



RESEARCH ARTICLE

Radon and cancer mortality among underground uranium miners in the Příbram region of the Czech Republic

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Abstract

Background: This study aims to estimate the association between radon and site-specific cancer mortality among a large contemporary cohort of male uranium miners.

Methods: Annual occupational radon exposure was estimated based on a worker's duration of underground mining in a year and estimates of potential alpha energy of radon progeny in their location of work. Cancer mortality over the period 1977-1992 was ascertained for a cohort of 16 434 male underground uranium miners employed in the Czech Republic between 1946 and 1992. Poisson regression was used to estimate relationships between cumulative radiation exposure (in working level months [WLM]) and site-specific cancer mortality.

Results: Radon is positively associated with lung cancer mortality (excess relative rate [ERR] per 100 WLM = 0.2; 95% confidence interval [CI]: 0.10, 0.37). The best fit of the dose-response relationship between radon and lung cancer mortality was linear and estimates of radon-lung cancer associations varied by windows of time-since-exposure. Positive associations between radon and several types of cancer other than lung cancer were identified, notably chronic lymphocytic leukemia (CLL) (ERR/100 WLM = 0.24; 95% CI: [not determined [ND], 5.10]) and extrathoracic cancer (ERR/100 WLM = 0.12; 95% CI: [ND, 0.69]). We observed no associations between radon and stomach cancer, nor between radon and several hematopoietic cancer subtypes.

Conclusions: This study confirms the established radon-lung cancer association and suggests that radon may also be associated with other types of cancer mortality. Further investigations of extrathoracic and CLL cancer, with the aim of obtaining more precise estimates, are warranted to understand associations between radon and cancers other than lung.

KEYWORDS

cancer, lung cancer, radon, uranium mining

1 | INTRODUCTION

Positive associations between radon exposure and lung cancer have been reported in several studies.¹⁻³ Radon and its progeny is classified as a Group 1 carcinogen by the International Agency for Research on Cancer.⁴ Several cohort studies of underground uranium miners have demonstrated the association between radon exposure and lung cancer, although magnitudes of associations vary somewhat between studies. Strong positive associations between radon and lung cancer, similar in size to the pooled Committee on the Biological Effects of Ionizing Radiation (BEIR VI) analysis,^{2,5,6} have been reported in four North American cohorts,⁷⁻¹² in a cohort of Czech miners in Western Bohemia,¹³⁻¹⁵ in a cohort of French uranium miners,¹⁶⁻¹⁸ and in a large cohort of German uranium miners.

While several studies of uranium miners have confirmed positive radon-lung cancer associations, more research is needed examining associations at lower levels, lower exposure rates, and under conditions that are representative of modern occupational radon exposures. Compared with many other uranium miner cohorts, the Příbram cohort has a lower average radon exposure and a higher proportion of workers with low cumulative exposures and low exposure rates; and, many Příbram miners were exposed to conditions representative of modern occupational conditions. The International Committee for Radiological Protection (ICRP) currently recommends an occupational exposure limit of four working level months (WLM) per year averaged over 5 years,¹⁹ which is reflective of median exposures in the Příbram cohort. Příbram miners also have lower average exposures to other co-pollutants compared with some other uranium miner cohorts. Příbram miners were not occupationally exposed to diesel exhaust exposure and industrial hygiene surveys indicate low silica exposure in Příbram mines due to wet drilling practices (Supporting Information Appendix A).²⁰⁻²²

More research on radon-cancer associations other than lung is also needed. Epidemiological studies and dosimetric models suggest that radon progeny may be associated with cancer types other than lung.² Human and animal models have demonstrated that inhaled radon results in radon activity in blood, adipose tissue, and organs.²³⁻²⁵ Radon gas is soluble in water, so inhaled radon progeny enters the bloodstream close to the airway and may cause leukemias through irradiation of T lymphocytes. Radon gas is also soluble in fat, so radon progeny reaches organs through proximity to adipose tissue.^{25,26} Dosimetric models show that the liver, kidney, stomach, and red bone marrow receive doses of radon progeny, although the doses are orders of magnitude smaller than doses received by respiratory tissues.²⁷ Prior uranium miner studies have examined solid cancer subtypes other than lung and reported excess mortality from leukemia among miners in a Czech cohort,²⁰ stomach cancer among German and US miners,^{11,28,29} and kidney cancer among French miners.³⁰ While several uranium miner studies suggest exposure to radon progeny is associated with solid cancer subtypes other than lung, results are not consistent across studies, and several of the positive findings are based on standardized mortality ratios that use external comparison populations. Hematopoietic cancers have also

been investigated in some uranium miner cohorts. Investigators studying red bone marrow doses among the German uranium cohort reported associations between high-linear energy transfer radiation, mostly from radon gas, and myeloid leukemia.³¹ In an incidence case-cohort study of Příbram uranium miners, investigators reported positive associations between radon and both all leukemia combined and chronic lymphocytic leukemia (CLL).²⁰ Epidemiological studies of nuclear workers and mechanistic evidence suggest that radiation may increase CLL.³²⁻³⁴

When radon and its progeny are inhaled, the tissues of the extrathoracic respiratory system also receive radiation doses.³⁵ The association between cumulative radon exposure and rates of extrathoracic airway cancers has been characterized in only two groups of uranium miners. Recent studies of the Ontario and German uranium miners reported on the association between radon and extrathoracic cancer.^{10,36} The German study found a positive association between radon and extrathoracic cancer mortality while the Ontario study found a negative association with extrathoracic cancer incidence and mortality, although both studies had low statistical precision.

Dosimetric and epidemiological studies suggest radon exposure causes cancers other than lung. In this analysis, we report on radon exposure-mortality analyses for lung cancer and other types of cancer among a cohort of workers from the Příbram region of the Czech Republic. Previously, two case-cohort studies of cancer incidence have been conducted using a subset of participants included in the present cohort,^{20,21} and standardized mortality and incidence ratios have been reported for the full cohort.³⁷ This is the first report of cancer mortality excess relative rates (ERRs) in the full cohort. This study adds to the understanding of cancer mortality by analyzing a large and historically significant uranium mining cohort routinely exposed to levels of radon progeny reflective of modern occupational exposures, examining cancers other than lung, and extrathoracic cancers as a group.

2 | METHODS

2.1 | Study setting

Příbram uranium mine operations occurred between 1946 and 1991, during which time over 46 000 workers were employed, producing over 98 500 metric tons of uranium.²² Workers produced most of the country's uranium through the collapse of the Soviet Union; and by the 1960s over 70% of all uranium production took place in Příbram (Supporting Information Appendix A).

2.2 | Cohort definition

The Příbram miner study is based on information collected from employment records for the Příbram Uranium Industry (UI). Card records were kept for compensation purposes for each worker and subsequently computerized into an employment register containing

41 741 males and 6106 females. Records included unique personal identification numbers, dates of birth, dates of employment, and location of employment within the mines (eg, underground, surface, sorting ore).^{20,21} Male employees who worked at least 12 months underground between 1949 and 1991, and were alive and residing in Czechoslovakia on 1 January 1977 are included in the follow-up cohort.^{20,21}

2.3 | Exposure assessment

An annual estimate of exposure to radon progeny, expressed in WLM, was assigned to each miner based on their duration of underground mining and estimates of potential alpha energy of radon progeny in their location of work. Duration of time spent underground was derived from the Czech UI employment records. Annual radon exposure concentration estimates were based on measurements by the Czech UI using area monitors. Before 1968, potential alpha energy was estimated from more than 50 000 radon gas measurements throughout the mines.²⁰ Radon gas measurements were converted to working levels using an equilibrium factor based on mine ventilation practices (Supporting Information Appendix A). From 1968 onward, direct measurements of the potential alpha energy of radon progeny were measured. Over 190 000 direct measurements were taken through the mines between 1968 and 1992.²⁰ Cumulative WLM of radon exposure was calculated for each miner by summing annual estimates for each year of exposure.

2.4 | Other exposures

Diesel fumes and dust are a concern among miners and may cause confounding of radon-cancer associations. Unlike many other mining operations, Příbram miners were not occupationally exposed to diesel exhaust because all vehicles in the Příbram mines were electric (Supporting Information Appendix A). Dust was measured in Příbram mines at least monthly and is described in detail in prior studies.³⁷ Average area measurements of airborne dust in Příbram were the highest in the mid-1950s with an average concentration of 10.5 mg/m³ in 1956. Dust concentrations decreased in the 1970s with the introduction of a strong ventilation system; concentrations fell steeply and remained around 1 mg/m³ until the end of the mining operations. While respirable dust exposure was not measured for Příbram miners, a crude comparison shows that dust levels are lower than the Wismut cohort, which has estimated respirable dust shift average of 20 mg/m³.³⁸ Heavy metals in dust sediments were measured in a pilot study and contained higher levels of lead and lower levels of arsenic compared with the other major Czech mine in the Jáchymov region (Supporting Information Appendix A). The mean concentration of free crystalline silica in the total dust in Příbram was estimated to be 15%, which is considered to be lower than many other hard-rock mines; dry drilling was not common in Czech mines which may have contributed to lower silica levels (Supporting Information Appendix A).

2.5 | Outcome assessment

Vital status for the period 1977-1992 was obtained for each worker from the Czech Central Register of Inhabitants using personal identification numbers listed on employment records. Person-time for workers who emigrated after the start of follow-up was censored at the date of emigration. For workers who died in the Příbram region (approximately 30% of all deaths), the underlying cause of death was coded by a nosologist. For workers who died outside this region, underlying cause of death was obtained from district death registries, and if possible, hard copy death certificates were obtained. Additional sources of vital status follow-up included pensions, UI death records, and medical documentation. The last date of follow-up, and vital status at the end of follow-up were coded. The primary cause of death was coded to the International Classification of Diseases, 9th Edition (ICD-9).^{20,21}

Outcomes in this analysis were chosen based on epidemiological and dosimetric studies of uranium miners and include lung, stomach, kidney, liver, extrathoracic, and hematopoietic cancer subtypes. The category of extrathoracic cancers, defined as all respiratory tissues other than lung and bronchus, is grouped based on the ICRP dose calculations,³⁵ and includes the nasal passages, larynx, pharynx, oropharynx, and mouth.

2.6 | Statistical analyses

Miners contributed person-time from the start of follow-up (1 January 1977) until the earliest of the date of death among deceased miners, date of migration out of the Czech Republic, or end of the study period (12 December 1992). Person-years and events were enumerated and analyzed using Poisson regression analyses with single units of person-time without grouping, which yields comparable estimates to grouped analyses.³⁹

The relationship between cumulative radon exposure (in k categories) and cancer deaths of interest was modeled using the general model form: $\text{rate} = \exp(\beta_0 + \sum_{i=1}^{k-1} \beta_i d_i + \sum_{j=2}^p \beta_j x_j)$. $\beta_1 - \beta_{k-1}$ represents the log relative rate (RR) of cancer mortality per category of lagged cumulative radon exposure in k groups (relative to the referent group). β_0 is the log rate of cancer among workers with the referent level of cumulative WLM, and β_j are parameters for effects of the p covariates x_j . Cumulative WLM was categorized as <25, 25 to <50, 50 to <150, and 150+ WLM for subtypes of interest except lung cancer. Due to the larger number of lung cancer deaths, lung cancer rates were modeled with more exposure categories (<15, 15 to <25, 25 to <50, 50 to <75, 75 to <100, 100 to <150, 150 to <200, 200 to <250, 250+ WLM).

Because the model forms for some outcomes of interest, such as extrathoracic cancer, are not well established, we fitted both log-linear and linear regression model forms. A log-linear model was fit for continuous exposure, $\text{rate} = \exp(\beta_0 + \beta_1 d + \sum_{j=2}^p \beta_j x_j)$ where β_1 represents the log RR of cancer mortality per unit of lagged cumulative radon exposure and β_j are parameters for effects of the

covariates x_j . To account for an induction and latency times, 2-, 5-, and 10-year lags were applied to cumulative radon exposures. Model fit and precision were used to determine final lag-time choice.

Linear ERR and 95% confidence intervals [CIs] were estimated by fitting a model for the association between continuous cumulative WLM and deaths by cancer types of interest. ERRs were obtained using a model form: $\text{rate} = \exp(a_0 + \sum_{j=2}^p a_j x_j)(1 + a_1 d)$, where a_1 is the ERR per unit of lagged cumulative radon exposure d , and a_j are parameters for effects of the covariates x_j . Variation in the radon exposure-cancer mortality association with time since exposure was examined in analyses of lung cancer mortality; three windows of exposure (10-20 years, 20-30 years, and 30+ years) were modeled using a model form: $\text{rate} = \exp(a_0 + \sum_{j=4}^{p+2} a_j x_j)(1 + \sum_{i=1}^3 a_i d_i)$, where a_i represents ERRs per unit of lagged cumulative radon exposure in time windows d_i and a_j are parameters for effects of the covariates x_j .

Potential adjustment variables included age, year of follow-up, birth cohort groups (by decade of employment starting in 1890), duration of employment, and time since exposure. Model fit was assessed using Akaike information criterion. Due to the small number of measured potential confounders, the final adjustment set was mainly informed by a directed acyclical graph with the aim of selecting the most parsimonious model. For most cancer outcomes, a model with log-age and birth cohort terms was the best fit; some cancer outcomes with few deaths had improved fit when excluding birth cohort terms or including interaction terms between birth cohort and age.

In sensitivity analyses of the lung cancer models, cumulative WLM was restricted to workers with less than 250 WLM to evaluate the impact of a small proportion of workers with very high exposure estimates. All statistical analyses were conducted using SAS statistical software (SAS 9.4; SAS Institute Cary, NC); PROC NLP and PROC NLMIXED with an iterative search were used to obtain profile likelihood CIs for RRs and ERRs, respectively. CIs were considered not determined (ND) if the lower CI was less than the negative inverse of highest cumulative exposure, -0.09 .

3 | RESULTS

A total of 16 434 male underground uranium miners met cohort inclusion criteria. They contributed 231 499 person-years during 16 years of follow-up. During follow-up, 25.6% of workers died. Cause of death was available for 89.6% of deceased workers. Mean duration of employment was 7 years and mean cumulative radon exposure was 53 WLM (Table 1). During follow-up, 1416 malignant causes of death were identified. This included 705 lung cancer deaths, 102 stomach cancer deaths, 59 extrathoracic cancer deaths, and 58 hematopoietic cancer deaths (Table 2).

Figure 1 shows RRs and 95% CIs for the association between cumulative radon exposure under a 5-year lagged exposure assumption and lung cancer mortality using log-linear RR models and linear ERR models. The highest RR was observed in the 200 to less than 250 WLM category (RR = 1.88; 95% CI: 1.23, 2.87). A log-linear

TABLE 1 Characteristics of the male Příbram uranium miner cohort

Variable	
Miners, <i>n</i>	16 434
Follow-up period	1977-1992
Person-years	231 499
Employment factors, mean (range)	
Duration of employment, years	7.0 (1.1-37.9)
Year of birth	1935 (1886-1957)
Year of hire	1963 (1946-1975)
Age at hire	27.8 (18.0-69.7)
Age at death	62 (22-102)
Vital status, <i>n</i> (%)	
Alive	12 209 (74.3)
Deceased	4212 (25.6)
Emigrated	12 (0.07)
Vital status unknown	1 (0.01)
Availability of cause of death	3776 (89.6)
Duration of follow-up in years, mean (range)	14 (0.1-16)
Radon	
Cumulative radon in WLM, mean (range)	53.2 (1.2-1121.9)
<10 WLM radon exposure, <i>n</i> (%)	4883 (30)
<50 WLM, <i>n</i> (%)	11 678 (71)
<100 WLM, <i>n</i> (%)	13 502 (82)

Abbreviation: WLM, working level month.

RR model with continuous exposure was best fit with a quadratic term for WLM (RR at 100 WLM = 1.31; 95% CI: 1.17, 1.48; Table 2). The linear model of ERR is also plotted in Figure 1. Lung cancer mortality increased with higher cumulative radon exposure (ERR/100 WLM = 0.22; 95% CI: 0.10, 0.37). Lung cancer results were not sensitive to exposure lag assumptions, such that 2-, 5- and 10-year exposure lag assumptions yielded comparable estimates of association. Estimates with 5-year lag assumptions were reported to be more directly comparable to estimates from other studies. At most levels of cumulative exposure, the log-linear RR estimates were higher than the linear ERR estimates.

Lung cancer results by windows of time since exposure and restricted to cumulative radon exposure less than 250 WLM are shown in Table 3. Results were sensitive to restricting the model to workers with less than 250 cumulative WLM, which increased the ERR per 100 WLM to 0.32 (95% CI: 0.11, 0.53). Windows of exposure, where only exposures within specific time intervals are considered relevant,⁴⁰ showed substantial variations in rates across windows. In the 15- to 30-year window before case failure, the radon-lung cancer association was the highest (ERR/100 WLM = 0.44; 95% CI: 0.21, 0.67). In the 30+ year window before case failure, the radon-lung cancer association was lowest (ERR/100 WLM = 0.05; 95% CI: -0.11 , 0.20).

We examined cancer subtypes other than lung. Linear ERRs for other outcomes of interest are provided in Table 2. Positive but imprecise associations were observed between cumulative radon exposure and extrathoracic airway (ERR/100 WLM = 0.12; 95% CI: ND,

TABLE 2 Linear excess relative rate and log-linear relative rates^a of cancer types by cumulative working level month (WLM) radon exposure among male Příbram uranium miners 1977-1992

Cancer site (ICD-9)	Number of deaths	Crude death rate per 1000 person-years	Linear ERR (95% CI) per 100 WLM ^b	Log-linear rate ratio at 100 WLM (95% CI) ^b
Extrathoracic airway (140-148, 160, 161)	59	0.25	0.12 (ND, 0.69)	1.10 (0.87, 1.39)
Stomach (151)	102	0.44	0.00 (-0.03, 0.29)	1.00 (0.82, 1.21)
Liver (155)	48	0.21	0.06 (ND, 0.58)	1.08 (0.85, 1.37)
Lung (162) ^c	705	3.02	0.22 (0.10, 0.37)	1.31 (1.17, 1.48)
Kidney (189)	41	0.18	0.01 (-0.05, 0.70)	1.01 (0.74, 1.37)
Non-Hodgkin lymphoma (200, 202) ^d	17	0.07	0.11 (ND, 4.87)	0.99 (0.57, 1.72)
Hodgkin lymphoma (201) ^d	8	0.03	-0.09 (ND, 1.95)	0.52 (0.12, 2.21)
Myeloma (203) ^d	8	0.03	-0.09 (ND, 14.73)	0.98 (0.52, 1.86)
CLL (204.1)	11	0.05	0.24 (ND, 5.10)	1.15 (0.72, 1.82)
Myeloid leukemia (205.0, 205.1) ^d	12	0.05	-0.09 (ND, 1.37)	0.75 (0.33, 1.67)
All hematopoietic (200-208) ^d	58	0.25	-0.09 (ND, 0.33)	0.91 (0.67, 1.23)

Note: ND, not determined if lower CI is less than the negative inverse of highest cumulative exposure (-0.09).

Abbreviations: CI, confidence interval; CLL, chronic lymphocytic leukemia; ERR, excess relative rate; HL, Hodgkin lymphoma; ICD, International Classification of Diseases; NHL, non-Hodgkin lymphoma; WLM, working level month.

^a5-y exposure lag assumption: extrathoracic airway, stomach, liver, lung, kidney, myeloma, CLL, and all hematopoietic cancers. 2-y exposure lag assumption: NHL, HL, myeloid leukemia.

^bAdjusted for age and birth cohort unless specified otherwise.

^cAdjusted for age, birth cohort, and age-birth cohort interaction. Log-linear rate ratio model includes quadratic term for WLM.

^dLinear ERR model is adjusted for age only.

0.69), liver (ERR/100 WLM = 0.06; 95% CI: ND, 0.58), kidney cancers (ERR/100 WLM = 0.01; 95% CI: -0.05, 0.70), and CLL (ERR/100 WLM = 0.24; 95% CI: ND, 5.10). Log-linear RRs were similarly positive but imprecise for these subtypes, and the magnitudes of associations were similar for linear and log-linear models in all outcomes

with the exception of non-Hodgkin's lymphoma. RRs for subtypes other than lung were assessed by categories of cumulative radon exposure (Supporting Information Appendix B Table S1). Although RRs are imprecise, there was a positive dose-response between cumulative radon exposure and CLL mortality and extrathoracic cancer mortality.

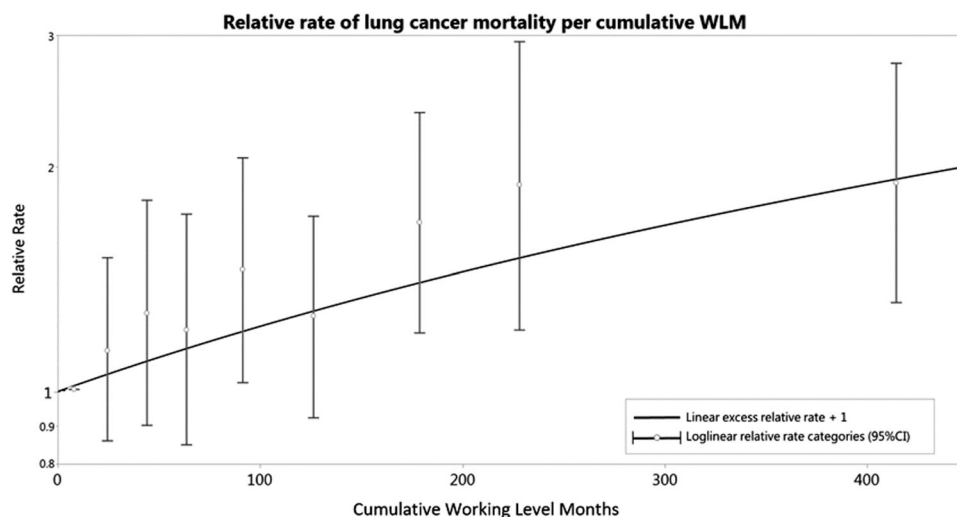
**FIGURE 1** Relative rate of lung cancer mortality per cumulative working level month (WLM) lagged 5 years among male underground uranium miners in the Příbram region of the Czech Republic, 1977-1992

TABLE 3 Lung cancer mortality by cumulative working level month (WLM)

Cumulative radon exposure (WLM)		Excess relative rate/ 100 WLM (95% CI)
Windows of exposure ^a	5-15 y	0.21 (-0.96,1.37)
	15-30 y	0.44 (0.21,0.67)
	30+ y	0.05 (-0.11,0.20)
Restricted to <250 WLM ^b		0.32 (0.11,0.53)

Note: Radon exposure by windows of time since exposure and by exposure less than 250 WLM, among male Příbram uranium miners 1977-1992. Abbreviations: CI, confidence interval; WLM, working level month.

^aAdjusted for age and birth cohort.

^bCumulative working level months under a 5-year lag assumption.

4 | DISCUSSION

We identified strong associations between radon and lung cancer mortality, and positive associations between radon and cancer mortality other than lung, namely extrathoracic cancers and CLL. Liver cancer was also elevated but the magnitude of the association was lower compared with lung and extrathoracic cancers or CLL. This study provides additional evidence regarding the positive exposure-response relationship between radon and lung cancer mortality. While the association between radon and lung cancer mortality has been observed in several other cohorts of uranium miners, estimates vary across studies as cohorts have different levels of radon exposure, rates of exposure, co-exposures, and smoking rates. This study provides lung cancer mortality estimates among a cohort of miners with low radon exposures and relatively few co-pollutants. Lung cancer mortality persisted throughout follow-up in this cohort despite having lower radon exposures than several other uranium miner studies.

Similar to other studies of uranium miners, a positive exposure-response relationship was observed between cumulative radon exposure and lung cancer mortality. Characteristics of several recently updated cohorts and the BEIR VI report are shown in Table 4, which illustrates the variation in estimates between cohorts. The BEIR VI analysis includes 11 cohorts of several types of miners, with a total of 60 606 workers. BEIR VI reports a mean cumulative radon exposure of 164.4 WLM and a combined ERR/100 WLM of 0.76.² Studies of the French, German, and Ontario uranium miners have been updated since the BEIR VI report. A study of 1785 French uranium miners with a mean 71.3 cumulative WLM radon exposure reported an ERR/100 WLM of 0.6 (95% CI: 0.1, 1.2).¹⁷ In the study of 58 987 German uranium miners with a mean 5-year lagged exposure of 280 WLM among the exposed, an ERR/100 WLM of 0.19 (95% CI: 0.17, 0.22) was reported.⁴¹ Among the Ontario miners, an ERR/100 WLM of 0.66 (95% CI: 0.44, 0.87) was reported in the cohort of 28 546 workers with a mean 21 WLM lagged 5 years.¹⁰ This study, the BEIR VI pooled analysis, and recent studies of the French, German, and Ontario cohorts all support a positive association between radon exposure and lung cancer mortality, however, effect estimates vary as a result of working conditions, occupational co-exposures, birth cohort effects, model choices, dose rate effects, and other factors.

TABLE 4 Summary of BEIR VI estimates and recent updates to several underground mining cohort

Study (publication)	Follow-up period	Lung cancer deaths	Mean cumulative WLM	Measured co-exposures	Mean duration of employment (y)	ERR/100 WLM (95% CI)
BEIR VI (NRC, 1999) ²⁴	Various cohorts	2674	164.4	None	1-18	0.59 (SE = 1.32)
Wismut, Germany (Walsh et al. 2010) ⁴²	1946-2003	3016	218	Dust, arsenic, long-lived radionuclides, external gamma radiation	12	0.19 (0.17, 0.22)
Western Bohemia, Czech Republic (Tomasek, 2012) ⁴⁴	1952-2010	1141	73	None	7	0.97 (0.74, 1.27)
Příbram, Czech Republic (Present study)	1977-1992	705	53	None	7	0.22 (0.10, 0.37)
CEA-COGEA, France (Rage et al. 2015) ³⁰	1946-2007	211	36.6	Long-lived radionuclides, external gamma radiation	17	0.71 (0.31, 1.30)
Ontario, Canada (Navaranjan et al. 2016) ¹⁰	1954-2007	1230	21	None	5.3	0.66 (0.44, 0.87)
WISMUT, Germany (Kreuzer et al. 2015) ⁶	1960-2008	334	17	Dust, arsenic, long-lived radionuclides, external gamma radiation, smoking	10	1.3 (0.7, 2.1)

Abbreviations: CI, confidence interval; ERR, excess relative rate; WLM, working level month.

The Příbram lung cancer mortality estimate is lower than many other cohorts, especially when compared with cohorts with similar mean cumulative WLM. This difference may be due to the factors mentioned above or because of delayed start of follow-up.

Estimates in this study are consistent with but slightly lower than other studies because follow-up began long after the start of mining operations. This means lung cancer deaths before the start of follow up are unobserved for 30 years after the start of mining operations. This has several implications for the interpretation of results, particularly among the earliest birth cohorts. Workers who were employed at the start of mining operations had higher average radon exposures because they worked before the implementation of a strong ventilation system. The older workers who were alive at the start of follow-up survived the peak epidemic of lung cancer, which likely occurred before the start of follow up for these workers. Older workers also may have experienced more competing risks due to advanced age. Birth cohort and interactions between age and birth cohort were important adjustment variables in linear lung cancer models. This may reflect missed deaths in the early birth cohorts that occurred before the start of follow-up. Thus, cohort selection criteria and limited duration of follow-up may have contributed to lower lung cancer mortality estimates than in other recent studies. Additionally, cause of death was missing for 10.4% of deceased workers, which reduces power and decreases the sensitivity of the death certificates.

Data on smoking were obtained only for the subcohort of miners and incident cancer cases that had developed at the time of selection for a case-cohort analysis. Therefore, we are unable to evaluate differences in lung cancer death rates by smoking status. However, many uranium miner studies have found that smoking is an effect measure modifier of the radon-lung cancer association, not a confounder.^{2,7,43} Therefore, we would not expect substantial changes in the overall point estimate for the association between radon and lung cancer. Smoking is an important risk factor for extrathoracic cancer as well, but to our knowledge smoking has not been evaluated as a potential confounder or modifier of the radon-extrathoracic cancer association in any uranium miner studies. In a forthcoming case-cohort study, researchers are investigating the effect of smoking on lung and extrathoracic cancer rate estimates in the case-cohort subpopulation.

The overall ERR/WLM was somewhat lower than in other uranium miner studies when restricted to workers with less than 250 WLM, suggesting an inverse dose rate effect. We observed a higher ERR for lung cancer when we restricted the cohort to miners with lower cumulative exposures, which has also been observed in studies of subcohorts of miners who worked in periods of lower exposures.^{6,30} ERR estimates were higher when adjusted for time since exposure, and varied substantially by windows of exposure with the highest estimate when exposures were in the 15- to 30-year window. Variation in risk with time since exposure has been observed in other uranium mining cohorts, including the West Bohemian Czech cohort, which reported substantial variations in estimates by time since exposure, with a decrease in ERR/WLM with increasing time since exposure.^{44,45} Variation by time since exposure was also observed in BIER VI models.²

Cancers other than lung have been investigated in several other uranium mining cohorts, as well as among Příbram miners. Two analyses of cancer incidence among the Příbram miners have been published to date.^{20,21} One report examined the incidence of leukemia, lymphoma, and multiple myeloma in a case-cohort study with a stratified random subcohort of 2393 workers and 177 incident hematopoietic cancer cases, of which 53 were CLL cases. This study found an elevated rate of leukemia, including CLL. Authors reported an RR of 1.75 (95% CI: 1.10, 2.78) for all leukemia combined and an RR of 1.98 (95% CI: 1.10, 3.59) for CLL comparing high radon exposure (110 WLM) to low radon exposure (3 WLM). Positive associations of radon exposure with myeloid leukemia and Hodgkin lymphoma were also found.²⁰ The present study supports the CLL incidence findings from the incidence study of Příbram miners, reporting a positive but imprecise ERR and RR for CLL mortality. However, the difference between incidence and mortality outcomes in these studies is apparent for CLL. CLL has a high relative survival⁴⁶; there are only 11 CLL deaths, 42 fewer CLL fatalities than incident cases reported by Rericha et al. Extended follow-up will be important for understanding radon-CLL associations in this cohort because median age at diagnosis of CLL is 70 years, and the average age at end of follow-up among Příbram miners is 58.

Extrathoracic cancer is another area of concern since inhalation of radon and its progeny delivers radiation to the respiratory tract, and the German study of uranium miners suggests radon may be associated with extrathoracic cancer mortality.^{35,36} Two other uranium miner cohorts have recently studied extrathoracic cancers as a group with conflicting results. A study of extrathoracic cancer among Ontario uranium miners found negative but imprecise associations with both incidence (ERR/100 WLM = -0.29; 95% CI: -0.57, 0.00) and mortality (ERR/100 WLM = -0.17; 95% CI: -0.64, 0.30).¹⁰ Another recent study of extrathoracic cancer mortality among German uranium miners showed a small but imprecise increase (ERR/100 WLM = 0.04; 95% CI: -0.01, 0.08).³⁶ Another case-cohort study of Příbram miners found no association between radon exposure and the incidence of non-lung solid cancers except for malignant melanoma and gallbladder cancer, but examined extrathoracic cancers only by individual subtypes, reporting no statistically significant associations.²¹ The current study aligns with the results of the German study, reporting a positive but imprecise association between radon progeny and extrathoracic cancer, although in our study we had fewer extrathoracic cancer deaths than reported in the large Wismut study. It is important to note that smoking is an important risk factor for extrathoracic cancer; smoking was not evaluated in this study. The present study also did not identify any statistically significant positive associations with non-lung solid cancers. However, there are several suggestive associations, particularly for the group of extrathoracic cancers. The combined study of extrathoracic cancer incidence in the case-cohort study of Příbram miners will be an important direction for future research, as more incident cases and more detailed exposure estimates should improve the precision of estimates.

In this cohort of miners exposed to relatively low radon levels and with less occupational co-pollutants compared with other

uranium mining cohorts, we see that the associations between radon and lung cancer persist. This study supports other findings that low-level, protracted radon exposure causes lung cancer. We also examined other cancer sites associated with radon inhalation in the epidemiologic and dosimetric literature and identified extrathoracic cancers and CLL as possible areas of concern. An extended follow-up of this cohort will improve the precision of these findings and allow for observation of cancers following protracted induction and latency. This study illustrates the importance of continuing to monitor both historical and contemporary populations of underground workers.

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CONFLICTS OF INTEREST

The authors declare that there are no conflicts of interest.

DISCLOSURE BY AJIM EDITOR OF RECORD

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

AUTHOR CONTRIBUTIONS

DPS and DS made substantial contributions to the conception of this study. KK-R, DBR, DPS, and DS led the initial design of this analysis. KK-R led the data analysis and manuscript writing. All authors reviewed and made substantial contributions to the analysis plan and manuscript drafts. All authors reviewed and approved the final version of the manuscript for publication.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS APPROVAL AND INFORMED CONSENT

The study protocol was reviewed by the Institutional Review Boards (IRBs) at the NIEHS and UNC Chapel Hill, and determined to be exempt from full IRB review, as it involved existing records and deidentified data.

DISCLAIMER

The findings and conclusions of this report are those of the authors and do not necessarily reflect those of the National Institute for Occupational Safety and Health. The views expressed are those of the authors and do not necessarily represent the decisions, policy or views of their respective institutions.

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REFERENCES

- Lubin JH, Boice JD Jr, Edling C, et al. Lung cancer in radon-exposed miners and estimation of risk from indoor exposure. *J Natl Cancer Inst.* 1995;87(11):817-827.
- National Research Council. *Health Effects of Exposure to Radon*. Washington, DC: National Academies Press; 1999. <https://doi.org/10.17226/5499>
- Tirmarche M, Harrison J, Laurier D, Blanchardon E, Paquet F, Marsh J. Risk of lung cancer from radon exposure: contribution of recently published studies of uranium miners. *Ann ICRP.* 2012;41(3-4):368-377. <https://doi.org/10.1016/j.icrp.2012.06.033>
- IARC. Monographs on the evaluation of carcinogenic risks to human. *Man-Made Mineral Fibres and Radon.* 1988;43:43-58.
- Grosche B, Kreuzer M, Kreisheimer M, Schnelzer M, Tschense A. Lung cancer risk among German male uranium miners: a cohort study, 1946-1998. *Br J Cancer.* 2006;95(9):1280-1287. <https://doi.org/10.1038/sj.bjc.6603403>
- Kreuzer M, Fenske N, Schnelzer M, Walsh L. Lung cancer risk at low radon exposure rates in German uranium miners. *Br J Cancer.* 2015;113(9):1367-1369. <https://doi.org/10.1038/bjc.2015.324>
- Hornung RW, Deddens J, Roscoe R. Modifiers of exposure-response estimates for lung cancer among miners exposed to radon progeny. *Environ Health Perspect.* 1995;103(suppl):49-53.
- Hornung RW, Deddens JA, Roscoe RJ. Modifiers of lung cancer risk in uranium miners from the Colorado Plateau. *Health Phys.* 1998;74(1):12-21.
- Lane RSD, Frost SE, Howe GR, Zablotska LB. Mortality (1950-1999) and cancer incidence (1969-1999) in the cohort of Eldorado uranium workers. *Radiat Res.* 2010;174(6):773-785. <https://doi.org/10.1667/RR2237.1>
- Navaranjan G, Berriault C, Do M, Villeneuve PJ, Demers PA. Cancer incidence and mortality from exposure to radon progeny among Ontario uranium miners. *Occup Environ Med.* 2016;73(12):838-845. <https://doi.org/10.1136/oemed-2016-103836>
- Schubauer-Berigan MK, Daniels RD, Pinkerton LE. Radon exposure and mortality among White and American Indian uranium miners: an update of the Colorado plateau cohort. *Am J Epidemiol.* 2009;169(6):718-730. <https://doi.org/10.1093/aje/kwn406>
- Samet JM, Pathak DR, Morgan MV, Key CR, Valdivia AA, Lubin JH. Lung cancer mortality and exposure to radon progeny in a cohort of New Mexico underground uranium miners. *Health Phys.* 1991;61(6):745-752.
- Tomásek L, Zárská H. Lung cancer risk among Czech tin and uranium miners—comparison of lifetime detriment. *Neoplasma.* 2004;51(4):255-260.
- Tomásek L. Czech miner studies of lung cancer risk from radon. *J Radiol Prot.* 2002;22(3A):A107-A112.
- Tomasek L, Rogel A, Tirmarche M, Mitton N, Laurier D. Lung cancer in French and Czech uranium miners: Radon-associated risk at low exposure rates and modifying effects of time since exposure and age at exposure. *Radiat Res.* 2008;169(2):125-137. <https://doi.org/10.1667/RR0848.1>

16. Rogel A, Laurier D, Tirmarche M, Quesne B. Lung cancer risk in the French cohort of uranium miners. *J Radiol Prot.* 2002;22(3A):A101-A106.
17. Laurier D, Tirmarche M, Mitton N, et al. An update of cancer mortality among the French cohort of uranium miners: extended follow-up and new source of data for causes of death. *Eur J Epidemiol.* 2004;19(2):139-146.
18. Vacquier B, Caer S, Rogel A, et al. Mortality risk in the French cohort of uranium miners: extended follow-up 1946-1999. *Occup Environ Med.* 2008;65(9):597-604. <https://doi.org/10.1136/oem.2007.034959>
19. Protection against radon-222 at home and at work. A report of a task group of the International Commission on Radiological Protection. *Ann ICRP.* 1993;23(2):1-45.
20. Reřicha V, Kulich M, Reřicha R, Shore DL, Sandler DP. Incidence of leukemia, lymphoma, and multiple myeloma in Czech uranium miners: a case-cohort study. *Environ Health Perspect.* 2006;114(6):818-822.
21. Kulich M, Reřicha V, Reřicha R, Shore DL, Sandler DP. Incidence of non-lung solid cancers in Czech uranium miners: a case-cohort study. *Environ Res.* 2011;111(3):400-405. <https://doi.org/10.1016/j.envres.2011.01.008>
22. Hu H, Yih K, Makhijani A. *Institute for Energy and Environmental Research, International Physicians for the Prevention of Nuclear War. Nuclear Wastelands: A Global Guide to Nuclear Weapons Production and Its Health and Environmental Effects.* MIT Press; 2000.
23. Ishimori Y, Tanaka H, Sakoda A, Kataoka T, Yamaoka K, Mitsunobu F. Measurements of radon activity concentration in mouse tissues and organs. *Radiat Environ Biophys.* 2017;56(2):161-165. <https://doi.org/10.1007/s00411-017-0682-9>
24. National Research Council. *Risk Assessment of Radon in Drinking Water.* Washington, DC: National Academies Press; 1999. <https://doi.org/10.17226/6287>
25. Nussbaum E, Hursh JB. Radon solubility in rat tissues. *Science.* 1957;125(3247):552-553.
26. Harley NH, Robbins ES. 222Rn alpha dose to organs other than lung. *Radiat Prot Dosimetry.* 1992;45(1-4):619-622.
27. Marsh JW, Blanchardon E, Gregoratto D, et al. Dosimetric calculations for uranium miners for epidemiological studies. *Radiat Prot Dosimetry.* 2012;149(4):371-383. <https://doi.org/10.1093/rpd/ncr310>
28. Darby SC, Whitley E, Howe GR, et al. Radon and cancers other than lung cancer in underground miners: a collaborative analysis of 11 studies. *J Natl Cancer Inst.* 1995;87(5):378-384.
29. Kreuzer M, Walsh L, Schnelzer M, Tschense A, Grosche B. Radon and risk of extrapulmonary cancers: results of the German uranium miners' cohort study, 1960-2003. *Br J Cancer.* 2008;99(11):1946-1953. <https://doi.org/10.1038/sj.bjc.6604776>
30. Rage E, Caer-Lorho S, Drubay D, Ancelet S, Laroche P, Laurier D. Mortality analyses in the updated French cohort of uranium miners (1946-2007). *Int Arch Occup Environ Health.* 2015;88(6):717-730. <https://doi.org/10.1007/s00420-014-0998-6>
31. Kreuzer M, Sobotzki C, Fenske N, Marsh JW, Schnelzer M. Leukaemia mortality and low-dose ionising radiation in the WISMUT uranium miner cohort (1946-2013). *Occup Environ Med.* 2017;74(4):252-258. <https://doi.org/10.1136/oemed-2016-103795>
32. Richardson DB, Wing S, Schroeder J, Schmitz-Feuerhake I, Hoffmann W. Ionizing radiation and chronic lymphocytic leukemia. *Environ Health Perspect.* 2005;113(1):1-5.
33. Linet MS, Schubauer-Berigan MK, Weisenburger DD, et al. Chronic lymphocytic leukaemia: an overview of aetiology in light of recent developments in classification and pathogenesis. *Br J Haematol.* 2007;139(5):672-686. <https://doi.org/10.1111/j.1365-2141.2007.06847.x>
34. Schubauer-Berigan MK, Daniels RD, Fleming DA, et al. Chronic lymphocytic leukaemia and radiation: findings among workers at five US nuclear facilities and a review of the recent literature. *Br J Haematol.* 2007;139(5):799-808. <https://doi.org/10.1111/j.1365-2141.2007.06843.x>
35. ICRP. Human respiratory tract model for radiological protection. *ICRP Publ.* 1994;66.
36. Kreuzer M, Dufey F, Marsh JW, Nowak D, Schnelzer M, Walsh L. Mortality from cancers of the extra-thoracic airways in relation to radon progeny in the Wismut cohort, 1946-2008. *Int J Radiat Biol.* 2014;90(11):1030-1035. <https://doi.org/10.3109/09553002.2014.909074>
37. Kelly-Reif K, Sandler DP, Shore D, et al. Mortality and cancer incidence among underground uranium miners in the Czech Republic 1977-1992. *Occup Environ Med.* 2019;76(8):511-518. <https://doi.org/10.1136/oemed-2018-105562>
38. Dahmann D, Bauer H-D, Stoyke G. Retrospective exposure assessment for respirable and inhalable dust, crystalline silica and arsenic in the former German uranium mines of SAG/SDAG Wismut. *Int Arch Occup Environ Health.* 2008;81(8):949-958. <https://doi.org/10.1007/s00420-007-0287-8>
39. Loomis D, Richardson DB, Elliott L. Poisson regression analysis of ungrouped data. *Occup Environ Med.* 2005;62(5):325-329. <https://doi.org/10.1136/oem.2004.017459>
40. Checkoway H, Pearce N, Hickey JLS, Dement JM. Latency analysis in occupational epidemiology. *Arch Environ Health Int J.* 1990;45(2):95-100. <https://doi.org/10.1080/00039896.1990.9935932>
41. Kreuzer M, Grosche B, Schnelzer M, Tschense A, Dufey F, Walsh L. Radon and risk of death from cancer and cardiovascular diseases in the German uranium miners cohort study: follow-up 1946-2003. *Radiat Environ Biophys.* 2010;49(2):177-185.
42. Walsh L, Tschense A, Schnelzer M, Dufey F, Grosche B, Kreuzer M. The influence of radon exposures on lung cancer mortality in German uranium miners, 1946-2003. *Radiat Res.* 2010;173(1):79-90. <https://doi.org/10.1667/RR1803.1>
43. Kreuzer M, Sobotzki C, Schnelzer M, Fenske N. Factors modifying the radon-related lung cancer risk at low exposures and exposure rates among German uranium miners. *Radiat Res.* 2018;189(2):165-176. <https://doi.org/10.1667/RR14889.1>
44. Tomasek L. Lung cancer mortality among Czech uranium miners—60 years since exposure. *J Radiol Prot.* 2012;32(3):301-314. <https://doi.org/10.1088/0952-4746/32/3/301>
45. Tomásek L, Darby SC. Recent results from the study of West Bohemian uranium miners exposed to radon and its progeny. *Environ Health Perspect.* 1995;103(suppl 2):55-57.
46. National Cancer Institute. Chronic Lymphocytic Leukemia—SEER Stat Fact Sheets. Cancer Stat Facts: Leukemia—Chronic Lymphocytic Leukemia (CLL); 2017. <http://seer.cancer.gov/statfacts/html/clyl.html>. Accessed 16 February 2016.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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