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Relation of Radon Exposure and Tobacco Use to Lung Cancer Among Tin Miners in Yunnan Province, China

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We studied the relation of radon exposure and tobacco use to lung cancer among tin miners in Yunnan Province in the People's Republic of China. Interviews were conducted in 1985 with 107 living tin miners with lung cancer and an equal number of age-matched controls from among tin miners without lung cancer to obtain information on lung cancer risk factors including a detailed history of employment and tobacco use. Occupational history was combined with extensive industrial hygiene data to estimate cumulative working level months (WLM) of radon daughter exposure. Similar data were also used to estimate arsenic exposure for control in the analysis.

Results indicate an increased risk of lung cancer for water pipe smoking, a traditional form of tobacco use practiced in 91% of cases and 85% of controls. Ever use of water pipes was associated with a twofold elevation in risk when compared with tobacco abstainers, and a dose-response relation was observed with increasing categories of pipe-year (dose times duration) usage. Estimated WLM of radon exposure varied from 0 to 1,761 among subjects but averaged 515 in cases versus only 244 in controls. Analyses indicated that the persons in the highest quarter of the radon exposure distribution had an odds ratio (OR) = 9.5 (95% confidence interval = 2.7–33.1) compared to persons without radon exposure after controlling for arsenic exposure and other potential confounders. Examination of duration and rate of radon exposure indicated higher risk associated with long duration as opposed to high rate of exposure. Cross-categorizations of radon exposure and tobacco use suggest greater risk associated with radon exposure than tobacco in these workers.

Key words: China, radon, tobacco, occupational exposure

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INTRODUCTION

Lung cancer in China accounts for about 7.4% of all cancer deaths (8.5% in males and 5.9% in females), ranking fourth among males and fifth among female cancer deaths, respectively. The highest risk area for lung cancer in males in China among the over 2,000 counties or cities is Gejiu City in Yunnan Province. Located there is the largest tin mining area in China, and mortality from lung cancer in Gejiu is about ten times higher than in males in the rest of China (mortality rates standardized to the world population = 102.08×10^{-5} person years versus 10.25×10^{-5}, respectively) [Li, 1981].

The Yunnan Tin Corporation (YTC) is located in Gejiu City, Yunnan Province, which borders on Burma, Laos, and Vietnam and is about 300 km south of Kunming, the capital of the province. The tin mines are located around Gejiu City, and the headquarters are in the city. The YTC is a large, complex, nonferrous metals industry, principally involved in the production of tin. Although the corporation was formed in 1883 and nationalized after 1949, mining dates back about 2,000 years. The total number of employees at the YTC in 1984 was 48,733, including more than 15,255 male miners who have had underground working and/or smelting experience. The search for etiologic factors for lung cancer among miners and eventual adoption of measures aimed at prevention is considered an important and urgent task as lung cancer represents 70–80% of all cancer seen annually among YTC employees [Yao and Zhang, 1984].

There are many suspected risk factors that may be associated with the high mortality rate of lung cancer in Gejiu City. These factors include occupational exposure (radon and radon daughter, arsenic, and other mining dusts), tobacco smoking (especially water-pipe smoking, which is very common in the Gejiu area), air pollution (arsenic and sulfur dioxide), and nutritional deficiencies [Mao and Dong 1984; Wang et al., 1984].

The objectives of the present study were to evaluate the relation of radon and tobacco exposure to lung cancer risk among past and present employees of the YTC.

MATERIALS AND METHODS

Study Subjects

All male lung cancer cases between the ages of 35–80 years who were reported to the Labor Protection Institute of the YTC during 1967–1984, lived in the Gejiu area, and who were alive in 1985 were included in this study. A pool of controls was chosen systematically by selecting every 20th person from a master list of all living past or present workers from the YTC living in the Gejiu area. The master list is organized hierarchically by census bureau, family, and street address. Controls were then matched to cases by year of birth (within the same 5-year age group). A total of 107 cases were confirmed by an independent panel of pathologists, clinicians, and cytologists according to diagnostic criteria for pulmonary carcinoma. Each case had one matched control (total = 107). Data concerning smoking, occupation, residence, diet, prior medical conditions, family history, and other information were collected by questionnaire during a personal interview that took 30–40 minutes to complete. Respondents were mostly the cases and controls themselves (90% and 94%, respectively), although for a few subjects the respondent was a close relative. The most common reason for interviewing surrogates instead of cases was poor health of the cases, while the most common reason for using surrogates of controls was their absence from the home at the time of interview. All completed questionnaires and medical abstracts were edited by a field supervisor or assistant for completeness and accuracy. Data were coded in Gejiu City by trained coders according to an established coding system and keypunched from coding sheets in Bethesda, MD.

Tobacco

A number of questions regarding use of tobacco were asked during the interview including questions on both use of water pipes and cigarettes. Individuals who had smoked regularly for 6 months or longer at any time were classified as ever smokers. To avoid ambiguity among subjects who quit smoking following diagnosis of cancer, ever/never smoking categorization was based on status 1 year prior to diagnosis (for cases) or 1 year prior to diagnosis of the matched case (for controls). Separate smoking indices to estimate lifetime consumption were calculated for water pipe and cigarette use, which incorporated level of use and duration. For water pipes, pipe-years were determined as average liang (50 g) smoked per month times the number of years of reported water pipe use. For cigarettes, pack-years were calculated as the average number of cigarettes per day (divided by 20) times the number of years of reported cigarette use.

Radon Exposure

A detailed occupational history was recorded that included information on job title, work site, and starting/stopping dates by year for each job held at the YTC for at least 1 year.

Exposure to radon daughters was estimated from industrial hygiene values measured or estimated for each individual mine (Laochang, Makuang, Songkuang, Kafang) and era (≤1952, 1953–1972, ≥1973). Radon daughter measurements were first made at the four principal mining areas of YTC in 1972 when a radon problem was initially recognized. Estimates were made for exposures that occurred prior to the actual collection of industrial hygiene data. Large-scale tunnel production started at the YTC in 1953. In order to estimate exposure values for the era prior to 1953, 117 samples were taken from 13 small pits that operated pre-1949 and were still available for testing. With the assistance of old miners, primitive mining work environments were simulated in these pits for the testing [Zhang et al., 1981]. Scientists from the Labor Protection Institute of the YTC and the Institute of Radiomedicine of the Chinese Academy of Medical Sciences used values from the 413 samples for radon daughters measured in the mines in 1972 as the basis for estimating values for the era 1953–1972. Since then, systematic monitoring of radioactivity in the YTC has been carried out, and over 26,000 samples have been collected and analyzed. Median values (and ranges) for radon daughters as WL (working level) for the three eras are summarized below [Wang et al., 1984]: (era, radon daughter [WL]) ≤1952, 1.64 (0.65–2.65); 1953–1972, 1.94 (0.23–4.27); 1973–1980, 0.77 (0.52–1.14).

Mine-, job-, and era-specific exposure to radon daughters was estimated as WLM for each job for each subject using the following formula [Mao, 1982]:

$$\text{WLM} = \frac{285 \text{ days/year} \times 8 \text{ hours/day}}{170 \text{ hours/month}} \times \text{WL} \times \text{exposure time (in years)}.$$

A cumulative exposure estimate for each subject was obtained by summing across the estimated WLM for each job held at the YTC prior to the diagnosis for cases or to the matched case for controls.

Other Exposures

Arsenic exposure was also estimated from industrial hygiene data obtained separately for each of the four mines (Laochang, Makuang, Songkuang, Kafang) over five eras (≤1949, 1950–1959, 1960–1969, 1970–1979, ≥1980) and from three smelters over three periods. Airborne dust concentration and arsenic content in dust were measured in the 1950s and 1960s, while direct air arsenic measures were made beginning in the 1970s. Calculated or measured mean values ranged from a high of 0.42 mg/m^3 before 1952 to a low of 0.01 mg/m^3 in the 1980s. Cumulative arsenic exposure was estimated by summing the exposure levels from each job prior to diagnosis for cases or to the matched case for controls.

Statistical Methods

Statistical analyses were performed using the Statistical Analysis Software (SAS) [SAS Institute, 1982]. Chi-square values were calculated using the Mantel-Haentzel procedure when conducting univariate analyses, or from the likelihood ratio test procedure when conducting multivariate analyses. Means of differences were computed parametrically using paired t-tests and repeated with the Wilcoxon signed rank test, a nonparametric test. PROC LOGIST was used to estimate the exposure odds ratio (OR) as a surrogate for the relative risk (RR) in bivariate and multivariate analyses. All analyses were run with age (the matching factor) as a main effect term. Confidence intervals (CI) of the regression coefficients were estimated under the assumption of normal distribution of the estimates of the coefficients.

RESULTS

Table I shows the general characteristics of the study population. The average age of first YTC employment for cases and controls was 16 and 20 years, respectively. As shown in Table II, over 40% of the cases were diagnosed in 1984. The average age at diagnosis for cases was 57 years. The average duration of YTC employment for the cases was 37 years (for controls it was 33 years). The average time from initial employment in the tin mines to diagnosis of lung cancer was 41 years. Lung cancer cases were categorized by method of diagnosis as follows: all but one had a positive X-ray, 67% had positive sputum cytology, and 53% had positive histology from a biopsy. Over 80% of cases with cytologic or histologic results were squamous cell carcinomas.

Table III shows estimates of the relative risk of lung cancer by various categories of smoking status. Compared to no tobacco use at all, modest elevations in risk were seen for ever use of water pipe only, use of water pipe and cigarettes, and any tobacco use. No increased risk was observed for cigarette use only. Although not included in Tables III or IV, opium smoking, a practice that was common before 1949, was also more common among cases than controls (37% versus 19%, $\chi^2 = 9.2$, $p = .002$).

Table IV shows the distribution of pipe-years and estimated cumulative radon exposure. The mean of the differences in pipe-years between case-control pairs, was

TABLE I. General Characteristics of Study Population of Tin Miners in Yunnan Province, 1985

	Cases (%)	Controls (%)
No.	107	107
Average age (years)	61	62
Age range (years)	49–78	47–79
Self-respondents	96 (90)	101 (94)
Education		
None	68 (64)	50 (47)
1–5 years	27 (25)	37 (35)
>5 years	12 (11)	20 (19)
Age started employment at YTC (years)		
6–11	27 (25)	18 (17)
12–13	21 (20)	14 (13)
14–16	25 (23)	9 (8)
17–21	19 (18)	28 (26)
22–51	15 (14)	38 (36)

57 ($t = 3.41$, $p = .0009$), while the mean of the differences in estimated cumulative radon exposure between case-control pairs was 271 WLM ($t = 4.93$, $p = .0001$).

Table V shows the bivariate (controlled for age only) and multivariate risk estimates by quarter of pipe-years use compared to never water pipe use. Evidence for a dose-response is seen in both analyses (statistically significant only in the bivariate analysis), but the ORs for the multivariate model are approximately one-half those seen in the bivariate model.

When cigarette use by pack-years compared to never cigarette use was examined in a multivariate model controlling for age at diagnosis, year first employed, and exposure to radon, arsenic, and pipe tobacco use, the ORs for quarters of the distribution of pack-years were 1.0, 0.9, 1.4, and 1.6 for none, 0.1–7.2, 7.3–15.5, and 15.6–61.0 pack-years, respectively.

A total of 22 subjects (14 cases and 8 controls) reported quitting water pipe smoking from 2 to 53 years before diagnosis for cases or before diagnosis of matched case for controls. Among these 22 quitters, risk in the 11 who had quit longest (10–53 years ago) was less than one-half that of the shorter-term quitters (2–9 years ago) (data not shown).

Bivariate (controlled for age only) and multivariate risks by quarter of radon exposure are shown in Table VI. Mean values within quarters 1–4 of the distribution of radon exposure are 0, 121, 376, and 1,011 WLM, respectively. Risk increases with exposure in these analyses except for the highest category where a slight decline is observed. Somewhat lower risks are observed in the multivariate as compared with the bivariate analysis, a result attributable to confounding by arsenic. Radon and arsenic exposures were highly correlated in these data (Spearman $r = 0.70$, $p = .0001$). The age-adjusted relative risks for arsenic exposure for quarters 1–4 were 1.0, 6.5, 24.6, and 21.1, respectively. Because of interest in risk from levels of radon exposure at or below 120 WLM, additional analyses were performed. The relative risks for radon exposure of 0, 1–120, and 120+ WLM were 1.0, 3.9, and 9.2, respectively, in the multivariate model.

Some radon exposure was reported in 100 cases and 62 controls. Among these radon-exposed individuals, cases had a median duration of exposure of 23 years

TABLE II. Diagnostic Characteristics of Cases Among Tin Miners, Yunnan Province, 1985

	No.	Percent
Year of diagnosis		
1967–1980	33	31
1981–1983	29	27
1984	45	42
Age at diagnosis		
39–49	20	19
50–59	45	42
60–69	30	28
70–79	12	11
Years worked before diagnosis		
7–30	25	23
31–40	38	36
41–50	39	36
51–61	5	5
Method of diagnosis		
Clinical	4	4
X-ray	106	99
Sputum cytology	72	67
Endoscopy	57	53
Biopsy	60	56
Thoracotomy	37	35
Histologic type (from biopsy)		
Squamous cell	49	82
Large cell	0	0
Oat cell	1	2
Adenocarcinoma	3	5
Mixed	3	5
Other	4	7
Histologic type (from sputum cytology)		
Squamous cell	59	82
Large cell	1	1
Oat cell	1	1
Adenocarcinoma	3	4
Mixed	2	3
Other	6	8

TABLE III. Age-Adjusted Relative Risk of Lung Cancer by Type of Tobacco Use Among Tin Miners, Yunnan Province, 1985

	Cases No.(%)	Controls No.(%)	OR	95% CI
Never[a]	3 (3)	5 (5)	1.0	—
Water pipe only	24 (22)	23 (22)	1.9	0.4–9.4
Cigarettes only	7 (7)	17 (16)	0.9	0.1–5.4
Water pipe + cigarettes	73 (68)	62 (58)	2.1	0.5–9.1
Any tobacco	104 (97)	102 (95)	1.7	0.4–7.6
Total	107 (100)	107 (100)		

[a]Reference category.

TABLE IV. Distribution of Pipe-Years and Estimated Cumulative Radon Exposure for Cases and Controls Among Tin Miners

	Cases	Controls
Pipe-years	(N = 106)	(N = 107)
Mean	177	122 [a]
SD	128	114
Median	160	111
Range	0–560	0–480
Radon (WLM)	(N = 107)	(N = 107)
Mean	515	244 [b]
SD	423	387
Median	374	61
Range	0–1,565	0–1,761

[a]Paired difference = 56.6, t = 3.41, p = .0009; Wilcoxon signed rank statistic = 934, p = .002.
[b]Paired difference = 271, t = 4.93, p = .0001; Wilcoxon signed rank statistic = 1,535, p = .0001.

TABLE V. Age-Adjusted Relative Risk of Lung Cancer Among Tin Miners From Water Pipe Smoking

	Quarter of pipe-years (range)[a]			
	Quarter 1[b] (0)	Quarter 2 (1–115)	Quarter 3 (116–200)	Quarter 4 (201–560)
No. Cases	10	26	35	35
No. Controls	22	35	25	25
OR[c]	1.0	1.7	3.2	3.4[d]
(95% CI)	(—)	(0.8–4.1)	(1.2–8.0)	(1.3–8.1)
Multivariate				
OR[e]	1.0	1.2	1.8	1.8[f]
(95% CI)	(—)	(0.5–3.3)	(0.7–5.1)	(0.6–5.0)

[a]Average liang per month times No. of years smoked.
[b]Reference category (never users of water pipe).
[c]Controlling for age.
[d]Chi-square for trend = 8.72, p = .003.
[e]Multivariate model includes age, radon, arsenic, and year first worked at YTC.
[f]Chi-square for trend = 1.68, p = .194.

(range 1–55), while the median for controls was only 12 years (range 1–47). The estimated rate of exposure, however, was less in cases than controls (medians = 21 versus 27 WLM per year, respectively). Table VII shows relative risks separately for categories of duration and rate of radon exposure. A dose-response is seen with a relative risk of 20 in the 20+ years duration exposure category. For rate of radon exposure, the magnitude of the risk estimates is lower, and a similar increase in risk with exposure is not seen.

Crosscategorization of radon exposure and tobacco use (as pipe-years) are shown in Table VIII (controlled for age and arsenic exposure). In the lowest category of tobacco use (0–84 pipe-years), a monotonic increase in risk with radon exposure was seen (ORs = 1.0, 8.8, 19.4 for low, medium, and high radon exposure, re-

TABLE VI. Age-Adjusted Relative Risk of Lung Cancer Among Tin Miners From Radon Exposure

	Quarter of WLM (range)[a]			
	Quarter 1[b] (0)	Quarter 2 (1–240)	Quarter 3 (241–541)	Quarter 4 (542–1,762)
No. cases	7	24	39	37
No. controls	45	31	14	17
OR[c]	1.0	5.0	18.1	14.0[d]
(95% CI)	(—)	(1.9–13.2)	(6.6–49.9)	(5.3–37.4)
Multivariate				
OR[e]	1.0	4.8	15.0	9.5[f]
(95% CI)	(—)	(1.6–14.8)	(4.4–50.8)	(2.7–33.1)

[a]WLM = working level months.
[b]Reference category.
[c]Controlling for age.
[d]Chi-square for trend = 35.30, $p < .0001$.
[e]Multivariate model includes age, arsenic, year first worked at YTC, and pipe-years (in addition to radon).
[f]Chi-square for trend = 13.21, $p = .0003$.

TABLE VII. Comparison of Lung Cancer Risk by Categories of Duration and Rate of Radon Exposure Among Tin Miners

	Duration of radon exposure (years)		
	0[a]	1–19	20–55
No. cases	7	38	62
No. controls	45	42	20
Multivariate			
OR[b,c]	1.0	5.8	20.0
(95% CI)	(—)	(1.9–17.6)	(4.9–82.7)
	Rate of radon exposure (WLM/year)		
	0[a]	1–22.8	22.9–57.4
No. cases	7	53	47
No. controls	45	28	34
Multivariate			
OR[b,d]	1.0	7.5	4.2
(95% CI)	(—)	(2.5–23.0)	(1.2–14.3)

[a]Reference category.
[b]Multivariate model includes age, arsenic, year first worked at YTC, pipe-years, and total radon exposure (WLM).
[c]Model chi-square = 61.3, $p < .0001$.
[d]Model chi-square = 56.8, $p < .0001$.

spectively). A monotonic increase was also seen for tobacco use in the lowest category of radon exposure (0–89 WLM); however, it was of lower magnitude (ORs = 1.0, 3.1, and 3.2 for low, medium, and high tobacco use).

DISCUSSION

We studied the relation of tobacco use and radon exposure to lung cancer among tin miners in southern China. Tobacco use was difficult to evaluate because of the use

TABLE VIII. Relative Risk for Lung Cancer by Crosscategories of Radon and Tobacco Exposure in Study of Tin Miners*

			Radon category (range)[a]			
			Low third (0–89)	Mid third (90–414)	High third (415–1,762)	Total
Tobacco pipe-years (range)[b]	Low third (0–84)	No. cases	4	11	11	26
		No. controls	34	8	3	45
		OR	1.0[c]	8.8	19.4	1.0
		(95% CI)	(—)	(2.0–37.9)	(3.4–110.8)	(—)
	Mid third (85–185)	No. cases	5	14	18	37
		No. controls	14	14	7	35
		OR	3.1	5.8	11.6	1.1
		(95% CI)	(0.7–13.8)	(1.4–24.3)	(2.5–54.3)	(0.5–2.4)
	High Third (186–560)	No. cases	4	19	20	43
		No. controls	10	5	12	27
		OR	3.2	23.1	8.5	1.6
		(95% CI)	(0.7–15.7)	(5.1–104.5)	(1.9–37.8)	(0.7–3.6)
	Total	No. cases	13	44	49	
		No. controls	58	27	22	
		OR	1.0	5.2	5.6	
		(95% CI)	(—)	(2.1–12.6)	(2.1–15.5)	

*Controlling for age and arsenic exposure.
[a]Working level months (WLM).
[b]Average liang per month times No. of years smoked.
[c]Reference category.

of different types of tobacco products and because almost all cases (97%) and controls (95%) had a history of some form of prior tobacco use. Elevated risk was suggested for cigarette use with or without water pipe use when compared to tobacco abstainers. Analysis of cigarettes by pack-years also suggested an increased risk for cigarette use in the highest two quarters of the pack-year distribution. However, no elevation in risk was observed in these data for the few subjects who smoked only cigarettes. This unexpected finding is likely due to the small number of subjects whose only tobacco exposure was cigarettes (7 cases and 17 controls), the relatively short duration of use among cigarette users (median ~27 years), and the low intensity of exposure (median use of ~7 cigarettes per day). The highest quarter of the distribution of pack-years was only 15.5–61. Alternatively, at least one other study of miners has also failed to observe a risk for smoking on lung cancer, and a potential biological cause has been proposed as the explanation [Edling and Axelson, 1983]. The traditional method of smoking tobacco in Yunnan is by water pipe. The workers' preference for water pipe use may also reflect the pre-1949 mine policy to distribute free pipe tobacco as a work incentive. It was only in 1984 that smoking in the underground mines was expressly prohibited. Ever use of the water pipe (compared to never pipe use) was associated with an approximately two- to threefold elevation in lung cancer risk. Examination of the intensity and duration of water pipe use (as pipe-years) suggested a dose response. Evaluation of reduction in risk from quitting use was limited by small numbers but was consistent with a reduction in risk for those who had quit longest ago compared to more recent quitters.

The dominant risk factor identified in this analysis was for exposure to radon, where a relative risk of 9.5 was observed when comparing the highest to lowest quarters of the exposure distribution after controlling for arsenic exposure and other potential confounders.

Our observations on duration and concentration of radon exposure suggest that duration of radon exposure is more important as a risk factor for lung cancer than intensity. This may have important implications for occupational as well as nonoccupational groups exposed to radon.

This study has a number of strengths, including the relatively large number of cases among radon-exposed workers, the wide range of exposure to radon, concurrent information on arsenic exposure, and the detailed environmental data available to allow estimation of individual exposures. The major weakness of the study is the potential bias introduced by use of prevalent cases whose diagnoses date back as far as 18 years. To minimize this potential bias, we repeated our analyses using only the 45 cases (and their matched controls) diagnosed within 1 year of interview. The results were only minimally different and did not affect the conclusions. Moreover, the use of prevalent rather than incident cases would have biased our radon estimates upward only if higher levels of radon exposure, relative to lower levels, prolonged survival. In other words, upward bias would have resulted only if the lung cancer cases who did not live to be interviewed has less radon exposure than those who did live long enough to be interviewed. This scenario is extremely unlikely. Other limitations of the study include the restricted range of tobacco exposure among miners, the high correlation between radon and arsenic exposure, the lack of direct individual exposure data, and the fact that job histories were obtained only from the interview (unverified by company records).

The relation of tobacco consumption (the most important overall lung cancer risk factor) and radon exposure to lung cancer risk is of great importance to disease prevention strategies. Several studies of the joint relationship of smoking and radon exposure have been reported [Archer et al., 1973; Axelson, 1983; Bank et al., 1980; Carroll et al., 1984; Damber and Larsson, 1985; Edling et al., 1984; Hornung and Meinhardt, 1987; Lees et al., 1987; Lubin, 1987; Lundin et al., 1971; National Research Council, 1988; Radford and St. Clair Renard, 1984; Saccomanno et al., 1986, Whittemore and McMillan, 1983]. Summaries of the results of these epidemiologic studies suggest that the additive relative risk model is not consistent with available data [Lubin, 1988; National Research Council, 1988]; however, formal analyses based on fitting statistical models have been carried out only in two study populations [Lubin, 1988; National Research Council, 1988; Whittemore and McMillan, 1983]. In the largest data set that is currently available, the additive model was statistically rejected. In those analyses, the association between smoking and radon are most consistent with a range of relative risk models from intermediate between additive and multiplicative to supermultiplicative.

In conclusion, we examined the relation of tobacco use and radon exposure to lung cancer in one of the largest case groups reported to date. Both tobacco and radon exposure increased risk, but in these data, radon was the greater risk.

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