

A marked limitation of the earlier studies in the petroleum industry is the likely presence of a healthy worker effect due to an overall mortality and overall cancer incidence among these workers that are significantly lower than in the general population used as a reference [12, 13, 22]. The healthy worker effect might mask increased risks

of both multiple myeloma and non-Hodgkin lymphoma even in studies capable of showing an increased risk of acute myelogenous leukemia.

We studied whether workers employed in Norway's upstream offshore petroleum industry have a higher risk of developing hematologic neoplasms than the general working population in Norway. We focused on the differences in risk of leukemia subtypes, multiple myeloma and non-Hodgkin lymphoma in the cohort combined and among different job categories.

Materials and methods

Study population and study design

We performed a historical cohort study of the cancer incidence in Norway's upstream petroleum industry. Statistics Norway established the cohort using the information from the Norwegian Registry of Employers and Employees, which is owned by the Norwegian Labour and Welfare Organisation. All employers are required to register their employees with a personal identification number, industrial classification code (International Standard Industrial Classification (ISIC) or the Classification of Economic Activities in the European Union (NACE)), county of work, and the first and last date of all their engagements. The Registry requires that all engagements with a mean of 4 h of work per week, provided that the engagement lasts for at least 6 weeks, must be registered. The Registry included on July 31, 2004, a total of 1,961,711 workers contributing with 2,126,699 work engagements [23].

The Norwegian Registry of Employers and Employees was established in 1978, became operational in 1983 and contains engagements from 1981 and onwards. Since the Cancer Registry, at time of study, only included cases until 2003, we used engagements from 1981 until 2003. Norway's petroleum industry has been operating offshore since the early 1970s and thus the cohort does not include all workers who were engaged during the period 1970–1980. Still, many of these workers might be included in the cohort with possible new engagements registered after 1981. This means that some of these early subjects might have had a longer engagement offshore than registered in our cohort. The criteria we used for the cohort of petroleum workers were workers registered with one of the following offshore-related industrial classification codes: ISIC 22 (extraction of crude oil and natural gas), ISIC 5032 (oil drilling), NACE 11100 (extraction of crude oil and natural gas), and NACE 11200 (service activities incidental to oil and gas extraction excluding surveying), or having Norway's continental shelf (North Sea) as the work location.

Based on the workers' location of work (onshore or offshore) and the industrial classification codes for their first registered engagement in the offshore-related petroleum industry, we categorized the petroleum workers into five job categories: (1) upstream operator offshore, (2) drilling and well maintenance offshore, (3) catering offshore, (4) others offshore and (5) petroleum workers onshore. The category "upstream operator offshore" contained solely workers registered with the NACE and ISIC code "extraction of crude oil and natural gas". These workers mainly work in the production and processing unit. This includes job categories such as process technicians, laboratory engineers, control operators, and other job groups involved in the production process including stabilization, separation, and fractionation of the crude oil, natural gas, and natural gas liquids. The category "drilling and well maintenance offshore" includes the ISIC code 50230 (oil drilling) and NACE code 11200 (service activities incidental to oil and gas extraction excluding surveying). NACE code 11200 comprises activities such as drilling of wells and installation, disassembling, and maintenance of drilling towers at site on contract and includes job groups such as drill floor crew, derrick employees, mud loggers and engineers, shale shaker operators, and well service crew. The category "catering offshore" includes job groups such as catering crew, chefs and housekeeping personnel. The category "others offshore" includes miscellaneous industrial codes and comprises activities contracted out to oil field service companies, such as construction and maintenance personnel and logistics. Finally, "petroleum workers onshore" contains workers registered with an offshore-related engagement without being registered with the North Sea as the location of work. This job category contains workers involved in administering, planning, and coordinating the activities offshore.

We drew up to six referents per petroleum worker at random from the general working population, using the same Norwegian Registry of Employers and Employees and the same year of the first engagement of the corresponding petroleum worker. We matched the referents to the petroleum worker by gender, age, and community of residence. The crude historical cohort included 71,018 workers from the petroleum industry ("at risk") and 424,584 referents. We excluded subjects from the cohort if they had a cancer diagnosis before entering into the cohort, and referents if they had an earlier engagement in the petroleum industry before they were drawn as referents even if they were not considered exposed in the engagement. We allowed subjects to serve as referents for more than one "subject at risk". The final cohort included 27,919 offshore workers (89% men) distributed on the four

Table 1 Characteristics of the study population studied to determine whether workers employed in Norway's upstream offshore petroleum industry have a higher risk of developing hematologic neoplasms than the general working population in Norway, 1981–2003

Variable	Referents	Petroleum workers (all)	Onshore workers (all)	Offshore workers			
				Upstream operator offshore	Drilling and well maintenance	Catering offshore	Others offshore
Number of subjects	366,114	70,600	42,681	6,734	7,049	2,417	11,719
Male (%)	283,002 (77.3)	55,376 (78.4)	30,611 (71.7)	5,853 (86.9)	6,722 (95.4)	1,231 (50.9)	10,959 (93.5)
Female (%)	83,112 (22.7)	15,224 (21.6)	12,070 (28.3)	881 (13.1)	327 (4.6)	1,186 (49.1)	760 (6.5)
Age, mean (standard deviation)							
At inclusion into the cohort	33.8 (9.5)	33.8 (9.5)	33.9 (9.7)	33.8 (8.1)	32.6 (8.6)	32.6 (10.0)	34.3 (9.6)
At the end of follow-up	46.3 (11.5)	46.4 (11.4)	46.3 (11.5)	49.6 (11.3)	43.4 (11.2)	47.9 (11.4)	46.7 (10.7)
Mean education level (1–6)	4.2 (1.5)	4.7 (1.6)	5.1 (1.6)	4.2 (1.2)	4.0 (1.2)	3.5 (1.1)	4.0 (1.3)
Tertiary education (%)	28.4	34.4	46.8	18.4	13.9	8.7	15.7
Intermediate education (%)	59.0	53.8	41.7	72.5	74.4	73.6	70.8
Compulsory education (%)	11.4	6.4	4.3	7.2	9.6	16.4	9.8
Start date in industry (%)							
Before 1986	28.3	28.3	29.0	49.1	15.0	47.7	18.0
1986–1990	19.4	19.3	16.1	22.8	17.2	19.9	30.3
1991–2003	52.3	52.3	54.9	28.1	67.8	32.4	51.7
Average follow up (years)	11.5	11.5	11.3	14.6	9.7	13.9	11.2
Person-years at follow-up	4,213,716	815,049	482,987	98,341	68,238	33,677	131,808

offshore job categories comprising 332,064 person-years (Table 1).

Statistics Norway established and linked the total cohort to the Cancer Registry of Norway in April 2006, including all cases of cancer reported up to December 31, 2003 with information on the date of diagnosis and the diagnosis (location, morphology, and histology). For the localization of the neoplasms, the cancer cases were coded according to a modified version of the International Classification of Diseases (ICD-7, three-digit codes). For subjects with more than one cancer, only the first was used to identify hematological neoplasms. The Cancer Registry of Norway is based on reporting from multiple sources, such as physicians, pathology laboratories, and death certificates from Statistics Norway mentioning cancer or cancer-related illnesses, ensuring a high degree of accuracy and completeness. Statistics Norway also linked the cohort to the Norwegian Cause of Death Registry and the Norwegian Education Registry, including the variable highest completed education, ranging from 1 (elementary school) to 6 (PhD degree).

Statistical analysis

We estimated the rate ratios comparing the various working categories with the general working population using the Cox proportional hazard regression model. We censored subjects at the end of follow-up (December 31, 2003), the date of death or date of diagnosis of another type of cancer than the one being studied, whichever occurred first.

We checked the proportional hazards assumption for overall cancer and all hematologic neoplasms by comparing the estimated—ln–ln survivor curves for the different groups being investigated. There was no marked deviation from the proportional hazards assumption. We performed multivariate analysis including the independent covariates age, gender, year of first registered engagement and educational level. Age was defined at time of entering into the cohort (time of first registered engagement) and used as a continuous variable in the model.

To ensure a sufficient adjustment for the year of first engagement, we repeated all analyses of the "upstream operators offshore" using only the referents drawn for this specific job category. We also repeated the analysis excluding the upstream operators offshore being registered only 1 year or less in the offshore related industry offshore.

Finally, we also performed subanalysis in 5 years periods according to the year of first registered engagement.

We performed all analysis using SPSS 14.0.1 (SPSS Inc., Chicago, IL, USA).

Ethical considerations

We conducted the study with the approval of the Western Norway Regional Committee for Medical Research Ethics, the Norwegian Data Inspectorate and the Directorate for Health and Social Affairs. Rikstrygdeverket (now merged into the Norwegian Labour and Welfare Organisation) gave us permission to use the Norwegian Registry of Employers and Employees, the Cancer Registry of Norway provided data, and Statistics Norway (Ministry of Finance) approved the use of information from the Norwegian Cause of Death Registry and the Norwegian Education Registry.

Results

The incidence of overall cancer (all sites) among the offshore workers did not differ significantly from that of the general working population in any job category (Table 2). However, the overall mortality was slightly increased among the offshore workers, ascribed to an increased mortality from all causes in the job categories "catering personnel offshore" (rate ratio (RR) 1.44) and "other personnel offshore" (RR 1.30). The mortality ratio was below unity for the job category "upstream operators offshore" with borderline significance (RR 0.87).

"Upstream operators offshore" had an excess risk of hematologic neoplasms (RR 1.90) (Table 2). The increased risk among "upstream operators offshore" was ascribed to an increased risk of acute myelogenous leukemia (RR 2.89) and multiple myeloma (RR 2.49) (Table 3). The other job categories had no increased risk of either hematologic neoplasms combined (blood and bone marrow), acute myelogenous leukemia or multiple myeloma.

We also compared "upstream operators offshore" to a reference group comprising only referents drawn for this specific job category during the establishment of the cohort (n = 35,634). The risk increased slightly in this subanalysis for both hematologic neoplasms localized to blood and bone marrow (RR 2.00, 95% CI 1.18.3.38), acute myelogenous leukemia (RR 3.67, 95% CI 1.30–10.34), and multiple myeloma (RR 2.54, 95% CI 1.09–5.90). The mortality from all causes and incidence of cancer (all sites) for "upstream operators offshore" did not differ from that of this alternative reference group. Further, by excluding the upstream operators offshore being registered only for 1 year or less in the offshore-related industry offshore (n = 71), no change in the risk estimates was found.

The risk of lymphoma for the total group of offshore workers was significantly lower than in the general working population (RR 0.64) (Table 2). However, no significant difference was found within any of the job categories

Table 2 Rate ratios (RR) for overall mortality (all causes of death), cancer incidence (all sites of cancer), hematologic neoplasms localized to blood and bone marrow and hematologic neoplasms localized to lymphatic tissues (lymphomas) for workers in the job categories in the upstream petroleum industry versus referents from the general working population, Norway 1981–2003 adjusted for gender, age at inclusion into the cohort, year of first exposure, and education using the Cox proportional hazards model

	All causes of death			All sites of cancer			Hematologic neoplasms (blood and bone marrow)			Lymphomas		
	n	RR	95% CI	*n*	RR	95% CI	*n*	RR	95% CI	*n*	RR	95% CI
Referents	10,002	–	–	11,271	–	–	394	–	–	655	–	–
All petroleum workers offshore	898	**1.13**	1.06–1.21	815	1.01	0.94–1.09	37	1.24	0.88–1.74	33	**0.64**	0.45–0.91
Upstream operators offshore	227	**0.87**	0.76–1.00	251	0.93	0.82–1.06	20	**1.90**	1.19–3.02	14	0.82	0.47–1.42
Drilling and well maintenance	160	1.08	0.92–1.27	150	0.96	0.82–1.13	9	1.55	0.80–3.02	7	0.66	0.31–1.40
Catering offshore	123	**1.44**	1.20–1.73	102	1.04	0.85–1.27	2	0.68	0.17–2.73	1	0.20	0.03–1.41
Others offshore	388	**1.30**	1.17–1.44	312	1.10	0.98–1.23	6	0.58	0.26–1.30	11	0.60	0.33–1.08

Rate ratios significantly different from unity are given in bold. The letter *n* denotes number of cases

offshore or for any of the subtypes of lymphomas (Table 3).

In the subanalyses in 5-year periods according to the first registered engagement we found strong effects for the first 5-year period 1981–1985 for both acute myelogenous leukemia (RR 3.26), and multiple myeloma (RR 2.85). The RRs for having the first registered engagement prior to 1986 and in the period 1986–2003, respectively, are given in Table 4 for all offshore workers combined and the job category "upstream operators offshore". Among the "upstream operators offshore", 29 of the total of 34 cases of hematologic neoplasms occurred among the workers participating in the first 5-year period. Compared with the general working population, the overall mortality (all causes) and overall cancer (all sites) was relatively stable for these periods both among all offshore workers combined and for "upstream operators offshore".

Discussion

Offshore petroleum workers employed on Norway's continental shelf from 1981 to 2003 had a higher risk of developing hematologic neoplasms, especially multiple myeloma and acute myelogenous leukemia, than the general working population. The risk was elevated among "upstream operators offshore". These are the workers assumed to have had the most extensive contact with different phases of crude oil and other products containing benzene. No increased risk of developing lymphoma in this group of workers was found.

Given the established association between benzene exposure and hematologic neoplasms [1, 2], benzene exposure probably caused the observed increased risk of acute myelogenous leukemia and multiple myeloma. At present, it is unclear at which level of exposure benzene poses an increased risk of developing hematologic neoplasms [9, 17, 24–27]. Previous studies that assessed the association between benzene exposure and hematologic neoplasms in cohorts of petroleum workers were limited by the lack of good exposure estimates including information on the variability of benzene exposure. This is also a major limitation of our study. Information about past exposure to benzene through contact with petroleum streams in Norway's offshore petroleum industry is scarce [28], and we do not have any objective data on a possible additional exposure through the use of benzene as a degreasing agent, as a laboratory chemical or as a component in drilling mud. However, crude oil assays from different regions of the Norwegian continental shelf ($n = 14$) reported a mean and median value of 0.28% benzene by weight, within a range of <0.01–0.66% [19]. Pooled full shift measurements from processing and drilling areas in the period 1994–2003

Table 3 Rate ratios (RR) and 95% confidence intervals (95% CI) for hematologic neoplasms among workers in job category "upstream operators offshore" versus referents from the general working population, Norway 1981–2003

	Referents	Upstream operators offshore		
	n	*n*	RR	95% CI
All hematologic neoplasms localized to blood and bone marrow	393	20	**1.90**	1.19–3.02
Multiple myeloma	132	9	**2.49**	1.21–5.13
Acute lymphocytic leukemia	17	1	2.17	0.29–16.6
Chronic lymphocytic leukemia	73	3	1.62	0.51–5.20
Acute myelogenous leukemia	86	6	**2.89**	1.25–6.67
Chronic myelogenous leukemia	31	1	1.44	0.19–10.7
Other hematologic neoplasms	54	0	–	–
All lymphomas	655	14	0.82	0.47–1.42
Non-Hodgkin lymphoma	524	14	1.01	0.58–1.75
Hodgkin disease	114	0	–	–
Unspecified and undefined lymphomas	17	0	–	–

Rate ratios are adjusted for gender, age at inclusion into the cohort, year of first exposure, and education using the Cox proportional hazard regression model. Rate ratios significantly different from unity are given in bold. The letter *n* denotes number of cases

Table 4 Rate ratios (RR) and 95% confidence intervals (95% CI) for different types of hematologic neoplasms, all cancer sites and overall mortality (all causes of death) for all offshore workers combined and workers in the job category "upstream operators offshore" versus referents from the general working population

	Referents	Offshore workers combined			Upstream operators offshore		
	n	*n*	RR	95% CI	*n*	RR	95% CI
First exposure 1981–1985							
All hematological neoplasms	549	45	1.08	0.79–1.48	29	1.38	0.93–2.03
All leukemia	107	14	**1.84**	1.05–3.22	10	**2.49**	1.30–4.78
Acute myelogenous leukemia	45	7	**2.24**	1.00–5.01	5	**3.26**	1.28–8.30
Multiple myeloma	83	11	1.74	0.90–3.38	9	**2.85**	1.37–5.93
Non-Hodgkin lymphoma	271	19	0.93	0.57–1.50	10	0.96	0.49–1.86
All cancers	6,075	411	1.00	0.90–1.11	187	0.91	0.78–1.06
All causes of death	5,884	487	**1.13**	1.02–1.24	184	0.89	0.76–1.03
First exposure 1986–2003							
All hematological neoplasms	500	25	**0.65**	0.43–0.97	5	0.78	0.32–1.89
All leukemia	100	4	0.50	0.18–1.37	1	0.80	0.11–5.75
Acute myelogenous leukemia	41	4	1.23	0.44–3.44	1	1.76	0.24–12.86
Multiple myeloma	49	5	1.52	0.60–3.86	0	—	—
Non-Hodgkin lymphoma	253	10	**0.50**	0.27–0.95	4	1.22	0.45–3.29
All cancers	5,196	404	1.04	0.93–1.15	64	0.97	0.76–1.25
All causes of death	4,118	411	**1.15**	1.03–1.27	43	0.79	0.59–1.08

Rate ratios are stratified on the year of the first engagement in the offshore-related petroleum industry ("first exposure") and adjusted for gender, age at inclusion into the cohort, year of first exposure, and education using the Cox proportional hazard regression model. Rate ratios significantly different from unity are given in bold. The letter *n* denotes number of cases.

(n = 367) show an arithmetic mean benzene exposure of 0.037 ppm, ranging from below level of detection to 2.6 ppm [28]. Recent studies report a benzene exposure averaged over a full shift well below 0.1 ppm during ordinary activity, ranging from below 0.001 to 0.69 ppm [19, 29]. Low full shift exposures for most job categories are also reported internationally from the upstream petroleum industry [20, 30–32]. However, specific tasks causing high short-term exposures, such as cleaning of tanks containing residues of crude oil with a reported maximum of

16.8 ppm benzene [19], are major determinants of exposure and may contribute significantly to the total benzene exposure [19, 29]. Collins et al. [33] reported that the number of peak exposures to benzene (above 100 ppm), rather than cumulative exposure, might be the best predictor of risk of hematologic neoplasms.

Nevertheless, in spite of the lack of good exposure estimates for the groups included in our study, we assume that the "upstream operators offshore", who have had the most extensive contact with crude oil and natural gas, was highest and most homogenously exposed to benzene. The reported exposure levels, and the low content of benzene in the crude oil, still indicate that the atmospheric exposure from the crude or condensate has been well below the exposure levels that most studies have reported to be necessary for inducing hematologic neoplasms. This increased risk thus implies that the exposure levels have been higher than published for this industry, or that the increased risk for these neoplasms can be found at lower levels of exposure than previously assumed. In support of the latter interpretation a few studies have reported an association between a mean benzene exposure around, and even below, 1 ppm and increased risk of acute myelogenous leukemia [9], increased single-strand breaks in DNA of leukocytes [34, 35], chronic hematotoxic effects including reduced neutrophil, lymphocyte and platelet counts in peripheral blood [36], and acute alterations of the immune system including levels of circulating lymphocytes and immunoglobulins [37], respectively. The sensitivity to benzene's toxic effects differs between individuals, partly explained by genetic polymorphisms in enzymes involved in the metabolism of benzene and genes which are of importance in DNA repair pathway or the regulation of hematopoiesis [38–42]. Hence, the present and previous observations suggest that benzene even at low exposure levels may contribute to the risk of hematologic neoplasm, especially in genetically susceptible individuals. As cigarette smoke is a known source of benzene exposure [43], a leukemogenic effect at low benzene-exposure is further supported by the reported increase in acute myelogenous leukemia and cytogenetic abnormalities in smokers [44]. Smokers not occupationally exposed to benzene reached a morning concentration of benzene in blood of up to 13 nmol/l after smoking four or five cigarettes [45], which is equivalent to a benzene exposure in the breathing zone of approximately 0.3 ppm averaged over an 8-h shift [46].

The association between benzene exposure and the development of specific subtypes of leukemia is still unclear. Our results showing the highest risk for acute myelogenous leukemia are in accordance with findings in previous studies [1, 2]. The risk of acute lymphocytic leukemia was also elevated but was based only on two cases in the exposed groups and therefore not statistically significant. Hence, the statistical power of our study to detect an increased risk for the more infrequent subtypes of leukemias might be too low. This is also reflected in the wide confidence intervals for these subtypes. The most recent meta-analysis of benzene exposure and leukemia subtypes including nine cohorts and 13 case–control studies from several industries, found a high and significant risk of acute myelogenous leukemia, with a positive dose–response relationship across study designs [2]. The risk for developing chronic lymphocytic leukemia was increased in the case–control studies, but not in the cohort studies. The data for chronic myelogenous leukemia and acute lymphocytic leukemia were sparse and inconclusive.

The association between benzene exposure and multiple myeloma is a contentious issue [3, 4, 47]. A meta-analysis of 22 cohort mortality studies consisting of 250,000 petroleum workers concluded that these workers do not have an increased risk of multiple myeloma as a result of their exposure to benzene, benzene-containing liquids or other petroleum products in their work environment [16]. In contrast, a more recent meta-analysis including seven cohort studies focusing on benzene-exposed workers reported a significant excess in the relative risk of multiple myeloma in relation to benzene exposure (relative risk 2.13, 95% CI: 1.31–3.46) [47]. The majority of the studies included in the negative meta-analysis [16] were performed on refinery and distribution workers, and it has been questioned whether the cohort members were sufficiently exposed to benzene to detect any effect [47]. Our finding of an increased risk of multiple myeloma among the upstream petroleum workers, also showing an increased risk of acute myelogenous leukemia, provides further evidence of an association between benzene exposure and the risk of multiple myeloma.

The risk of acute myelogenous leukemia and multiple myeloma was highest among the workers who had their first registered engagement in the offshore petroleum industry at the beginning of the study period. A plausible explanation for this finding might be a general improvement of the working environment offshore, including reduced benzene exposure, following regulations and other initiatives in the 1990s. Another explanation might be that the follow-up time for workers starting later was too short to detect any increased risk. While maximum follow-up in the present study is truncated at 22 years for both offshore workers and referents, the average follow-up periods were 14.6 and 11.5, respectively. Several authors have discussed the temporal variation of the risk of developing leukemia after exposure to benzene. For the Pliofilm-cohort [27], the increased risk was reported to be attributable primarily to exposures occurring during the 10 years preceding the death of the case rather than the more distant exposure [48, 49], and

that the risk was highest in the first few years after cessation of exposure [49]. Glass et al. [24] have reported a similar pattern prior to diagnosis of leukemia in the Health Watch cohort from the Australian petroleum industry. Further, in the large cohort of benzene-exposed Chinese workers the relative risk was increased even for workers exposed to benzene less than 5 years [25]. On the other hand, mortality studies of workers from the petroleum industry have shown an increased risk of acute myelogenous leukemia along with increasing duration of employment, with the highest risk among workers employed for more than 20–30 years [10, 11, 50]. Although the time estimates reported in these studies represent a combination of latency and the effect of cumulative exposure, these observations are compatible with a wide range of latency periods for acute myelogenous leukemia induced by benzene, and indicate that an increased risk might be found also for work in the later periods in the present study after longer follow-up period.

Previous studies report that the time from first exposure till diagnosis or death of multiple myeloma possibly related to benzene is above 20 years [27, 33, 47]. In our study, the median time between the first year of registered engagement and diagnosis of acute myelogenous leukemia and multiple myeloma for cases in the job category "upstream operators offshore" included into the cohort prior to 1986 was 6 (range 5–21) and 18 (range 13–20) years, respectively. This is compatible with a longer latency in multiple myeloma, but the rather short follow-up time together with the low number of cases, limit the possibility of a powerful discussion on the latency issue based on our data.

The etiology of lymphomas is still largely unknown, but given the potential for benzene to affect the immune system an association between benzene exposure and particularly non-Hodgkin lymphoma has been suggested [7, 8, 25]. We found that the total cohort of offshore workers had a decreased risk of lymphomas. However, there were no statistical difference in the risk of neither non-Hodgkin lymphoma nor Hodgkin disease in any of the job categories. This is in line with what has been found in most other cohorts of petroleum workers [15, 17]. The increased risk of both acute myelogenous leukemia and multiple myeloma indicates a sufficient exposure to benzene in this cohort to induce hematologic neoplasms, and the negative findings on lymphomas therefore argue against an association between benzene and lymphomas at these exposure levels. However, in the large cohort of Chinese workers [25] it was reported a relative risk of non-Hodgkin lymphoma of 4.2 for workers with 10 or more years of benzene exposure, as compared to a relative risk of 0.7 for workers with exposure less than 5 years. The increased risk was found only for workers with an average exposure of ≥25 ppm benzene (RR 4.7). Thus, in our study the follow-up time to detect an increased risk of non-Hodgkin lymphoma might also have been too short.

Smoking is associated with risk of acute myelogenous leukemia [44] and might also be associated with multiple myeloma [51]. We do not have data on smoking in our study. However, the risk estimates were adjusted for the level of education, which is sometimes used as a surrogate measure of social class and smoking [52, 53]. The "upstream operators offshore" had a modest and non-significantly increased risk of cancer in lung and bronchus, while a slightly higher increased risk was found for the two groups "catering offshore" and "others offshore" where no increased risk of hematologic neoplasms was found (data not shown). Further, the percentages of smokers among operators in offshore oil industry in Norway in 1997 was reported to be 31% [54], while the percentage of smokers in the general male working population in Norway was estimated to be 35% in 1997–1999 [55]. All these factors indicate that smoking did not contribute substantially to the increased risk of hematologic neoplasms among "upstream operators offshore".

Given the complexity of the exposure to crude oil and to other agents at offshore installations, other factors might have contributed to the increased risk of hematologic neoplasms. Ionizing radiation has been shown to cause both acute myelogenous leukemia [56] and multiple myeloma [57]. Some petroleum workers are potentially exposed to ionizing radiation due to nondestructive testing of welding seams, well-logging, and contact with sediments emitting low-level ionizing radiation. The majority of exposure measurements relevant for the petroleum industry offshore have been reported to be well below the present recommended annual limit values of 1 mSv, and all below that of 20 mSv for occupational radiation exposure [58, 59]. From naturally occurring radioactive materials in the oil and gas industry, maximal effective doses ranging from 0.04 to 0.60 mSv for normal activities and from 0.08 to 1.20 mSv during revision stops have been estimated [60].

The healthy worker effect is a bias that might occur in occupational mortality studies comparing the working population of interest with general populations, possibly masking an increased risk of the disease under study. This has been shown for mortality risks for both chronic diseases and cancer [61], and is a potential limitation of previous studies in the petroleum industry reporting a significantly lower overall mortality of causes and overall cancer incidence among these workers than in the general population [11–13, 22, 50]. In addition to using a historical prospective design, we drew our referents from the general working population and from the same

registry as the subjects "at risk", hence reducing this possible healthy worker effect. We also matched the subjects and referents for level of education and place of residence, thereby reducing a potential bias due to culture, ethnicity, lifestyle and/or regional environmental pollution, as discussed by Leonard et al. [61]. The Cancer Registry of Norway was the source for cases of cancer among both petroleum workers and referents, thereby avoiding classification bias of the outcome. The incidence of overall cancer (all sites) among the offshore workers did not differ significantly from that of the general working population in any job category, indicating that our study design has sufficiently reduced such possible information and selection biases. However, the overall mortality was slightly increased among the offshore workers compared with the general working population (RR 1.13), ascribed to a significantly increased mortality from all causes in the job categories "catering offshore" (RR 1.44) and "others offshore" (RR 1.30). The mortality ratio was below unity for the job category "upstream operators offshore" (RR 0.87) with borderline significance, indicating that a healthy worker effect still might have been present in this specific work category.

In conclusion, workers in the upstream petroleum industry exposed to crude oil and other hydrocarbons had a significantly increased risk of developing acute myelogenous leukemia and multiple myeloma, but not non-Hodgkin lymphoma. The workers employed early in the study period had the highest risk. Although we cannot exclude a possible contribution of other types of specific or combined exposure, occupational exposure to benzene is the most likely candidate for the increased risk. However, given the lack of detailed information on occupation, job tasks, and exposure in the groups studied, exposure was probably nondifferentially misclassified in this historical prospective study. Such nonspecific exposure indicators might have caused an underestimation of the risk for the individuals with substantial exposure. A case–control study nested within the cohort should be performed to improve the estimates of the association between the various types of exposure and the risk of the subtypes of hematologic neoplasms.

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