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Updated cancer mortality among uranium miners on the Colorado Plateau: interactions of radon exposure with smoking and temporal factors

Mary K. Schubauer-Berigan^{1,*}, Stephen J. Bertke², Kaitlin Kelly-Reif², Robert D. Daniels³

¹International Agency for Research on Cancer, Evidence Synthesis and Classification Branch; Lyon, France.

²National Institute for Occupational Safety and Health; Division of Field Studies and Engineering; Cincinnati, OH.

³National Institute for Occupational Safety and Health (retired).

Abstract

Objectives: Understanding of long-term lung cancer risks from radon decay products (RDP) exposure derives largely from studies of uranium miners. We aimed to compare mortality for lung and other cancers to the general population, to estimate excess absolute rate (EAR) and excess relative rate (ERR) from RDP exposure, and to estimate the joint effects of RDP and cigarette smoking in extended follow-up of a cohort of 4137 male uranium miners from the U.S. Colorado Plateau.

Methods: We extended mortality follow-up through 2016 and re-evaluated RDP exposure against original work history and mine records. We calculated standardized mortality ratios (SMRs) compared to a regional population, evaluated EAR of lung cancer mortality using standardized rate ratios, and modeled ERR using Cox proportional hazards regression. We evaluated interactions of RDP with smoking pack-years, attained age (AA) and time-since-exposure (TSE).

Results: There were 695 lung cancer deaths, including 146 among never- and light smokers. The overall SMR was >4; the EAR per unit RDP exposure increased substantially with smoking

*Corresponding author, Correspondence to Mary K Schubauer-Berigan; beriganm@iarc.who.int.
Contributors

MS-B led the acquisition of the mortality data, the development of the smoking imputation method, and initial drafting of the manuscript. She is the study guarantor. SJB conducted the statistical modelling analyses. KKR participated in acquisition of data and development of the analytic file. RDD led the development of the updated radon decay product estimates. All authors contributed to the design and interpretation of the analyses; to drafting, critically revising, and final approval of the manuscript; and to ensuring the integrity and accuracy of the results.

Competing interests

All authors declare no competing interests.

Ethics approval

Ethics approval was provided by the National Institute for Occupational Safety and Health Human Subjects Review Board (NIOSH HSRB #89-DSHEFS-20).

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pack-years and decades of follow-up. Lung cancer ERR decreased with AA and TSE. ERR attenuation at high exposure-rates was smaller than observed elsewhere. Joint effects of RDP and smoking were sub-multiplicative but greater-than-additive, appearing closer to multiplicative at lower RDP exposures. Pancreas was the only other site showing a significantly positive ERR per unit exposure.

Conclusions: Excess rates of lung cancer mortality persist throughout the lifespan among this cohort of uranium miners. Information about RDP-smoking interactions is of interest for occupational and general population exposure.

Keywords

Lung Neoplasms; Radon; Smoking; Risk Assessment; Occupations; Cohort studies

Introduction

In 1964, the U.S. Public Health Service published the first epidemiologic evaluation of lung cancer mortality among uranium miners.¹ This seminal cohort study of miners on the Colorado Plateau of the southwestern U.S. found a fourfold elevation in risk of respiratory cancers, which was subsequently definitively linked to exposure to radon decay products (RDP).^{2–6} Studies of this cohort have contributed to the evidence base for risk assessment of occupational and residential RDP exposure.^{7,8}

Studies of uranium miner cohorts have demonstrated that relative risk of lung cancer decreases with increasing time since exposure and attained age and suggest a sub-multiplicative but greater-than-additive interaction between cigarette smoking and RDP exposure.^{4,9–11} However, lifetime follow-up of these key cohorts has been incomplete. Understanding the evolution of relative and absolute excess rates of lung cancer over time and the persistence of the lung cancer burden in the cohort compared to the general population are of interest. The Pooled Uranium Miners Analysis (PUMA) recently published estimates of lung cancer mortality risk combining 7 cohorts in the USA, Czechia, Canada, France, and Germany, including (with follow-up through 2005) the Colorado Plateau cohort.^{12,13} PUMA analyses examined evolution of risk in the pooled cohort with attained age, time since exposure, and exposure rate. However, excess absolute rates (EARs) or excess relative rates (ERRs) for lung cancer have not been examined in detail for the Colorado Plateau cohort since the late 1990s,⁴ and not all cohorts in PUMA have information on smoking. With extended follow-up, more cases have emerged among never and light smokers, permitting a more thorough analysis of the joint effects of RDP and cigarette smoking exposure.⁶ Lastly, there is renewed interest in whether cancers other than lung are associated with exposure to RDP.¹⁴

Our analysis of Colorado Plateau uranium miner cohort, with follow-up extended through 2016, addresses the following specific aims:

1. Compare mortality rates for specific causes of death to the general population, to assess the cancer burden and estimate trends in EAR by dose category.

2. Model lung cancer mortality rates per unit RDP exposure with time-since-exposure (TSE), attained age, and dose rate, comparing findings to estimates from the Biological Effects of Ionizing Radiation (BEIR) VI committee⁸ and PUMA¹³ and examining whether temporal risk patterns vary by smoking level.
3. Examine joint effects of RDP and cigarette smoking for lung cancer mortality, including miners of all races and ethnicities, to increase the amount of data on never and light smokers.
4. Evaluate the association of RDP with mortality from cancers other than lung, including several individual cancers and all cancers combined other than respiratory and ill-defined cancers (which may represent under-diagnosed lung cancer).

Methods and Materials

Cohort assembly and follow-up

The Colorado Plateau cohort has been described previously.⁶ Briefly, the cohort was assembled by compiling records from a series of cross-sectional examinations held periodically between 1950 and 1960 among active uranium miners in southwestern USA.^{1,2} The cohort consists of all male miners who participated in a medical examination and questionnaire at least once between 1950 and 1960 and worked underground in a uranium mine for at least one month (n=4137). Initially, miners were followed up triennially via interview and physical examination and later by record linkage to multiple sources. Since the previous reported follow-up,⁶ we linked records for all miners not known to be deceased with the National Death Index (NDI), death records of the Social Security Administration, and tax records of the Internal Revenue Service, which confirmed status as either alive or deceased. Causes of death for deceased miners were obtained from the NDI or death certificates, which were coded to the revision in effect at the time of death. Mortality follow-up was extended through 31 December 2016.

Assessment of exposure to RDP

RDP exposure estimates are based on thousands of measurements collected from hundreds of mines between 1951 and 1969.^{1,2} Exposures from both uranium mining and other hard rock mining are based on the historical unit “working level month” (WLM), equivalent to a potential alpha energy exposure of 3.54 mJ hour m⁻³.¹⁵ In previous analyses,⁶ available data consisted of the dates on which each miner’s RDP exposure reached 9 pre-specified cumulative exposure levels. Here, we made extensive effort to link the cohort to original dosimetry records to verify employment data and exposure estimates by mine and year. Data are available at the level of the combination of individual miners’ work history data and the periodic exposure estimation (usually, annual) made for each mine. We interpolated daily rates of exposure between these dates for each worker. We included estimated exposure to RDP from previous non-uranium hard rock mining according to the dates estimated for each miner before beginning uranium-mine employment. Uranium mine exposure is subject to uncertainties, particularly before 1960, including exposure measurement and estimation error;¹⁶ however, consideration of these uncertainties is beyond our scope here.

Smoking data

Quantitative cigarette smoking histories were collected for nearly all cohort members using surveys conducted in the 1950s-1970s, and (for white miners) 1986.³ Data were available in two forms: smoking category at the last survey (never, former, current <1 pack per day, current 1 pack per day, current >1 pack per day), and cumulative number of cigarettes smoked (expressed in pack-years) for ever-smokers. To facilitate analyses based on pack-years, we estimated a quit date to reflect a more realistic lifetime smoking quantity, given the long follow-up period. We created a detailed smoking history for each miner, individually imputing the last smoking date for each current smoker at the time of last questionnaire (Supplemental Materials, Supplemental Tables 1–3), conditional on expected values for single-year age- and 5-year birth cohort-specific cessation probabilities for U.S. men.¹⁷

Cancers of interest

We examined associations between RDP exposure and mortality for the following cancer types with at least 10 cases: all cancers excluding lung and neoplasms of uncertain type overall or in the respiratory system (ICD-9 codes: 140–208, except 162, 165, 195, 199); lung (162); extrathoracic airways (140–148, 160–161, 164); digestive cancers as a group (150–159); esophagus (150); stomach (151); intestine (152–153); liver and gall bladder (155–156); pancreas (157); prostate (185); melanoma (172); all skin combined (172–173); lymphatic & hematopoietic (200–208, 273.3) and its subcategories non-Hodgkin lymphoma (200, 202, 273.3), multiple myeloma (203), and leukemia (204–208).

Statistical analyses

For Aim 1, we used the NIOSH Life Table Analysis System (LTAS)^{18,19} to estimate standardized mortality ratios (SMRs) compared with the male population of Arizona, Colorado, New Mexico, and Utah (for white miners) and with those in Arizona and New Mexico (for miners of other races), as described previously.⁶ Person-time and event tabulation began at the later of date of first examination or 1/1/1960 (when American Indian miners' follow-up⁵ and general population rates began) and ended at the earliest of date of emigration ($n < 5$), loss to follow-up, death, or 31/12/2016. SMRs were indirectly standardized on race, age, and calendar period, stratifying by dose category and decade of follow-up for lung and other cancers. We also calculated internally adjusted standardized rate ratios (SRRs) directly standardized to the race, age, and calendar year distribution of the entire cohort. Using SRRs, we estimated EAR trends across RDP exposure in lung cancer mortality rates.¹⁹

For Aims 2–4, to evaluate temporal patterns in RDP-associated lung cancer mortality rates and effect modification by smoking, we used full risk sets with attained age as the time scale, also caliper-matching on birth cohort within 2.5 years of the case.^{20,21} Partial likelihoods when using the full risk set are identical to those from Cox proportional hazards regression. We estimated the ERR per 100 WLM using models commonly explored in other studies of uranium miners.^{8,13} Analyses were conducted using the PHREG procedure in SAS (ver. 9.4).

To address Aim 2, we fitted cubic b-spline models, with two equally spaced knots,²² to flexibly examine the shape of exposure-response patterns and their variation with TSE, attained age, and smoking level. We fit the following model, based on the BEIR VI⁸ model considering effect modification by attained age, TSE, and exposure rate

$$\text{ERR} = \beta \cdot (w_{5-14} + \theta_1 \cdot w_{15-24} + \theta_2 \cdot w_{25-34} + \theta_3 \cdot w_{35+}) \cdot \phi_{\text{age}} \cdot \phi_{\text{dose rate}}$$

where w_{5-14} , w_{15-24} , w_{25-34} and w_{35+} represent windows of cumulative exposure accrued 5–14, 15–24, 25–34 and 35+ years prior to attained age, respectively, and, therefore, their sum equals a worker's cumulative exposure lagged 5 years. β represents the ERR of the weighted sum of cumulative exposures (weighted by parameters θ_i), ϕ_{age} represents a modifying factor of attained age in categories <55, 55–64, 65–74 and 75+ years old, and $\gamma_{\text{dose rate}}$ represents modifying factors of the radon progeny alpha energy decay airborne concentration (mJ m^{-3}), in categories <10 and 10+ working levels (WL, calculated as WLM/number of months in uranium mining). Studies of RDP suggest that, at a given total exposure, low exposure rates are more effective than high exposure rates in causing cancer. In previous analyses of this cohort,⁴ a cutpoint of 10 WL was found to capture most of these effects. The above model does not control for smoking (which is not related to RDP exposure in this cohort; Pearson $r = -0.00123$, $p=0.9370$) but matches on age and birth date. The ability to differentiate attained age from TSE effects is limited at their lower and upper extremes, due to their strong correlation in this cohort (Supplemental Table 4).

We addressed Aim 3 using three approaches:

- a. We employed previously developed models,⁴ including a parameter in the ERR model to estimate whether the form of the ERR–smoking pack-year interaction is multiplicative, sub-multiplicative, or additive. The baseline model was specified as:

$$\text{ERR} = (1 + \beta_1 \text{WLM}/100)(1 + \beta_2 \text{Pack-years}) \exp(\beta_3 \text{TSLE} + \beta_4 \text{Dose Rate} > 10\text{WL}), \text{ where } \text{TSLE} = \text{time since last exposure}$$

- b. We estimated the coefficients for a multiplicative (λ) and additive ($1 - \lambda$) contribution in a geometric mixture model.^{4,9}
- c. We tabulated the internally standardized rates by WLM and smoking category and evaluated whether additive or multiplicative joint effects better summarize the observed rates across the range of smoking and exposure categories.²³

For Aim 4, we examined the other cancer types under consideration, matching on age and birth cohort. Because other cancers may have a different latency pattern than lung cancer, we identified an optimal lag through a grid search by fitting all yearly lags between 0 and 40 and choosing the model with the lowest $-2 \log$ -likelihood (as for studies of US nuclear workers²⁴).

Results

This analysis excludes 116 miners who died or were lost to follow-up before 1960 (Table 1). There were 128,578 person-years and 3568 deaths through 2016, representing an increase of 8141 and 604, respectively, in the 11 years since last reported follow-up;⁶ 89% of the cohort is now deceased. Fourteen (0.34%) cohort members were lost to follow-up, and cause-of-death was unavailable for 22 (0.62%) decedents. These low percentages indicate that follow-up mechanisms were adequate.

Lung cancer mortality rates compared to regional population

With 695 deaths, the overall lung cancer SMR was 4.55 (95% CI: 4.21, 4.90). The highest SMRs were seen among miners exposed to more than 120 WLM, monotonically increasing above this level to nearly 10 above 1000 WLM (Supplemental Table 5a). Stratified by decade of follow-up, we observed a clearly decreasing pattern of SMRs over time, from 6.3 in the 1960s to 3.7 in the 2010s; however, within exposure categories the patterns were more equivocal. The EAR per 100 WLM increased across decades, from 2.8 to 16 cases per 10,000 person-years from the 1960s to the 2000s, declining in the 2010s (Supplemental Fig. 1).

Lung cancer SMRs increased substantially across cigarette pack-years, in the cohort overall and within categories of RDP exposure (Supplemental Table 5b). However, the relative increase in smoking-related SMRs was much greater for miners exposed to 0-<60 WLM than for miners exposed to more than 1000 WLM. Within each smoking category, a clear pattern of RDP-related exposure-response was seen above 120 WLM, with RDP-related SRR increases much higher among the 0-<10 pack-year smoking category than in the ≥ 50 pack-year category (Supplemental Table 5b). However, the EAR/100 WLM for lung cancer mortality increased monotonically across smoking categories, from 5 to 15 deaths per 10,000 person-years in the lightest to heaviest smoking groups.

Lung cancer exposure-response overall and effect modification with temporal factors

The shape of the exposure-response curve for lung cancer mortality with RDP appears linear in the lower-exposure region, with curvilinearity above approximately 1200 WLM (Supplemental Fig. 2a). In the BEIR VI exposure-age-concentration model, at 5–14 years since exposure the estimated ERR/100 WLM at age <55 was 4.04 for dose rates <10 WL and 2.14 for higher dose rates (Table 2). ERR/100 WLM decreased notably with TSE: stratified on dose rate at 10 WL, exposures received 15–24, 25–34, and ≥ 35 years before age-at-risk were 87%, 49%, and 36% as effective, respectively, as those received in the 5–14-year window. Spline models confirm this pattern (Fig. 1a), with ERR/100 WLM stabilizing by about 40 years post-exposure.

ERR/100 WLM did not vary greatly by age-at-exposure up to age 40; however, above this age, rate per unit exposure increased, although with widening confidence intervals (Fig. 1b). By contrast, strong heterogeneity ($p < 0.001$) was observed by attained age: compared to age <55, the ERRs/100 WLM for ages 55–64, 65–74 and ≥ 75 were 61%, 30%, and 16% as high, respectively (Table 2). Spline models suggest this decline in ERR with attained age

levelled off by about age 70 (Fig. 1c). Examining ERR/100 WLM by smoking category, Supplemental Fig. 3 illustrates the diminishment of RDP-associated risk after about 25 years post-exposure for the heaviest smokers, with rates declining less steeply among lower smoking categories.

Joint effects of RDP and smoking

We used three approaches to evaluate the interaction between RDP exposure and cigarette smoking. In the first approach, the interaction term for pack-years and WLM exposure was negative and marginally significant ($p=0.042$) in a multiplicative model adjusting only for age, birth cohort, and race (Table 3). However, in a model that included the interactions of attained age with both WLM and smoking pack-years, interaction for pack-years and WLM exposure was not significant (deviance $\chi^2=3.5$, 3 df, $p=0.321$). Supplemental Fig. 2b indicates steeper RDP exposure-response curves for lower compared to higher smoking pack-years, and Fig. 1d shows the relatively modest decrease in ERR/100 WLM across increasing smoking pack-years.

In the second approach, the estimate of λ in a geometric mixture model was 0.288 (95% CI: 0.0250, 0.551), indicating a supra-additive but sub-multiplicative interaction between WLM and pack-year exposure. At cumulative exposure levels below 400 WLM, λ was 0.438 (95% CI: -0.183, 1.058), moving towards multiplicative.

In the third approach, the interaction appeared supra-additive (Supplemental Table 6). In an examination of departures from additive joint effects, only one combination of WLM and pack-year categories had an observed joint absolute risk (AR) less than the expected joint AR. The mean ratio of the observed to expected joint AR was 1.9, with no clear pattern across smoking categories. However, the observed-to-expected joint AR values tended to decrease across WLM exposure categories, suggesting an interaction closer to additive at higher RDP exposures. This was confirmed in the examination of joint multiplicative effects (Supplemental Table 7): overall, the interaction appeared sub-multiplicative, in that the mean of the observed-to-expected joint rate ratio (RR) across all dose and smoking categories was 0.74. However, at RDP exposures >400 WLM, the interaction was clearly sub-multiplicative (observed-to-expected ratio of joint RRs ranged from 0.29 to 0.60), while below 260 WLM, the interaction appeared super-multiplicative (observed-to-expected joint RRs ranged from 1.1 to 1.9). As smoking increased, the interaction moved away from multiplicative to additive across WLM categories (Supplemental Table 7).

Association of RDP exposure with other cancers

Pancreas was the only individual cancer site other than lung that was significantly positively associated with RDP exposure (Table 4; Supplemental Table 8): under the best-fitting lag of two years, the ERR/100 WLM was 0.07 (95% CI: 0.01, 0.3). Estimated exposure-response coefficients were weakly and imprecisely positive for extrathoracic airways, intestine, and prostate cancers and were significantly negative for leukaemia and multiple myeloma (Table 4).

Discussion

With more than 50 years of follow-up, lung cancer mortality remains highly elevated among miners on the Colorado Plateau, compared with the regional population. SMRs have not declined notably since the 1990s. The heaviest smokers who were most highly RDP-exposed had 12 times the expected mortality, demonstrating the high combined burden of RDP and tobacco smoking in lung cancer among these miners. A longstanding limitation of the Colorado Plateau cohort study is the use of the entire non-white population of Arizona and New Mexico as a comparison for the light-smoking American Indian (primarily Navajo) uranium miners. This is likely to have led to underestimates of the SMRs for lung cancer.^{5,6}

In the main effects ERR/WLM model, compared with previous analyses of the cohort,⁴ overall parameter estimates were much more precise, reflecting more cases with additional follow-up. As with the most recent modelling in this cohort,⁴ we found that relative rates decreased with time since exposure and attained age. However, spline and categorical analyses showed that this decline in ERR/100 WLM levelled off by about age 70 and 40 years since exposure and remained substantially elevated throughout the lifespan of the miners. We also found the ERR/100 WLM was about 60% higher at attained age ≥ 70 compared with earlier follow-up.⁴ Notably, the EAR rose as the cohort aged (Supplemental Fig. 1), declining only in the period from 2010–2016, reinforcing the persistence seen in the highly elevated SMRs compared to the regional population as the cohort aged.

As seen in Table 2, ERR/WLM at older attained ages was higher than in BEIR VI,⁸ but lower than in PUMA¹³ (which had much more precise estimates than seen here). However, estimates based on time since exposure were similar among the three analyses. Attenuation at high exposure rates was about half as severe in our cohort analysis, even though the dose rate was much higher, as in the BEIR VI and PUMA analyses. Notably, parameters in some of the stratified analyses were estimated imprecisely.

An important limitation of our study is the potential for bias from unavoidable errors in individual RDP estimates. Lacking personal measurements, exposure estimates were obtained using dose reconstruction methods that relied on available data that varied between and within mines in both content and quality. For example, processing and employment recordkeeping, as well as environmental monitoring techniques, likely improved over time. The effects of measurement error on the exposure-response have not been fully explored; however, model-based corrections applied in earlier follow-up led to stronger exposure-response estimates, particularly at higher exposure rates,¹⁶ suggesting that we may have underestimated high exposure-rate effects. This should minimally bias estimates for the lower exposure-rates typically observed in current occupational and environmental settings.

Tobacco smoking is not a confounder in this cohort (Table 3), but the joint effects of smoking and RDP are of great interest. Previous analyses of this cohort found that the joint effect of RDP and cigarette smoking tended to move from multiplicative,²⁵ to sub-multiplicative,²⁶ towards additive⁴ with increased follow-up. We found that a sub-multiplicative but supra-additive model continues to describe the data well with several decades of additional follow-up. However, with extended follow-up the negative interaction

between RDP and pack-year categories in a multiplicative model that included important effect modification of WLM ERR by attained age was no longer statistically significant and its magnitude was reduced, compared with previous follow-up.⁴ Furthermore, with more lung cancer deaths among never and light smokers, we observed heterogeneity by dose category: joint effects appeared closer to multiplicative at exposures below about 400 WLM than at higher exposures. This finding contrasts with that from the pooled European nested case-control study, in which a sub-multiplicative joint effect was observed below 300 WLM²⁷ but appears similar to that found in the German Wismut cohort.²⁸ Interaction estimates from the pooled 11-country study ranged from sub-additive in the China tin miners to multiplicative in the Beaverlodge (Canada) cohort.⁹ The joint effects found at low exposures in this study should be more relevant than those at high exposures in modern occupational and environmental exposure settings. A slight limitation of our study was the assumption of a fixed quit date for current smokers at last survey, conditional on age and birth year, which may have led to increased uncertainty in estimation of these joint effects.

RDP's interaction with smoking not only affects the magnitude of radiation risk across pack-year categories, but also reflects a delayed temporal pattern, wherein peak risks were observed earlier for heavy smokers and later for never- or light-smokers. This may explain the early lack of excess lung cancer mortality among the light-smoking American Indian miners, which was initially attributed to "stringent health standards used by the industry in the employment of Indians and the tendency to discharge ill Indians from mining and return them to the reservation for medical care".¹

We found no evidence for an association between RDP and deaths from all cancers combined (excluding respiratory and ill-defined cancers). The only cancer type besides lung positively associated with RDP was pancreas, for which we found an ERR/100 WLM of 0.07 (95% CI: 0.01–0.3) under a best-fitting lag of 2 years. This is similar to a finding reported in the 11-cohort pooled study,²⁹ which reported an ERR/100 WLM of 0.02 for pancreatic cancer (the only specific cancer type besides lung showing an elevation). By contrast, a null association was seen for pancreatic cancer in the large Wismut cohort,³⁰ which was not part of the previous pooled study. It is unclear why we found an inverse association for leukaemia and RDP. Competitive mortality from lung cancer may have depleted susceptible individuals, given that the lung would be expected to receive a much higher dose than bone marrow.

Our use of mortality rather than cancer incidence outcomes is a limitation, which is of particular concern for some cancer types other than lung (e.g., skin, prostate, and haematolymphoid cancers). We did not incorporate uncertainty in the selection of optimal lags for cancer types other than lung; however, for most outcomes the 10-year and optimal lags produced similar results.

In conclusion, with near-complete follow-up of uranium miners on the US Colorado Plateau, persistent elevation in lung cancer mortality rates remain even into miners' oldest ages. Information about the supra-additive but sub-multiplicative joint effects of smoking and RDP, particularly at lower exposure levels, may be useful for risk assessment. Further

analyses of joint effects from PUMA should help elucidate the form of this interaction at lower exposures.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Wagoner JK, Archer VE, Carroll BE, et al. Cancer mortality patterns among U.S. uranium miners and millers, 1950 through 1962. *JNCI* 1964;32(4):787–801.
2. Lundin FE, Wagoner JK, Archer VE. Radon Daughter and Respiratory Cancer Quantitative and Temporal Aspects. Springfield, VA: Public Health Service, US Department of Health, Education, and Welfare; 1971. (Joint monograph no. 1).
3. Hornung RW, Deddens J, Roscoe R. Modifiers of exposure-response estimates for lung cancer among miners exposed to radon progeny. *Environ Health Perspect* 1995;103(Suppl. 2):49–53.
4. Hornung RW, Deddens JA, Roscoe RJ. Modifiers of lung cancer risk in uranium miners from the Colorado Plateau. *Health Phys* 1998;74(1):12–21. [PubMed: 9415577]
5. Roscoe RJ, Deddens JA, Salvan A, Schnorr TM. Mortality among Navajo uranium miners. *Am J Public Health*. 1995;85(4):535–540. [PubMed: 7702118]
6. Schubauer-Berigan MK, Pinkerton LE, Daniels RD. Radon exposure and mortality among White and American Indian uranium miners: An update of the Colorado Plateau cohort. *Am J Epidemiol* 2009;169:718–730. [PubMed: 19208723]
7. National Institute for Occupational Safety and Health (NIOSH). A recommended standard for occupational exposure to radon progeny in underground mines. U.S. Department of Health and Human Services (DHHS) Public Health Service. DHHS Publication No. 88–101, 1987.
8. National Research Council (NRC), Committee to Assess Health Risks from Exposure to Radon. Health Effects of Exposure to Radon: BEIR VI. Washington, DC: National Academy Press; 1999.
9. Lubin JH, Boice JD Jr, Edling C, et al. Radon and Lung Cancer Risk: a Joint Analysis of 11 Underground Miners Studies. Washington, DC: US Department of Health and Human Services, Public Health Service, National Institutes of Health; 1994. (NIH Publication No. 94–3644).
10. Leuraud K, Schnelzer M, Tomasek L, et al. Radon, smoking and lung cancer risk: results of a joint analysis of three European case-control studies among uranium miners. *Radiat Res* 2011; 176(3):375–87. [PubMed: 21714633]
11. Tomasek L Interaction of radon and smoking among Czech uranium miners. *Radiat Prot Dosimetry*. 2011;145(2–3):238–42. [PubMed: 21471126]
12. Richardson DB, Rage E, Demers PA, et al. Lung cancer and radon: pooled analysis of uranium miners hired in 1960 or later. *Environ Health Perspect*. 2022 May;130(5):57010. doi: 10.1289/EHP10669. Epub 2022 May 23. [PubMed: 35604341]
13. Kelly-Reif K, Bertke SJ, Rage E, et al. Radon and lung cancer in the pooled uranium miners analysis (PUMA): highly exposed early miners and all miners. *Occup Environ Med* 80(7):385–391. doi: 10.1136/oemed-2022-108532

14. Rage E, Richardson DB, Demers PA, et al. PUMA: Pooled Uranium Miners Analysis: Cohort profile. *Occup Environ Med* 2020;77(3):194–200. doi: 10.1136/oemed-2019-105981. [PubMed: 32005674]
15. International Commission on Radiological Protection. Protection against radon-222 at home and at work. A report of a task group of the International Commission on Radiological Protection. *Ann ICRP*. 1993;23(2):1–45.
16. Stram DO, Langholz B, Huberman M, et al. Correcting for exposure measurement error in a reanalysis of lung cancer mortality for the Colorado Plateau uranium miners cohort. *Health Phys* 1999;77(3):265–275. [PubMed: 10456497]
17. Holford TR, Levy DT, McKay LA, et al. , Patterns of birth cohort-specific smoking histories, 1965–2009. *Am J Prev Med* 2013;46(2).
18. Bertke SJ, Kelly-Reif K. Introducing LTASR, a new R package based on the NIOSH Life Table Analysis System. *Occup Environ Med* 2022 Sep 20:oemed-2022-108462. Cause-of-death categories available <https://cran.r-project.org/web/packages/LTASR/vignettes/Minors119.pdf>; accessed 13 April 2025
19. Schubauer-Berigan MK, Hein MJ, Raudabaugh WM, et al. Update of the NIOSH Life Table Analysis System: a person-years analysis program for the Windows computing environment. *Am J Ind Med* 2011; 54:915–24. [PubMed: 22068723]
20. Beaumont JJ, Steenland K, Minton A, et al. A computer program for incidence density sampling of controls in case-control studies nested within occupational cohort studies. *Am J Epidemiol* 1989;129:212–9. [PubMed: 2910063]
21. Schubauer-Berigan MK, Deddens JA, Couch JR, et al. Risk of lung cancer associated with quantitative beryllium exposure metrics within an occupational cohort. *Occup Environ Med* 2011;68:354–60. [PubMed: 21084327]
22. Prautzsch H, Boehm W, Paluszny M. Bézier and B-Spline Techniques. *Mathematics and Visualization*. 2002; Berlin, Heidelberg: Springer Science & Business Media.
23. Szklo M, Nieto J. *Epidemiology: beyond the basics*, second edition. 2007; Burlington, Mass: Jones & Bartlett Publishers.
24. Schubauer-Berigan MK, Daniels RD, Bertke SJ, et al. Cancer mortality through 2005 among a pooled cohort of U.S. nuclear workers exposed to external ionizing radiation. *Radiat Res*, 183:620–631, 2015. [PubMed: 26010709]
25. Hornung RW. Modeling occupational mortality data with applications to US uranium miners. Chapel Hill, NC:University of North Carolina; 1985. Dissertation
26. Hornung RW, Meinhardt TJ. Quantitative risk assessment of lung cancer in US uranium miners. *Health Phys* 1987; 52:417–430. [PubMed: 3032855]
27. Hunter N, Muirhead CR, Tomasek L, et al. Joint analysis of three European nested case-control studies of lung cancer among radon exposed miners: exposure restricted to below 300 WLM. *Health Phys* 2013;104(3):282–92. [PubMed: 23361424]
28. Kreuzer M, Sobotzki C, Schnelzer M, Fenske N. Factors modifying the radon-related lung cancer risk at low exposures and exposure rates among German uranium miners. *Radiat Res* 2018;189(2):165–176. [PubMed: 29215327]
29. Darby SC, Whitley E, Howe GR, et al. Radon and cancers other than lung cancer in underground miners: a collaborative analysis of 11 studies. *J Natl Cancer Inst* 1995;87(5):378–384. [PubMed: 7853419]
30. Fenske N, Deffner V, Schnelzer M, et al. Does radon cause diseases other than lung cancer? Findings on mortality within the German uranium miners cohort study, 1946–2018. *Occup Environ Med Online First*: 23 April 2025. doi: 10.1136/oemed-2024-109923

Key messages:**What is already known on this topic**

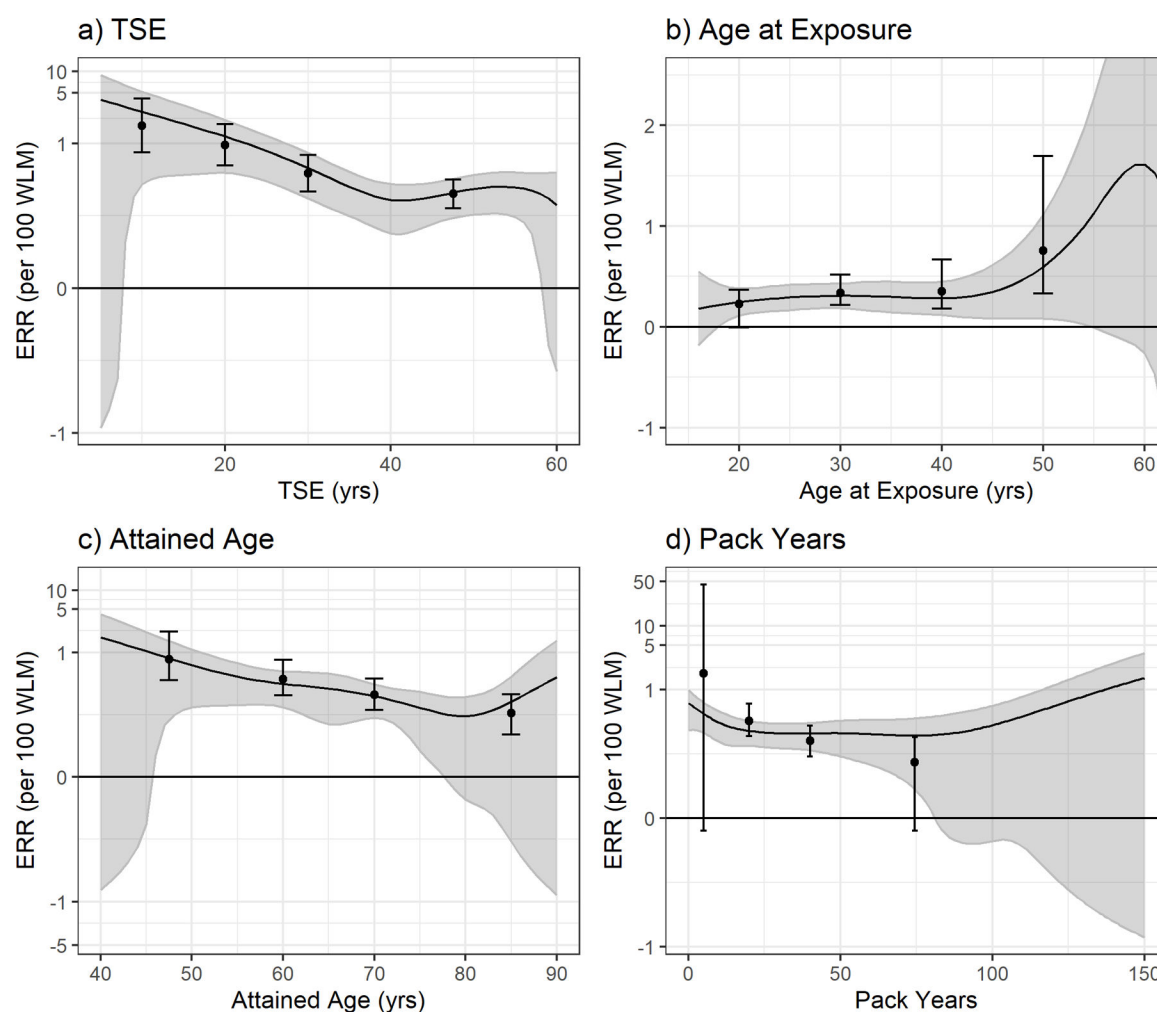
For decades, studies of lung cancer risk among uranium miners, including those on the Colorado Plateau of the southwestern USA, have estimated quantitatively the risk from exposure to radon decay products, demonstrating that excess relative rates per unit exposure decrease with time since exposure and attained age. However, risks of lung and other cancers at ages greater than 70 have been less available. The Colorado Plateau cohort also has near-complete smoking information on the cohort, which is available in few other studies.

What this study adds

This cohort of Colorado Plateau uranium miners exposed mainly in the 1950s-60s has been followed up for cancer mortality for 56 years, making this among the most complete prospective occupational cohorts. We found that high excess absolute and relative rates of lung cancer mortality from exposure to radon decay products persist into old age, and that the joint effects of radon decay products and tobacco smoking remain sub-multiplicative but supra-additive. We also identified a positive association with pancreatic cancer.

How this study might affect research, practice or policy

Findings of persistent excess lung cancer risk may inform compensation policy for U.S. uranium miners. The quantitative estimates of risk at old ages and long time since exposure, as well as among never and light smokers, may inform risk assessment for protective workplace exposure limits.

**Fig. 1.**

Variation in excess relative rate (ERR) per 100 working level months (WLM) for lung cancer mortality by (a) time since exposure (TSE); (b) age at exposure; (c) attained age; (d) cigarette smoking pack-years, in models matched on attained age and year of birth.

Table 1. Description of Colorado Plateau uranium miners cohort

Variable	White miners	American Indian miners ^a	Total
Total (N)	3358	779	4137
Alive on 1 Jan 1960	3254	767	4021
Mean year of birth, SD (interdecile range)	1921, 11.0 (1905, 1936)	1924, 10.6 (1908, 1935)	1922, 11.8 (1906, 1936)
Deceased through 2005	2428 (74.6%)	536 (69.9%)	2964 (73.7%)
Deceased through 2016	2983 (91.7%)	675 (88.0%)	3568 (88.7%)
Mean cumulative RDP exposure, SD (interdecile range)	834.6, 1226 WLM (54, 2054)	686.6, 752 WLM (46.7, 1842)	806.3, 1152 WLM (53, 1999)
Mean radon progeny dose rate, SD (interdecile range)	10.0, 22.9 WL (2.6, 12.3)	11.3, 12.2 WL (4.3, 14.3)	10.2, 21.3 WL (2.9, 12.8)
Last reported smoking category: Never	526 (16.2%)	417 (54.3%)	943 (23.5%)
Former	1199 (36.8%)	108 (14.1%)	1307 (32.5%)
Current < 1 pack per day	329 (10.1%)	210 (27.4%)	539 (13.4%)
Current 1 pack per day	732 (22.5%)	20 (2.6%)	752 (18.7%)
Current >1 pack per day	468 (14.4%)	3 (0.4%)	471 (11.7%)
Missing	0	9 (1.2%)	9 (0.2%)
Cumulative pack-years: 0 ^b	527 (16.2%)	427 (55.7%)	954 (23.7%)
>0 to <10	254 (7.8%)	270 (35.2%)	524 (13.0%)
10 to <20	322 (9.9%)	47 (6.1%)	369 (9.2%)
20 to <30	432 (13.3%)	10 (1.3%)	442 (11.0%)
30 to <40	460 (14.1%)	11 (1.4%)	471 (11.7%)
40 to <50	496 (15.2%)	2 (0.3%)	498 (12.4%)
50 to <60	296 (9.1%)	0	296 (7.4%)
60+	467 (14.4%)	0	467 (11.6%)
Mean cumulative pack-years, SD (interdecile range)	33.8, 27.6 (0, 68.5)	3.1, 6.3 (0, 9.0)	29.2, 27.8 (0, 64.0)

Abbreviations: RDP, radon decay products; SD, standard deviation

^aIncludes 2 Asian and 3 Black miners.

^bIncludes 1 White miner and 10 American Indian miners missing information on smoking status or quantity

Table 2.

Comparison of parameter estimates for excess relative rate (ERR) per 100 WLM of lung cancer mortality from an exposure-age-concentration model to those reported in BEIR VI⁸ and in the pooled uranium miners analysis (PUMA).¹³

Parameter (95% CI)	Colorado Plateau cohort, present study	BEIR VI Table 3-3, "Updated data"	PUMA full cohort	PUMA full cohort, no employment duration adjustment	PUMA, excluding Colorado Plateau
β per 100 WLM ^a	4.04 (-2.81, 10.9)	7.68	4.68 (2.8, 6.96)	3.42 (2.05, 4.82)	3.82 (2.14, 5.73)
Time-since-exposure windows					
θ_{5-14} yrs	1	1	1	1	1
θ_{15-24} yrs	0.87 (0.33, 1.41)	0.78	0.77 (0.56, 1.05)	0.63 (0.48, 0.84)	0.80 (0.57, 1.15)
θ_{25-34} yrs	0.49 (0.10, 0.88)	0.51 ^b	0.54 (0.38, 0.76)	0.44 (0.32, 0.60)	0.54 (0.37, 0.80)
θ_{35+} yrs	0.36 (0.03, 0.70)		0.39 (0.26, 0.58)	0.30 (0.21, 0.43)	0.38 (0.25, 0.59)
Attained age					
$\phi_{<55}$	1	1	1	1	1
ϕ_{55-64}	0.61 (-0.57, 1.79)	0.57	0.55 (0.38, 0.82)	0.61 (0.44, 0.83)	0.52 (0.35, 0.78)
ϕ_{65-74}	0.30 (-0.27, 0.87)	0.29	0.38 (0.25, 0.57)	0.39 (0.27, 0.55)	0.37 (0.24, 0.57)
ϕ_{75+}	0.16 (-0.16, 0.49)	0.09	0.40 (0.24, 0.66)	0.39 (0.25, 0.60)	0.40 (0.24, 0.68)
Exposure rate					
$\gamma_{<10}$ (Colorado) or $\gamma_{<5}$ (BEIR VI, PUMA)	1	1	1	1	1
$\gamma_{\geq 10}$ (Colorado) or $\gamma_{\geq 5}$ (BEIR VI, PUMA)	0.53 (0.42, 0.63)	0.26 ^c	0.25 ^d	0.31 ^d	0.28 ^d

Abbreviations: BEIR VI, Biological Effects of Ionizing Radiation, 6th committee; PUMA, Pooled Uranium Miners Analysis; WL, working level; WLM, working level month

^aRepresents ERR/100 WLM at 5–14 years since exposure, attained age <55, and exposure rate <10 WL (for Colorado Plateau cohort) and <5 WL, based on the mean of $\gamma_{<0.5}$, $\gamma_{0.5-1.0}$, $\gamma_{1.0-3.0}$, $\gamma_{3.0-5.0}$ estimates (for BEIR VI and PUMA data).

^bValue is for category 25+ years since exposure

^cCoefficient was derived by dividing the mean of the γ_{5-15} and γ_{15+} estimates by the mean of estimates for $\gamma_{<0.5}$, $\gamma_{0.5-1.0}$, $\gamma_{1.0-5.0}$

^dCoefficient was derived by dividing the γ_{75+} estimate by the mean of estimates for $\gamma_{<0.5}$, $\gamma_{0.5-1.0}$, $\gamma_{1.0-5.0}$

Table 3.

Parameter estimates for attained age and smoking effect modification for lung cancer mortality, using models from Table 5 of Hornung et al. 1998,⁴ WLM/smoking/age interaction.

Parameter ^a	Estimate	Std Err	95% Confidence Limits (Wald-based)		-2LL	Diff ^b	df	p-value
Main effects model: (1 + β ₁ WLM/100)(1 + β ₂ Pack-years)exp(β ₃ TSLE + β ₄ Dose Rate>10WL)								
WLM/100	0.308	0.0658	0.178	0.437	7121.7			
Pack-years	0.062	0.0091	0.044	0.080				
Radon-attained age interaction:								
WLM/100 age <60	0.819	0.314	0.202	1.44	7104.5	17.2	2	0.0002
WLM/100 age 60-<70	0.235	0.0816	0.0744	0.395				
WLM/100 age ≥70	0.147	0.0453	0.0577	0.236				
Pack-years	0.0616	0.0090	0.0439	0.0794				
Radon/age & smoking/age interactions:								
WLM/100 age <60	0.828	0.318	0.203	1.45	7104	0.5	2	0.779
WLM/100 age 60-<70	0.235	0.0816	0.0744	0.395				
WLM/100 age ≥70	0.147	0.0454	0.0579	0.236				
Pack-years age <60	0.051	0.0157	0.0201	0.0819				
Pack-years age 60-<70	0.0637	0.0168	0.0307	0.0968				
Pack-years age ≥70	0.0666	0.0144	0.0383	0.0950				
Interaction model: (1 + β ₁ WLM/100)(1 + β ₂ Pack-years)(1 + β ₃ WLM/100×Pack-years)exp(β ₄ TSLE + β ₅ Dose Rate>10 WL)								
Radon/smoking interaction:								
WLM/100	0.332	0.0709	0.1923	0.4709	7117.6	4.1	1	0.0429
Pack-years	0.0681	0.0100	0.0485	0.0877				
WLM/100×Pack-years	-0.0001	0.0000	-0.0002	0.0000				
Radon/smoking/age								
WLM/100 age <60	0.857	0.339	0.192	1.52	7100.5	3.5	3	0.321
WLM/100 age 60–70	0.249	0.0891	0.0739	0.424				
WLM/100 age ≥70	0.182	0.0591	0.0662	0.298				
Pack-years age <60	0.0563	0.0182	0.0205	0.0920				
Pack-years age 60-<70	0.0680	0.0181	0.0326	0.104				
Pack-years age ≥70	0.0765	0.0170	0.0432	0.110				
WLM*Pack-years (age <60)	-0.0001	0.0001	-0.0003	0.0001				
WLM*Pack-years (age 60-<70)	-0.0001	0.0001	-0.0002	0.0000				
Pack-years age ≥70	-0.0002	0.0001	-0.0003	0.0000				

Abbreviations: TSLE, time since last exposure; WL, working level; WLM, working level month

^aAll models adjust for time since last exposure and dose rate, as in Table 5 of Hornung et al. (1998)⁴

^bDifference in model deviance (-2 log likelihood) in nested models interpreted as χ^2 test with degrees of freedom equal to number of terms added to model

Table 4.

Parameter estimates for linear excess relative rate (ERR) per 100 WLM (maximum likelihood-based optimal lag) for cancer mortality at sites of a priori interest.

Outcome	NIOSH LTAS categories	N	ERR/100 WLM (10 yr lag) ^a	Best Lag (years)	ERR/100 WLM (best lag)
All Cancer excl lung, respiratory, ill-defined	4–15, 17, 19–35, 37–40	362	0 (-0.01, 0.02)	30	0 (-0.01, 0.02)
Extrathoracic airways	5–7, 15, 18	18	-0.01 (-0.19, 0.06)	39	0.02 (-0.5, 0.29)
All digestive cancers	8–14	152	0.01 (-0.01, 0.03)	0	0.01 (-0.01, 0.04)
Oesophagus	8	15	-0.06 (-0.13, -0.03)	0	-0.06 (-0.13, -0.03)
Stomach	9	33	0 (-0.17, 0.07)	32	0 (-0.36, 0.14)
Intestine	10	45	0.02 (-0.02, 0.11)	20	0.02 (-0.32, 0.13)
Liver and gall bladder	12	17	-0.01 (-0.05, 0.27)	7	0 (-0.42, 0.28)
Pancreas	13	31	0.06 (-0.41, 0.24)	2	0.07 (0.01, 0.3)
Prostate	24	67	0.02 (-0.2, 0.08)	40	0.02 (-0.03, 0.12)
Skin	29–30	20	-0.01 (-0.3, 0.11)	0	-0.02 (-0.04, 0.07)
Melanoma	29	13	-0.01 (-0.3, 0.12)	0	-0.02 (-0.24, 0.09)
Lymphatic & Hemopoietic	37–40	63	-0.02 (-0.09, 0.01)	29	-0.02 (-0.1, 0.01)
Non-Hodgkin lymphoma	38	23	0.01 (-0.02, 0.12)	31	-0.01 (-0.23, 0.08)
Multiple myeloma	39	18	-0.05 (-0.16, 0)	0	-0.05 (-0.16, 0)
Leukaemia	40	20	-0.07 (-0.08, -0.04)	0	-0.07 (-0.13, -0.05)
Lung	16	695	0.27 (0.2, 0.38)	5	0.31 (0.22, 0.45)

Abbreviations: ERR, excess relative rate; LTAS, life table analysis system; NIOSH, National Institute for Occupational Safety and Health; WLM, working level month

^a All models matched on attained age and birth cohort