



## Original Contribution

# Radon Exposure and Mortality Among White and American Indian Uranium Miners: An Update of the Colorado Plateau Cohort

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Studies of uranium miners on the US Colorado Plateau have identified associations between exposure to radon progeny and risk of lung cancer. This study added 15 years of mortality follow-up for the 4,137 miners (primarily white or American Indian) in the Colorado Plateau cohort. The cohort experienced 209 new lung cancer deaths. For white miners, the standardized mortality ratio for lung cancer compared with the regional population was 3.99 (95% confidence interval: 3.43, 4.62) for the period 1991–2005. For American Indian miners, the lung cancer standardized mortality ratio was 3.27 (95% confidence interval: 2.19, 4.73). These standardized mortality ratios have not declined substantially since the 1980s. Internally standardized rate ratios by radon exposure category over the entire follow-up period are similar to those based on earlier follow-up, although estimates within smoking categories demonstrated improved precision. The apparent interaction between radon and smoking in causing lung cancer remains submultiplicative but greater than additive. Mortality rates from silicosis remain highly elevated in the cohort. Elevated mortality rates were observed from interstitial pulmonary fibrosis, multiple myeloma, and non-Hodgkin lymphoma. Significant trends were observed with increased radon exposure in silicosis and pulmonary fibrosis mortality and in the incidence of diabetes-related end-stage renal disease among white miners.

lung neoplasms; lymphoma, non-Hodgkin; multiple myeloma; pulmonary fibrosis; radiation, ionizing; silicosis

Abbreviations: CI, confidence interval; COPD, chronic obstructive pulmonary disease; ESRD, end-stage renal disease; WLM, working level months.

The carcinogenicity of radon and its progeny has been established conclusively by studies of miners exposed during the extraction of uranium from underground mines during the 1950s and 1960s (1, 2). One of the most influential is the cohort of US miners from the Colorado Plateau (3–5). This prospective study enrolled several thousand primarily white and American Indian uranium miners in the 1950s, evaluating mine work history data and smoking through questionnaires administered from the 1960s to the 1980s, combined with radon measurements in the mines. This permitted the observation of an exposure-response relation for radon and lung cancer, as well as the form of interaction between smoking and radon in causing lung cancer. Studies have found an inverse dose-rate effect and variability of the rate ratio with increasing attained age and time since last exposure (6). These data have been useful for quantitative

risk assessment (2) and mechanistic modeling of the effect of radon on lung cancer risk (7). At the last reported follow-up (December 31, 1990), about half the cohort remained alive (4, 5).

The purposes of the present study were 1) to evaluate the association between radon (and smoking-radon interactions) and lung cancer among miners with 15 years of additional mortality follow-up, and 2) to evaluate the risks of certain other diseases. Stomach and kidney cancers, as well as non-malignant diseases of the kidney (including end-stage renal disease (ESRD)), are of interest given the likely exposure of these organs to uranium through clearance of inhaled uranium or accidental ingestion during mining. We also evaluated nonmalignant lung diseases found to be elevated in previous analyses. Lymphohematopoietic malignancies, specifically chronic lymphocytic leukemia, non-Hodgkin

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lymphoma, and multiple myeloma, were of interest for several reasons: Thoracic lymph nodes could receive high doses of radon progeny from inhaled exposure, the diseases are expected to have long latencies, and the incidence of chronic lymphocytic leukemia has been found to be elevated in other studies of uranium miners (8, 9).

## MATERIALS AND METHODS

This study was conducted under the review and approval of the Human Subjects Review Board of the National Institute for Occupational Safety and Health.

### Cohort follow-up

The cohort consists of 4,137 men who worked in a uranium mine for at least 1 month and agreed to at least 1 health screening between January 1, 1950, and December 31, 1960 (5). Follow-up through 1990 is as described in previous studies (4, 5). Additional follow-up through December 31, 2005, was obtained by linking workers to the National Death Index and the Social Security Administration's mortality file by name, Social Security number, and date of birth. Manual review of each likely but imperfect match was carried out. Miners not found in these databases were presumed to be alive. Fourteen miners (0.34%) were lost to follow-up before 1979 (when the National Death Index began). No cause of death was obtained for 22 miners (<1% of decedents).

To evaluate the incidence of end-stage renal disease, we made linkage to the Renal Management Information System maintained by the US Centers for Medicare and Medicaid Services. This database covers all Medicare beneficiaries with ESRD during the period 1977–2004 and includes about 93% of US ESRD cases (10). Workers were linked to this database by Social Security number, name, and date of birth.

### Exposure assessment

As in previous studies (5, 6, 11), radon exposures relied on estimates from the early 1970s (12). Exposure levels to radon progeny from both uranium mining and other hard rock mining were expressed by using the historical unit, working level month (WLM), equivalent to a potential alpha energy exposure of  $3.54 \text{ mJ} \cdot \text{hour} \cdot \text{m}^{-3}$  (13). Available data consisted of the dates on which each miner's uranium mine exposure to radon progeny reached 1 of 9 cumulative exposure levels (0, 60, 120, 240, 360, 600, 840, 1,800, and 3,720 WLM). Daily rates of exposure were interpolated between these dates for each worker. Exposure to radon progeny from previous non-uranium mining was included and was assigned on the day before the worker began uranium mine employment. We included 11 previously excluded miners (5) whose WLM exposures we located. Information on cigarette smoking was collected in surveys from the 1950s, 1960s, and 1985 (5). For the present analysis, we used the smoking status determined at the time of the 1985 survey (or, for nonrespondents, their status as of the previous surveys) and the same classifications as in previous cohort studies (5).

## Statistical methods

Analyses were conducted by using a modified life table analysis program, LTAS.NET (14). For most analyses, person-years for each worker began on the later of January 1, 1960 (when rates began), or the date of first medical screening and ended on the earlier of the date of death, date of loss to follow-up, or December 31, 2005. For the ESRD analysis, person-years began on January 1, 1977 (when rates began). Cohort members who died or were lost to follow-up before this date ( $n = 933$ ) were excluded from this analysis. As in previous analyses (4, 5), expected mortality rates were calculated by using, for white miners, the combined rates for whites in Arizona, Colorado, New Mexico, and Utah, and for American Indian miners, the combined rates for all races other than white in Arizona and New Mexico.

Mortality rates for underlying causes of death used 1960–2005 data obtained from the National Center for Health Statistics (15). Deaths were classified into 1 of 119 cause-of-death categories, called “minors” (15). Additional rate files for ESRD incidence (10) and pulmonary fibrosis mortality (both based on US rates) were also created (Appendix 1). Person-years and deaths were stratified on age, race, and calendar year (the standardizing variables) and on cumulative radon exposure (lagged 5 years for lung cancer, silicosis, and pulmonary fibrosis and 10 years for non-Hodgkin lymphoma and multiple myeloma) and smoking category. Indirectly standardized mortality ratios and standardized incidence ratios were calculated as the number of observed deaths for each minor divided by the number expected on the basis of the age-, calendar year-, and race-specific combined state rates for males. Two-sided 95% confidence intervals for each standardized mortality ratio and standardized incidence ratio were calculated by using either the exact Poisson distribution of the number of observed ( $N$ ) deaths or incident ESRD cases for  $N < 5$  or Byar's approximation of the Poisson distribution of  $N$  for  $N \geq 5$  (16).

For some analyses, internal comparisons were done by using directly standardized rate ratios. These ratios in LTAS.NET are calculated as the ratio of standardized rates for “exposed” groups to that for a baseline (e.g., unexposed) category, using the entire cohort's age-, race-, and calendar year-specific person-years as standardizing weights. In this analysis, miners exposed to higher radon levels (120–<400 WLM, 400–<1,000 WLM, and  $\geq 1,000$  WLM) were compared with those exposed to less than 120 WLM; 95% confidence intervals on the standardized rate ratios and 2-sided tests of linear trend in directly standardized rates (cases per WLM  $\cdot$  person-year) were conducted as described elsewhere (17).

## RESULTS

The Colorado Plateau cohort consists of 3,358 white miners and 779 miners of another race, of whom 99% were American Indian (Table 1). Approximately 97% of white and 98% of American Indian miners were alive in 1960, the start of follow-up; 84% of white miners and 45% of American Indian miners were current or former smokers. Among current smokers in the 2 racial groups, whites (78%)

**Table 1.** Characteristics of the Colorado Plateau Uranium Miners Cohort (All Male) by Race, Western United States, 1950–1960

Variable <sup>a</sup>	Race				Total	
	White		American Indian <sup>b</sup>		No.	%
	No.	%	No.	%		
Total, no.	3,358		779		4,137	
Alive on January 1, 1960	3,255		767		4,022	
Deceased through December 31, 1990	1,602	49.2	306	39.9	1,908	47.4
Deceased through December 31, 2005	2,428	74.6	536	69.9	2,964	73.7
Median year of birth (interquartile interval)	1922 (1912–1931)		1926 (1918–1932)		1923 (1913–1931)	
Total person-years at risk	95,867		24,570		120,437	
Average length of follow-up, years	29.5		32.0		29.9	
Smoking						
Never smoked	526	16.2	417	54.4	943	23.4
Former smoker	1,199	36.8	108	14.1	1,307	32.5
Current smoker						
<1 pack/day	329	10.1	210	27.4	539	13.4
1 pack/day	733	22.5	20	2.6	753	18.7
>1 pack/day	468	14.4	3	0.4	471	11.7
Unknown	0		9	1.2	9	0.2
Cumulative radon exposure, WLM						
From uranium mining						
Mean (SD)	806 (1,130)		742 (840)		794 (1,090)	
Median (interdecile interval)	426 (44.1–2,070)		392 (43.7–2,010)		422 (44.1–2,050)	
Including hard rock mines						
Mean (SD)	824 (1,140)		742 (840)		808 (1,090)	
Median (interdecile interval)	439 (55.0–2,080)		392 (43.7–2,030)		434 (53.2–2,060)	

Abbreviations: SD, standard deviation; WLM, working level months.

<sup>a</sup> All percentages and statistics except "Total, no." are based on workers alive on January 1, 1960.

<sup>b</sup> Includes 2 Asian-American and 3 African-American miners.

were much more likely than American Indians (10%) to smoke at least 1 pack per day.

### Overall rates

A total of 2,964 deaths and 120,437 person-years occurred through 2005, representing an accrual of 1,056 deaths and 23,292 person-years since the last follow-up. Approximately 90% of total person-time accrued after employment ceased by the late 1960s. The all-cause mortality rate was elevated by about 60% for the entire study period among white miners but was not elevated for American Indian miners (Table 2). For the most recent follow-up period (1991–2005), the all-cause mortality rate for the latter group was 29% higher than expected. The standardized mortality ratio for all cancers combined was significantly elevated for both groups.

Among the causes of death of a priori interest, lung cancer was elevated from 3- to 5-fold both overall and during the most recent follow-up period (Table 2). By the 10-year calendar period (Figure 1), standardized mortality ratios for white miners changed little since 1980–1989. Lung cancer standardized mortality ratios for American Indian miners increased over the period 1960–1999 and decreased slightly in the period 2000–2005. American Indian miners had much lower overall lung cancer mortality rates than did white miners (standardized rate ratio = 0.44, 95% confidence interval (CI): 0.33, 0.57). The standardized rate ratios for American Indian compared with white miners were 1.04 (95% CI: 0.65, 1.65) among never smokers, 0.73 (95% CI: 0.41, 1.33) among former smokers, and 0.51 (95% CI: 0.27, 0.96) among the lightest smokers.

The stomach cancer standardized mortality ratio was elevated among American Indian, but not white, miners

(Table 2). Kidney cancer rates were not significantly elevated among either group. Leukemia risk was not elevated; 2 of 14 leukemias of known subtype were chronic lymphocytic leukemia. The non-Hodgkin lymphoma and multiple myeloma mortality rates were approximately doubled among white miners in the most recent follow-up period. The chronic obstructive pulmonary disease (COPD) rate was doubled among white miners compared with the rate for the regional population (Table 2), although the elevations were restricted to current or former smokers (combined standardized mortality ratio = 2.50, 95% CI: 2.16, 2.89). Among American Indian miners, COPD was not elevated in any smoking group. Standardized mortality ratios for silicosis and other pneumoconiosis (excluding asbestosis, which was not elevated) were highly elevated among all miners. The latter category includes unspecified pneumoconioses ( $n = 11$ ). Tuberculosis standardized mortality ratios were also elevated among the miners.

The mortality rates of chronic or unspecified nephritis or chronic renal failure were not elevated (Table 2). Among white miners, the standardized mortality ratio of acute glomerulonephritis and acute renal failure was elevated, particularly within the latest follow-up period. The overall standardized incidence ratios for ESRD related to diabetes mellitus and nonsystemic ESRD were 1.4 (95% CI: 0.84, 2.1) and 1.4 (95% CI: 0.45, 3.2), respectively. The ESRD standardized incidence ratio related to diabetes among American Indian, but not white, miners was elevated (Table 3). Standardized incidence ratios for nonsystemic ESRD were similar between the 2 groups.

Other causes of death, not of a priori interest, showed elevated rates (Appendix Table 1). Among white miners, standardized mortality ratios were elevated for all causes combined (excluding lung cancer, COPD, and pneumoconioses) and all cancers combined other than lung, nonmalignant diseases of the blood and blood-forming organs, and pneumonia. The standardized mortality ratios among all miners combined were 2.73 (95% CI: 1.00, 5.93) for nonmelanoma skin cancer, 2.55 (95% CI: 1.10, 5.03) for "benign and unspecified nature" neoplasms other than nervous system, and 1.63 (95% CI: 1.23, 2.11) for malignant neoplasms of other and unspecified sites. The mortality rates of conductive disorders of the heart and "other heart diseases" were elevated for both white and American Indian miners. Among white miners, the mortality rates were elevated from several injury categories; however, these excesses were restricted to follow-up before 1990 (data not shown).

The mortality rate for "other respiratory diseases" was highly elevated among the miners (Appendix Table 1). Among the 69 deaths in this category, the most common cause was interstitial pulmonary fibrosis ( $n = 30$ ), followed by unclassifiable diseases of the lung ( $n = 20$ ). Compared with the US population, the standardized mortality ratios for interstitial pulmonary fibrosis were highly elevated for both white and American Indian miners (Table 2). Pulmonary fibrosis standardized mortality ratios by smoking category were 4.1 (95% CI: 1.7, 8.5) for never smokers, 4.8 (95% CI: 2.5, 8.4) for former smokers, 3.8 (95% CI: 0.79, 11) for smokers of <1 pack per day, 6.6 (95% CI: 2.1, 15) for

smokers of 1 pack per day, and 4.6 (95% CI: 0.55, 17) for smokers of >1 pack per day.

### Associations with radon exposure

For all miners combined and for white miners, lung cancer mortality rates compared with those of the regional population were significantly elevated at each exposure category above 120 WLM (Table 4). Among American Indian miners, significantly elevated rates were observed in the 2 highest exposure categories. In internal analyses, standardized rate ratios were elevated for each exposure category compared with miners exposed to less than 120 WLM, and standardized rate ratios increased monotonically with WLM exposure category. A highly significant positive linear trend in standardized rate per WLM • person-year was observed for both white and American Indian miners ( $P < 0.0001$ ).

The 2 chronic lymphocytic leukemia deaths occurred in the intermediate exposure groups. No trends in standardized rates with increasing exposure were observed for multiple myeloma or non-Hodgkin lymphoma. All silicosis deaths were observed among miners exposed to 120 or more WLM; standardized mortality ratios increased monotonically above this level. A positive trend in the pulmonary fibrosis death rate with increasing dose was observed. The incidence of ESRD due to diabetes mellitus showed a positive exposure-response trend for white miners ( $P = 0.033$ ) but not for American Indian miners ( $P > 0.5$ ). All nonsystemic ESRD cases ( $n = 6$ ) occurred among miners exposed to 120 WLM or greater; these miners experienced nonsignificantly elevated rates compared with the rates for the US population (standardized incidence ratio = 1.8, 95% CI: 0.66, 4.1).

Nearly half ( $n = 34$ ) of the 76 lung cancer deaths among never smokers occurred among American Indian miners. Lung cancer mortality rates showed strong heterogeneity by smoking and WLM categories (Table 5). Within each smoking category, standardized mortality ratios increased directly with WLM exposure level. Standardized rate ratios increased monotonically with WLM exposures for most smoking categories (Table 5). Tests of trend were highly significant for never smokers, former smokers, and those who smoke at least 1 pack per day and were of borderline significance for miners who smoke less than 1 pack per day. The slope (in standardized rate per WLM • person-year) was highest for those who smoke at least 1 pack per day and former smokers and was lowest for light smokers and never smokers; however, the standardized rate ratios for each WLM category above the baseline decreased nearly uniformly with increasing smoking frequency.

### DISCUSSION

More than 30 years after major uranium mining operations ceased in the late 1960s on the US Colorado Plateau, lung cancer remains substantially elevated among former miners. From 1991 to 2005, lung cancer caused 1 in 5 deaths among the miners—similar to previous years of follow-up.

**Table 2.** Standardized Mortality Ratios for Causes of Death of a Priori Interest Among Colorado Plateau Uranium Miners, 1960–2005 and 1991–2005

Cause of Death	Minor Cause-of-Death Category <sup>a,b</sup>	Whites			American Indians		
		No.	SMR <sup>c</sup>	95% Confidence Interval	No.	SMR <sup>c</sup>	95% Confidence Interval
All causes	1–119						
1960–2005		2,428	1.58	1.51, 1.64	536	1.03	0.95, 1.12
1991–2005		826	1.47	1.37, 1.58	230	1.29	1.13, 1.47
All cancers	4–40						
1960–2005		844	2.38	2.22, 2.55	117	1.41	1.16, 1.68
1991–2005		301	2.01	1.79, 2.25	61	1.62	1.24, 2.08
Lung cancer	16						
1960–2005		549	4.96	4.55, 5.39	63	3.18	2.45, 4.07
1991–2005		180	3.99	3.43, 4.62	29	3.27	2.19, 4.73
Stomach cancer	9						
1960–2005		17	1.33	0.78, 2.13	13	1.92	1.02, 3.28
1991–2005		4	1.06	0.29, 2.70	6	2.41	0.88, 5.49
Kidney cancer	26						
1960–2005		7	0.76	0.30, 1.56	5	1.65	0.54, 3.85
1991–2005		5	1.29	0.42, 3.21	4	2.60	0.71, 6.64
Lymphohematopoietic cancers	37–40						
1960–2005		51	1.38	1.03, 1.82	3	0.41	0.08, 1.20
1991–2005		25	1.57	1.02, 2.34	0	0	
Non-Hodgkin lymphoma	38						
1960–2005		19	1.40	0.84, 2.19	3	1.32	0.27, 3.85
1991–2005		12	1.86	0.96, 3.31	0	0	
Multiple myeloma	39						
1960–2005		13	1.97	1.05, 3.37	0	0	
1991–2005		8	2.52	1.09, 5.13	0	0	
All leukemia	40						
1960–2005		17	1.17	0.68, 1.88	0	0	
1991–2005		4	0.66	0.18, 1.68	0	0	

Table continues

This represents nearly quadruple the expected age- and calendar year-adjusted rate of lung cancer for white miners and more than triple the expected rate for American Indian miners. There is little evidence that radon-related lung cancer standardized mortality ratios have substantially decreased over the 15-year period since the last follow-up.

Overall lung cancer rates were much lower among American Indian than white miners; however, adjustment for smoking largely accounted for this difference. In the general population of Arizona, Colorado, New Mexico, and Utah, whites have age-adjusted lung cancer mortality rates from 2.5- to 3-fold higher than do American Indians and Asian Americans combined (18), presumably because of higher past smoking rates among whites. Considering data for white and American Indian miners together (as in Table 5), the radon-associated rate ratios are very similar to

those estimated previously among white miners (5). The number of lung cancer deaths among never smokers has tripled since the last reported follow-up (11), with all but 2 of 76 lung cancers among never smoking white and American Indian miners occurring among those exposed to more than 120 WLM.

This is among the few uranium miner cohorts with near-complete smoking information; thus, it provides key information regarding the radon-smoking interaction in producing lung cancer. The increase in absolute standardized rates (per WLM • person-year) appeared to be higher for heavier smokers and former smokers than for light smokers and never smokers, which suggests a superadditive relation between smoking and WLM. However, the rate ratios at a given exposure level were generally highest for never smokers and light smokers compared with heavier

Table 2. Continued

Cause of Death	Minor Cause-of-Death Category <sup>a,b</sup>	Whites			American Indians		
		No.	SMR <sup>c</sup>	95% Confidence Interval	No.	SMR <sup>c</sup>	95% Confidence Interval
COPD	66						
1960–2005		197	2.07	1.79, 2.38	9	0.78	0.36, 1.49
1991–2005		78	1.85	1.47, 2.32	4	0.66	0.18, 1.70
Silicosis	69						
1960–2005		37	42.5	29.9, 58.6	6	24.2	8.89, 52.7
1991–2005		8	64.7	27.9, 132	3	33.3	6.87, 97.4
Other and unspecified pneumoconiosis, excluding asbestosis	70						
1960–2005		21	27.8	17.2, 42.6	5	31.6	10.3, 73.7
1991–2005		9	37.1	16.9, 72.4	2	28.3	3.43, 102
Pulmonary fibrosis							
1960–2005		20	3.95	2.41, 6.11	10	8.70	4.17, 16.0
1991–2005		11	3.56	1.77, 6.51	7	10.0	4.00, 21.4
Tuberculosis	1, 2						
1960–2005		13	3.44	1.83, 5.99	14	2.40	1.31, 4.04
1991–2005		0	0		2	2.39	0.29, 8.62
Acute glomerulonephritis and acute renal failure	81						
1960–2005		6	3.17	1.16, 6.89	0	0	
1991–2005		4	4.28	1.17, 10.9	0	0	
Chronic and unspecified nephritis and renal failure	82						
1960–2005		14	1.20	0.65, 2.01	4	0.56	0.15, 1.44
1991–2005		5	0.82	0.27, 2.04	1	0.31	0.01, 1.73

Abbreviations: COPD, chronic obstructive pulmonary disease; SMR, standardized mortality ratio.

<sup>a</sup> For all causes of death except pulmonary fibrosis, the minor cause-of-death category was from National Institute for Occupational Safety and Health Life Table 119-cause rate file (15).

<sup>b</sup> For pulmonary fibrosis, the minor cause-of-death category was based on the special rate file created for the US population of (for white miners) whites and (for American Indian miners) American Indians, Asians, and Pacific Islanders (combined).

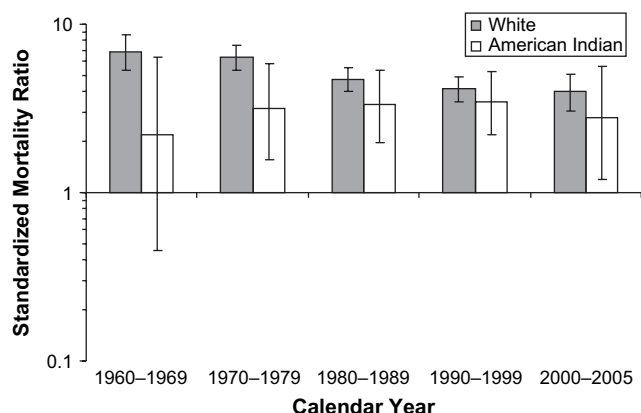
<sup>c</sup> Based on (for white miners) the combined Arizona, Colorado, New Mexico, and Utah rates for white men and (for American Indian miners) the combined Arizona and New Mexico rates for men of all other races, adjusted for age, calendar year, and race.

smokers, suggesting a submultiplicative interaction, as found previously in this cohort (6).

The increased risk of non-Hodgkin lymphoma among white miners, particularly during 1991–2005, extends findings of earlier follow-up, in which the rate was elevated between 1980 and 1990 (5). Multiple myeloma rate elevation was seen for the first time here, with 8 of 13 deaths occurring in the most recent follow-up period. Although neither non-Hodgkin lymphoma nor multiple myeloma was associated with WLM exposure, this may be a poor surrogate for uranium dust exposure, a hypothesized etiologic agent for these 2 diseases (19, 20). We did not see an association between radon progeny and chronic lymphocytic leukemia as observed recently among Czech miners

(9). Our study had low power for lymphatic and hematopoietic cancers because of the lack of cancer incidence data and small cohort size.

Certain nonmalignant diseases were also elevated in the Colorado Plateau cohort. Silicosis and other pneumoconiosis (besides asbestosis) remained highly elevated among all miners. Tuberculosis rates remained elevated among American Indian miners and are likely related to heavy silica exposures. The elevated rate of COPD among white miners appears to be explained by cohort smoking patterns. Archer et al. (21) describe chronic diffuse interstitial lung fibrosis among former uranium miners. The elevated rate of interstitial pulmonary fibrosis that we found corroborates findings from that case series. This elevation showed a positive



**Figure 1.** Standardized mortality ratios for lung cancer by calendar period among Colorado Plateau uranium miners, 1960–2005. Cohort standardized mortality ratios are compared with those for the regional population, and error bars indicate 95% confidence intervals.

trend with radon exposure. The authors (21) attributed the case series findings to radon progeny, as they estimated that most were exposed to more than 1,000 WLM. In our study, pulmonary fibrosis deaths occurred at all radon exposure levels. Rate elevation was not associated with smoking category, which suggests an occupational etiology. Since the early 1920s, acute irradiation of the lung has been observed to cause pulmonary fibrosis in radiotherapy patients (22). More recently, lung fibrosis in radiotherapy patients was correlated with an increase in fractionated total dose greater than 30–35 Gy (23, 24), and the lung volume irradiated is associated with probability of fibrosis (25). This dose threshold is roughly equivalent to 400 WLM, applying a lung equivalent dose coefficient for mining atmospheres of 75 mSv per WLM (26).

Miners exposed to more than 120 WLM had a near 2-fold elevation in the incidence rate of nonsystemic end-stage

renal disease, compared with the rate for the US population. Although this category's components, glomerulonephritis and interstitial nephritis, may plausibly be related to uranium exposure, the estimate had wide confidence intervals. Mortality from chronic renal failure was not significantly elevated, compared with the regional population.

The Colorado Plateau cohort has several limitations. Smoking data have not been updated since the mid-1980s. However, the differences in standardized mortality ratios observed by last reported smoking status are consistent with the expected association of lung cancer and smoking, suggesting that this limitation had minimal impact. Comparison population mortality rates (excluding pulmonary fibrosis) for American Indian miners were derived from the nonwhite population of Arizona and New Mexico. As described in previous analyses of this cohort (4), this likely led to an underestimation of the standardized mortality ratios, because of the very low background lung cancer rate among American Indians in the southwestern United States. The incidence rate for ESRD is based on the entire US population. For American Indian miners, this may have led to an overestimate of the standardized incidence ratio for diabetes-related ESRD. The Navajo population (to which most American Indian Colorado Plateau miners belong) has exhibited a near 10-fold elevation in rates of diabetes-related ESRD compared with whites (27). The comparison population that we used for ESRD (predominantly African American) may experience lower diabetes-related ESRD than the American Indian population in the southwestern United States (28, 29). The excess incidence of nonsystemic ESRD observed among white miners was likely not caused by regional differences in rates, as the combined rates in the southwestern states of Arizona, Colorado, Nevada, New Mexico, Utah, and Wyoming are lower than those in the combined US population (29).

Potential confounding exposures include silica, gamma radiation, and diesel exhaust. Death certificate diagnoses may be particularly unreliable in differentiating pulmonary fibrosis from pneumoconioses and obstructive lung diseases

**Table 3.** Standardized Incidence Ratios for Reported End-Stage Renal Disease Associated With Systemic and Nonsystemic Diseases Among Colorado Plateau Uranium Miners, 1977–2004

Cause of Death	Whites			American Indians		
	No.	SIR	95% Confidence Interval	No.	SIR	95% Confidence Interval
Systemic end-stage renal disease	9	0.54	0.25, 1.0	16	1.1	0.64, 1.8
Diabetes mellitus	5	0.65	0.21, 1.5	15	2.2	1.3, 3.7
Hypertension	4	0.60	0.16, 1.5	0	0	
Hereditary congenital nephropathy	0	0		1	35	0.89, 190
Nonsystemic end-stage renal disease <sup>a</sup>	4	1.4	0.37, 3.5	2	1.4	0.17, 5.2
Other and unknown	3	0.78	0.16, 2.3	0	0	

Abbreviation: SIR, standardized incidence ratio based on comparison with US rates.

<sup>a</sup> Glomerulonephritis and interstitial nephritis.

**Table 4.** Standardized Mortality Ratios and Standardized Rate Ratios by Radon Progeny Exposure Category and Race for Lung Cancer, Non-Hodgkin Lymphoma, Multiple Myeloma, Silicosis, and Pulmonary Fibrosis Among Colorado Plateau Uranium Miners, 1960–2005

	Cumulative Exposure to Radon Progeny From Uranium Mining <sup>a</sup>			
	<120 WLM	120–<400 WLM	400–<1,000 WLM	≥1,000 WLM
<b>Lung cancer<sup>b</sup></b>				
All miners				
No.	37	111	180	284
SMR <sup>c</sup> (95% CI)	1.3 (0.88, 1.7)	2.9 (2.4, 3.5)	5.3 (4.5, 6.1)	9.9 (8.8, 11)
SRR <sup>c</sup> (95% CI)	1.0 <sup>d</sup> (Referent)	2.4 (1.6, 3.5)	4.2 (2.9, 6.1)	9.2 (6.3, 13)
White miners				
No.	34	102	162	251
SMR (95% CI)	1.4 (0.94, 1.9)	3.2 (2.6, 3.9)	5.5 (4.7, 6.4)	10 (9.2, 12)
SRR (95% CI)	1.0 <sup>d</sup> (Referent)	2.3 (1.6, 3.5)	4.0 (2.7, 5.9)	8.1 (5.6, 12)
American Indian miners				
No.	3	9	18	33
SMR (95% CI)	0.66 (0.14, 1.9)	1.5 (0.69, 2.9)	4.0 (2.3, 6.3)	7.0 (4.8, 9.9)
SRR (95% CI)	1.0 <sup>d</sup> (Referent)	2.5 (0.66, 9.9)	7.2 (2.0, 26)	24 (6.1, 95)
<b>Non-Hodgkin lymphoma<sup>b</sup></b>				
All miners				
No.	7	5	3	7
SMR (95% CI)	1.7 (0.67, 3.4)	1.1 (0.36, 2.6)	0.77 (0.16, 2.2)	2.2 (0.87, 4.5)
SRR (95% CI)	1.0 (Referent)	0.68 (0.21, 2.2)	0.39 (0.10, 1.6)	1.1 (0.40, 3.2)
White miners				
No.	6	5	3	5
SMR (95% CI)	1.7 (0.62, 3.7)	1.3 (0.42, 3.0)	0.87 (0.18, 2.5)	1.8 (0.60, 4.3)
SRR (95% CI)	1.0 (Referent)	0.72 (0.21, 2.5)	0.42 (0.10, 1.7)	0.88 (0.26, 3.0)
<b>Multiple myeloma<sup>b</sup></b>				
White miners				
No.	4	3	5	1
SMR (95% CI)	2.4 (0.67, 6.3)	1.6 (0.33, 4.7)	2.9 (0.95, 6.8)	0.73 (0.02, 4.1)
SRR (95% CI)	1.0 (Referent)	0.65 (0.14, 3.0)	1.1 (0.29, 4.1)	0.23 (0.03, 2.0)
<b>Silicosis<sup>b</sup></b>				
All miners				
No.	0	6	17	20
SMR (95% CI)	0 (0, 16)	20 (7.2, 43)	57 (33, 92)	71 (43, 110)
SRR (95% CI)	0	1.0 (Referent)	3.1 (1.2, 8.0)	4.6 (1.8, 12)
<b>Pulmonary fibrosis<sup>b</sup></b>				
All miners				
No.	4	6	11	9
SMR (95% CI)	2.7 (0.74, 6.9)	3.3 (1.2, 7.2)	7.0 (3.5, 12)	6.8 (3.1, 13)
SRR (95% CI)	1.0 <sup>e</sup> (Referent)	1.1 (0.30, 3.9)	2.3 (0.73, 7.4)	1.8 (0.61, 5.1)

Abbreviations: CI, confidence interval; SMR, externally standardized mortality ratio; SRR, internally standardized rate ratio; WLM, working level months.

<sup>a</sup> One miner's date of death was reduced by 1 day to avoid creating a stratum with 1 observed event and 1 person-day.

<sup>b</sup> WLM lagged 5 years for lung cancer, silicosis, and pulmonary fibrosis and 10 years for non-Hodgkin lymphoma and multiple myeloma.

<sup>c</sup> SMR compared with combined Arizona, Colorado, New Mexico, and Utah rates (whites) or combined Arizona and New Mexico rates (American Indians) for all but pulmonary fibrosis, which was compared with the US population. SMRs and SRRs are standardized on race, age, and calendar year.

<sup>d</sup>  $P < 0.0001$  for the trend in standardized rate (cases/WLM • person-year).

<sup>e</sup>  $P = 0.042$  for the trend in standardized rate (cases/WLM • person-year).

**Table 5.** Standardized Mortality Ratios and Standardized Rate Ratios by Smoking Status and Cumulative Radon Progeny Exposure Category (Lagged 5 Years) for Lung Cancer Among Colorado Plateau Uranium Miners, 1960–2005

	Cumulative Exposure to Radon Progeny From Uranium Mining <sup>a</sup>				Trend Slope, cases/WLM • person-year
	<120 WLM	120–<400 WLM	400–<1,000 WLM	≥1,000 WLM	
Never smoker					
No.	2	9	22	43	
SMR <sup>b</sup> (95% CI)	0.25 (0.03, 0.89)	0.87 (0.40, 1.7)	2.9 (1.8, 4.4)	6.3 (4.6, 8.5)	
SRR <sup>b</sup> (95% CI)	1.0 (Referent)	3.5 (0.75, 16)	13 (3.0, 54)	29 (7.0, 120)	4.5 × 10 <sup>-6c</sup>
Former smoker					
No.	7	41	67	119	
SMR (95% CI)	0.69 (0.28, 1.4)	2.9 (2.0, 3.9)	4.6 (3.6, 5.9)	8.8 (7.3, 10)	
SRR (95% CI)	1.0 (Referent)	4.6 (2.0, 11)	6.6 (3.0, 15)	14 (6.3, 31)	7.7 × 10 <sup>-6c</sup>
Current smoker					
<1 pack/day					
No.	4	12	12	24	
SMR (95% CI)	0.97 (0.26, 2.5)	2.8 (1.4, 4.8)	3.1 (1.6, 5.5)	7.6 (4.9, 11)	
SRR (95% CI)	1.0 (Referent)	2.8 (0.85, 9.4)	2.6 (0.79, 8.4)	11 (3.3, 34)	4.2 × 10 <sup>-6d</sup>
1 pack/day					
No.	14	29	47	60	
SMR (95% CI)	3.2 (1.8, 5.5)	5.1 (3.4, 7.4)	9.6 (7.1, 13)	18 (14, 23)	
SRR (95% CI)	1.0 (Referent)	1.8 (0.95, 3.6)	3.3 (1.8, 6.0)	5.7 (3.1, 11)	9.5 × 10 <sup>-6c</sup>
>1 pack/day					
No.	10	20	32	38	
SMR (95% CI)	3.8 (1.8, 6.9)	6.0 (3.7, 9.3)	9.5 (6.5, 13)	21 (15, 29)	
SRR (95% CI)	1.0 (Referent)	1.6 (0.70, 3.5)	2.5 (1.2, 5.3)	9.5 (3.7, 25)	9.4 × 10 <sup>-6e</sup>

Abbreviations: CI, confidence interval; SMR, externally standardized mortality ratio; SRR, internally standardized rate ratio; WLM, working level months.

<sup>a</sup> One miner's date of death was reduced by 1 day to avoid creating a stratum with 1 observed event and 1 person-day.

<sup>b</sup> SMR compared with the regional population as described in Table 2. SMRs and SRRs are standardized by race, age, and calendar year.

<sup>c</sup>  $P_{\text{trend}} < 0.0001$ .

<sup>d</sup>  $P_{\text{trend}} = 0.051$ .

<sup>e</sup>  $P_{\text{trend}} = 0.0026$ .

(21). However, it is unlikely that the severity of this problem is directly related to the radon progeny level within the uranium mining cohort. More likely is that exposure to quartz dust in mines confounds the association that we found of both silicosis and pulmonary fibrosis with radon. Although silica levels were found not to be associated with radon progeny exposure in unventilated mines in the 1960s and 1970s (30), cumulative silica exposure is likely related to cumulative radon exposure, as both are correlated with duration of mine employment. The strong gradient that we observed between silicosis standardized mortality ratios and radon exposure (Table 4) suggests that workers with high radon exposures also had elevated silica exposures, perhaps during early time periods when silica exposures were not well controlled. Alternatively, radon-related pulmonary diseases may have been misattributed as silicosis, leading to elevations in the silicosis standardized mortality ratios for the higher WLM groups.

Lastly, the WLM exposure data's apparent precision belies substantial uncertainty in the individual estimates for each mine, which are based on average data over long periods of time and extrapolation to mines and periods for which no monitoring data were available. The available data on exposure require the presumption that WLM exposures were received uniformly between the predetermined cumulative exposure levels. Correction for these limitations affected mechanistic models of dose rate, exposure age, and attained age on lung cancer risk (31). Because such factors were not evaluated in the present study, the impact of these limitations should be minimal. The feasibility of improving exposure estimates through modeling techniques (32) and the use of individual miner work histories to improve the accuracy of dose estimates is currently being explored; nevertheless, the updated mortality experience of the Colorado Plateau miner cohort should prove useful for additional quantitative risk evaluation and mechanistic

modeling of the association between radon progeny and lung cancer risk, as well as evaluation of the temporal aspects of the interaction of cigarette smoking and radon in causing lung cancer.

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## APPENDIX

## Creation of Rates for End-Stage Renal Disease and Pulmonary Fibrosis

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An ESRD rate file for 1977–2004 was created by using all incident cases of reported ESRD arising from systemic diseases (e.g., diabetes mellitus, hypertension, malignancy, cystic nephropathy) and from nonsystemic diseases (i.e., glomerulonephritis and interstitial nephritis), based on the Renal Management Information System of the Centers for Medicare and Medicaid Services, combined with US Census data (10). US rates were created for whites (used for white miners) and for all other races combined (used for American Indian miners).

A special rate file was also created to analyze underlying cause mortality rates from pulmonary fibrosis (interstitial pulmonary disease). This is based on US rates for *International Classification of Diseases*, Revisions 6 and 7, code 525; Revision 8, code 517; Revision 9, codes 515 and 516.3; and Revision 10, code J84.1. US rates in 10-year age and 5-year calendar year intervals were obtained from the National Center for Health Statistics (18) for the period 1979–2005. Rates for the period 1979–1982 were applied to the period 1960–1978, which should have overestimated expected numbers. Available race categories include “white,” “black or African American,” and “other race”; therefore, rates were developed for whites (for white miners) and the “other race” group (for American Indian miners).

**Appendix Table 1.** Standardized Mortality Ratios for White and American Indian Uranium Miners Compared With Regional Rates, With Follow-up From January 1, 1960, Through December 31, 2005

Minor Cause-of-Death Category <sup>a</sup>	Cause of Death	Whites			American Indians		
		No.	SMR <sup>b</sup>	95% Confidence Interval	No.	SMR <sup>b</sup>	95% Confidence Interval
1–15, 17–65, 67, 71–119	All causes except lung cancer, COPD, and pneumoconioses	1,623	1.22	1.16, 1.28	453	0.93	0.85, 1.02
4–15, 17–40	All cancers other than lung	295	1.21	1.08, 1.36	54	0.85	0.64, 1.11
4–7	Malignant neoplasm buccal cavity and pharynx	6	0.86	0.32, 1.88	0	0	0, 2.24
8	Malignant neoplasm esophagus	11	1.17	0.58, 2.09	0	0	0, 1.43
10, 11	Malignant neoplasm intestine and rectum	34	0.93	0.64, 1.30	5	0.73	0.24, 1.82
12	Malignant neoplasm liver, gall bladder, and biliary	12	1.33	0.68, 2.31	4	0.71	0.19, 1.81
13	Malignant neoplasm pancreas	27	1.33	0.89, 1.97	3	0.65	0.13, 1.91
14	Malignant neoplasm peritoneum and other and unspecified digestive organs	3	2.12	0.44, 6.19	1	2.18	0.06, 12.2
15	Malignant neoplasm larynx	6	1.67	0.61, 3.64	1	1.16	0.03, 6.47
18	Malignant neoplasm other nonpleura respiratory	2	2.36	0.29, 8.54	0	0	0, 10.7
19	Malignant neoplasm breast	1	2.60	0.07, 14.5	0	0	0, 46.3
24	Malignant neoplasm prostate	40	1.08	0.77, 1.47	6	0.51	0.19, 1.11

Table continues

Appendix Table 1. Continued

Minor Cause-of-Death Category <sup>a</sup>	Cause of Death	Whites			American Indians		
		No.	SMR <sup>b</sup>	95% Confidence Interval	No.	SMR <sup>b</sup>	95% Confidence Interval
27	Malignant neoplasm bladder and other urinary site	8	0.78	0.34, 1.54	2	1.65	0.20, 5.96
28	Malignant neoplasm bone	3	3.91	0.81, 11.4	0	0	0, 32.4
29	Malignant neoplasm melanoma	8	1.28	0.55, 2.52	0	0	0, 9.85
30	Malignant neoplasm other skin	5	2.52	0.82, 5.89	1	4.56	0.12, 25.4
33	Malignant neoplasm nervous system	6	0.65	0.24, 1.41	0	0	0, 4.25
37	Hodgkin lymphoma	2	0.93	0.11, 3.34	0	0	0, 19.8
36	Malignant neoplasm other and unspecified site	47	1.77	1.30, 2.35	9	1.14	0.52, 2.17
41–43	Benign and unspecified nature neoplasms	10	1.82	0.87, 3.35	4	3.13	0.85, 8.01
44–47	Diseases of blood and blood-forming organs	12	2.07	1.07, 3.61	0	0	0, 2.19
48	Diabetes mellitus	32	1.10	0.75, 1.55	24	1.16	0.74, 1.73
49	Alcoholism	14	1.35	0.74, 2.26	6	0.46	0.17, 1.00
50	Other mental disorders	17	1.54	0.90, 2.47	0	0	0, 0.94
51, 52	Nervous system disorders	32	1.02	0.70, 1.44	10	1.32	0.63, 2.43
53	Rheumatic heart disease	15	1.49	0.83, 2.46	0	0	0, 1.47
55	Ischemic heart disease	459	1.05	0.96, 1.15	46	0.54	0.39, 0.72
56	Chronic disease of endocardium	5	0.74	0.24, 1.73	0	0	0, 2.91
57	Cardiomyopathy	10	0.93	0.55, 1.71	3	0.71	0.15, 2.07
58	Conductive disorder	31	1.78	1.21, 2.52	18	1.85	1.09, 2.92
54, 61	Hypertension (with and without mention of heart disease)	7	0.48	0.19, 1.02	3	0.37	0.08, 1.07
59	Other heart diseases	42	1.62	1.17, 2.19	16	1.62	0.93, 2.63
60	Cerebrovascular disease	78	0.98	0.78, 1.23	14	0.53	0.29, 0.90
62	Diseases of arteries, veins, lymphatic system	47	1.03	0.76, 1.37	3	0.33	0.07, 0.98
64	Influenza	2	1.35	0.16, 4.88	0	0	0, 10.1
65	Pneumonia	61	1.43	1.09, 1.84	31	1.33	0.91, 1.89
67	Asthma	7	1.84	0.74, 3.79	2	1.44	0.17, 5.19
68	Asbestosis	1	3.72	0.09, 20.7	0	0	0, 72.3
71	Other respiratory disease	39	1.94	1.38, 2.65	30	2.79	1.88, 3.98
74	Cirrhosis and other liver disease	31	0.92	0.63, 1.31	11	0.53	0.27, 0.95
72, 73, 75	Other digestive disease	45	1.16	0.85, 1.56	7	0.43	0.17, 0.93
76, 77	Diseases of skin and subcutaneous tissues	3	2.18	0.45, 6.38	0	0	0, 3.50
78–80	Diseases of musculoskeletal and connective tissue	7	1.49	0.60, 3.06	3	1.98	0.41, 5.78
83–89	Other genitourinary diseases	11	1.24	0.62, 2.26	4	0.74	0.20, 1.90
90	Symptoms and ill-defined conditions	20	1.15	0.70, 1.77	33	1.60	1.10, 2.25
92–96	Motor vehicle injury	51	1.38	1.03, 1.82	32	0.98	0.67, 1.39
91, 97	Other transportation injury	7	1.05	0.42, 2.24	3	0.78	0.16, 2.29

Table continues

Appendix Table 1. Continued

Minor Cause-of-Death Category <sup>a</sup>	Cause of Death	Whites			American Indians		
		No.	SMR <sup>b</sup>	95% Confidence Interval	No.	SMR <sup>b</sup>	95% Confidence Interval
98	Falls into hole	9	2.48	1.13, 4.70	2	0.95	0.12, 3.45
99–102	Other and unspecified falls	10	1.12	0.54, 2.11	2	0.51	0.06, 1.86
103	Collision with objects	22	8.40	5.26, 12.7	3	3.38	0.70, 9.89
104	Machine injury	9	4.90	2.24, 9.29	3	3.62	0.75, 10.6
105	Explosion injury	2	4.19	0.51, 15.1	0	0	0, 19.6
106–115	Other injury	56	2.22	1.68, 2.89	25	0.95	0.62, 1.41
116	Intentional self-harm	44	1.24	0.90, 1.67	8	1.34	0.58, 2.64
117	Assault and homicide	8	1.01	0.44, 2.00	8	0.60	0.26, 1.19
119	Other and unspecified causes <sup>c</sup>	40	1.48	1.06, 2.01	27	1.84	1.21, 2.68

Abbreviations: COPD, chronic obstructive pulmonary disease; SMR, standardized mortality ratio.

<sup>a</sup> Minor cause-of-death category from National Institute for Occupational Safety and Health Life Table 119-cause rate file (15).

<sup>b</sup> Based on (for white miners) the combined Arizona, Colorado, New Mexico, and Utah rates for white men and (for American Indian miners) the combined Arizona and New Mexico rates for men of all other races, adjusted for age, calendar year, and race.

<sup>c</sup> Includes 22 with unknown cause of death.