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Incidence of non-lung solid cancers in Czech uranium miners: a case-cohort study

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Abstract

Objectives—Uranium miners are chronically exposed to radon and its progeny, which are known to cause lung cancer and may be associated with leukemia. This study was undertaken to evaluate risk of non-lung solid cancers among uranium miners in Příbram region, Czech Republic.

Methods—A retrospective stratified case-cohort study in a cohort of 22,816 underground miners who were employed between 1949 and 1975. All incident non-lung solid cancers were ascertained among miners who worked underground for at least 12 months (n = 1020). A subcohort of 1707 subjects was randomly drawn from the same population by random sampling stratified on age. The follow-up period lasted from 1977 to 1996.

Results—Relative risks comparing 180 WLM (90th percentile) of cumulative lifetime radon exposure to 3 WLM (10th percentile) were 0.88 for all non-lung solid cancers combined (95% CI 0.73 – 1.04, n = 1020), 0.87 for all digestive cancers (95% CI 0.69 – 1.09, n = 561), 2.39 for gallbladder cancer (95% CI 0.52 – 10.98, n = 13), 0.79 for larynx cancer (95% CI 0.38 – 1.64, n = 62), 2.92 for malignant melanoma (95% CI 0.91 – 9.42, n = 23), 0.84 for bladder cancer (95% CI 0.43 – 1.65, n = 73), and 1.13 for kidney cancer (95% CI 0.62 – 2.04, n = 66). No cancer type was significantly associated with radon exposure; only malignant melanoma and gallbladder cancer showed elevated but non-significant association with radon.

Conclusions—Radon was not significantly associated with incidence of any cancer of interest, although a positive association of radon with malignant melanoma and gallbladder cancer cannot be entirely ruled out.

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Keywords

Environmental carcinogens; Ionizing radiation; Neoplasms; Occupational exposure; Radon; Smoking

1. Introduction

Uranium miners are chronically exposed to many external risk factors, most prominent among them being ionizing radiation whose carcinogenic effect is generally known. The first type of cancer that was found to be associated with ionizing radiation in uranium miners was bronchogenic lung cancer (Saccomanno et al., 1964; Řeřicha and Šnajberk, 1966). Consequently, lung cancer has been long acknowledged as an occupational disease in uranium miners (BEIR VI, 1999). A recent study (Řeřicha et al., 2006) reported a significant association of radon exposure with leukemia, especially chronic lymphocytic leukemia, a leukemia type that has been previously considered non-radiogenic.

Several studies have investigated mortality from other types of cancer in uranium miners and other workers exposed to radon (Tomášek et al., 1993; Darby et al., 1995; Vacquier et al., 2008; Tirmarche et al., 1993; Laurier et al., 2004; Checkoway et al., 1988; Kreuzer et al., 2008, 2010). Some of them found increased mortality from various cancers of the digestive tract (Tomášek et al., 1993; Darby et al., 1995; Kreuzer et al., 2008) or renal and urinary tract cancers (Tomášek et al., 1993; Vacquier et al., 2008). One study reported excess mortality from larynx cancer (Tirmarche et al., 1993). A large German study (Kreuzer et al., 2010) has recently identified a positive association between radon and mortality from cancer of extrathoracic airways and trachea.

Nearly all reported positive findings were all based on standardized mortality ratios (SMR) comparing cancer mortality in the miners to that in the general population, with no clear association between radon exposure and mortality among the miners themselves. All previous miner studies share several of the following important design limitations: they investigated mortality instead of incidence and could have missed a number of cases, especially of less aggressive cancers; they included small number of cases because of insufficient cohort size or follow-up duration; the primary analysis made use of comparisons with the general population (SMR) rather than of trends with exposure to radon; and, last but not least, they did not account for smoking, an important risk factor for many of the cancers of interest (Kuper et al., 2002). Thus, despite the lack of consistent positive associations between working exposure and non-lung cancer mortality, it is yet unclear whether underground work in uranium mines, and in particular exposure to prolonged low levels of radon, can cause solid cancers other than lung cancer.

This paper reports the results of a case-cohort incidence study conducted in uranium miners working in Příbram region in the Czech Republic to evaluate and test associations of radon exposure with the incidence of various types of cancer. The study differs from the previous studies in that it investigated incidence rather than mortality and included a substantially larger number of cases. The case-cohort design allowed more detailed evaluation of work-related exposures and assessment of smoking status. Lymphoma, myeloma, and leukemia results from the case-cohort study were published earlier (Řeřicha et al., 2006). This report focuses on the incidence of non-lung solid cancers.

2. Methods

2.1. Location and study population

Most of the uranium produced in the former Czechoslovakia was mined near the town of Příbram. Uranium mines operated in that area from 1949 till 1991 and over that time employed a total of almost 50 thousand people. The employer, Uranium Industry, maintained a registry of all workers as well as special employment logs for those who were at risk for radiation exposures. The Uranium Industry registry was used to define a population for this study. First, we identified all 27,441 male workers who were listed in the employment registry at any time between January 1, 1949, and December 31, 1975, and who, according to the registry records, worked underground for at least one month prior to January 1, 1976. These workers were matched against the National Registry of Inhabitants and the National Pension Funds registry, with a success rate of 92%. The 22,816 workers who were alive and residing in the former Czechoslovakia as of 1/1/1977 formed the study cohort.

2.2. Case ascertainment

Czech regional oncological registries and the Slovak national cancer registry were used to identify incident cancer cases among the miners. Reporting cancer cases to the registries was mandatory and enforced; nevertheless the overall coverage is not known. All cancers recorded in the registries were histologically confirmed. The cancer registries are available in an electronic form since 1977. The follow-up period for case ascertainment was Jan. 1, 1977, to Dec. 31, 1996. The miners were matched to the cancer registries using unique state-issued identification numbers. All cancers were recoded according to the 9th revision of the International Classification of Diseases (ICD). A total of 2841 subjects with incident cancers were identified, of which 1508 had cancer type of interest (all cancers except lymphatic and hematopoietic neoplasms, lung cancer, and cancers of the skin other than malignant melanoma; ICD-9 codes 140 – 161, 162 – 172, 174 – 195, and 199).

2.3. Subcohort

A subcohort of 2393 subjects was selected from the cohort by stratified random sampling. The cohort was classified according to age on 1/1/1977 (5-year groups) and duration of employment (less than 12 months according to the employment registry versus 12 months or more). The subcohort was sampled from each of the resulting strata so that the number of subcohort subjects sampled from a stratum was approximately equal to the total number of all cancer cases in the stratum.

2.4. Employment history

General employment history (dates of start and end of work in different occupations and rough estimates of total radon exposures) was available for the whole study cohort from the employment registry. Since the employment registry data were not entirely accurate, employment and exposure history was reassessed for the cases and the selected subcohort subjects from employment logs of individual employees. The logs provided much more detailed and specific information on the exact duration of employment in different professions and workplaces, including those in other uranium mines, which was used to assess duration of work in underground occupations and radiation and dust exposures.

2.5. Exclusions

We excluded 66 cases and 108 subcohort subjects who, according to the detailed employment logs, failed the criteria for inclusion in the main cohort, and 402 cases and 578 subcohort subjects who worked in underground occupations for less than 12 months. We

excluded 20 cases who had been previously diagnosed with another cancer. The final study population consisted of 1020 cases and a 1707-person subcohort, which included 1486 subjects who were not diagnosed with any of the cancers of interest.

2.6. Radiation exposures

The exposure to radon and its progeny was calculated from the potential alpha energy of radon progeny (the energy of alpha particles emitted by radioactive decay products of radon contained in a given volume of air) in the mine during the period of interest, the duration of the period, and the estimated proportion of working time spent underground, and converted to working level months (WLM; 1 WLM = 3.5×10^{-3} Jhm^{-3}). Direct measurements of the potential alpha energy of radon progeny were available since 1968. In the earlier period (1949 – 1967), the potential alpha energy was estimated from detailed industry tables of mean annual concentrations of ^{222}Rn and from an equilibrium factor. The equilibrium factor, which related the radiation activity of the short-lived radon progeny to the activity of ^{222}Rn, was calculated from a number of direct measurements conducted in the mines under varying ventilating conditions in the 1960's. Up to 1959, the equlibrium factor was 0.864 for ^{222}Rn concentrations over 37,000 Bq m^{-3} and 0.550 for lower concentrations. In 1960 – 1967, the equlibrium factor was 0.550 for concentrations over 7,400 Bq m^{-3} and 0.364 for lower concentrations. Additional details on the methodology of radiation exposure assessment in this study have been provided elsewhere (Řeřicha et al., 2006).

2.7. Smoking exposure

The primary source of smoking information were archives of medical records with initial job-entry examination results complemented by review of records from mandatory annual check-ups of Uranium Industry employees, personal communication with living subjects or with the relatives of the deceased ones, and mail-in questionnaires. Because details of smoking history were limited, smoking status was classified into two groups: (a) non-smokers and light smokers who smoked less than 10 cigarettes a day for a period not exceeding 5 years; (b) moderate and heavy smokers (who exceeded the limit for light smokers). Subjects with unknown smoking status (7% of all cases and 4.8% of subcohort subjects) were included as a separate group in some analyses.

2.8. Other exposures

Dust measurements were recorded monthly for each workplace. Concentrations of airborne dust in the mine air reached 10 mg/m^3 in the 1950's, gradually dropped to 2 – 4 mg/m^3 in the 1960's, and stabilized below 2 mg/m^3 later. The average concentration of arsenic in Příbram ore was low and was unlikely to confound cancer incidence results. The long-term average content of arsenic in samples of load ore was 25 mg/kg, about the same as the natural background level in the area. This is an important difference from other uranium mines: in Joachimsthal (Tomášek et al., 1993), the average content of arsenic was 200 times higher.

2.9. Statistical methods

Current age was used as the underlying time variable. The subjects entered follow-up on Jan. 1, 1977, and were removed at the first recorded occurrence of any type of cancer, at death, or on Dec. 31, 1996, whichever occurred first. Thus, subjects who were diagnosed with another cancer before the cancer of interest was detected were censored at the diagnosis of the first cancer. Exposures were cumulated over working histories, with a 5-year lag. Population descriptive statistics such as proportions, mean exposures or crude incidence rates were calculated by weighting subcohort subjects by inverse sampling fractions depending on the sampling stratum. The cases were assigned unit weights even if they happened to be in the subcohort. Thus, all the reported results are adjusted for the sampling

design. Age-standardized incidence rates were calculated from crude incidence rates in age-exposure cells and estimated person-years accrued by the whole cohort in the age groups divided by estimated total person-years for the whole cohort. For this purpose, age was categorized into five-year groups. Total person-years were calculated from the subcohort by inverse probability weighting; time-varying cumulative exposures were taken into account by dividing the at-risk period into calendar years and plugging in the lagged cumulative exposure acquired on Dec. 31 of the previous year.

The proportional hazards model was used to estimate the relative risks (RR) for cancer due to radon and dust exposures, working time, and number of underground shifts worked. All analyses were adjusted for smoking and calendar time. We used Estimator II for stratified case-cohort studies proposed by Borgan et al. (2000), where cases of incident cancer that occurred outside of the subcohort were only included in the analysis of the particular outcome. Confidence intervals and tests were based on estimated parameters and their asymptotic robust standard errors. The effects of radiation and dust exposures, working time, and number of shifts were modeled in two alternative ways. First, the cumulative lagged exposures were classified into 4 – 6 categories, and RR's of each category compared to baseline were estimated. The second model involved continuous log-transformed exposures. The resulting relative risk function had the form $RR(y) = (c + y)^{\beta}$, where y was the cumulative exposure and c was an exposure-specific adjustment, whose purpose was to capture lifetime exposure from non-occupational sources (such as residential radon) and to standardize the shapes of the dose-response curves for different exposures (for radon, we took $c = 30$ WLM). Additional details on the choice of c and its effect on the relative risk function are discussed in the online supplement to this article (Kulich et al., 2011).

The results are reported in the form of model-based relative risks comparing a “high” exposure (the estimated 90th percentile of the exposure in the selected population) to a “low” exposure (the estimated 10th percentile). The test of $\beta = 0$ in this model is sensitive against a monotonic dose-response trend. Software for analyzing two-phase studies was used to fit proportional hazards models and to calculate weighted summary statistics (R library “survey”, Lumley, 2004).

2.10. Ethics

The study protocol was reviewed by the chair of the Institutional Review Board (IRB) at the NIEHS and determined at the time to be exempt from full IRB review because it involved linkage of existing records and analysis of coded data without identifiers.

3. Results

A total of 1020 cases of incident cancer at the sites of interest were identified among eligible miners who worked underground for 12 months or more. The most frequent diagnosis was rectal cancer (145 cases), followed by stomach cancer (138 cases), and colon cancer (109 cases). Other relatively common sites included bladder, kidney, prostate, mouth, larynx, and pancreas. Basic characteristics of the study population are summarized in Table 1. For comparison, the table also presents estimated characteristics for the whole cohort of 22,816 miners. The study subjects were on average older than miners from the original cohort, largely due to the age-stratified sampling designed to choose a subcohort similar in age to the cancer cases. Study subjects also were more likely to have started working in earlier periods and at older age, and had higher duration of underground work and higher radon exposures. Cancer cases had higher rates of moderate and heavy smoking compared to subcohort controls. The average age at the start of the follow-up was 50.4 years (SD 10.8). The follow-up lasted for up to 20 years; the median was 16.5 years. The duration of employment ranged from 12 months to 38 years, with mean of 7.9 years (SD 6.6). The

lifetime radon exposure ranged from less than 1 WLM to 960 WLM, with mean 84.0 WLM (SD 105.9 WLM). Over 30% of workers selected into the study had exposures higher than 100 WLM, compared to an estimated 15% in the whole cohort.

Table 2 summarizes numbers of incident cancers grouped by lifetime radon exposures. Incidence rates (per 100,000 person-years) standardized to the age distribution of the whole cohort and relative risks comparing the rates to the lowest exposure group are also shown. Overall, the combined incidence rates appear to decrease with increasing radon exposure, with similar trends for several sites. The rates suggest that incidence of malignant melanoma and perhaps liver cancer may be related to radon exposure. Colon cancer also showed some increased risk, but only in the intermediate exposure categories. Cancers at other sites seem to have no clear relation to exposure levels.

In proportional hazards analyses, no significant positive association of radon with cancer incidence (adjusted for age, smoking and calendar time) was found (Table 3). Malignant melanoma and gallbladder cancer had elevated but non-significant risks: the model-based estimated relative risk (comparing 180 WLM, the 90^{th} percentile of radon exposure, to 3 WLM, the 10^{th} percentile) for malignant melanoma ($N = 23$) was 2.92 (95% CI 0.91 – 9.42, $p = 0.072$); for gallbladder cancer ($N = 13$), the relative risk was 2.39 (95% CI 0.52 – 10.98, $p = 0.26$). The numbers of cases of these cancer types were, however, small.

For most other cancers, the estimated relative risks were around unity or showed a non-significant deficit; the confidence intervals were wide. Not surprisingly, all cancers of interest combined and several of the individual cancer sites showed significant positive associations with smoking: all cancers combined had smoking RR = 1.37 (95% CI 1.18 – 1.59); oral cancers had RR = 2.32 (95% CI 1.17 – 4.59); digestive cancers had RR = 1.32 (95% CI 1.08 – 1.60); rectal cancer had RR = 1.48 (95% CI 1.01 – 2.16); bladder cancer had RR = 2.62 (95% CI 1.34 – 5.11)). Even though the reported relative risks for smoking compare moderate and heavy smokers to non-smokers and light smokers combined, the results agree quite well with published estimates of smoking risks (Kuper et al., 2002).

The effect of radon exposure on malignant melanoma was found significant in a model where radon was categorized into 4 exposure groups with breakpoints 10, 50, and 100 WLM. Relative to ≤ 10 WLM, RR was 2.16 (95% CI 0.67 – 6.90) for 10 – 50 WLM; RR=5.55 (95% CI 1.83 – 16.86) for 50 – 100 WLM; and RR=3.38 (95% CI 0.82 – 13.94) for > 100 WLM. The overall *p*-value for testing the unity of all the three relative risks was 0.002. The estimated risks seem high but the confidence intervals are wide. Complete results of the categorized radon analyses are available in the online supplement to this article (Kulich et al., 2011).

The risk of gallbladder cancer did not increase with radon exposure category: relative to ≤ 10 WLM, RR was 1.26 (95% CI 0.13 – 12.11) for 10 – 50 WLM; RR=0.71 (95% CI 0.05 – 9.23) for 50 – 100 WLM; and RR=2.89 (95% CI 0.31 – 27.16) for > 100 WLM. The overall *p*-value for testing the unity of all the three relative risks was 0.086. However, gallbladder cancer seemed to be related to the number of shifts worked rather than to cumulative radon exposure: relative to ≤ 600 shifts, RR was 2.61 (95% CI 0.16 – 43.85) for 600 – 1200 shifts; RR=5.87 (95% CI 0.72 – 47.66) for 1200 – 2400 shifts; and RR=6.44 (95% CI 0.90 – 45.91) for > 2400 shifts. The overall *p*-value for testing the unity of all the three relative risks was 0.038. However, numbers of cases of both malignant melanoma and gallbladder cancer were very small and the results should be interpreted with caution.

We also investigated associations of cancer incidence with duration of employment, number of underground shifts and cumulative dust exposure. In most cases, the results were very similar to those from radon analyses.

Even though lung cancer was not included among the outcomes discussed in this paper, we perfomed lung cancer analysis using the same methodology and exclusion rules as with the other cancer types. A total of 825 lung cancer cases were observed. The resulting relative risk comparing 180 WLM to 3 WLM (estimated from the log-transformed exposure model adjusted for age, smoking, and calendar time) was 1.69 (95% CI 1.41 – 2.02, $p < 0.001$). The relative risks comparing exposure categories to < 10 WLM were RR=1.26 (95% CI 0.99 – 1.60) for 10 – 50 WLM; RR=1.11 (95% CI 0.85 – 1.45) for 50 – 100 WLM; and RR=1.65 (95% CI 1.30 – 2.09) for > 100 WLM. The overall *p*-value for testing the unity of all the three relative risks was < 0.001. The relative risk comparing non-smokers and light smokers to moderate and heavy smokers was 2.68 (95% CI 2.18 – 3.29, $p < 0.001$).

4. Discussion

The present study does not indicate unequivocally that uranium miners are at increased risk for non-lung solid cancers. The results do not rule out a positive association of radon with incidence of malignant melanoma and/or gallbladder cancer, but these cancer types are too rare to be evaluated with sufficient precision even in a study of this size. A link between radon and malignant melanoma is biologically plausible, though no previous human or animal studies have demonstrated an increased risk of malignant melanoma after radon exposure (Charles, 2007). Tomášek et al. (1993) reported somewhat increased SMRs for malignant melanoma, gallbladder cancer, and liver cancer in another cohort of Czech uranium miners, albeit with smaller number of cases. The assessment of lung cancer risk was not among the objectives of this paper. It is well known that radon causes lung cancer (BEIR VI, 1999), the most common cancer type among the miners. Lung cancer analyses require a different focus and more elaborate modeling methods; they will be published separately.

The strengths of this study are relatively complete ascertainment of incident cancer cases, long duration of follow-up, and, due to the case-cohort design, precise evaluation of working histories. The number of cases we had available for all the cancer sites of interest was higher than in any previous study of uranium miners. E.g., the highest previously reported number of larynx cancer cases was 38 in the joint analysis of 11 miner cohorts (Darby et al., 1995), our study included 61 larynx cancer cases. Assessment of radon exposure was better than in most other studies because the worker employment logs included detailed descriptions of their occupations and workplaces over time and a large number of radon measurements were available to estimate the exposures even in early periods. Our smoking data was limited; however, to our knowledge, the previous studies of cancer risk in uranium miners collected no smoking data at all. The case-cohort design was very efficient; the loss of precision compared to a full cohort study of nearly 23 thousand miners was negligible. For example, in the analysis of all non-lung solid cancers, the standard error for the estimated radon parameter of the log-transformed proportional hazards model would be approx. 0.04805 in the full cohort analysis compared to 0.04838 in the case-cohort analysis, which is a very small difference.

Naturally, the study had limitations as well. The follow-up started years after many of the most exposed miners left their jobs. They could have had incident cancers before the follow-up started, and these were not included in the study. We may have lost some subjects who left the country after 1989 and thus did not have incident cancers included in the national registry.

The original subcohort was stratified on age and employment duration, and included a group of miners who had had less than 12 months of underground work. Many of them were temporary workers hired on short-term contracts. Several cancers of interest had

disproportionately high incidence among workers with very short working periods so we excluded all miners who did not work at least 12 months underground from all analyses.

Given that radon is an important risk factor for lung cancer in uranium miners, it is interesting that epidemiological studies, including ours, fail to demonstrate an association of radon with other malignancies of the upper respiratory tract, in particular cancer of the larynx. With some exception (e.g. true vocal chords) larynx epithelium is similar to that of other sites of the upper respiratory tract and main lobar lung bronchi, which is the most frequent site of primary bronchogenic lung cancer, and is exposed to the same risk factors, particularly radon and its progeny, during the inhalation of underground air. A Czech clinical study (Tichý and Janisch, 1973) reported that 9 out of 10 larynx tumors diagnosed in Příbram uranium miners employed between 1964 and 1970 were supraglotic, and 8 were observed in patients younger than 50. In the general population at that time, only about 30% of larynx tumors were diagnosed in patients younger than 50 and only about 25% were supraglotic. Even though their findings are based on a small sample with no control group and were never followed by a larger epidemiological study, they might imply that larynx tumors in uranium miners develop differently and that the reported atypically high percentage of supraglotic tumors in uranium miners could be related to radiation.

One potential explanation for the lack of association between radon exposure and larynx cancer is competition between the incidence and development of lung and laryngeal cancers in uranium miners. If the initiation of the carcinogenetic process occurs simultaneously in both organs, bronchogenic lung cancer, especially the small-cell type, would progress to clinical manifestation faster and would lead to poor prognosis. On the other hand, supraglotic laryngeal cancer is characterized by mild symptoms early in disease and prolonged clinical course. It is usually diagnosed later, often when already metastatic. If most laryngeal cancers in uranium miners were of the supraglotic type, they could be masked by a concurrent or subsequent lung cancer and remain undiagnosed. In Czech uranium miners, lung cancer was diagnosed relatively early thanks to mandatory annual medical check-ups that included thorax x-ray examination.

We conclude that most non-lung solid cancers are either not associated with radon exposure among uranium miners, or that the increase in risk is quite small. For malignant melanoma and gallbladder cancer, however, this conclusion is not definitive. In both cases, elevated but statistically non-significant risks were observed and a potential positive association with radon cannot be excluded. In the case of larynx cancer, increased risk could be masked by concurrent rapidly progressing lung tumors. Further research is needed to clarify the role of radon in the development of these cancer types.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Characteristics of general worker population, eligible cases and subcohort controls.

Group	Whole cohort *n* = 22816	Cancer cases *n* = 1020	Subcohort controls *n* = 1486
Age at start of study [years]			
<30	6614 (29.0%)	75 (7.4%)	84 (5.7%)
30 – 39	5095 (22.3%)	127 (12.5%)	142 (9.6%)
40 – 49	5732 (25.1%)	351 (34.4%)	543 (36.5%)
50 – 59	3468 (15.2%)	266 (26.1%)	457 (30.8%)
60 – 69	1649 (7.2%)	184 (18.0%)	233 (15.7%)
≥ 70	258 (1.1%)	17 (1.7%)	27 (1.8%)
Year of start of work			
1945 – 55	—[a] (30.5%)	480 (47.1%)	736 (49.5%)
1956 – 65	—[a] (27.4%)	354 (34.7%)	524 (35.3%)
1965 – 76	—[a] (42.1%)	186 (18.2%)	226 (15.2%)
Age at start of work [years]			
<20	—[a] (11.1%)	73 (7.2%)	91 (6.1%)
20 – 29	—[a] (57.3%)	435 (42.6%)	629 (42.3%)
30 – 39	—[a] (21.2%)	307 (30.1%)	504 (33.9%)
≥ 40	—[a] (10.4%)	205 (20.1%)	262 (17.6%)
Duration of work [years]			
<1	—[a] (28.4%)	0 (0.0%)	0 (0.0%)
1 – 3	—[a] (30.5%)	374 (36.7%)	525 (35.3%)
3 – 10	—[a] (16.2%)	260 (25.5%)	358 (24.1%)
>10	—[a] (25.0%)	386 (37.8%)	603 (40.6%)
Lifetime radon exposure [WLM]			
<10	—[a] (50.9%)	213 (20.9%)	271 (18.2%)
10 – 50	—[a] (25.3%)	340 (33.3%)	463 (31.2%)
50 – 100	—[a] (9.3%)	169 (16.6%)	274 (18.4%)
100 – 200	—[a] (9.7%)	203 (19.9%)	311 (20.9%)
>200	—[a] (4.9%)	95 (9.3%)	167 (11.2%)
Smoking			
Smoker	—[a] (74.2%)	711 (74.7%)	969 (68.0%)
Nonsmoker	—[a] (25.8%)	241 (25.3%)	456 (32.0%)

[a] In the whole cohort, exact counts are unknown; percentages are estimated from the subcohort by inverse probability weighting.

Table 2

Descriptive analyses of number of cases, follow-up duration, crude rates and crude relative risks by radon exposure in miners with 12 or more months of underground work.

	Radon [WLM]					
	<10	**10–50**	**50–100**	**100–200**	**>200**	**All**
All non-lung solid (ICD 140–195, 199, except 162, 173)						
N (PY)	217 (52.9)	336 (32.8)	169 (14.9)	203 (14.5)	95 (7.1)	1020 (122.2)
Rate	876.7	894.5	792.6	741.0	665.8	834.7
RR	1.00	1.02	0.90	0.85	0.76	
Oral (ICD 140 – 149)						
N (PY)	28 (52.0)	18 (31.7)	10 (14.8)	9 (13.5)	4 (6.9)	69 (118.8)
Rate	105.1	48.5	40.4	39.7	29.7	58.1
RR	1.00	0.46	0.38	0.38	0.28	
All digestive (ICD 150 – 159)						
N (PY)	99 (51.9)	191 (32.2)	103 (14.6)	114 (14.3)	54 (6.9)	561 (120.0)
Rate	437.5	520.8	507.9	420.2	369.4	467.7
RR	1.00	1.19	1.16	0.96	0.84	
Stomach (ICD 151)						
N (PY)	28 (51.9)	44 (31.7)	30 (14.9)	26 (13.7)	10 (6.8)	138 (118.9)
Rate	115.3	120.6	163.0	98.2	67.9	116.0
RR	1.00	1.05	1.41	0.85	0.59	
Colon (ICD 153)						
N (PY)	17 (51.7)	33 (31.6)	20 (14.5)	28 (13.8)	11 (6.8)	109 (118.3)
Rate	85.0	92.5	121.0	109.7	76.5	92.1
RR	1.00	1.09	1.42	1.29	0.90	
Rectum (ICD 154)						
N (PY)	24 (51.4)	55 (31.7)	22 (14.7)	28 (13.8)	16 (6.9)	145 (118.4)
Rate	119.7	152.2	52.2	109.3	113.2	122.4
RR	1.00	1.27	0.77	0.91	0.95	

	Radon [WLM]					
	<10	**10–50**	**50–100**	**100–200**	**>200**	**All**
Liver (ICD 155)						
N (PY)	4 (51.8)	21 (31.6)	9 (14.8)	12 (13.7)	4 (6.8)	50 (118.7)
Rate	13.0	58.9	36.2	43.5	25.8	42.1
RR	1.00	4.54	2.79	3.36	1.99	
Gallbladder (ICD 156)						
N (PY)	2 (51.7)	3 (31.6)	1 (14.7)	4 (13.6)	3 (6.9)	13 (118.5)
Rate	11.5	7.8	3.9	14.6	19.1	11.0
RR	1.00	0.68	0.34	1.27	1.66	
Pancreas (ICD 157)						
N (PY)	16 (51.9)	18 (31.7)	9 (14.8)	12 (13.7)	6 (6.8)	61 (118.9)
Rate	70.7	49.1	36.4	43.8	40.8	51.3
RR	1.00	0.70	0.52	0.62	0.58	
Larynx (ICD 161)						
N (PY)	18 (51.9)	20 (31.8)	9 (14.8)	11 (13.6)	4 (6.9)	62 (118.9)
Rate	56.3	53.1	48.2	45.7	32.4	52.1
RR	1.00	0.94	0.86	0.81	0.58	
Melanoma (ICD 172)						
N (PY)	5 (51.8)	6 (31.6)	7 (14.8)	3 (13.5)	2 (6.9)	23 (118.5)
Rate	6.0	16.1	28.4	13.9	18.2	19.4
RR	1.00	2.69	4.74	2.32	3.04	
Genitourinary (ICD 185 – 189)						
N (PY)	49 (52.0)	76 (31.9)	29 (14.8)	50 (13.8)	27 (6.9)	231 (119.6)
Rate	225.2	207.8	128.3	176.7	176.8	193.2
RR	1.00	0.92	0.57	0.78	0.79	
Prostate (ICD 185)						
N (PY)	12 (51.9)	25 (31.8)	9 (14.8)	19 (13.7)	8 (6.9)	73 (119.0)
Rate	69.5	69.9	36.0	64.8	49.7	61.4

	Radon [WLM]					
	<10	**10–50**	**50–100**	**100–200**	**>200**	**All**
RR	1.00	1.00	0.52	0.93	0.71	
Bladder (ICD 188)						
N (PY)	13 (51.7)	29 (118.7)	7 (14.8)	15 (13.7)	9 (6.9)	73 (118.7)
Rate	73.1	79.6	28.2	57.5	57.7	61.5
RR	1.00	1.09	0.39	0.79	0.79	
Kidney (ICD 189)						
N (PY)	12 (51.9)	19 (31.6)	11 (14.8)	14 (13.6)	10 (6.8)	66 (118.7)
Rate	53.9	51.2	56.2	50.5	72.1	55.6
RR	1.00	0.95	1.04	0.94	1.34	

N: number of cases

PY: person-years of follow-up [thousands]

Rate: age-adjusted incidence rate [per 10^5 person-years]

RR: relative risk with respect to lowest exposure group

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Table 3

Model-based estimates of radon and smoking effects.

				Radon		Smoking	
Outcome group	**ICD**	**n**	**RR**	**CI**	**P**	**RR**	**CI**
All non-lung solid	*a*	1020	0.88	0.73–1.04	0.14	1.37	1.18–1.59
Oral	140–149	69	0.48	0.21–1.12	0.089	2.32	1.17–4.59
All digestive	150–159	561	0.87	0.69–1.09	0.22	1.32	1.08–1.60
Stomach	151	138	0.66	0.43–1.03	0.067	1.17	0.80–1.70
Colon	153	109	1.23	0.74–2.07	0.42	1.24	0.81–1.92
Rectum	154	145	0.78	0.50–1.20	0.25	1.48	1.01–2.16
Liver	155	50	1.17	0.55–2.50	0.69	1.21	0.64–2.30
Gallbladder	156	13	2.39	0.52–10.98	0.26	6.55	0.76–56.11
Pancreas	157	61	0.89	0.41–1.92	0.76	1.16	0.65–2.07
Larynx	161	62	0.79	0.38–1.64	0.52	1.42	0.80–2.51
Melanoma	172	23	2.92	0.91–9.42	0.072	0.88	0.36–2.17
Genitourinary	185–189	231	0.82	0.57–1.18	0.28	1.41	1.04–1.91
Prostate	185	73	0.68	0.36–1.28	0.23	0.92	0.56–1.49
Bladder	188	73	0.84	0.43–1.65	0.61	2.62	1.34–5.11
Kidney	189	66	1.13	0.62–2.04	0.69	1.64	0.92–2.93

n: number of cases

Radon RR: compares 180 WLM to 3 WLM based on the continuous loglinear model, adjusted for age, calendar time, and smoking

Radon CI: 95% confidence interval for radon RR

Radon *p*: tests hypothesis of no radon effect based on the continuous loglinear model, adjusted for age, calendar time, and smoking

Smoking RR: compares moderate and heavy smokers (more than 10 cig./day for more than 5 years) to non-smokers and light/irregular smokers

Smoking CI: 95% confidence interval for smoking RR

[a]Non-lung solid cancer ICD : 140–195, 199, except 162, 173