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Radon and Lung Cancer in the Pooled Uranium Miners Analysis (PUMA): Highly-exposed Early Miners and All Miners

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Abstract

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CONTRIBUTORSHIP STATEMENT

K.K.R., D.B.R., E.R., D.L., J.S., P.A.D., L.T., L.B.Z., M.S.B. and M.K. developed the research questions and designed the study. E.R. and D.L. worked on provision of the French data; M.S.B. and K.K.R. worked on provision of the US Colorado Plateau data; J.S. and C.W. worked on provision of the US New Mexico data; L.B.Z. worked on provision of the Canadian Eldorado data; P.A.D. worked on provision of the Canadian Ontario data; and V.D. and N.F. worked on provision of the Wismut data. S.B., E.R., K.K.R., and D.B.R. were responsible for data management and processing. K.K.R. produced the initial draft of the manuscript, which was revised and approved by all authors.

COMPETING INTEREST STATEMENT

The authors declare no conflicts of interest.

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. Where authors are identified as personnel of the International Agency for Research on Cancer / World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer / World Health Organization.

Objectives: Radon is a ubiquitous occupational and environmental lung carcinogen. We aim to quantify the association between radon progeny and lung cancer mortality in the largest and most up-to-date pooled study of uranium miners.

Methods: The Pooled Uranium Miners Analysis combines seven cohorts of male uranium miners with 7,754 lung cancer deaths and 4.3 million person-years of follow-up. Vital status and lung cancer deaths were ascertained 1946-2014. The association between cumulative radon exposure in working level months (WLM) and lung cancer was modelled as the excess relative rate (ERR) per 100 WLM using Poisson regression; variation in the association by temporal and exposure factors was examined. We also examine analyses restricted to miners first hired before 1960.

Results: In a model that allows for variation by attained age, time since exposure, and annual exposure rate, the ERR/100 WLM was 4.68 (95% CI: 2.88, 6.96) among miners who were less than 55 years of age and were exposed in the prior 5-<15 years at annual exposure rates of <0.5 WL. This association decreased with older attained age, longer time since exposure, and higher annual exposure rate. In analyses restricted to men first hired before 1960 we observed similar patterns of association but a slightly lower estimate of the ERR per 100 WLM.

Conclusions: This new large, pooled study confirms and supports a linear exposure-response relationship between cumulative radon exposure and lung cancer mortality which is jointly modified by temporal and exposure factors.

Keywords

Radon; Lung Cancer; Uranium Mining; Ionizing Radiation

INTRODUCTION

Epidemiologic studies of uranium miners play a central role in understanding the health effects of radon progeny exposure. In 1999, the US National Academies of Sciences Biological Effects of Ionizing Radiation (BEIR) VI Committee developed models to describe the excess relative rate (ERR) of lung cancer following exposure to radon progeny.[1] BEIR estimates have informed occupational radon protection and indoor radon risks for the general population.[1 2] Based on 11 epidemiologic studies of several types of underground miners,[1 3] the committee's main model described the exposure-response association between radon and lung cancer mortality as modified by attained age, time since exposure, and exposure rate. In the BEIR committee's report, higher ERRs of lung cancer mortality per unit of radon progeny exposure were observed at younger attained ages, shorter time since exposure, and lower exposure rates.[1] Cohort-specific analyses,[4-7] and several combined European studies[8-10] have also reported modification by temporal and exposure factors, although there are study-specific variations.

Radon is a known carcinogen[11] and an important occupational and environmental cause of lung cancer. Lung cancer is the fifth leading cause of death globally and causes of 1.5 million deaths annually.[12] Approximately 15% of lung cancer deaths worldwide are attributable to residential radon exposure.[13] While some studies have evaluated residential radon-lung cancer risks in the general population, studies of uranium miners continue to serve as a basis for both occupational and environmental radon protection standards. We aim to strengthen and expand upon the evidence outlined in BEIR and other pooled analyses of the association between radon progeny and lung cancer by examining modifying factors of the radon-lung cancer association in the largest pooled study of uranium miners to date. The Pooled Uranium Miners Analysis (PUMA) includes seven of the eight uranium miner cohorts that were included in analyses reported by the BEIR VI committee (including additional follow-up), and adds a large German cohort. PUMA excludes the non-uranium cohorts (tin, fluorspar, and iron miners) and uranium miner cohorts that are not active or have incomplete follow-up (Australian uranium miner cohort). The resulting pooled analysis has twice the number of workers, three times as many lung cancer deaths, and 3.5 million more person-years of follow-up than BEIR VI. This provides the power to examine the role of modifying factors in the full cohort and in important sub-cohorts such as workers employed in early periods. Using PUMA data, we aim to describe with high statistical precision variations in the association between cumulative radon progeny exposure and lung cancer mortality by attained age, age at exposure, time since exposure, and exposure rate.

METHODS

The Pooled Uranium Miners Analysis consortium

PUMA is an international consortium composed of seven underground uranium miner cohorts from Canada, the Czech Republic, France, Germany, and the United States. Cohorts of uranium miners with individual worker estimates of radon progeny exposure and active research programs are included in PUMA.[14] Cohorts contain workers employed in uranium mining and exclude workers who were employed as uranium millers. PUMA includes 119,709 male miners from four North American cohorts and three European cohorts. Two Canadian cohorts consist of 28,546 underground miners in Ontario starting in 1954,[15] and 13,574 miners employed by the Eldorado Mining and Refining Company in the Northwest Territories and Saskatchewan starting in 1942.[16] Two US cohorts consist of 4,137 underground uranium miners from the Colorado Plateau region who participated in a US Public Health Service health exam between 1950 and 1960,[17] and a cohort of 3,469 miners from New Mexico enumerated from personnel and clinical records since the 1950s.[18] European cohorts consist of 9,978 miners from the Czech Republic, based on Western and Central Bohemian mine records starting in 1948,[4] a French cohort of 5,086 uranium miners, employed by CEA-COGEMA, with records starting in 1946,[19] and 54,919 miners employed at the SAG/SDAG Wismut in Eastern Germany, based on company records starting in 1946.[20] Detailed cohort-specific information on vital status ascertainment, radon exposure estimates and co-exposures is presented elsewhere.[14]

Exposure data

Annual occupational radon progeny exposure estimates were available for each miner from every cohort.[14] Radon progeny exposure, henceforth referred to as radon, is expressed in Working Level Months (WLM). One WLM is equivalent to working 170 hours at a radon concentration of 2.08×10^{-5} joules of potential energy per cubic meter of air. Radon exposure assessment techniques differed by cohort and calendar period.[14] In general, radon estimates in early periods of operation were based on company records of employment and mine operations, and relied on expert evaluation. In mid to late periods of mine operations, data from ambient radon gas monitoring was converted into WLM using equilibrium factors. In some instances, individual worker monitoring was conducted.[14] Estimates of exposure for employment in earlier periods are generally higher prior to the implementation of engineering controls, and possibly subject to greater uncertainties than in later periods.[21]

The annual exposure rate is expressed as average annual Working Level (WL) concentration and was calculated by dividing a miner's annual radon exposure in WLMs by the number of months a miner was employed in that year. Miners in the Czech and German cohorts regularly worked longer than 170 hours in a single month. In these instances, annual exposure rate calculations were adjusted to reflect longer work hours.[22] This approach allows for variation in the annual exposure rate by worker-year, and differs from the BEIR VI pooled analysis which defined a worker's average exposure rate at a given attained age as their cumulative exposure accrued to that age divided by their duration of exposure up to that age.[1]

Mortality ascertainment and follow-up

Investigators from each cohort have obtained vital status and cause of death from their respective national, regional, and local registration offices or death records systems, and in some instances, from company records.[14] In the United States, vital status was also ascertained from Social Security Administration records. Duration of follow-up varied by cohort. Vital status and underlying cause of death were ascertained through 1999 at the earliest (Eldorado cohort) and 2014 at the latest (Czech cohort); the average miner was eligible to be followed through 2010.

Miners entered the study based on cohort-specific criteria. Inclusion was based on a minimum duration of employment, which ranged from 0 to 1 year. Cohort-specific start of follow-up ranged from 1946 to 1960. Detailed characteristics of each cohort can be found in prior publications.[14] All miners exited the study at the earliest date of death, loss to follow-up, or cohort-specific end of follow-up.

Statistical methods

Data from each cohort were transformed into a data structure tabulated by person time (in person-days) and events (number of lung cancer deaths), grouped by explanatory variables of interest.[23] All explanatory variables originally measured continuously were categorized as follows: cumulative exposure to radon progeny was categorized as 0, −5, −10, −20, −30, −40, −50, −60, −70, −80, −90, −100, −125, −150, −175, −200, −250, −300, −500, −750, −1000, −1250, −1500, −2000, −3000, −4000, −5000, and ≥6000 WLM, attained age in five-year categories (15-19, 20-24, …, 80-84, >=85), calendar period in five-year categories, and duration of employment in five categories (0-<5, 5-<10, 10-<20, 20-<30, 30+ years).

Cumulative exposure was treated as a time-dependent variable defined by four time-since-exposure windows (5-<15, 15-<25, 25-<35, 35+ years before attained age), three age at exposure windows (<35, 35-<50, 50+ years old), and four annual exposure-rate windows (<0.5, 0.5-<1, 1-<5, and 5+ WL).

All statistical models were calculated using background stratified Poisson regression, [23] and all parameter precision measures were represented by 95% profile likelihood confidence intervals. As in BEIR VI, we considered adjustment for study cohort and categories of attained age. Additionally, in this analysis we adjusted for calendar period at risk, and we also adjusted for duration of employment as a means of controlling for healthy worker survivor bias, which may be substantial in uranium miners.[24] All models are linear ERR models; this decision was based on evaluations of linearity published in prior PUMA analyses,[25] the results of the BIER IV analyses,[1] and from evidence of linearity from several cohorts within PUMA.[4 22 26]

Two model forms for the ERR were estimated for this study. Let $d_{t,a,r}$ define the cumulative exposure lagged by five years accrued in the window at time since exposure t, age at exposure a and annual exposure rate r, and therefore, $\sum d_{t,a,r}$ defines the total five-year lagged cumulative exposure. The first model form, which is similar to that used in BEIR VI, is defined as:

$$ERR = (1 + \beta \sum f_j AA_j \sum b_t e_r d_{t,a,r})$$

where AA_j represents indicators for attained age periods of <55, 55-<65, 65-<75 and 75+ years. The parameters f_j, b_t, and e_r represent weighting factors for attained age, time since exposure and exposure rate, respectively, that modify this risk from the reference level. As in BEIR VI, the parameters f_j for attained age period <55 years, b_t for time since exposure window 5-<15 years and e_r for exposure rate 0-<0.5 WL were set to 1. Therefore, the interpretation of β is an overall ERR at reference level of <55 years attained age, 5-<15 years since exposure, and 0-<0.5 WL exposure rate. Note that this model has no direct modifying effect of age at exposure, a. Age at exposure is attained age minus time since exposure [5] so age at exposure is indirectly accounted for with the inclusion of these other two factors.

A second model was also considered and defined as in order to provide more information for risk assessment models:

$$ERR = (1 + \beta \sum f_j AA_j \sum g_a e_r d_{t,a,r})$$

with g_a set to one for age at exposure window 50+ years, with three categories of age at exposure (50+, 35-<50, and <35). The parameters of this model have a similar interpretation as the first described model, and time since exposure is indirectly accounted for as the difference in attained age and age at exposure. Although model convergence is a potential problem in these types of linear models, we did not encounter any convergence problems in any of the model fittings.

Analyses were repeated restricting to miners first hired before 1960 to evaluate risks for early miners exposed to high levels of cumulative radon progeny, and analyses were repeated restricting to person time and events among those with <100 WLM of cumulative exposure to evaluate workers exposed to lower levels of cumulative radon progeny in the full cohort. Sensitivity analyses were considered, including: 1) restricting to person time and events among those employed for at least one year and at least five years, to assess the effect of exclusion of shorter term workers, 2) fitting models that do not background stratify by duration of employment to assess the impact of adjustment for duration of employment, and 3) removing each cohort from the main model to assess the impact of individual cohorts on overall results. Likelihood ratio test (LRT) statistics were used to evaluate goodness of fit for nested models, including a test for heterogeneity between cohort-specific summary estimates. Additionally, we fit a model with a random effect for slope by cohort, which allows for heterogeneity by cohort and provides an overall estimate that is less influenced by cohort size. All analyses were conducted using R.[27] Institutional Review Board approval and waiver of informed consent were obtained from the US National Institute for Occupational Safety and Health.

RESULTS

This analysis of PUMA data included 7,754 lung cancer deaths and 4.3 million person-years of follow-up (Table 1). The Wismut cohort contributed almost half of all deaths and person time in the combined analysis. Nearly 85% of lung cancer deaths, and 57% of person time were contributed by miners hired prior to 1960 (Table 1). Approximately half (49%) of lung cancer deaths occurred among miners employed <10 years, 67% of lung cancer deaths occurred between the ages of 55 and 75 years, and 67% of lung cancer deaths occurred among workers with cumulative radon exposure higher than 50 WLM. Miners in PUMA were predominately white. Descriptive statistics by individual cohort are presented in Supplementary Table S1.

In the full cohort, a simple linear ERR model (without effect modifiers) yields an estimated ERR/100 WLM of 0.22 (95% CI: 0.19, 0.24) and provides strong evidence of a positive association between cumulative exposure (lagged five years) and lung cancer. A model which also includes time since exposure indicates that there is strong evidence of modification by time since exposure (LRT=95.7, 3 d.f., p-value <0.001). The ERR/100 WLM was largest when time since exposure was shortest (ERR/100 WLM= 0.90, 95% CI: 0.51, 1.16, in the period 5-<15 years after exposure) and decreased monotonically with increasing time since exposure (Figure 1). Similar model fits and trends were observed in the pre-1960 hire cohort.

Table 2 describes a model with attained age, time since exposure, and exposure rate for miners first hired before 1960, and for the full cohort. In both the pre-1960 hires and in the full cohort a model that allows for modification of the ERR/100 WLM by attained age and time since exposure fitted substantially better than a model that allows only for modification of the ERR/100 WLM by time since exposure (LRT=19.1, 3 d.f., p-value <0.001 for the full cohort); and a model that further allowed for modification by annual exposure rate further improved model fit (LRT=121.6, 3 d.f., p-value <0.001 for full cohort). A model with attained age, time since exposure, and exposure rate (Table 2) describes a set of modifiers that is similar to the BEIR VI model (Supplementary Table S4); the estimated ERR/100 WLM was highest in earliest window of time since exposure, youngest category of attained age, and lowest exposure rate (ERR/100 WLM = 4.68, 95% CI: 2.88, 6.96 for full cohort). We observed similar patterns of association among the pre-1960 hires and among the full cohort, but there was a slightly lower estimate of ERR/100 WLM at the reference level of the effect measure modifiers, and the magnitudes of the estimated coefficients for time since exposure and exposure rate were slightly smaller in analyses restricted to the pre-1960 hires.

We estimated results for a model with attained age, time since exposure, and exposure rate with each cohort removed (Supplementary Table S2). Additionally, we fit a model of attained age, time since exposure, and exposure rate allowing for separate betas for each cohort, which suggested heterogeneity (LRT= 40.2, d.f. = 6, p-value <0.0001). An estimate of the ERR/100 WLM at the reference levels of the effect measure modifiers when derived from a random slope model was larger than the fixed effects model (6.14; 95% CI: 2.63, 9.64).

A model was fitted without background stratification by duration of employment; this led to some reduction in the reference estimates of linear association between cumulative radon exposure and lung cancer mortality, as well as changes in estimates for some categories of effect modifiers. Modification of the ERR/100 WLM by annual exposure rate was more pronounced in a model that adjusted for duration of employment (Supplementary Table S3).

We restricted models to person time and events observed among those employed at least one year and at least five years (Supplementary Table S3). A model restricted to workers employed at least one year resulted in an increase in the magnitude of the ERR/100 WLM at the reference levels and changes in estimated coefficients of the modifiers. This model was also sensitive to the removal of duration of employment. A model restricted to workers employed at least five years was similar in magnitude to the unrestricted model estimates for both the reference level of effect modifiers and the directions and magnitudes of the estimated coefficients of the modifiers. These estimates were not sensitive to removal of duration of employment.

A model was fitted restricting person time and events to those accrued <100 WLM of cumulative radon exposure. While the reference estimate was nearly similar to that of the full cohort, no clear trend in attained age was observed and the ERR/100WLM in the 15-<25 years since exposure increased to 1.02 (95% CI: 0.52, 2.39). Risk estimates in the restricted cohort were less precise than the full cohort estimates due to the smaller size of the restricted cohort.

Finally, we fitted a model which allows for variation by attained age, age at exposure, and exposure rate as presented in Table 3. This model provides additional information of the modification of lung cancer risk by age at exposure, used by some risk assessment models.[28] The ERR was highest among miners who were older when exposed, at earlier attained ages, and at exposure lower rates (ERR/100 WLM = 6.47, 95% CI: 3.39, 10.06). Rates were lower with younger ages at exposure, older attained ages, and higher exposure rates.

DISCUSSION

With the large PUMA dataset we more precisely modelled the joint effects of several modifying variables, which was not feasible to this extent in past studies; this strengthens the epidemiological basis for occupational and environmental radiation protection standards.

We confirmed that there are several temporal and exposure modifiers that simultaneously impact the magnitude of the radon-lung cancer association. The inclusion of the Wismut cohort nearly doubles the size of the pooled analysis compared to BEIR VI, with three times as many lung cancer deaths and five times as many person-years of follow-up. In addition to more precise risk estimates in the full cohort, we estimated risks relevant to miners previously exposed to high levels of radon, a research gap identified by investigators of prior analyses.[3]

The results of this pooled analysis are generally consistent with the BEIR VI report; however, the ERR/100 WLM estimates are in many categories lower in magnitude than BEIR estimates (Supplementary Table S4). This may be due to the inclusion of the Wismut cohort which was not in the BEIR VI analyses. The Wismut cohort contributes about half of the information in PUMA, and has substantial influence on the overall estimates of ERR/100 WLM (see Supplementary Table S2). Individual cohorts differ by exposure levels, age at first exposure, attained age effects, duration of exposure, duration of follow-up, inclusion of non-exposed workers, occupational co-exposure scenarios, and cohort selection attributes (e.g., enumeration of cohorts after the start of mining operations, prior hard rock mining experience, or screening as a condition of employment). All these factors may account for some of the observed differences between individual cohorts and the different pooled studies.

The majority of miners in PUMA are pre-1960 hires and have higher average cumulative exposures due to early-period mining conditions, and probably more uncertainty in exposure estimates because monitoring information was less comprehensive in early periods. Early miners on average had the highest exposures; virtually all lung cancer deaths among workers with cumulative exposure higher than 500 WLM were among pre-1960 hires (Table 1). While the full cohort merits independent examination for its precise estimates from long follow-up, older attained ages, and a wide range of exposures and exposures rates, analyses of the pre-1960 hires provide insights into the impacts of the early period and its associated higher exposure scenarios and exposure measurement uncertainties (Table 2). The pre-1960 hires have impact on the PUMA overall summary estimate of association, and also influence estimates of trends in time since exposure and exposure rate within the full cohort. A separate analysis on the subset of miners hired after 1960 provides understanding of the effects of chronic low exposure rate scenarios experienced by more contemporary miners with high quality exposure estimates.[25]

We assumed an *a priori* lag of five years for comparability with prior studies. Different exposure lags will be evaluated in future analyses. It is worth noting that the 5-year lag does not affect baseline rates. We also fitted a model that described the modifying effects of age at exposure, attained age and annual exposure rate (Table 3). Prior work suggests that a model that allows for effect modification by age at exposure should be adjusted for time since exposure [4] [5] [10], a related but somewhat different modelling approach to the one used here.

We observed an inverse exposure rate effect in all models and, when other parameters were held constant, excess relative rates by exposure rate declined (Supplementary Table

S4), which has been observed in several other studies.[1 7 29] In the report of the BEIR VI committee, exposure rates were estimated as a worker's cumulative exposure divided by their duration of employment at any attained age, while in our analysis we partitioned a worker's cumulative exposure according to windows defined by annual exposure rate; we still observed similar trends in exposure rate.

Neither occupational co-exposures nor smoking were assessed in this analysis. Known occupational co-exposures from uranium mining such as silica, arsenic, gamma radiation, long lived radionuclides, and diesel exhaust could influence rates of lung cancer.[1 30] Other analyses have indicated that the influence of occupational co-exposures on the radon-lung cancer risk is minimal. And, while smoking is a strongly associated with lung cancer risk, smoking modifies, rather than confounds, the association between radon exposure and lung cancer mortality.[7 17 31-33] However, differences in unmeasured occupational co-exposures and smoking rates may be responsible for the heterogeneity observed between cohorts. The effect of smoking and occupational co-exposures among PUMA data will be explored in future research, noting that few of the cohorts in PUMA have individual-level smoking history data (but some have such information on case-control sub-samples).[14] Health-related selection out of employment (healthy worker survivor effect) is a potential concern in occupational studies in which workers need to maintain a certain level of fitness to retain employment. In the current analysis, there are indications of such a pattern of bias; exclusion of miners employed for less than a year led to a modest change in the estimates, as did adjustment for duration of employment.

There was evidence that although short term workers (<1 year employment) tended to accrue lower cumulative exposures than longer term workers (5+ years), short term workers had higher baseline rates of lung cancer. The different rates between shorter- and longer-term workers are illustrated in Supplementary Table S3; when comparing models adjusted for duration of employment, the exclusion of workers employed in uranium mining for <1 year tended to slightly increase the reference ERR/100 WLM and subsequently for categories of modifiers. However, exclusion of workers employed in uranium mining for <5 years did not substantively change the ERR/100 WLM for the reference estimate or modifiers. Note that cohorts had different exclusion criteria for short term workers (Supplementary Table S1).

Epidemiological studies of underground miners are the basis for occupational and indoor radon risk estimates. PUMA has three times as many lung cancer deaths as BEIR VI, is composed solely of uranium miners, and extends mortality follow-up by decades. This study demonstrates with several modelling approaches that the association between radon and lung cancer varies by attained age, age at exposure, time since exposure, and exposure rate, with the highest estimates in the lowest attained ages, least time since exposure, highest ages at exposure and lowest exposure rates.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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KEY MESSAGES

What is already known on this topic:

Prior studies have established an exposure-response association between radon progeny and lung cancer mortality, but more precise estimates of the temporal- and exposure-related modifiers of this association are needed.

What this study adds:

The Pooled Uranium Miners Analysis (PUMA) is the largest and most up-to-date pooled study of uranium miners, with three times as many lung cancer deaths and five times as many person-years of follow-up than the last National Academies of Science pooled analysis.

How this study might affect research, practice or policy:

PUMA data confirms a linear exposure-response relationship between cumulative radon exposure and lung cancer mortality, and supports modification of the association by temporal and exposure factors.

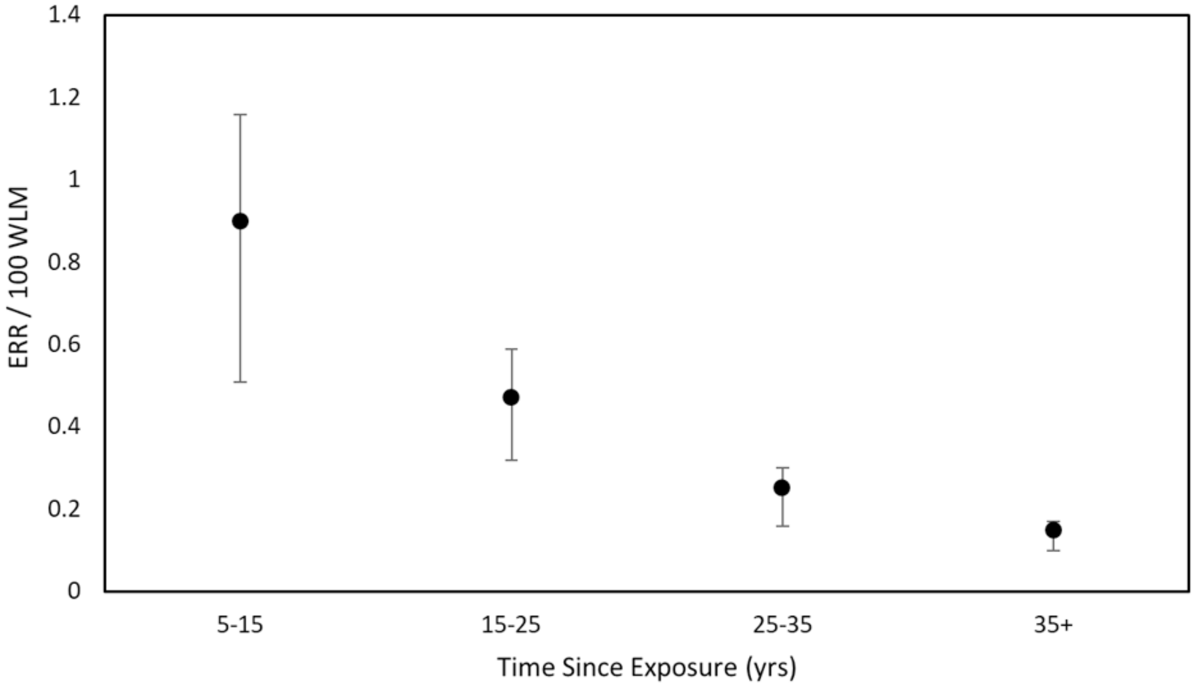

Figure 1.

Excess relative rate (ERR) of lung cancer mortality (circles), and 95% profile likelihood confidence intervals (lines), by windows of time since exposure to cumulative radon measured in WLM. PUMA study of male uranium miners.

ERR/100 WLM = Excess relative rate per 100 working level months. Cumulative radon exposure is lagged 5 years, adjusted via background stratification for study cohort, attained age, calendar period, and duration of employment in uranium mining.

Table 1.

PUMA study characteristics among males: count and proportion of lung cancer deaths and person-years (pyrs) of follow-up by categories of covariates of interest, and cumulative exposure in working level months (WLM), miners hired before 1960 and full cohort.

	Pre-1960 hires		**Full cohort**	
	Lung cancer (*n* = 6537)	**Person time (2 456 293 pyrs total)**	**Lung cancer (*n* = 7754)**	**Person time (4 343 384 pyrs total)**
	n	**pyrs**[a]	**n**	**pyrs**[a]
Attained age (years)				
<55	1078	14.8	1380	30.5
55–<65	2078	4.9	2568	7.2
65–<75	2289	3.4	2640	4.1
75+	1092	1.5	1166	1.6
Calendar period				
<1955	8	1.1	8	1.1
1955-1965	251	5.1	251	5.2
1965-1975	910	5.6	926	7.2
1975-1985	1489	5.0	1572	9.1
1985-1995	1711	4.0	1946	9.4
1995-2005	1531	2.8	1978	7.6
2005+	637	1.0	1073	3.8
Duration of employment				
0– < 5 years	1595	11.3	2124	21.1
5 – < 10 years	1492	5.4	1666	9.1
10 – < 20 years	1643	4.0	1946	8.1
20 – < 30 years	959	2.2	1167	3.4
30+ years	848	1.7	851	1.7
Cohort				
Colorado Plateau	596	1.1	612	1.2
Czech Republic	948	1.3	1176	3.2
Eldorado	426	2.6	517	4.2
France	194	1.2	213	1.8
Wismut	3289	12.7	3759	21.6
New Mexico[b]	137	0.3	231	1.3
Ontario	947	5.4	1246	10.1
Cumulative radon exposure[c]				
0	358	2.9	499	5.4
>0-5	312	2.6	699	11.3
>5-50	1157	3.7	1342	12.3
>50-100	827	2.5	690	3.2
>100-250	871	5.7	1236	4.0

	Pre-1960 hires		**Full cohort**	
	Lung cancer (*n* = 6537)	**Person time (2 456 293 pyrs total)**	**Lung cancer (*n* = 7754)**	**Person time (4 343 384 pyrs total)**
	n	**pyrs**[a]	**n**	**pyrs**[a]
>250-500	566	2.5	839	2.5
>500-750	619	1.6	619	1.6
>750	1827	3.1	1830	3.1

[a] Per 100,000 person-years

[b] 20 less deaths than previously reported because workers who are also included in the Colorado Plateau cohort were removed from the New Mexico cohort, there are no overlapping workers between cohorts in this analysis

[c] Working level months, unlagged.

Table 2.

Model for the association between cumulative radon exposure and lung cancer mortality with effect modification by time since exposure, attained age and exposure rate with 95% profile likelihood confidence intervals. PUMA study of male uranium miners, miners hired before 1960 and full cohort.

	Pre-1960 hires	Accrued <100 WLM of cumulative exposure	Full cohort
ERR/100WLM[a]	4.49 (2.49, 6.85)	4.35 (1.67, 8.80)	4.68 (2.88, 6.96)
Time since exposure			
5-<15	1	1	1
15-<25	0.74 (0.53, 1.04)	1.02 (0.52, 2.39)	0.77 (0.56, 1.05)
25-<35	0.45 (0.30, 0.66)	0.61 (0.27, 1.45)	0.54 (0.38, 0.76)
35+	0.34 (0.22, 0.53)	0.33 (0.06, 1.02)	0.39 (0.26, 0.58)
Attained age			
<55	1	1	1
55–<65	0.53 (0.35, 0.82)	0.66 (0.33, 1.41)	0.55 (0.38, 0.82)
65–<75	0.40 (0.26, 0.64)	0.37 (0.13, 0.89)	0.38 (0.25, 0.57)
75+	0.46 (0.26, 0.80)	0.60 (0.10, 2.00)	0.40 (0.24, 0.66)
Exposure rate (WL)			
0–<0.5	1	1	1
0.5–<1.0	0.43 (0.15, 0.95)	0.79 (0.35, 1.60)	0.60 (0.31, 1.08)
1.0–<5.0	0.44 (0.30, 0.71)	0.51 (0.28, 0.94)	0.42 (0.31, 0.64)
5.0+	0.18 (0.12, 0.27)	−0.01 (−0.28, 0.37)[b]	0.17 (0.12, 0.25)

[a] Excess relative rate per 100 working level months. Cumulative radon exposure is lagged 5 years. Background stratification by study cohort, attained age, calendar period, and duration of employment in uranium mining.

[b] Only 2% of person years were accrued and 138 deaths occurred in this stratum.

Table 3.

Model for the association between cumulative radon exposure and lung cancer mortality with effect modification by age at exposure, attained age and exposure rate with 95% profile likelihood confidence intervals. PUMA study of male uranium miners.

ERR/100WLM[a]	6.47 (3.39, 10.06)
Age at exposure	
50+	1
35-<50	0.83 (0.54, 1.39)
<35	0.55 (0.36, 0.92)
Attained age	
<55	1
55–<65	0.40 (0.28, 0.59)
65–<75	0.21 (0.15, 0.31)
75+	0.19 (0.12, 0.29)
Exposure rate (WL)	
0-<0.5	1
0.5-<1.0	0.57 (0.29, 1)
1.0-<5.0	0.39 (0.28, 0.58)
5.0+	0.15 (0.11, 0.22)

[a] Excess relative rate per 100 working level months. Cumulative radon exposure is lagged 5 years. Background stratification for study cohort, attained age, calendar period, and duration of employment in uranium mining.