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Lung and extrathoracic cancer incidence among underground uranium miners exposed to radon progeny in the Příbram region of the Czech Republic: a case-cohort study

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Abstract

Objectives: Radon is carcinogenic, but more studies are needed to understand relationships with lung cancer and extrathoracic cancers at low exposures. There are few studies evaluating associations with cancer incidence or assessing the modifying effects of smoking.

Methods: We conducted a case-cohort study with 16,434 underground uranium miners in the Czech Republic with cancer incidence follow-up 1977–1996. Associations between radon exposure and lung cancer, and extrathoracic cancer, were estimated with linear excess relative rate (ERR) models. We examined potential modifying effects of smoking, time since exposure, and exposure rate.

Results: Under a simple ERR model, assuming a 5-year exposure lag, the estimated ERR of lung cancer per 100 Working Level Months (WLM) was 0.54 (95%CI:0.33,0.83) and the estimated ERR of extrathoracic cancer per 100 WLM was 0.07 (95%CI:−0.17,0.72). Most lung cancer cases were observed among smokers (82%), and the estimated ERR of lung cancer per 100 WLM was larger among smokers (ERR/100 WLM=1.35;95%CI:0.84, 2.15) than among never smokers (ERR/100 WLM=0.12;95%CI:−0.05,0.49). Among smokers, the estimated ERR of lung cancer

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per 100 WLM decreased with time since exposure from 3.07 (95%CI:−0.04,10.32) in the period 5–14 years after exposure to 1.05 (95%CI:0.49,1.87) in the period 25+ years after exposure.

Conclusions: We observed positive associations between cumulative radon exposure and lung cancer, consistent with prior studies. We observed a positive association between cumulative radon exposure and extrathoracic cancers, although the estimates were small. There was evidence that the association between radon and lung cancer was modified by smoking in a multiplicative or super-multiplicative fashion.

Keywords

Cancer; Radon; Miners; Ionizing Radiation

Background

Inhalation of radon and its decay products (referred to as radon) are an occupational cause of lung cancer.[1] Globally, inhalation of radon is a leading cause of lung cancer death.[2,3] Uranium miners are occupationally exposed to radon, and several cohort studies of underground uranium miners provide strong evidence of positive exposure-response relationships between radon and lung cancer mortality.[4–10]

While radon is an established lung carcinogen,[11] more studies are needed to understand exposure-response relationships at concentrations that reflect contemporary occupational and environmental settings. Additionally, it is unclear if radon exposure causes cancers of the extrathoracic respiratory system. Dosimetric models indicate that α-radiation exposure to the extrathoracic airways occurs upon inhalation.[12] Although the magnitude of these exposures are smaller than lung exposures, they may still be substantial. Recently, the rates of extrathoracic cancer in uranium miners were examined as a group based on the International Commission on Radiological Protection (ICRP) models for energy deposition following radon inhalation in two studies of uranium miners.[7,13] Radon was associated with extrathoracic cancer mortality in the German Wismut cohort, but radon was not associated with extrathoracic cancer mortality or incidence in the Ontario cohort.[7,13]

Also of interest is the modifying effect of smoking on radon-cancer associations. This was characterized in other cohorts[2,14,15] but more information is needed to understand the modifying effect of smoking at lower exposures. Modification by smoking has been studied in several populations of uranium miners, namely in analyses from the Committee on Health Risks of Exposure to Radon (BEIR VI) report, a pooled case control study of three European uranium mining studies, and the US Colorado Plateau cohort.[2,14–16] All concluded that there is sub-multiplicative interaction between radon and smoking. However, the mean cumulative radon exposures in these studies were higher than levels experienced in modern occupational settings. More research is needed to understand the effect of smoking at low cumulative radon exposures and at low exposure rates [e.g., <4 Working Level Months (WLM) per year).[1]

To investigate associations between radon exposure and lung and extrathoracic cancer incidence in an occupational cohort with individual information on smoking status, we

analyzed a case-cohort study of uranium miners in the Czech Republic. In 1996, the National Institute of Environmental Health Sciences in collaboration with the Health Institute of the Uranium Industry of the Czech Republic created a study of underground uranium miners in the Příbram region of the Czech Republic to better understand the health effects caused by radon exposure.[17–19] This is a large cohort with 20 years of follow-up with low average exposures compared to other uranium mining cohorts, and some workers experienced exposures comparable to modern occupational exposures.

The objectives of this study were to estimate the exposure-response relationships between radon exposure and lung cancer incidence, and extrathoracic cancer incidence within a case-cohort of underground uranium miners. We also examined exposure rates, windows of time since exposure, and the effects of cigarette smoking.

Methods

Study setting and population.

Between World War II and the Cold War, extensive uranium mining activities occurred in the former Czechoslovakia, notably in the Jáchymov mines of Western Bohemia and in the Příbram regions.[19] A cohort of Jáchymov miners has been studied extensively, and mortality has been examined relative to national death rates and in relation to cumulative estimates of radon exposure.[20,21] That cohort was expanded to include some miners in the Příbram region.[20] The current study focuses on a cohort of miners employed in the Příbram region which was developed separately from the cohort of Czech miners reported on by Tomášek et al.[17,18,20,22,23]

Příbram mine operations occurred between 1946 and 1991, during which over 46,000 workers were employed. The Příbram Uranium Industry (UI) kept a card register for each employee that contained a personal identification number and occupational history. The cohort included male workers who were listed in the employment registry between January 1, 1949 and December 31, 1975, worked underground for at least 1 year, and were alive and living in the former Czechoslovakia on January 1, 1977. A total of 16,434 workers satisfied cohort selection criteria and were followed for cancer incidence and mortality outcomes from 1977 through 1996.[17,18]

Case-cohort study.

In the late 1990’s, a case-cohort study was developed with the goal to investigate radon-cancer associations using more precise radon exposure estimates than those in the full cohort, and to collect additional data on smoking and co-pollutants.[17–19] It includes all lung and extrathoracic cancer cases diagnosed from the start of follow-up through 1996, and a subcohort of cases and non-cases. The subcohort of 1,826 workers was selected by stratified random sampling based on the age of lung and extrathoracic cancer cases at start of follow-up in 5-year intervals. Members of the case-cohort study were then assigned more detailed radon exposure estimates (as described below), and medical records were reviewed to obtain smoking status, described below.

Exposure estimates.

For the cohort of 16,434 workers who met the study definition, cumulative exposure to radon progeny, which in this study is measured in WLM, was estimated based on the duration of underground mining in a calendar year and annual radon concentration estimates, derived from industry records. Duration of underground mining was based on start and end of employment and annual radon exposure concentration estimates were based on measurements from area monitors.

Members of the case-cohort study were assigned more precise annual WLM estimates than the full cohort by combining the radon exposure measurements recorded in the original hygiene records with information from a detailed archive of employee work histories that contained locations of work within mines and entry and exit times for these locations. Prior to 1968, employment records were abstracted by investigators to estimate the time spent underground per month. In 1968, with the introduction of individual dosimetric cards, exposures were estimated by number of shifts. Area radon measurements were taken in each specific workplace during each shift.

Smoking information was derived mainly from job-entry medical records and annual check-ups conducted by the UI. Cigarette smoking was categorized as a fixed variable as ever smoker and never smoker, using information obtained from UI medical records, and in some instances, direct contact with miners or next of kin.

Outcome assessment.

Vital status and emigration status for the period 1977 – 1996 were obtained from the Czech Central Register of Inhabitants using personal identification numbers listed on employment records. Incident cancer cases among the miners were identified between 1977 and 1996 by matching individual government identification numbers, names, and date of birth with the Czech and Slovak national cancer registries. Reporting to the cancer registries was mandatory. All cancers were coded according to the International Classification of Diseases, Ninth Revision.[18] Workers diagnosed with cancer were not allowed to work underground. Therefore, all workers alive in 1977 and still working underground were assumed to be cancer free at the start of follow-up.[17,18] Cancer subtypes of interest for this analysis include trachea, bronchus, and lung (ICD-9 162) and extrathoracic cancers. Extrathoracic cancers are reported as a group based on the ICRP models for energy deposition following radon inhalation.[12] The extrathoracic group includes the nasal passages (ICD-9 160), larynx (ICD-9 161), pharynx (ICD-9 147–148), oropharynx (ICD-9 146), mouth, including salivary glands (ICD-9 141–145).

Statistical analyses.

To estimate the association between cumulative WLM of radon exposure and cancer incidence, linear and log-linear models with age as the underlying time scale were fit to the case-cohort data. Birth cohort by decade, duration of employment, and active *vs.* inactive employment were investigated for potential confounding. Smoking was investigated both as a potential confounder and effect modifier. The final adjustment set was informed by Directed Acyclical Graph (DAG) theory with the aim of selecting the most parsimonious

model, and, potential confounders were also systematically evaluated for changes in the WLM parameter estimate compared to a model with all other covariates and assessed for change in model fit based on Akaike's information criterion. The interaction between smoking and radon exposure was tested with likelihood ratio tests (LRT). Evidence of statistical interaction was defined *a priori*, as $P < 0.1$.[24]

Linear relative rates.

Linear excess relative rates (ERR) per 100 WLM were estimated using Poisson regression with SAS PROC NLMIXED. We used the general model form $rate = \exp\left(a_0 + \sum_{i=1}^{p-1} a_i x_i\right)\left(1 + a_p d\right)$ where $\boldsymbol{a_0}$ is the intercept of the log-linear term of the model, a_p is the excess relative rate per unit of lagged cumulative radon exposure, d, and a_i are parameters for effects of covariates x_i. Five-year and 10-year lagged exposures were compared. In addition to cumulative WLM, windows of time since exposure (5–14, 15–24, and 25+ years) and exposure-rate windows (<5 and ≥5 Working Levels (WL)) were modeled to investigate timing and rate of radon exposure.[25] Excess relative rates by windows of time since exposure and windows of exposure-rate were fit, respectively, using the general model form $rate = \exp\left(a_0 + \sum_{i=1}^{p-1} a_i x_i\right)\left(1 + \sum_{j=p}^{k} a_j d_j\right)$ where a_j represents excess relative rates per unit of lagged cumulative radon exposure in time since exposure windows or exposure rate windows, d_j. Modification by smoking was investigated by adding smoking and product terms between smoking and exposure to the models.

To model excess relative rates (ERR) with a linear exposure in the random stratified case-cohort design, we used the approach described by Richardson et al, where a risk-set data structure is generated.[26] A weighted bootstrapping method was used to calculate confidence intervals of ERRs.[26] A random weight from an exponential distribution is assigned to each person for each weighted regression model which accommodates the random stratified case-cohort design well since risk sets only need to be enumerated once, retaining the case failures from the full cohort and the observed failure times.[26]

Log-linear models.

Proportional hazards regression models were used to estimate the log relative rate (RR) per 100 WLM using SAS PROC PHREG with a robust variance estimator (covsandwich option). For comparison to, log-linear RRs per 100 WLM were also estimated by SAS PROC NLMIXED using the approach outlined by Richardson et al., described above.[26] RRs were estimated using the general model form $rate = \exp\left(\beta_0 + \sum_{i=1}^{p-1} \beta_i x_i + \sum_{j=p}^{k} \beta_j d_j\right)$ where β_j represent the log RR of cancer incidence per category of lagged cumulative radon exposure, d_j, β_0 is the log rate of cancer among workers with the referent cumulative WLM, and β_i are parameters for effects of covariates x_j. Modification by smoking was investigated by adding smoking and product terms between smoking and exposure categories to the model. A model with a quadratic term for radon exposure was also examined and assessed for model fit using AIC and LRT tests.

Evaluation of the joint effects of smoking.

The joint effects of radon exposure and smoking were evaluated formally in a mixture model that allows for model forms intermediate between the linear ERR model and the log-linear (i.e., exponential rate) model. A mixture model of the form $rate = \exp(\beta_i d + \beta_j s)^{\alpha}(1 + \beta_i d + \beta_j s)^{1-\alpha}$ was fitted, where β_j and β_i are parameters for the effects of smoking and radon exposure, respectively, and $\alpha = 1$ indicates a strictly multiplicative model and $\alpha = 0$ indicates a strictly additive model.

Results

During follow-up there were 890 lung cancer cases (190 subcohort cases and 700 non-subcohort cases), 127 extrathoracic cancer cases (13 subcohort cases and 114 non-subcohort cases) and 1621 subcohort members that had neither extrathoracic nor lung cancer (Table 1). The most common extrathoracic cancer subtype was larynx (63 cases). The mean duration of follow-up was 13.6 years. The mean age at start of follow-up was 50.7 years (standard deviation = 10 years). The members of the case-cohort study were on average older than in the full cohort due to the age-stratified subcohort sampling based on the age distribution of cases.[18] Mean cumulative WLM among the lung cancer cases was higher than the subcohort or among extrathoracic cancer cases (Table 1). Estimates with 10-year lags were marginally larger than estimates with 5-year lags; the AIC was the same for 5- and 10-year lagged models. For comparability with other studies of radon among uranium miners, a 5-year lag was chosen.

Table 2 presents relative rates of lung cancer incidence among smokers and never smokers by category of cumulative radon exposure. Birth cohort is an important covariate identified in DAG analyses and substantially improved model fit; it was adjusted for in all models. Based on DAG analyses, smoking was included in the model as an effect modifier; results are reported separately for smokers and never smokers (overall results are reported in Appendix Table 1). Workers with missing smoking information were removed from models that included smoking. Because smoking was missing for 38 lung cancer cases and 8 extrathoracic cases, 852 lung cancer cases and 119 extrathoracic cases were included in the analyses.

For lung cancer, modification by smoking was observed on both the linear and log-linear scales. In log-linear models, statistically significant RRs above the null were observed in each exposure category only among smokers. Although there was not a strictly monotonic increase across categories, rates of lung cancer generally increased with higher radon exposures among smokers. Compared to the reference category (<10 WLM), the RR at cumulative exposures 10 – <50 WLM was higher among smokers (1.67 (95%CI: 1.24, 2.26)). Among never smokers, the RR at cumulative exposures 10 – <50 WLM was 1.27 (95%CI: 0.71, 2.27). On the log-linear scale with continuous WLM, smoking was observed to be a modifier and relative rates were higher among smokers (RR/100 WLM = 2.88; 95%CI: 1.93, 4.30) than never smokers (RR/100 WLM = 1.11; 95%CI: 0.94, 1.31).

Relative rate estimates of the exposure-response association between radon exposure and extrathoracic cancer did not increase monotonically (Appendix Table 2). When analyzed by

categories, the highest and most precise relative rates appear in the 3 to <5 and the 5 to <10 WLM categories (RR = 3.85; 95%CI: 1.58, 9.39 and RR = 2.42; 95%CI: 1.19, 4.93, respectively). Exposure categories above 10 WLM have lower estimates. We estimated the RR of extrathoracic cancer with a quadratic term for radon exposure. The addition of the quadratic term improved model fit, and the observed positive associations at low WLM decreased (RR at 100 WLM = 0.73; 95%CI: 0.50 – 1.07). Smoking was not a modifier of the radon-extrathoracic cancer association based on LRT tests.

Excess relative rates of lung cancer by continuous WLM, windows of time since exposure, and windows of exposure rate, adjusted for age, birth cohort, and smoking are shown in Table 3. Smoking was a modifier of the radon-lung cancer association in linear ERR models, and estimates are reported separately among smokers and never smokers. The ERR per 100 WLM among never smokers was 0.12 (95%CI: −0.05, 0.49) and among smokers 1.35 (95%CI: 0.84, 2.15). The estimate from our mixture model approached the upper bound of 1, which indicates that the interaction is multiplicative.

Among smokers, we observed variations between windows of time since exposure, where ERRs/100 WLM were lower in windows of time since exposure that occurred further in the past. Among never smokers, ERRs/100 WLM for all time since exposure windows were imprecise. We also fitted a model that partitioned cumulative radon exposure by two categories of radon exposure rate, and lower exposure rates were associated with higher ERR/100 WLM among both smokers and never smokers, although estimated associations were imprecise. Adjustment for active employment and duration of employment did not change model estimates or improve model fit.

An elevated association between cumulative radon exposure (5-year lag) and extrathoracic cancers was observed (ERR/100 WLM = 0.07; 95%CI: −0.17, 0.72) in a model of continuous exposure adjusted for age, birth cohort, and smoking. Models adjusting for smoking interaction, windows of time since exposure, exposure rate, active employment, and duration of employment did not improve model fit.

Discussion

This study describes lung cancer incidence among the Příbram uranium miners. The positive exposure-response relationship between cumulative radon exposure and lung cancer incidence is consistent with conclusions published from prior mortality studies.[4–8] This study also provides evidence of radon-lung cancer associations at levels more similar to those encountered in contemporary occupational settings than many cohorts of earlier uranium miners. A positive ERR was observed at exposure rate levels less than 5 WL, and modification by smoking was also observed at this level. Similar to the BEIR VI models, we observed an inverse exposure rate effect. We also observed that overall and among smokers, time since exposure was a temporal modifier of the radon-lung cancer association, with ERRs highest in the earliest windows of time since exposure.

This study provides evidence of the radon-lung cancer association based upon incidence rather than mortality. While lung cancer has a high fatality rate, incidence-based studies

are less liable to outcome misclassification because cancer classifications based on cancer registry information tend to have better sensitivity and specificity than classifications based on death certificates. Extrathoracic cancers are rare, and since some subtypes have a lower case fatality rate than lung cancer, incidence data provides more case information than mortality data. Even with incidence information, there were relatively few extrathoracic cancers in this cohort and the statistical power to estimate associations between radon exposure and extrathoracic cancers, even as a group, was low.

Two other studies of uranium miners examined associations between radon exposure and extrathoracic cancer as a group. A positive association between radon and extrathoracic cancer mortality (ERR/100 WLM = 0.036; 95%CI: −0.009, 0.080) was observed in the German miner study.[13] A negative association with extrathoracic cancer incidence (ERR/100 WLM = −0.29; 95%CI: −0.57, 0.0034) and mortality (ERR/100 WLM = −0.17; 95%CI: −0.64, 0.30) was observed in the study of Ontario miners.[7] Neither the German nor the Canadian study included smoking information. In several other miner studies individual subtypes of extrathoracic cancer were investigated, but in all of them had very low case counts.[13,17,27–30]

We report here a modification of the radon-lung cancer association by smoking when both linear and log-linear rate models were fitted. Presence of modification on both the linear and log-linear scales, and results from the mixture model, suggest that the joint effects of radon exposure and smoking is greater than additive. In several other uranium miner studies interaction between radon and smoking was observed to be less than multiplicative.[2,14,15] BEIR VI reported a sub-multiplicative interaction between radon exposure and smoking.[2] Similarly, a combined case-control analysis of three studies of European uranium mining cohorts and an analysis of a sub-cohort of the German Wismut cohort found an attenuation of the ERR among smokers, which suggests a sub-multiplicative interaction between radon and smoking.[10,14] The Colorado Plateau uranium miner study reported modification with an interaction between additive and multiplicative.[31] While the presence of modification is consistent with other studies, our results are more consistent with a multiplicative or super-multiplicative interaction because the ERR among smokers was higher than among never-smokers. This may be due to differences in quality of information on smoking status. In the European pooled case-cohort and the Colorado Plateau studies, smoking information was more detailed and included information on duration of smoking whereas our study only included smoking status typically from the start of employment. Another reason for difference in modification scale may be because our study population experienced lower average exposures to radon than the BEIR VI, European, and Colorado studies. Radon exposures in the Wismut sub-cohort are also low, but smoking information was missing for a large proportion of the cohort.[10]

In this study, adjustment for birth cohort improved the model fit for lung and extrathoracic cancers. This was observed in the mortality analyses for this cohort and may be related to a cohort selection criterion that workers be alive at the start of follow-up in 1977. This is unlike most other uranium mining cohorts, where follow-up usually begins at the start of mining operations. Workers who were employed at the start of mining operations had higher average radon exposures until a strong ventilation system was installed in the

1970s. Many of the earlier workers may have died of lung cancer prior to the start of follow-up. Additionally, the older workers who were still alive at the start of follow-up had higher exposures but may have had lower lung cancer rates than other birth cohorts due to competing risks associated with advanced age.

The case-cohort design is advantageous because it was an efficient way to obtain smoking data and more precise radon exposure information that could not easily be obtained for the entire cohort of uranium miners.[32,33] Previously it was challenging to fit ERR models or other non-log-linear models with a random stratified case-cohort design, but recently a method was developed using standard statistical software. Here, linear ERR models were estimated with case-cohort data by restructuring data into risk-sets, and weighted bootstrapping were used to calculate confidence intervals.[26] The point estimates and CIs calculated with this method[26] closely matched the estimates generated from SAS PROC NLMIXED. In two instances the bootstrapped estimates did not match the NLMIXED estimates as closely as the other results. The differences occurred in the 5–15-year time since exposure windows for smokers and never smokers but did not change the direction of the association or the overall interpretation of results (Table 3). Examining the distribution of the bootstrap samples indicated that the difference may be due to sparse data or influential observations. Nevertheless, this method was advantageous because we estimated linear ERR models from the case-cohort data derived from a stratified random sample.[26] Other approaches are constrained to log-linear model forms or data derived from a simple random samples. The method[26] leads to a flexible modeling approach and better specified models, more accurately representing the exposure-response association between exposure and disease.

While this study adds to our understanding of smoking as a modifier of the radon-lung cancer association, we did not evaluate other potential modifiers such as silica dust, heavy metals, or gamma radiation. Other studies of uranium miners suggest that the impact of these exposures is minor.[6] Diesel exhaust exposure is a potential confounder of concern in some studies of underground miners. However, in Příbram, diesel was never used in mining operations because all vehicles were electric.

The results of this study are consistent with prior studies indicating that there is a positive exposure-response relationship between cumulative exposure to radon and lung cancer.[4–8] The results are also consistent with prior findings that smoking modifies the association between radon exposure and development of lung cancer.[2,14,15]. It should be noted that smoking data are crude, incomplete, and time invariant. Extrathoracic cancer analyses were less precise, but the results suggest that miners may experience an elevated rate of extrathoracic cancers even at low levels of cumulative radon exposure (<50 WLM). To obtain more precise estimates of extrathoracic cancer rates and determine exposure-response relationships, more pooled studies of radon-extrathoracic cancer are needed. Studies with individual dosimetric estimates of radon to the extrathoracic tissues, and larger studies with more cases and extended follow-up would improve understanding of radon-extrathoracic cancer associations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Messages

What is already known about this subject?

Radon is a lung carcinogen, but more information is needed about radon exposure at low levels, and the role of smoking as a modifier of the radon-lung cancer association. Other types of cancer such as extrathoracic cancers also require more investigation.

What are the new findings?

We observed positive associations between radon and lung cancer incidence, and radon and extrathoracic cancer incidence. The joint effects of radon and smoking were multiplicative.

How might this impact on policy or clinical practice in the foreseeable future?

Cancer risks from exposure to radon at lower levels is important for estimating radon-related risks among contemporary workers and the general population. Pooled studies should investigate extrathoracic cancer risks to uranium miners.

Table 1:

Characteristics of a case-cohort study of male underground uranium miners in the Příbram region of the Czech Republic 1977–1996

	Subcohort non-cases	Lung cancer cases	Extrathoracic cancer cases
Total cases, n	1621	890	127
Year of birth, n (%)			
< 1910	87 (5)	30 (3)	4 (3)
1910 – 1919	342 (21)	185 (21)	17 (13)
1920 – 1929	677 (42)	403 (45)	39 (31)
1930 – 1939	367 (23)	212 (24)	33 (26)
≥1940	148 (9)	60 (7)	34 (27)
Age at start of employment (years), n(%)			
<20	99 (6)	59 (7)	12 (9)
20-<30	677 (42)	379 (43)	63 (50)
30-<40	528 (33)	313 (35)	36 (28)
≥40	317 (20)	139 (16)	16 (13)
Duration of employment (years)			
1-<3	632 (39)	250 (28)	61 (48)
3-<10	351 (22)	190 (21)	24 (19)
≥10	638 (39)	450 (51)	42 (33)
Cumulative exposure, mean (range)			
Radon (WLM)	78 (0– 959)	115 (0– 1022)	69 (0– 866)
Smoking status			
Ever Smoker	1027 (63)	731 (82)	95 (75)
Never Smoker	506 (31)	121 (14)	24 (19)
Missing	88 (5)	38 (4)	8 (6)

Table 2:

Relative rates (RR) of lung cancer incidence among smokers and never smokers by categories of cumulative radon exposure (5-year lag) among male uranium miners in the Příbram region of the Czech Republic, 1977–1996

WLM Categories	Total lung cancer cases (n)	Smokers			Non-smokers		
		Smoking cases (n)	Relative Rate (RR)	95%CI	Never smoking cases (n)	Relative Rate (RR)	95%CI
0 - <10	112	92	1 (ref)		20	1 (ref)	
10 - <50	227	186	1.67	1.24, 2.26	41	1.27	0.71, 2.27
50 - <100	139	121	1.60	1.15, 2.23	18	0.93	0.47, 1.85
100 - <150	117	104	1.86	1.30, 2.66	13	0.88	0.42, 1.86
150 - <200	93	85	3.41	2.28, 5.09	8	1.55	0.61, 3.92
200+	164	143	3.56	2.50,5.09	21	1.79	0.90, 3.57

*All models are adjusted for age, birth cohort, and smoking, and included statistical interaction terms between smoking status and categories of WLM. a. WLM = Working Level Months

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Table 3a-3c:

Excess relative rates of lung cancer incidence per 100 working level months (ERR/100 WLM[^]) among male uranium miners in the Příbram region of the Czech Republic, 1977–1996. Modeled as continuous WLM (3a), exposure rate (3b), and windows of time since exposure (3c).

3a. Continuous WLM

	Never Smokers		Smokers		Overall	
	ERR/100 WLM	**95%CI**	**ERR/100 WLM**	**95%CI**	**ERR/100 WLM**	**95%CI**
	0.12	−0.05, 0.49	1.35	0.84, 2.15	0.54	0.33, 0.83

3b. Exposure rate

	Never Smokers		Smokers		Overall	
	ERR/100 WLM	**95%CI**	**ERR/100 WLM**	**95%CI**	**ERR/100 WLM**	**95%CI**
<5 WL	0.35	0.01, 0.91	1.73	1.08, 2.66	0.76	0.49, 1.14
≥ 5 WL	−0.16	−0.28, 0.31	0.72	−0.16, 2.42	0.09	−0.22, 0.58

3c. Windows of time since exposure

	Never Smokers		Smokers		Overall	
	ERR/100 WLM	**95%CI**	**ERR/100 WLM**	**95%CI**	**ERR/100 WLM**	**95%CI**
5–15	−0.86[*]	−1.26, 1.51	3.07[**]	−0.04, 10.32	1.70	−0.14, 3.92
15–25	0.15	−0.31, 0.83	2.30	1.02, 4.09	0.91	0.41, 1.56
25+	0.14	−0.07, 0.58	1.05	0.49, 1.87	0.43	0.19, 0.74

[^] All models adjusted for age, birth cohort, and smoking. Reported estimates for never smoker and smoker estimates were obtained by including interaction terms between smoking status and radon exposure. Radon exposure is lagged 5 years

[*] Table estimates use weighted bootstrapping approach. Standard PROC NLMIXED results were −1.39 (95%CI −4.00, 1.21)

[**] Table estimates use weighted bootstrapping approach. PROC NLMIXED results were 4.78 (95%CI 0.18, 9.37)