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Non-Radiation Risk Factors for Leukemia: A case-control study among Chernobyl Cleanup Workers in Ukraine

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Abstract

Background—Occupational and environmental exposure to chemicals such as benzene has been linked to increased risk of leukemia. Cigarette smoking and alcohol consumption have also been found to affect leukemia risk. Previous analyses in a large cohort of Chernobyl clean-up workers in Ukraine found significant radiation-related increased risk for all leukemia types. We investigated the potential for additional effects of occupational and lifestyle factors on leukemia risk in this radiation-exposed cohort.

Methods—In a case-control study of chronic lymphocytic and other leukemias among Chernobyl cleanup workers, we collected data on a range of non-radiation exposures. We evaluated these other potential risk factors in analyses adjusting for estimated bone marrow radiation dose. We

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Competing Interests:

The authors declare they have no competing interests.

Authors' Contributions:

Drs. Gudzenko, Bazyka, Zablotska, Hatch and Mabuchi contributed to the design and conception of the study.

Drs. Gudzenko, Hatch, Brenner, and Zablotska contributed to analysis and interpretation of the data.

Drs. Dyagil, Chumak and Reiss contributed specialized expertise.

Drs. Gudzenko and Hatch drafted the manuscript.

Drs. Bazyka, Mabuchi, Reiss, and Zablotska helped revise the manuscript critically.

Dr. Babkina was responsible for acquisition of the data.

calculated Odds Ratios and 95% Confidence Intervals in relation to lifestyle factors and occupational hazards.

Results—After adjusting for radiation, we found no clear association of leukemia risk with smoking or alcohol but identified a two-fold elevated risk for non-CLL leukemia with occupational exposure to petroleum (OR=2.28; 95% Confidence Interval 1.13, 6.79). Risks were particularly high for myeloid leukemias. No associations with risk factors other than radiation were found for chronic lymphocytic leukemia.

Conclusions—These data – the first from a working population in Ukraine – add to evidence from several previous reports of excess leukemia morbidity in groups exposed environmentally or occupationally to petroleum or its products.

Keywords

leukemia; Ukraine; Chornobyl cleanup workers; petroleum; benzene

1. Introduction

Leukemia as an early and late health effect of exposure to ionizing radiation has long been recognized (UNSCEAR 2008; Preston et al., 1994; Little MP, 2008; Ron E, 2003; Vrijheid et al., 2008; Kesminiene et al., 2008; Hsu et al., 2013; Pearce et al., 2012; Matthews et al., 2013). In addition to ionizing radiation, occupational and environmental exposure to certain chemicals, principally benzene, has also been found to increase the risk of leukemia (Polychronakis et al. 2013; Vlaanderen et al., 2011; Infante PF, 2013). Benzene as a single compound, or as part of a mixture of solvents, has most often been linked to acute myeloid leukemia (AML). However, some studies suggest it may be related to other subtypes as well, including chronic lymphocytic leukemia (CLL) (Vlaanderen et al., 2011; Cocco et al., 2010). Relatively low-level exposure to benzene experienced by petroleum distribution workers has also been associated with an increased risk of myelodysplastic syndrome (MDS), some types of which are recognized precursors to AML (Schnatter et al., 2013). Several studies have reported excess morbidity from leukemia or MDS in population groups either residentially or occupationally exposed to petroleum or its products (Schnatter et al., 2012; Barregard et al., 2009; Talbott et al., 2011; Stenehjem et al., 2014). While less toxic solvents have been substituted for benzene, it is still a component of petroleum products. Other chemicals implicated in leukemia risk include specific categories of pesticides such as phenoxy-herbicides (Polychronakis et al., 2013; Cocco et al., 2013), as well as chemicals used in the synthetic rubber industry (e.g., formaldehyde) (Polychronakis et al., 2013; Infante PF, 2013).

In terms of lifestyle factors, cigarette smoking has been reported to increase the risk of myeloid leukemia, particularly AML (Musselman et al., 2013; Strom et al., 2012; Fircanis et al., 2014; Slager et al., 2014), while, in one study (Slager et al., 2014), an inverse association was found between current smoking and CLL. In the UK Million Women Study (Kroll et al., 2012), higher levels of smoking were associated with increased risk of MDS but not CLL. The study found no association between alcohol consumption and increased risk of either CLL or MDS. In comparison with non-drinkers, the risk of some lymphoid tumors

(principally non-Hodgkin lymphoma and multiple myeloma) was reduced with increasing amounts of alcohol consumed, a pattern observed in some (Gapstur et al., 2012; Besson et al., 2006) but not all (Heinen et al., 2013) other studies. Thus, there is evidence, not altogether consistent, suggesting that smoking is a risk factor for myeloid forms of leukemia while drinking appears to be associated with reduced risk for lymphoid neoplasms.

We previously reported the results of a case-control study of leukemia risk after radiation exposure among Chernobyl clean-up workers in Ukraine, in which we found increased dose-dependent risks for both CLL and non-CLL leukemias (Romanenko et al., 2008; Zablotska et al., 2013). In the course of the study, we also collected interview data on lifestyle factors and subjects' history of occupational exposure to hazardous chemicals. We report here results of the analysis of these potential non-radiation risk factors in this Ukrainian worker population.

2. Material and Methods

A nested case-control study of leukemia was conducted in a cohort of 110,645 male clean-up workers who resided in one of 5 oblasts of Ukraine (Cherkassy, Chernihiv, Dnipropetrovsk, Kharkiv, Kiev) or Kiev city (Romanenko et al., 2008; Zablotska et al., 2013). The cohort was formed based on data from the Chernobyl State Registry. A total of 162 cases of leukemia was identified among cohort members during the period 1986–2006 and confirmed by an international review panel consisting of 6 hematopathologists from the USA, France, Great Britain, and Ukraine. Incidence density sampling was used to identify and interview 5 controls for each leukemia case from among cohort members without leukemia. Controls were matched to cases by year of birth (+/–2 years) and oblast of residence and had to be alive at the time of diagnosis of the corresponding case.

Individual bone marrow radiation doses for both cases and controls were estimated using a time-and-motion method, known as RADRUE (Realistic Analytical Dose Reconstruction with Uncertainty Estimates) (Kryuchkov et al., 2009; Chumak et al., 2008), based on personal interviews with a special questionnaire to gather data on the workers' exposure history (including place, period, duration of clean-up work and residence in the 70-km zone around the Chernobyl nuclear power plant). Radiation doses were reconstructed for 137 (85%) of 162 confirmed leukemia cases, with little variation in verification rate for different leukemia types (Table 1). Based on the data for cases with reconstructed dose and corresponding controls, a significant linear dose-response was found for all leukemia (ERR/Gy = 1.26 (95% CI: 0.03, 3.58)). There were nonsignificant positive dose-response associations for both CLL and non-CLL (ERR/Gy = 0.76 and 1.87, respectively).

Besides the information needed to estimate radiation dose from clean-up work, the questionnaire administered to study subjects included sections designed to collect data on other work-related exposure to radiation either before or after the Chernobyl cleanup work (e.g., in industrial radiography or nuclear energy production). In addition, questions were asked about whether subjects had 'ever worked' in specified Hazardous Industries' (namely, oil refining, chemical plants, resin factories, shoemaking factories, the mechanical repair industry, the electrical industry and Army service). Cohort members were also asked about

‘ever’ working with three categories of Hazardous Chemicals (organic solvents, pesticides, petroleum products). In addition, questions were asked about lifestyle factors such as history of alcohol consumption and smoking (frequency and intensity).

The study was approved by IRBs in both Ukraine and the U.S., and all subjects gave their signed informed consent.

Statistical methods

To evaluate the possible leukemia risks associated with exposure to factors other than Chernobyl radiation, we carried out categorical analyses of 137 cases and 863 controls with reconstructed radiation doses. Conditional logistic regression adjusted for estimated bone marrow dose (continuous) was used to calculate odds ratios (OR) and 95% confidence intervals (CIs) for all leukemias and leukemia types and subtypes in relation to the following variables: work at hazardous enterprises, contact with hazardous chemicals, marital status, education, alcohol consumption, smoking, type of residency (urban/rural), and exposures to diagnostic x-rays. Statistical significance for main effects and interactions was assessed by likelihood ratio tests, with $P < 0.05$ set as the criterion for statistical significance. All tests were two-sided. The models were fitted using the EPICURE statistical package (Preston, 1993).

3. Results

Results of analyses of occupational exposure categories, adjusted for Chernobyl radiation bone marrow dose, are shown in Table 2. Occupational radiation exposure other than Chernobyl was not associated with leukemia risk ($p > 0.5$). Similarly, no association was found for work in a “Hazardous Industry” or for exposure to “Hazardous Chemicals” as a group (both $p > 0.2$). Results were similar for all leukemia types (not shown). Analyses of pesticides, solvents and ‘other chemicals’ also showed no association with leukemia risk, although the numbers of exposed subjects were few (≤ 5) (Table 3). However, we noted that 19 subjects had reported exposure to petroleum. Detailed analysis (Table 4) showed the odds ratio for petroleum exposure to be significantly elevated for non-CLL leukemias (OR=2.28, 95% CI: 1.13, 6.79, $P = 0.03$). This excess was due to the high OR for myeloid leukemia (OR=3.48; $p = .037$), especially chronic myeloid leukemia (CML). Petroleum exposure was not associated with risk of CLL ($p > 0.5$). We tested for interactions between bone marrow dose and exposure to petroleum but found no indication of a significant modifying effect of radiation ($p = 0.58$ from the Likelihood Ratio Test) (data not shown).

Our results from analyses of medical radiation (diagnostic x-rays), and social factors (marital status, education, type of residence (rural/urban)) did not suggest any associations with leukemia (data not shown).

We found no clear relationship with cigarette smoking, for leukemia as a group or by type (Table 5). Although categorical analyses of smoking intensity (packs per day) and pack-years categories did not show significant associations with increased risk of leukemia, the data did suggest a possible decreased risk of non-CLL leukemia with higher smoking intensity; this inverse trend was not statistically significant however ($p = 0.08$). Inverse trends

were also seen with alcohol consumption (Supplemental Table 2). As in the case of petroleum, we found no significant interaction effects between radiation exposure and smoking ($p=0.30$) or alcohol consumption ($p=0.60$) (data not shown).

4. Discussion and Conclusions

Previously we reported a statistically significant monotonic increase in radiation risks of leukemia from a case-control study nested in a large cohort of 110,645 male Chernobyl clean-up workers in Ukraine (Romanenko et al., 2008; Zablotska et al., 2013). The current analysis presents the results with regard to independent effects of other potential risk factors, including lifestyle and occupational factors. In this unique cohort from Ukraine, where work conditions may potentially lead to higher levels of hazardous substances, we found that after adjusting for radiation doses from Chernobyl clean-up work, there were no additional exposure-related increases in risk for CLL, either with self-reported employment in a 'Hazardous Industry' or exposure to 'Hazardous Chemicals'. For non-CLL leukemias, however, we found that exposure to petroleum, over and above effects of radiation, was a significant risk factor ($OR=2.28$, $p=0.03$), and that this relationship was chiefly due to an increased risk for myeloid leukemia, primarily CML ($OR=5.43$, $p=0.03$). Although the relationship is based on relatively few cases ($n=30$), the association we observed in Ukrainian cleanup workers between petroleum exposure and myeloid leukemia, but not CLL, is generally consistent with findings reported in a number of occupational and environmental groups in other countries (Schnatter et al., 2012; Barregardt et al., 2009; Talbott et al., 2011; Stenehjem et al., 2014). Results from a pooled analysis of benzene exposure in recent petroleum worker cohorts, however, with benzene exposures much below the levels seen previously, did not show associations either CML (Glass et al., 2014) or CLL (Rushton et al., 2014), although one of the pooled studies did find an increased risk of CLL among refinery workers, a group that may have had a more diverse exposure. We should note that, as in several other studies, our data on petroleum exposure come from self-reports. However, a review of the occupations and industries where these subjects were employed showed the reports of exposure to be plausible.

Our findings for smoking and leukemia risk differ from those in some recent studies that found associations with increased risk of AML (Strom et al., 2012; Fircanis et al., 2014; Kroll et al., 2012; Besson et al., 2006). Although after adjustment for radiation we did not observe significant associations with smoking, this may reflect changes in smoking intensity among subjects with the disease or be due to a potential recall bias. The design of the questionnaire was such that it was not possible to determine the timing of reported smoking intensity in relation to the date of diagnosis for cases/reference date for controls. (The same caveat applies to the alcohol data.) The limitations of the retrospective smoking data, especially in view of potential changes in smoking habits related to leukemia diagnosis, do not allow us to rule out the association of smoking and increased risk of AML found in other studies. In addition, we note that our smoking data are not entirely inconsistent with a recent pooled analysis from the InterLymph consortium showing a modest protective effect of current smoking for CLL [36].

Conclusions

Although our study has some limitations due to sample size and lack of details/verification of exposure, our results are among the few epidemiological data on leukemia risk factors in a working Ukrainian population and they add to the accumulating evidence on the leukemogenic effect, especially for non-CLL, of petroleum exposure and its benzene component.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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List of Abbreviations

AML	Acute Myeloid Leukemia
CI	Confidence Interval
CLL	Chronic Lymphocytic Leukemia
CML	Chronic Myeloid Leukemia
IRB	Institutional Review Board
MDS	Myelodysplastic Syndrome
Non-CLL	non-Chronic Lymphocytic Leukemia
OR	Odds Ratio
RADRUE	Realistic Analytical Dose Reconstruction with Uncertainty Estimates
USA	United States of America

Highlights

- A unique population - a cohort of 110,645 Chernobyl clean-up workers from Ukraine
- Followed 1986–2006 for leukemia, interviewed about non-radiation risk factors
- Petroleum exposure increased risk for non-CLL leukemias, particularly CML
- No risk factor other than radiation was found for CLL

Table 1

Distribution of Cases of Leukemia Among Ukrainian Chernobyl Cleanup Workers by Subtype, 1986–2006.

Cell Type	Confirmed ^a cases	Cases with doses ^b (% confirmed cases)
All leukemias	162	137 (84.6)
Non-CLL^c	73	58 (79.5)
Including:		
Myeloid leukemia	48	40 (83.3)
Acute myeloid leukemia (AML) ^d	20	16 (80.0)
Chronic myeloid leukemia	28	24 (85.7)
Acute lymphocytic leukemia	8	6 (75.0)
Acute leukemia otherwise not specified	11	7 (63.6)
Other chronic leukemia ^e	6	5 (83.3)
CLL	89	79 (88.8)

^a Cases confirmed by the International Hematopathology Panel.

^b Bone marrow doses estimated by RADRUE method from dosimetric questionnaires of participants or their proxies.

^c CLL – Chronic lymphocytic leukemia

^d Combined AML group includes 4 Myelodysplastic syndrom (MDS) RAEB-t cases.

^e 1 Hairy cell leukemia initially was in CLL group and then was transferred to Other chronic leukemia group.

Table 2

Odds Ratios and 95 % Confidence Intervals for Exposure to Hazardous Factors and leukemia (n=137)

Subtype of Leukemia	Variable	Cases	%	Controls	%	OR ^a	95 % CI
All leukemias	Radiation exposure ^b , No	113	87.6	749	87.1	1	
	Yes	16	12.4	111	12.9	0.82	0.46 – 1.49
	Hazardous industry ^c , No	111	86.7	718	83.4	1	
	Yes	17	13.3	143	16.6	0.71	0.41 – 1.26
	Hazardous chemicals ^d , No	102	78.5	666	77.5	1	
	Yes	28	21.5	193	22.5	1.03	0.64 – 1.65
Non CLL	Radiation exposure No	47	88.6	329	87.2	1	
	Yes	6	11/3	48	12.7	0.80	0.31 – 2.06
	Hazardous industry No	46	88.4	311	82.5	1	
	Yes	6	11.5	66	17.5	0.56	0.22 – 1.40
	Hazardous chemicals No	39	72.2	293	77.5	1	
	Yes	15	27.7	85	12.5	1.48	0.75 – 2.92
CLL	Radiation exposure No	66	86.8	420	86.9	1	
	Yes	10	13.1	63	13.0	1	0.48 – 2/14
	Hazardous industry No	65	85.5	407	84.1	1	
	Yes	11	14.5	77	15.9	0.84	0/41 – 1.74
	Hazardous chemicals No	63	82.9	373	77.5	1	
	Yes	13	17.1	108	22.5	0.74	0.38 – 1.45

^a OR from conditional logistic regression with adjustment for radiation dose to the bone marrow lagged by 2 years.^b data on radiation exposure (other than Chernobyl) are missing for 8 cases and 3 controls^c data on hazardous industry (oil refining, chemical plants, resin factories, shoemaking factories, the mechanical repair industry, the electrical industry and Army service) exposure are missing for 9 cases and 2 controls^d data on hazardous chemicals exposure are missing for 7 cases and 4 controls

Table 3

Odds Ratios and 95 % Confidence Intervals for Exposure to Hazardous Chemicals and leukemia (n=137)

Variable (chemical)	Cases	%	Controls	%	OR ^a	95 % CI
Pesticides ^b	No	129	821	95.2	1	
	Yes	5	41	4.8	0.78	0.28 – 2.13
Solvents ^b	No	133	846	98.1	1	
	Yes	1	16	1.85	0.30	0.03 – 3.14
Petrol ^b	No	115	765	88.7	1	
	Yes	19	97	11.3	1.56	0.86 – 2.81
Other chemicals ^b	Yes	129	807	93.6	1	
	No	5	55	6.4	0.52	0.20 – 1.40

^a OR from conditional logistic regression with adjustment for radiation dose to the bone marrow lagged by 2 years.^b data on hazardous chemicals exposure are missing for 3 cases and 1 control

Table 4

Odds Ratios and 95 % Confidence Intervals for Petrol Exposure by subtypes of leukemia (n=137).

Subtype of leukemia	Cases	%	Controls	%	OR ^a	95 % CI
All leukemias ^b						
No	115	85.8	765	88.7	1	
Yes	19	14.2	97	11.3	1.56	0.86 – 2.81
Non-CLL ^c						
No	45	81.8	339	89.4	1	
Yes	10	18.2	40	10.6	2.28	1.13 – 6.79
Including:						
Myeloid leukemia						
No	30	81.1	229	90.9	1	
Yes	7	18.9	23	9.1	3.48	1.09 – 11.12
Acute myeloid leukemia						
No	11	84.6	85	88.5	1	
Yes	2	15.4	11	11.5	1.85	0.29 – 11.72
Chronic myeloid leukemia						
No	19	79.2	144	92.3	1	
Yes	5	20.8	12	7.7	5.43	1.11 – 26.54
CLL						
No	70	88.6	426	88.2	1	
Yes	9	11.4	57	11.8	1.03	0.45 – 2.33

^a OR from conditional logistic regression with adjustment for radiation dose to the bone marrow lagged by 2 years.

^b data on petroleum exposure are missing for 3 cases and 1 control

^c Includes all types of myeloid leukemia, non lymphoid chronic leukemia, leukemia otherwise not specified.

Table 5

Odds ratios and 95 % Confidence intervals for smoking categories and leukemia subtypes

Variable	All leukemias				CLL				non-CLL			
	Cases N (%)	Controls N (%)	OR ^a (95% CI)		Cases N (%)	Controls N (%)	OR ^a (95% CI)		Cases N (%)	Controls N (%)	OR ^a (95% CI)	
Smoking status^b												
Never smoked ^c	35	217	reference		19	124	reference		16	93	reference	
Ever smoked	95	646	1.09 (0.72 – 1.67)		57	360	1.09 (0.62 – 1.92)		38	286	0.72 (0.38 – 1.37)	
Former smoker	65	311	1.25 (0.77 – 2.02)		35	191	1.08 (0.56 – 2.10)		30	120	1.46 (0.72 – 2.93)	
Current smoker	30	335	0.66 (0.37 – 1.18)		19	124	1.20 (0.57 – 2.53)		8	166	0.25 (0.09 – 0.69)	
Regular smoking (ever smoked vs never smoked)												
<1 pack/day	53	281	1.11 (0.68 – 1.82)		31	157	1.27 (0.65 – 2.45)		22	124	0.94 (0.45 – 1.97)	
>1 pack/day	36	340	0.67 (0.39 – 1.14)		21	188	0.88 (0.43 – 1.80)		15	152	0.46 (0.20 – 1.05)	
Pack-years for ever smoked^d												
0	35	217	Reference		19	124	Reference		16	93	Reference	
>0–15	30	190	1.39 (0.82 – 2.36)		10	103	1.17 (0.60 – 2.30)		20	87	0.81 (0.38 – 1.70)	
>15–30	32	207	1.38 (0.79 – 2.39)		23	112	0.79 (0.35 – 1.78)		9	95	0.43 (0.18 – 1.02)	
>30	25	221	0.98 (0.55 – 1.74) P, trend>0.5		17	128	1.04 (0.52 – 2.07) P, trend=0.281 ^b		8	93	0.39 (0.15 – 0.98) P, trend=0.080 ^b	

^aOR from conditional logistic regression with adjustment for radiation dose to the bone marrow lagged by 2 years.^bdata on smoking are missing for 7 cases^creference group is “never smoked” for all models^ddata on pack-years are missing for 8 cases and 28 controls