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RESEARCH ARTICLE

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Residential proximity to oil and gas production sites and hematologic malignancies: A case-control study

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Abstract

Background: We investigated the association between residential proximity to oil and gas production sites and hematologic malignancies, due to a cancer cluster in the German state of Lower Saxony.

Methods: A registry-based case-control study was conducted including 3978 cases of hematologic malignancies diagnosed within 2013–2016 and 15,912 frequency-matched controls randomly drawn by population registries. Residential proximity to 5333 oil and gas production sites at the time of diagnosis was calculated. Unconditional logistic regression models were used to estimate the association between living within 1 km of any exposure site and developing a hematologic malignancy. Models were adjusted for matching variables sex, age group, district, and year of diagnosis as well as for proximity to main streets and to agricultural land.

Results: We found no association between the development of hematologic malignancies and the proximity to all oil and gas production sites (odds ratio: 0.97; 95% confidence interval: 0.85, 1.11). Focusing on gas production sites increased the odds of developing hematologic cancer (odds ratio: 1.19; 95% confidence interval: 0.97, 1.45). In stratified analyses, associations were stronger in women and for acute myeloblastic leukemia. We also found an association in the district where the initial cluster occurred.

Conclusions: Our results suggest that residential proximity to oil and gas production is not a risk factor for all hematologic malignancies in general. Sporadic and past exposures are the most likely scenarios for mechanisms involving oil and gas production, leading to increased risk for certain subtypes of cancer in certain populations.

KEYWORDS

case-control studies, hematologic neoplasms, leukemia, lymphoma, oil and gas industry

1 | INTRODUCTION

The German state of Lower Saxony is one of Germany's most important areas of oil and gas production, with the second most oil and the single most gas produced among German states.[1] Within the state, production sites are located in a belt in the east-west direction which roughly covers half of the state's area. In one district's subarea located in the oil and gas belt, an investigation by the Cancer Registry of Lower Saxony for malignancies diagnosed between 2003 and 2012 showed an increased incidence of hematologic cancer, especially multiple myeloma (MM) and non-Hodgkin lymphoma (NHL), in men.[2] Similar results were found for a city located nearby, although MM and to lesser extent leukemia were the subtypes of cancer with increased incidence while the numbers for NHL were as expected.[3] In an explorative analysis that was part of the following cluster investigation, proximity of the place of residence to gas production sites was found as one possible explanation of the described cluster.[4]

Although the literature points to a relation between oil and gas production and hematologic malignancies,[5,6] the biological pathway from residential proximity to oil and gas production sites toward hematologic malignancies is still not completely clear. Butadiene, benzene, or other substances that are used, produced, or emitted in oil and gas production might be part of it. Some of these substances are categorized as carcinogenic for leukemia or lymphoma by the International Agency for Research on Cancer (IARC), especially when including hydraulic fracturing.[7,8] These substances might be distributed by water or air. Another explanation would be a higher exposure in some areas due to spills and leaks.[9,10] In addition, light pollution,[11] noise,[12] and radiation[13] are discussed as potential pathways.

The presented study was conducted to further investigate the results from the explorative cancer cluster investigation.[4] We conducted a case-control study to investigate the association between residential proximity to oil and gas production sites as well as to gas production sites only (including hydraulic fracturing) and hematologic malignancies in the oil and gas production belt in the German state of Lower Saxony.

2 | METHODS

2.1 | Study design

A registry-based case-control study was conducted in 15 districts of the German state Lower Saxony which roughly form the state's oil and gas production belt. The districts cover half the area of Lower Saxony and with around 3.3 million people 42% of its inhabitants.[14,15] Cities with more than 50,000 inhabitants were excluded to avoid bias by inner-city air pollution. Cases were defined as adults that were known by the cancer registry of Lower Saxony to be diagnosed with a hematologic malignancy (International Statistical Classification of Diseases and Related Health Problems 10 [ICD-10] diagnoses C81-C96) between 2013 and 2016 and lived within the study region at the time of diagnosis. Before 2013, addresses were only available for a small proportion of cases, and after 2016, data were not yet available in the expected quality. We focused on adults based on previous results of the cluster investigation. Of the resulting 5028 cases, 1050 were excluded because of the missing year of diagnosis due to only death certificates being available ($n = 440$), previous diagnoses of hematologic malignancies ($n = 20$), missing consent for linking personal data to registry information ($n = 51$), imprecise addresses, that is, missing house number or missing street and house number ($n = 445$), conflicting addresses or coordinates ($n = 78$), or a correction of the year of diagnosis at a later date ($n = 16$), leaving 3978 cases for inclusion. Controls were drawn randomly by the population registries of the study region and frequency-matched based on the variables sex, age group (5-year categories), district, and living within the district the same year as the year of diagnosis of the cases to ensure similar marginal distributions for cases and controls. For each case, four controls were selected leading to a study population of 3978 cases and 15,912 controls. To avoid the selection of controls that are also cases, controls were checked for presence in the cancer registry before matching and were excluded if hematologic malignancies have been diagnosed previously.

The study was approved by the Ethics Committee of the University Hospital Munich (Munich, Germany). Since the study was registry-based and only data from the cancer registry of Lower Saxony or population registries was used, the participants were not contacted and no informed consent was necessary. The registry data were used based on the cancer registry state law.[16]

2.2 | Exposure

Residential proximity to oil or gas wells was investigated as exposure. All wells within the study region where oil or gas were actually produced within the 30 years before diagnosis (1983–2012) were considered relevant. Because of the long history of oil and gas production in the area, the hydrocarbon well database did not contain information on production for all wells. The main set of wells included exposure sites for which the Lower Saxony State Authority for Mining, Energy and Geology (LBEG) was reasonable certain that oil or gas was produced within 1983–2012 based on available information. Wells that were constructed to store oil and gas were not included since there were no such wells in the area where the described cluster occurred. To investigate the proximity of cases and controls to production sites, surface coordinates of wells were considered. In total, 5333 coordinates were considered as primary exposure sites. The distribution of production sites in the study region is shown in Figure 1A. Although several wells could start at the same surface coordinates, each surface coordinate was only considered once. For sensitivity analysis, exposure sites were restricted to 1510 wells for which production data were available and production was therefore certain.

Since the production of oil and gas are hard to separate, the 5333 production sites included wells where mainly oil was produced as well as wells where mainly gas was produced. For a secondary analysis, LBEG identified 637 surface coordinates where mainly gas was produced based on a comparison with maps of gas fields.[18] The distribution of coordinates where mainly gas was produced is shown in Figure 1B.

In addition, 273 instances of hydraulic fracturing at 121 production sites in the study region and neighboring districts between 1983 and 2012 from another LBEG database were considered.[19] Fracking sites used for producing geothermal energy were excluded.

Based on exposure coordinates, binary exposure variables were calculated. A case was considered exposed if the address at the time of

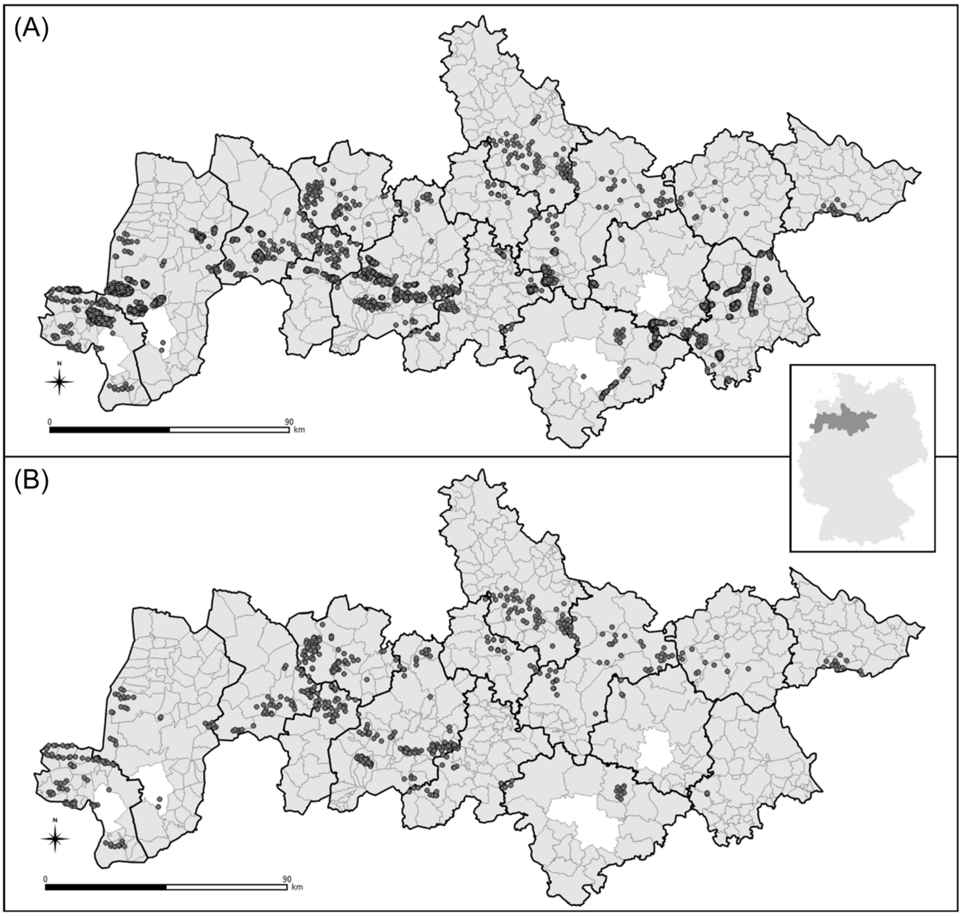

FIGURE 1 (A) Distribution of all oil and gas production sites (*N* = 5333) in the study region; (B) distribution of gas production sites (*N* = 637) in the study region; white areas are excluded cities with more than 50,000 inhabitants; small map shows location of study region in Germany; map of Germany by Federal Agency for Cartography and Geodesy Germany.[17]

diagnosis was within 1 kilometer (km) of any exposure site to allow comparison to previous studies.[20] A control was considered exposed if the address provided by the population registry for the corresponding year was within 1 km of any exposure site. For hydraulic fracturing, 178 unexposed participants living within 1 km of the state border were excluded, since the actual exposure status was unknown because no information on neighboring countries and states was available.

2.3 | Potentially confounding factors

Apart from the matching variables, sex, age group, district, and living within the district the same year as the year of diagnosis of the cases, the proximity to main streets and to agricultural land was considered as potential confounders. Since the participants were not contacted, other potential confounders like smoking, occupational exposure, or nutrition could not be taken into account. Proximity to main streets was considered since on the one hand exposure sites need a link to transportation infrastructure.[21] On the other hand, traffic is one of the main sources of benzene and other air pollutants, which might play a role in the biological mechanism of the association under study.[22–25] Main streets included country roads up to highways. The street map from the Lower Saxony State Authority for Road Construction and Transportation on January 1, 2012, was used to identify streets.[26] Because of the agricultural character of the study region, exposure sites might often be close to agricultural land. Exposure to some of the used pesticides might be a risk factor for certain cancer types, thus distance to agricultural land was considered another potential confounder.[27–31] For this, land use data from the Coordination of Information on the Environment (CORINE) Land Cover System from 2012 was used; categories "non-irrigated arable land" and "fruit tree and berry plantations" were considered.[32] Binary variables were created to indicate if the participant's address lay within a distance of 1 km of a main street or agricultural land.

2.4 | Statistical analysis

Absolute and relative frequencies of matching and potentially confounding variables were described (apart from the district). For the primary exposure, frequencies were shown separately for cases and controls and stratified for matching and potentially confounding variables.

Unconditional logistic regression models were calculated to estimate the association between exposure variables (residential proximity to all oil and gas production sites, residential proximity to gas production sites) and the development of hematologic malignancies. Models were adjusted for matching variables (Model 1) and, in a second step, additionally for potential confounders (Model 2). We also considered the proximity to fracking sites as an exposure. For this, unconditional regression models were only adjusted for matching variables (Model 1), since the number of exposed was low. All models were stratified by sex to assess potential effect modification by sex as seen in the previous results of investigations of the described cluster. Models investigating the primary exposure as well as the proximity to gas production sites were additionally stratified by aggregated age group (18–49, 50–69, 70+ years) and subtype of cancer (NHL, chronic lymphocytic leukemia [CLL], and MM [ICD-10 C82-C88, C91.1, C90]; only MM [ICD-10 C90]; and acute myeloblastic leukemia [AML; ICD-10 C92.0]). These groups were formed based on previous results of the described cluster investigation. In addition, in sensitivity analyses, we restricted exposure sites to those with confirmed production as described above and we restricted cases and controls to those who lived in the district of Rotenburg which is where the initial cluster of hematologic malignancies was found.

For logistic regression models, odds ratios (OR) and 95% confidence intervals (95% CI) were calculated. After the selection of cases and controls as mentioned above, the data set contained no missing data. Analyses were conducted in R version 3.4.3[33] and QGIS version 2.18.15 Las Palmas.[34]

3 | RESULTS

More cases were male (56.8%) than female (43.2%). At the time of diagnosis, almost 60% of cases were between 65 and 84 years old (58.2%; Table 1). More than 95% of participants lived within a

TABLE 1 Comparison of relative and absolute frequencies of matching and potentially confounding variables among all cases (ICD-10 C81-C96) and controls; frequencies of subtypes of cancer used in stratified analyses

Variable	Categories	Cases (N = 3978)		Controls (N = 15,912)	
		%	n	%	n
Sex	Female	43.2	1718	43.0	6845
Age group (years)	18–24	1.2	46	1.0	162
	25–29	1.2	47	1.1	177
	30–34	1.6	62	1.5	237
	35–39	1.7	69	1.7	264
	40–44	1.6	64	1.7	266
	45–49	3.9	154	4.1	657
	50–54	6.2	245	6.2	983
	55–59	8.1	324	7.7	1220
	60–64	8.9	355	9.0	1435
	65–69	12.3	489	12.2	1946
	70–74	15.3	609	15.4	2446
	75–79	18.9	753	18.7	2979
	80–84	11.7	467	12.8	2034
	85 and older	7.4	294	7.0	1106
Year of diagnosis	2013	24.6	978	25.5	4060
	2014	26.4	1049	26.0	4145
	2015	24.1	959	23.4	3722
	2016	24.9	992	25.0	3985
Main streets	≤1 km	95.8	3812	96.0	15,268
Agricultural land	≤1 km	96.6	3844	96.4	15,342
Subtype of cancer	NHL + CLL + MM	77.2	3071		
	MM	18.9	750		
	AML	5.9	235		

Abbreviations: AML, acute myeloblastic leukemia; CLL, chronic lymphocytic leukemia; MM, multiple myeloma; NHL, non-Hodgkin lymphoma.

distance of 1 km to main streets and agricultural land. Most subtypes of cancer fell into the group of NHL, CLL, and MM (77.2%).

Relative frequencies of exposure to all oil and gas production sites were similar between cases (7.6%) and controls (7.5%; Table 2). Within strata, the largest differences were found for year of diagnosis, for example, 6.5% (cases) versus 8.8% (controls) in 2014 or 9.4% (cases) versus 4.9% (controls) for 2016.

Logistic regression models showed no association between the proximity to oil and gas production sites and the development of hematologic malignancies (OR: 0.97; 95% CI: 0.85, 1.11; Table 3). Stratification by sex, or age group leads to similar results. Stratification by subtype of cancer showed differences with the strongest association among the three subtypes for AML (OR: 1.34; 95% CI: 0.86, 2.07). Living within 1 km of a gas production site increased the odds of developing hematologic cancer (OR: 1.19; 95% CI: 0.97, 1.45). When stratifying by sex, only the odds in women were increased (OR: 1.51; 95% CI: 1.13, 2.03). Stratification by subtype of cancer showed a similar pattern to all exposure sites. Effect estimates for residential proximity to fracking sites tended toward increased odds, but interval estimates were large.

When focusing only on the subset of exposure sites with confirmed production, results were similar to results including all oil and gas production sites (OR: 0.92; 95% CI: 0.75, 1.12). When restricting cases and controls to those living in the district of Rotenburg where the initial cluster appeared, we were able to replicate the association between the proximity to gas production sites and the development of hematologic malignancies from the previous cluster investigation (OR: 1.97; 95% CI: 1.01, 3.84). Results were similar when considering all oil and gas production sites because, due to the high percentage of gas production in the area, all exposed cases and controls were also exposed to gas production sites only.

TABLE 2 Comparison of relative and absolute exposure frequencies to all oil and gas production sites (N = 5,333) by case status

Variable	Categories	Cases (*N* = 3978) Exposed %	*n*	Controls (*N* = 15,912) Exposed %	*n*
Total		7.6	302	7.5	1201
Sex	Male	7.3	166	7.6	686
	Female	7.9	136	7.5	515
Age group[a] (years)	18–49	8.1	36	7.5	133
	50–69	8.1	114	7.6	426
	70 and older	7.2	152	7.5	642
Year of diagnosis	2013	7.6	74	7.3	296
	2014	6.5	68	8.8	366
	2015	7.0	67	9.2	343
	2016	9.4	93	4.9	196
Main streets	>1 km	6.0	10	6.2	40
	≤1 km	7.7	292	7.6	1161
Agricultural land	>1 km	7.5	10	7.2	41
	≤1 km	7.6	292	7.6	1160

[a]Age groups were combined for data confidentiality reasons.

4 | DISCUSSION

The presented registry-based case-control study included 3978 adult cases of hematologic malignancies diagnosed within 2013–2016 and 15,912 frequency-matched controls randomly drawn by population registries. Living within a distance of 1 km to an oil and gas production site showed no association with the development of all hematologic cancer. Stratification by subtype of cancer indicated stronger associations for AML compared to other investigated subtypes. Living in the proximity of a gas production site increased the odds of developing a hematologic malignancy with a similar pattern regarding subtypes of cancer. Although residential proximity to fracking sites tended toward increased odds as well, there was not enough data to confidently conclude such an association. Stratification by sex showed an association for living in the proximity of gas production sites only in women. This was in contrast to the initial cluster investigation, however, which found an increased risk in men and mainly for MM.

In the literature, living close to the petrochemical industry or oil and gas production sites is suggested to be a risk factor for hematologic malignancies, although results are inconsistent. In a systematic review and meta-analysis on residential proximity to petrochemical facilities and hematological malignancies, Jephcote et al.[5] found that living closer than 5 km from a petrochemical facility increased the risk of leukemia, while the results for NHL and MM incidence were inconclusive. The authors mentioned several limitations, especially the difficulty to disentangle residential and occupational risk, missing adjustment for socioeconomic status in several studies, and indirect exposure measurements. Although several included studies stratified by sex, no apparent differences were reported. The largest differences were found for MM incidence with higher effect estimates for women, but again, results for MM incidence were inconclusive. A second review by Onyije et al.[6] found an elevated risk for childhood leukemia to be associated with living close to petroleum facilities, while no effect was found for other hematologic malignancies. The review reported no sex-specific estimates. When focusing on oil and gas production sites, a case-control study from the United States (which was also part of the review by Onyije et al.) found an association between residential proximity to oil and gas production sites (many of them using hydraulic fracturing) and acute lymphocytic leukemia in age group 5–24 years, while none was found for NHL. Stratified results by sex were not available.[35] In terms of differences between subtypes of cancer, the presented study found weaker associations for NHL + CLL + MM, while associations for AML were stronger. However, a

TABLE 3 Estimation of association between exposure measures and hematologic malignancies by unconditional logistic regression

	Exposure to				
	All oil and gas production sites (5333)		Gas production sites (637)		Fracking sites (273)
	OR				
	95% CI				
	Model 1[a]	Model 2[b]	Model 1[a]	Model 2[b]	Model 1[a]
Total study population	0.97	0.97	1.19	1.19	1.22
	0.85–1.11	0.85–1.11	0.97-1.45	0.97–1.45	0.75–2.00
Stratification by:					
Sex					
Women	1.03	1.03	**1.51**	**1.51**	1.09
	0.84–1.26	0.84–1.26	**1.13–2.02**	**1.13–2.03**	0.50–2.39
Men	0.93	0.93	0.98	0.98	1.27
	0.78–1.12	0.78–1.12	0.74–1.29	0.74–1.29	0.67–2.42
Subtype of cancer					
NHL + CLL + MM	0.95	0.95	1.18	1.18	
	0.81–1.10	0.82–1.10	0.95–1.47	0.95–1.47	
MM	1.10	1.10	1.21	1.21	
	0.83–1.44	0.84–1.44	0.80–1.84	0.80–1.83	
AML	1.32	1.34	1.58	1.58	
	0.85–2.04	0.86–2.07	0.79–3.18	0.79–3.17	
Age group					
18–49 years	1.05	1.04	1.56	1.55	
	0.70–1.56	0.70–1.55	0.87–2.80	0.87–2.78	
50–69 years	1.04	1.04	1.27	1.26	
	0.84–1.30	0.84–1.30	0.90–1.78	0.90–1.77	
70+ years	0.91	0.91	1.07	1.08	
	0.75–1.09	0.75–1.10	0.82–1.42	0.82–1.42	

Note: Bold—Interval estimate excludes 1.

Abbreviations: AML, acute myeloblastic leukemia; CI, confidence interval; CLL, chronic lymphocytic leukemia; MM, multiple myeloma; NHL, non-Hodgkin lymphoma; OR, odds ratio.

[a]Model 1: adjusted for matching variables age group, sex, district, and year of diagnosis.

[b]Model 2: adjusted for matching variables age group, sex, district, and year of diagnosis and potential confounders proximity to main streets and proximity to agricultural land.

difference in associations between different subtypes of cancer cannot be concluded confidently.

With a study population of almost 4000 cases and four controls per case, we were able to find relatively small differences and estimate associations in subgroup analyses. In registry-based studies, the completeness of case collection is one important quality criterion. Using the mortality-incidence ratio, the Cancer Registry of Lower Saxony was estimated to collect >95% of all existing cases within the relevant years 2013–2016.[36–38] Ten percent of cases had to be excluded because of imprecise addresses. However, the age and sex distributions of excluded cases were similar to those of included cases. Since registry data were used instead of contacting participants directly, deceased cases and controls could be included as well. Controls were based on the total population since only 5 of 162 population registries within the study region (3%) were not able to contribute controls for technical reasons. The risk of selection bias should therefore be limited.

The main limitation was exposure measurement. Due to limited data regarding, for example, surface, wind, and well emissions, only the distance between oil and gas production sites and the place of residence at the time of diagnosis could be calculated. We were also limited in accounting for individual differences between potential exposure sites. We could, for example, not include any data on production volume.

As cases and controls were not contacted individually, duration of stay at the place of residence and other sources of potentially causal exposures were unknown. Because of the skewness of the distribution of distance to exposure sites, only binary exposure variables could be used with the cut-off for the distance introducing an additional source of uncertainty. Misclassification therefore probably affected estimates of association.

We were, however, able to replicate the association in the district of Rotenburg where the initial cluster of hematologic malignancies occurred. Unfortunately, the sample size was too small to stratify by sex and subtype of cancer within the district of Rotenburg. Therefore, we were not able to investigate if the stratified results that are in contrast to the initial cluster analysis are similar within Rotenburg. In general, replication of an association in Rotenburg speaks for sporadic exposures as potential causes rather than for an exposure that is present in all oil and gas production sites at all time. Since potential exposures vary substantially between individual sites, this scenario is not implausible. Many substances used or produced in the context of oil and gas production have some toxic effect to humans, especially when taking unconventional production into account.[8,25] However, the exposure varies due to variations in e.g. regulation and control, geology, drinking water sources, fracking fluid recipes, and the occurrence of spills and leaks.[25] Several investigations looked at potential exposures and individual differences in our study region. To investigate substances in soil and sediments in Lower Saxony, a large number of samples were taken from the vicinity of gas production sites.[39] Although some elevated values were found especially for mercury and benzo(a) pyrene, they did not cover the whole area. In addition, the geographic distribution showed no clustering of elevated values in specific regions, for example, in the district of Rotenburg which showed high incidences of hematologic malignancies. Additionally, during a 9-month period of measurements of air concentrations of benzene, toluene, ethylbenzene, and xylene as well as mercury in a gas field in Rotenburg that included periods of flaring, no elevated concentrations were found.[40] Leaks and spills were also reported repeatedly in the study region but the affected amount of soil and groundwater was usually low.[25] In addition, the current exposure assessment regarding benzene and mercury, which was also part of the described cluster investigation, did not indicate any elevated levels in nearby residents.[41] Therefore, sporadic exposures which occurred in the past and for which, due to the long latency, effects may only be seen today, appear as the most likely scenario if oil and gas production was in fact part of a causal mechanism. These exposures probably would be linked to gas production, potentially via hydraulic fracturing.

In conclusion, this study found no indication for increased odds of developing hematologic malignancies due to living in the proximity of oil and gas production sites in general but indicated an association with AML. An association was also found for living close to gas wells as compared to living farther away. Together with results from additional investigations in the study region, this suggests that sporadic and past exposures are the most likely scenarios for mechanisms involving oil and gas production.

AUTHOR CONTRIBUTIONS

Katja Radon, Michael Hoopmann, and Joachim Kieschke made substantial contributions to the conception and design of the study. Joachim Kieschke, Bernhilde Deitermann, Felix Forster, and Katja Radon made substantial contributions to the acquisition of data. Ronald Herrera, Katja Radon, Michael Hoopmann, and Felix Forster made substantial contributions to the analysis and interpretation of data. Felix Forster and Katja Radon were involved in drafting the manuscript. All authors revised the manuscript and gave final approval of the version to be published.

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CONFLICTS OF INTEREST

R. H. started working for Bayer AG after finishing the study and submitting the study report to the funder. The remaining authors declare no conflicts of interest.

DISCLOSURE BY AJIM EDITOR OF RECORD

John Meyer declares that he has no conflict of interest in the review and publication decision regarding this article.

ETHICS APPROVAL AND INFORMED CONSENT

The study was approved by the Ethics Committee of the University Hospital, Munich (Munich, Germany). Since the study was registry-based and only data from the cancer registry of Lower Saxony or population registries we used, the participants were not contacted and no informed consent was necessary. The registry data was used based on the cancer registry state law as referenced in the manuscript.

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