Lung Cancer Mortality Among Nonsmoking Uranium Miners Exposed to Radon Daughters

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Radon daughters, both in the workplace and in the household, are a continuing cause for concern because of the well-documented association between exposure to radon daughters and lung cancer. To estimate the risk of lung cancer mortality among nonsmokers exposed to varying levels of radon daughters, 516 white men who never smoked cigarettes, pipes, or cigars were selected from the US Public Health Service cohort of Colorado Plateau uranium miners and followed up from 1950 through 1984. Age-specific mortality rates for nonsmokers from a study of US veterans were used for comparison. Fourteen deaths from lung cancer were observed among the nonsmoking miners, while 1.1 deaths were expected, yielding a standardized mortality ratio of 12.7 with 95% confidence limits of 8.0 and 20.1. These results confirm that exposure to radon daughters in the absence of cigarette smoking is a potent carcinogen that should be strictly controlled.

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RADON daughters, both in the workplace and in the household, are a continuing cause for concern because of the well-documented association between exposure to radon daughters and lung cancer.[1-11] Few studies have, however, been able to assess the lung cancer risk from exposure to radon daughters in the absence of cigarette smoking. Studies among Navaho uranium miners, who were predominantly nonsmokers, have demonstrated rate ratios for lung cancer mortality of 4.2[3] and 14.4.[6] Studies of nonsmoking Swedish iron ore[5] and Czech clay shale[10] miners have both shown a rate ratio of 10.0 for mortality from lung cancer. These rate ratios for nonsmokers were generally higher than for cohorts of miners in which smokers and nonsmokers were combined.[3,5,10]

Various regression modeling techniques have been used to estimate the lung cancer mortality risks for nonsmokers from mixed cohorts of smokers and nonsmokers. Although these techniques are extremely powerful and useful, they require that certain assumptions be true, and the results are sometimes difficult to interpret. To provide additional information regarding the lung cancer mortality risks for nonsmokers exposed to radon daughters, we conducted a straightforward cohort mortality study of US, white, male uranium miners who never smoked cigarettes, pipes, or cigars.

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METHODS

Colorado Plateau Study Group

The cohort of white nonsmokers was selected from a larger cohort, also known as the Colorado Plateau study group and as the US Public Health Service (USPHS) uranium miners cohort, that consisted of 3359 white and 779 nonwhite men (total, 4138) who mined uranium on the Colorado Plateau.[1-3] These totals differ slightly from previous totals reported for this cohort because of racial reclassifications and duplications that have been corrected. To be included in the cohort, miners must have been examined in the USPHS medical surveys conducted between 1950 and 1960 and must have worked at least 1 month underground in a uranium mine by January 1, 1964. (Of the nonsmoking miners, all except 6 completed their first month of mining before the end of 1960.) Although lower before 1954, participation rates in the medical surveys reached approximately 90% of the miners in visited areas in 1957 and 1960.[1] Occupational, medical, and smoking histories were obtained during the examinations and updated during subsequent annual censuses of the miners conducted by the USPHS.

Selection and Verification of Nonsmokers Cohort

We selected for analysis only those white men who had never smoked cigarettes and were thus coded as "nonsmokers" according to their previously recorded computer codes from the periodic questionnaires administered by the USPHS between 1950 and 1969.[2] To further verify this information, we reexamined the previously collected questionnaire responses for the 681 miners previously coded as nonsmokers; we did not verify the smoking status of all 4138 cohort members.

Radiation Exposure

The working level months (WLM) of exposure to radon daughters were determined by multiplying the working months (170 hours) spent underground by the working level of the particular mine at that time. One working level is equal to any combination of radon daughters in 1 L of air that results in the ultimate release of 1.3×10^5 MeV of potential α-energy. Lundin et al[2] described the four following methods used to estimate the working level of radon daughters in a given mine during a given year: (1) actual measurements; (2) interpolation or extrapolation in time; (3) geographic area estimation; and (4) estimates before 1950 based on knowledge of ore bodies, ventilation practices, and earliest measurements. A coefficient of variation of 97% in these exposure data and the effect of the errors on relative risk estimation has been evaluated in a previous analysis done by the National Institute for Occupational Safety and Health.[8] For each miner, we had the date he entered the nine exposure categories predetermined by Lundin et al.[2] The nine categories were (1) 0 through 59 WLM, (2) 60 through 119 WLM, (3) 120 through 239 WLM, (4) 240 through 359 WLM, (5) 360 through 599 WLM, (6) 600 through 839 WLM, (7) 840 through 1799 WLM, (8) 1800 through 3719 WLM, and (9) 3720 WLM or more. Because there were only 14 lung cancer deaths among nonsmokers, we collapsed the nine categories into two categories for this analysis. We chose 360 WLM as the midpoint because it is the middle of the nine exposure categories and is close to the median exposure of 296 WLM for this cohort. Exposure to radon daughters from uranium mining ceased for most of the cohort members during the late 1960s.

Vital Status Follow-up

The miners were followed up from the date of their first USPHS medical examination through December 31, 1984, using the records of the Social Security Administration, Internal Revenue Service, National Death Index, and Health Care Financing Administration. Cohort members whose vital status was unknown were considered unavailable for follow-up on the date last observed. Death certificates were obtained for the deceased and coded by a qualified nosologist into the appropriate revision of the *International Classification of Diseases*, using the rules in effect at the time of death. Deceased miners for whom no certificate was located were assumed dead, with the cause of death unknown on the date specified by the reporting agency.

Method of Analysis

The nonsmoking uranium miners cohort was analyzed using a modified life table analysis system developed by the National Institute for Occupational Safety and Health.[12] Although latency and duration of exposure were calculated from the first date of employment underground in a uranium mine, the number of person-years at risk of dying were calculated from the date of the first USPHS medical examination or the date of completion of 1 month of underground uranium mining if that was later. The number of person-years was calculated for specific WLM exposure groups, age groups, calendar periods, and periods after first underground uranium mining. The expected number of deaths was calculated by multiplying the number of person-years by the lung cancer mortality rates from two separate nonsmoking comparison populations. The total number of expected lung cancer deaths was obtained by summing the results over the age groups. The standardized mortality ratios (SMRs) were calculated for lung cancer by dividing the observed number of deaths by the expected number of deaths. Test-based 95% confidence limits (CLs) (two-sided) for the SMR were calculated for cells where there were observed deaths, and 95% confidence limits (Fisher's Exact Test) were calculated for cells where there were no observed deaths.[13] The statistical power to detect various SMRs was determined using one-sided tests[14] because of the a priori belief that SMRs would be elevated.

Veterans' Rates Comparison

The US veterans' mortality rates[15,16] for lung cancer among nonsmoking, white men were used as the primary comparison population (A. Blair, PhD, written communication, February 1987). Because lung cancer rates for nonsmokers have changed little over time[17] and the numbers of observed deaths were small when the veterans' data were divided by calendar periods, we used one set of age-specific rates based on the entire period from 1950 through 1984. The actual age groupings and rates (per 10^6 person-years) used were as follows: 40 through 49 years, 77; 50 through 59 years, 100; 60 through 69 years, 213; 70 through 79 years, 375; and 80 years and older, 706. Since these rates were available for persons who had never smoked cigarettes, pipes, or cigars, we compared them with the rates for uranium miners who had also never smoked tobacco of any kind.

Axelson-Adjusted US Rates Comparison

As a verification of our primary comparison population of nonsmoking veterans, we calculated the rate ratio for lung cancer among non–cigarette-smoking miners using estimated US rates for non–cigarette smokers. To estimate the rates for non–cigarette smokers in the US, white, male population, we adjusted the overall US rate using four age and calendar time-specific adjustments, according to the method proposed by Axelson.[18] First we "decomposed" the known overall US lung cancer rate (I) into a weighted average of rates for non–cigarette smokers, ex-smokers, and smokers to derive an estimate of the rate for non–cigarette smokers (I_o).

$$I = (P_n)(R_n)I_o + (P_e)(R_e)I_o + (P_l)(R_l)I_o + (P_h)(R_h)I_o$$

where I indicates overall mortality from lung cancer in the US, white, male population; P_n, P_e, P_l, and P_h indicate US, white, male population proportions of non–cigarette smokers, ex-smokers, light smokers (20 cigarettes per day or fewer), and heavy smokers (more than 20 cigarettes per day), respectively; R_n, R_e, R_l, and R_h indicate known lung cancer relative risk estimates among non–cigarette smokers, ex-smokers, light smokers, and heavy smokers, respectively, taken from the large prospective study of US veterans. All terms in the equation were known except I_o. We solved for I_o. To adjust for age and calendar time, rates for US non–cigarette smokers were estimated for four age and calendar time combinations (ages 45 through 64 years and 65 years and older, calendar times 1950 through 1974 and 1975 through 1984). Then we used the four estimated rates for US non–cigarette smokers (I_o) to calculate expected deaths in our cohort of miners, after stratifying person-years from the cohort into the same four age and calendar time strata. The numbers of observed and expected deaths for all four strata were summed to derive an overall rate ratio.

The age and calendar time groupings were chosen to provide similar numbers of expected deaths from the cohort of non–cigarette-smoking miners in each of the four cells to be used in the analysis. The population proportions used in these calculations were taken from 1965 and 1980 National Center for Health Statistics survey data regarding smoking habits among white men in the United States.[19] The years 1965 and 1980 were chosen because they were approximately the midpoints of the two calendar periods—1950 through 1974 and 1975 through 1984. The smoking-specific relative risk estimates for lung cancer used in these calculations were taken from data regarding US veterans divided in the two age groups, 45 through 64 years and 65 years and older.[20] Since pipe and cigar smokers were included in the US proportions of non–cigarette smokers for 1965 and 1980, it was necessary for us to include pipe and cigar smokers in the veterans' risk estimates and in the cohort of non–cigarette-smoking uranium miners for the analysis based on US rates.

RESULTS

Accuracy in Smoking Codes

On review of the periodic questionnaires collected between 1950 and 1969 for the 681 white miners who had been previously computer coded as never having smoked cigarettes (nonsmokers), we found that some had actually smoked cigarettes (13%) and some had smoked pipes or cigars (11%). Those who ever smoked cigarettes were excluded from further analysis. Those who smoked only pipes or cigars were excluded from the analysis that used nonsmoking US veterans (no tobacco of any type) but were included in the second analysis that used estimated US nonsmoking rates. In total, 76% (516/681) reported never having smoked tobacco of any kind, and 87% (593/681) reported never having smoked cigarettes. We corrected all miscoding, including 3 persons with unknown smoking status.

Table 1.—Vital Status of White, Nonsmoking, Uranium Miners, With Follow-up Through 1984

Vital Status	No. (%) of Miners
Alive	387 (75)
Deceased	126 (24)
Certificate obtained	124 (98)
Certificate not obtained*	2 (0.02)
Unknown†	3 (0.01)
Total	**516 (100)**

*Includes one foreign death for whom no appropriate death certificate can be obtained.
†Persons with unknown vital status had their person-years at risk accumulated only until their last date observed.

Cohort Status

The 516 white nonsmokers had the following characteristics: mean year of birth, 1923; mean year first employed, 1952; mean age first employed, 29 years; mean time in underground uranium mining, 52 months; mean exposure to radon daughters, 720 WLM (median, 296 WLM); and mean rate of exposure to radon daughters, 16 WLM per month (median, 10 WLM/mo). The mean time since first employment in uranium mining until either death or the end of the study was 28 years; the mean time since last employment was 21 years. The mean age at the end of the study for the live cohort members was 56 years. Follow-up of the cohort through December 31, 1984, resulted in only 3 persons with unknown vital status and the identification of 126 deaths (Table 1). Fourteen deaths from lung cancer were found; characteristics of the 14 persons are reported in Table 2.

Lung Cancer: Veterans' Rates Comparison

When the number of observed deaths from lung cancer among the 516 nonsmoking uranium miners was compared with the expected number of deaths derived from the lung cancer mortality rates among white, male, nonsmoking US veterans, the SMR was 12.7 (95% CL, 8.0 and 20.1) (Table 3).

Lung Cancer: Axelson-Adjusted US Rates Comparison

The cohort of non–cigarette-smoking miners used in this secondary comparison consisted of the 516 nonsmokers plus 77 cigar and pipe smokers for a total of 593 nonsmokers. Cigar and pipe smokers were included because the data regarding the smoking habits of the US population included cigar and pipe smokers among nonsmokers of cigarettes. When the numbers of expected lung cancer deaths in the United States among white men were estimated for non–cigarette smokers by the Axelson method, we estimated the SMR to be 9.3 (95% CL, 5.6 and 14.5), based on 19 observed and 2.04 expected deaths.

Using the Axelson method, we estimated the following lung cancer rates for non–cigarette smokers in the United States: (1) 12% of the known overall US lung cancer rate for white men, aged 45 through 64 years, during the period 1950 through 1974; (2) 25% of the overall rate for ages 65 years and older, 1950 through 1974; (3) 12% for ages 45 through 64 years, 1975 through 1984; and (4) 24% for ages 65 years and older, 1975 through 1984.

Table 2.—Characteristics of White, Nonsmoking, Uranium Miners Who Died of Lung Cancer

Case No.	Year of Death	Age at Death, y	Years Since First Exposure*	Year First Employed	Age First Employed, y	Duration Employed, y	Years Since Last Exposure†	Uranium Exposure, WLM‡	Other§ Exposure, WLM‡	Total Exposure, WLM‡	Months Underground	Rate of Exposure, WLM/mo‡
1	1965	57.1	15.3	1949	41.8	12.6	2.7	403	62	465	41	10
2	1972	73.2	21.6	1950	51.6	9.5	12.1	16 467	0	16 467	90	183
3	1972	42.1	17.5	1955	24.6	13.0	4.5	520	0	520	134	4
4	1973	67.9	13.9	1959	53.9	8.1	5.8	709	74	783	96	7
5	1975	53.0	20.5	1954	32.6	10.2	10.3	555	7	562	116	5
6	1975	62.3	16.5	1958	45.7	8.9	7.6	2854	54	2908	62	46
7	1976	54.8	36.2	1940	18.6	28.6	7.6	2889	0	2889	214	14
8	1980	45.7	27.2	1953	18.5	15.9	11.3	2225	0	2225	124	18
9	1980	67.4	29.4	1950	37.9	13.6	15.9	4765	0	4765	157	30
10	1981	59.3	43.3	1938	15.9	30.8	12.5	4483	0	4483	347	13
11	1982	69.4	27.3	1955	42.1	9.1	18.2	952	0	952	101	9
12	1984	45.1	26.8	1957	18.3	10.9	15.9	1266	0	1266	93	14
13	1984	56.2	34.1	1950	22.1	17.0	17.1	1845	0	1845	162	11
14	1984	83.7	34.3	1950	49.5	15.6	18.7	1810	0	1810	163	11
Mean	1977	59.8	26.0	1951	33.8	14.6	11.4	2982	14	2996	136	27

*Time from first uranium mining until death, does not include other hard rock–mining employment.
†Time from last known uranium mining until death.
‡WLM indicates working level months.
§Other exposure to radon daughters from hard rock mining before uranium mining.

Table 3.—Lung Cancer Mortality Among Uranium Miners Aged 40 Years and Older Who Never Smoked Compared With Nonsmoking US Veterans

Time Since First Exposure to Uranium Mining, y	Exposure to Radon Daughters From Uranium Mining		
	1-359 WLM*	≥360 WLM*	Total
≤19			
No. of observed/expected deaths	0/0.2	4/0.2	4/0.4
Standardized mortality ratio	0.0	20.0	10.0
95% CL†	0.0-15.6	10.6-43.9	4.1-22.1
Person-years at risk	...	...	3436
WLM (N)‡	...	...	400 (50)
≥20			
No. of observed/expected deaths	0/0.3	10/0.4	10/0.7
Standardized mortality ratio	0.0	25.0	14.3
95% CL†	0.0-11.9	17.3-41.7	8.9-24.3
Person-years at risk	...	...	4425
WLM (N)‡	...	...	282 (466)
Total			
No. of observed/expected deaths	0/0.5	14/0.6	14/1.1
Standardized mortality ratio	0.0	23.3	12.7
95% CL†	0.0-6.8	17.2-37.6	8.0-20.1
Person-years at risk	4095	3766	7861
WLM (N)‡	114 (288)	989 (228)	296 (516)

*WLM indicates working level months.
†95% CL indicates 95% confidence limits for the standardized mortality ratio.
‡WLM (N) indicates median exposure from uranium mining for miners who did not progress to a higher category of exposure or time since first exposure, and parentheses indicate the number who did not progress to a higher category.

Nonmalignant Respiratory Disease

Because a significant excess risk of mortality from nonmalignant respiratory diseases (NMRDs) had been previously reported in studies of the Colorado Plateau miners[2-4] and because mortality from NMRDs is associated with smoking, we felt it would be important to report the NMRD mortality among this subcohort of nonsmokers. We calculated an SMR of 11.7 (95% CL, 5.1 and 23.1) for NMRD (*International Classification of Diseases, Ninth Revision*, disease codes 460 to 466, 470 to 478, 492, and 494 to 519) based on 8 observed and 0.682 expected deaths. Of the 8 observed deaths, 3 were caused by silicosis, 3 were caused by chronic obstructive pulmonary disease, 1 was caused by pulmonary fibrosis, and 1 was caused by pulmonary emphysema. The expected number of NMRD deaths was calculated by multiplying the rate of NMRDs among nonsmoking US veterans[20] in age groups 45 through 64 years and 65 years and older by the appropriate number of person-years from the nonsmoking uranium miners and adding the results.

COMMENT

Although models have been previously used to estimate the lung cancer risk among members of the US uranium miners cohort who never smoked (nonsmokers),[2] this is the first analysis of nonsmokers in which lung cancer mortality has been directly compared with a large referent group of nonsmokers. In this analysis, we also extended follow-up through 1984, assessed risk by personal cumulative exposure, and reviewed smoking status and corrected miscoding in this cohort. We found an overall SMR for lung cancer of 12.7 (95% CL, 8.0 and 20.1) for nonsmoking miners compared with a referent group of nonsmoking US veterans. In a secondary analysis that used a different referent group of US, white men adjusted for non–cigarette smoking via the Axelson method, we found an overall SMR of 9.3 (95% CL, 5.6 and 14.5) for non–cigarette smokers (including some pipe and cigar smokers).

Our overall lung cancer SMR of 12.7 (95% CL, 8.0 and 20.1) for white, nonsmoking uranium miners was in close agreement with the lower 95% CL of 14.4 for the odds ratio calculated in the study by Samet et al[6] of lung cancer among predominantly nonsmoking Navahos exposed to uranium mining. The relative risk of lung cancer of 10.0 reported for nonsmoking Swedish iron ore miners by Radford and Renard[5] and for nonsmoking Czech clay shale miners by Sevc et al[10] were also in close agreement with our estimate, although the mean exposure to radon daughters for nonsmokers in the Swedish study (84.3 WLM) and in the Czech study (31.7 WLM) were only 28% and 11%, respectively, of the median exposure of 296 WLM (mean, 720 WLM) in our analysis. However, a greater difference did exist between our relative risk estimate of 12.7 and the estimate of 4.2 (11.0/2.6) for predominantly nonsmoking Navahos calculated in a previous analysis of the USPHS uranium miners cohort by Archer et al.[3] This difference is probably caused by the substantial lung cancer mortality that occurred among nonsmokers after the 1974 follow-up date for Archer's analysis.

Besides relative risk, attributable risk is frequently used to compare the results of studies of the association between lung cancer and exposure to radon daughters. In previous reports,[5,7,9] attributable risk has been defined as follows: Attributable Risk = ([Observed − Expected] / [Person-Years × Mean Dose]) × 10^6. We estimated an attributable risk of 5.5 excess lung cancer deaths per WLM per 10^6 person-years in our analysis of nonsmoking uranium miners (Table 3). This result is in close agreement with the estimate of 5.56 excess lung cancer deaths per WLM per 10^6 person-years estimated for nonsmoking Newfoundland fluorspar miners by Morrison et al.[7] However, it is below estimates of 16.3 for nonsmoking Swedish iron ore miners[5] and 16.6 for nonsmoking Czech clay shale miners.[10] The difference in the number of excess deaths per WLM among the studies might be caused by differences in the levels of exposure analyzed. The mean exposure in our analysis was 720 WLM (median, 296 WLM). The mean was approximately 447 WLM for all miners, smokers and nonsmokers alike, in the Newfoundland study. The mean exposure to radon daughters for nonsmokers in the Swedish study was 84.3 WLM and 31.7 WLM for nonsmokers in the Czech study. Thus, the mean exposures analyzed in our study and the Newfoundland fluorspar study were more than three times greater than the mean exposures in the Swedish and Czech studies, also leading to higher rates of exposure. It has been reported that radon daughters above certain exposure rates might be redundant or superfluous in increasing the risk for lung cancer.[21]

Our examination of the USPHS questionnaire data regarding white nonsmokers from the Colorado Plateau study group revealed that 13% of the miners coded as nonsmokers should have been coded as smokers or ex-smokers of cigarettes. However, the miscoding appeared to be random with relation to lung cancer cases and noncases and, thus, did not have a significant effect on our overall risk estimate. In our analysis of the corrected nonsmokers group, the total number of lung cancer deaths declined from 20 to 14 (30%), the expected number of deaths declined from 1.7 to 1.1 (35%), and the overall SMR rose from 11.7 to 12.7. Although miscoding might also have occurred among miners coded as smokers or ex-smokers, it seems more likely that smokers would have been incorrectly coded as nonsmokers than the other way around.

Errors in the classification of exposure to radon daughters might also have occurred. The coefficient of variation for the radiation exposure for the entire cohort of white, US, uranium miners was previously estimated to be 97%.[8] This implies that many miners might be classified in the wrong exposure categories. This misclassification, however, is independent of the exposure-disease relationship because the exposures were determined without knowledge of the disease outcome. Random misclassification has been shown to bias the mortality ratio toward 1.00, causing an underestimation of risk.[22]

Miners are exposed to radon daughters, not only from uranium mining, but from other underground, hard-rock mining as well. One hundred forty-two of the miners (28%) in our cohort had exposure to radon daughters from previous hard-rock mining. Their mean exposure from previous hard-rock mining was 46 WLM (median, 21 WLM). Although we did not consider these prior exposures in our analysis (Table 3), they were relatively small and would not have caused any of the deaths from lung cancer to enter different categories of exposure to radon daughters.

Besides radon daughters, the miners in our cohort might also have been exposed to diesel exhaust, silica, arsenic, nickel, cobalt, γ-radiation, and other substances associated with mining. Although these exposures were not considered in our analysis, they might have acted synergistically with radon daughters to potentiate the effects of exposure to radon daughters.

In our SMR analyses, we observed no deaths and thus estimated a relative risk of 0.0 for lung cancer among nonsmokers who fell in the exposure category of less than 360 WLM (Table 3). However, our power to detect any excess risk at lower exposure levels was low. For example, to have attained statistical power of 0.80 in the exposure category of less than 360 WLM and greater than 20 years since first exposure, an SMR of 10.37 would have had to exist with 0.3 expected deaths from lung cancer.[14] The power to detect a risk of 2.00 was 0.12.

An important consideration in using both the US veterans comparison population and the smoking-adjusted US comparison population, which we used for corroboration, was our selection of rates[15,16] and risk estimates[20] from the study of US veterans. The authors of that study noted that the veterans were mostly from World War I and were drawn mainly from the middle and upper socioeconomic classes and hence might not be very similar to Colorado Plateau uranium miners. However, our results would have been largely unchanged had we used the rates calculated by Hammond and Seidman[23] for American Cancer Society volunteers, the only other principal US cohort of smokers and nonsmokers studied prospectively (1960 to 1972). The veterans' rates seemed more appropriate because they covered the entire study period for the uranium miners—1950 through 1984.

In conclusion, we have demonstrated a 12-fold mortality risk for lung cancer for nonsmoking uranium miners exposed to radon daughters at a median level of 296 WLM (mean, 720 WLM) when compared with nonsmoking nonminers. No deaths from lung cancer were observed among nonsmoking miners who had accumulated less than 465 WLM of exposure to radon daughters; however, our statistical power to detect risks at lower exposures relevant to current occupational and most household exposures was not adequate in this analysis. These results confirm that exposure to radon daughters in the absence of cigarette smoking is a potent carcinogen that should be strictly controlled.

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