Paper

MODIFIERS OF LUNG CANCER RISK IN URANIUM MINERS FROM THE COLORADO PLATEAU

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Abstract—**Given the scientific consensus that exposure to radon decay products causes lung cancer, most recent studies have focused on the nature of the exposure-response relationship. Since residential radon exposure is now a primary public health issue, a better understanding of the effects of low levels of radon as well as factors modifying risk estimates has become very important. Several factors are shown to affect risk estimates in the latest update of the vital status follow-up (through 1990) and smoking history for the cohort of underground uranium miners in the Colorado Plateau. This analysis confirms earlier results indicating a strong dependence of relative risk estimates upon attained age. Quantitative estimates of relative risk as a function of cumulative exposure to radon decay products (WLM) are provided for three age strata. The non-linearity often reported in the Colorado Plateau data is shown to be at least partially due to an inverse exposure-rate effect, i.e., low exposure rates for long periods are more hazardous than equivalent cumulative exposure received at higher rates for shorter periods of time. However, this effect is shown to diminish at lower exposure rates and cumulative exposures. In addition, use of the new smoking data indicates that the radon/smoking interaction is submultiplicative and may depend upon attained age.**
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INTRODUCTION

THE EXCESS relative risk of lung cancer in underground miners exposed to radon decay products has been well documented (Lundin et al. 1971; Archer et al. 1976; Waxweiler et al. 1981). More recent attention has been given to quantifying the excess risk as a function of measured and estimated cumulative exposure to radon decay products expressed in working level months (WLM) (Hornung and Meinhardt 1987; NAS 1988; Lubin et al. 1994). Since the number of underground miners in the U.S. exposed to high levels of radon has fallen dramatically over the past 40 y, the principal interest in continuing these studies centers around the risk to the general population from indoor radon. Because direct epidemiologic studies of persons exposed to indoor radon suffer from incomplete exposure assessment, low statistical power, and other problems, studies of underground miners may still be our best hope for a better understanding of the risks associated with protracted exposure to low levels of radon (Lubin et al. 1995b).

The oldest continuing study of underground uranium miners, initiated in 1950, is being conducted by the National Institute for Occupational Safety and Health (NIOSH). This study includes 3,347 white underground miners who worked at least 1 mo underground in the Colorado Plateau (located within Colorado, New Mexico, Arizona, and Utah) and who volunteered for at least one medical survey between 1950 and 1960. Data from several vital status updates of this study population have been previously reported (Lundin et al. 1971; Waxweiler et al. 1981; Hornung and Meinhardt 1987). In addition, the subcohort of 780 Native Americans has also been investigated and recently published (Roscoe et al. 1995). The vital status of the Colorado Plateau cohort has been updated to 31 December 1990. In addition, an attempt was made in 1986 to update smoking histories on members of the cohort through questionnaires sent to living members or next of kin for deceased members dying after 1965.

The purpose of the current analysis is to use these new data to investigate in more detail the factors that may modify lung cancer risk estimates associated with radon exposure. We use the term "modifiers" in a general sense to include the epidemiologic concepts of both confounding and effect modification, i.e., any factor for which lack of data or attention in the analysis may substantively alter the estimated risk. It is our contention that any quantitative risk assessment that does not specifically address changes in risk estimates based upon different levels of these modifiers may be seriously misleading.

METHODS

The objective of investigating the dependency of the exposure-response relationship upon various risk factors

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is best accomplished using a model of lung cancer mortality as a function of these factors. Since several previous analyses of underground miners, including the Colorado Plateau data, have found the relative risk model to provide a simpler description of the data than the additive risk model (NAS 1988; Lubin et al. 1994), we will use the relative risk model throughout our analyses.

The relative risk model is of the form

$$\lambda(t,z,w) = \lambda_{oj}(t)\, F(t,z,w), \qquad (1)$$

where

$\lambda(t,z,w)$ = the age-specific lung cancer mortality rate for exposure level z and other risk factors w;

$\lambda_{oj}(t)$ = the background or unexposed rate at age t in strata j where j indexes the birth decade; and

$F(t,z,w)$ = the risk function which may depend upon age t, cumulative exposure z, and other risk factors w.

The exposure response function component of $F(t,z,w)$ in many analyses of underground miner studies of radon has been the linear relative risk model: $f(z, t) = 1+\beta z(t)$ where $z(t)$ is cumulative exposure at age t. However, the previous analysis of the Colorado Plateau data (Hornung and Meinhardt 1987), based on 1982 vital status follow-up, indicated that the exposure-response was significantly non-linear and was better described as a power function model: $f(z, t) = z(t)^{\beta}$. The current analysis will investigate various forms of $f(z, t)$ with the objective of determining the best-fitting model while remaining biologically plausible.

Cumulative exposure is weighted to reduce the contribution of exposures received in close proximity to death when it is thought that such exposures have little if any etiological impact (redundant exposures). The most common weighting scheme is to apply a lag of k years, which gives a weight of zero to exposures received during the k years immediately prior to the time of observation. The previous analysis of these data indicated that a lag of 4 to 6 y provided the best fit to the data. In order to provide a better basis for comparison to the previous analysis as well as several other individual and combined analyses (NAS 1988; Lubin et al. 1994), we chose a 5-y lag for all analyses. To validate this assumption, however, several different lag intervals were used in preliminary analyses.

In addition to cumulative exposure to radon decay products, several other risk factors were examined for their potential impact upon the exposure-response analysis. These factors included cigarette smoking, attained age, age at initial exposure, average exposure rate, and time since last exposure. These factors were examined as both potential confounders and effect modifiers, i.e., inclusion in the model of a risk factor causing a substantial difference in the overall exposure risk coefficient (confounding) or interactions between cumulative exposure and another risk factor (effect modification).

The form of the relative risk model was the Cox proportional hazards model (Cox 1972). Another commonly used form of relative risk models is Poisson regression. A common feature to both of these models is that they are designed to adequately consider the time-dependent nature of many of the variables. At the age that a miner dies of lung cancer, his cumulative exposure (or any other time-dependent variable) is compared to all other surviving miners' cumulative exposures at that age (minus any lag period). Poisson regression requires categorization of all continuous variables, e.g., cumulative exposure, in order to assign person-years and observed lung cancer deaths to cells in the model in a fashion similar to a standardized mortality ratio (SMR) analysis. In the limiting case where the number of categories for each variable is large, the likelihood functions for the Cox model and Poisson regression are identical. In preliminary analyses, both methods were used and, as expected, the results were similar when many categories were employed in the Poisson models. In order to avoid the need to categorize continuous variables, the Cox model was subsequently employed in all analyses using the EPICURE software system (Hirosoft 1993).

DESCRIPTION OF NEW DATA

Vital status followup

The vital status of the white miners was ascertained from 1 January 1950, through 31 December 1990, using the records of the Social Security Administration, Internal Revenue Service, National Death Index, and the Health Care Financing Administration. Death certificates were obtained for the deceased and coded by a qualified nosologist into the appropriate revision of the International Classification of Diseases (ICD), using the ICD rules in effect at the time of death. Classification of the causes of death was based solely on the underlying cause of death. Vital status was ascertained for 99.6% of the cohort and death certificates were obtained for 99.5% of the deceased. Table 1 compares the vital status of the Colorado Plateau cohort used in this analysis to the previously analyzed data with vital status through 1982.

Table 1. Vital status and cohort description white uranium miners cohort, 1950–1990.

Vital status	31 December 1990	31 December 1982
Alive	1,634 (48.8%)	2,131 (63.7%)
Deceased	1,699 (50.8%)	1,215 (36.3%)
Lung cancer deaths	377	256
Unknown	14 (0.4%)	1 (0.03%)
Total	3,347	3,347
Cohort characteristics (mean)		
Year of birth	1920	
Age first employed (y)	32	
Underground uranium (mo)	61	
Uranium exposure[a] (WLM)	822	

[a] The distribution of uranium exposures was highly skewed. The median exposure was 430 WLM. The median exposure rate was 10 WL.

Update of cigarette smoking data

The data on cigarette smoking rates used to determine cumulative smoking history in this study have been updated from the original data collected from 1950 through 1969 and reported in prior publications (e.g., Hornung and Meinhardt 1987). The white uranium miners cohort received a questionnaire survey by mail or telephone in 1986. The survey attempted to reach all cohort members who were alive in 1986 and the next-of-kin of cohort members who died in 1965 or later. Three questions from the survey about the subject's history of cigarette smoking were used to update the original data: (1) the age smoking started, (2) the number of cigarettes per day on average and, (3) the age smoking stopped for former smokers.

The original data on smoking rates, collected from 1950 through 1969, consisted of rates of smoking in packs per day and the date (month and year) on which that rate was reported. Prior to the 1986 survey, the last rate of smoking reported in the original data was considered to be unchanged through the present. The following methods were used to combine the data collected in 1986 with the original data:

1. If the rate of smoking reported in 1986 was the same as last reported in the original data, then the rate of smoking remained unchanged;
2. If the subject was reported to have quit smoking in the 1986 survey and had been reported to smoke in the original data, then the rate of smoking was changed to 0.0 on the reported quit date;
3. If the rate of smoking reported in 1986 was different from the rate last reported in the original data and the subject was alive in 1986, the rate of smoking changed to the new rate on the date midway between 1986 and the date on which the last rate was reported. If the subject was deceased by 1986, the rate of smoking changed to the new rate on the date midway between the year of death and the date on which the last rate was reported;
4. If the rate of smoking reported in 1986 was different from the rate last reported in the original data and the subject was reported to have quit smoking by 1986, then the rate of smoking changed to the new rate on the date midway between the date quit and the date on which the last rate was reported, and the rate of smoking became 0.0 on the date quit; and
5. If data on smoking rates or dates reported in 1986 conflicted with the rates or dates reported in the original data in any way (e.g., original data reported quitting in 1955 while 1986 data reported quitting in 1947), then the original data were accepted and the rates and dates remained unchanged.

Results of smoking survey

Of the 3,347 white miners in the cohort, 285 (8%) died before 1965 and were not included in the survey due to problems with recall and locating next-of-kin. Thus the survey attempted to reach 3,062 subjects or next-of-kin. Of the 3,062 in the actual survey, 2,205 (72%) responded and 857 (28%) did not.

When compared to the respondents, the non-respondents (1) were born 5 y earlier; (2) started work 4 y older; (3) received 107 WLM more exposure to radon progeny from uranium mining; and (4) died 9 y earlier. By the time of the 1986 survey, 305 of the 377 lung cancer deaths had occurred. Questionnaire responses were received from next-of-kin for 224 (59%) of the 377 lung cancer deaths.

The changes in cigarette smoking categories that resulted from updating the original data are presented in Table 2. Among the 2,205 respondents, the percentage who reported quitting smoking (former smokers) jumped from 11% in the original data to 51% in the updated data. Since no changes were made for the 1,142 non-respondents, the percentage of former smokers for the entire cohort increased from 9.5% in the original data to 36% in the updated data.

Table 2. Original and updated smoking data for respondent status white uranium miners cohort, 1950–1990.

Cigarette smoking category	Respondents	Non-respondents[a]	Total
Original smoking category[b]			
Never smoked[c]	441 (20%)	153 (13%)	594 (18%)
Current smokers	1,526 (69%)	900 (79%)	2,426 (72%)
Former smokers	233 (11%)	85 (08%)	318 (9.5%)
Missing data	5 (.2%)	4 (.4%)	9 (.3%)
Total	2,205	1,142	3,347
Updated smoking category[d]			
Never smoked[c]	374 (17%)	153 (13%)	527 (16%)
Current smokers	707 (32%)	900 (79%)	1,607 (48%)
Former smokers	1,124 (51%)	85 (08%)	1,209 (36%)
Missing data	0 (0.0%)	4 (.4%)	4 (.1%)
Total	2,205	1,142	3,347

[a] Includes 857 subjects or next-of-kin who did not respond to the survey and 285 subjects who died before 1965 and were not surveyed.
[b] Original smoking categories were based on the last reported smoking rate from the data collected between 1950 and 1969; they did not change for the non-respondents.
[c] May include cigar and pipe smokers, tobacco chewers and users of snuff.
[d] Updated smoking categories were based on a combination of the last reported smoking rate from the original data and the smoking data collected in the 1986 questionnaire survey.

It should be noted that smoking data are self-reported and we have no way of evaluating their accuracy other than comparison to previous reports as outlined above. Since compensation issues began to arise prior to the 1986 survey, there may have been a tendency for some miners to underestimate their smoking status.

Preliminary analyses

Before investigating the exposure-response model best defining the radon-lung cancer relationship, other risk factors for lung cancer in this cohort were examined (Table 3). Cumulative cigarette smoking using the updated smoking data continued to be a strong risk factor ($\chi^2 = 66.5, p < .001$). Cigarette smoking, however, was not acting as a confounder in the relationship between radon and lung cancer since the effect of cumulative radon exposure was not altered by including cumulative smoking (pack years) in the model. The effects of both cumulative exposure to radon decay products and cigarette smoking were modeled using the power function as good preliminary fits to the data. Improvements in these functional relationships were investigated in the final phases of the analysis.

In the earlier analysis of data from the 1982 followup (Hornung and Meinhardt 1987), age at first exposure had a significant impact upon lung cancer risk. In the current followup through 1990, age at first exposure (or equivalently time since first exposure) was no longer found to be a significant risk factor ($\chi^2 = 2.24$, $p = .136$). However, time since last exposure continued to show a strong negative effect upon lung cancer risk when modeled as an exponential function ($\beta = -0.049$ y^{-1} $\chi^2 = 25.2$, $p < .001$). This would indicate, for example, that miners who were retired from uranium mining 10 y longer than another group of miners of equivalent age, radon, and smoking status, would only have 62% [exp(−0.049)10 = 0.62] the risk of lung cancer or a reduction of 38%.

Another risk factor showing a strong negative effect in the 1982 followup was exposure rate. In the preliminary analysis using 1990 followup the inverse exposure rate effect was again very strong ($\chi^2 = 11.4$, $p < .001$) using the exponential function for this term. Table 3 shows the effects of adding terms for average exposure rate, time since last exposure, and cumulative smoking to the power function model of cumulative exposure to radon decay products.

Exposure rate was also examined by categorizing the continuous variable to see if the effect reported in the preliminary analyses was consistently strong over the entire range of exposure rate. Results indicated that the effect of exposure rate was considerably higher when average levels of radon decay products exceeded 10 WL (where WL = working levels). In fact, a simple dichotomization of exposure rate at 10 WL fit almost as well as the continuous variable for exposure rate. The comparison of risk estimates above and below 10 WL indicated that miners whose average exposure level was greater than 10 WL had only exp (−.629) = 53% of the risk of miners exposed at lower levels for longer duration resulting in the same cumulative exposure. The inverse exposure rate effect was considerably reduced and not statistically significant at lower exposure rates.

Form of the dose-response relationship

In the previous analysis of the Colorado Plateau data (Hornung and Meinhardt 1987), a power function model of the form $f(z, t) = \exp\{\beta \ln[z(t)] + k_r)\} = [z(t) + k_r]^{\beta}$, where k_r is cumulative background radon exposure was found to provide a good fit over the full range of exposure to radon decay products. The exposure-response relationship was significantly non-linear. Over

Table 3. Preliminary relative risk models for radon and other risk factors.
Model: $\exp(\Sigma \beta_i Z_i)$

Model	Variables[a]	Coefficient	STD Error	Deviance	χ^2 [b]	p-value
Null model		—	—	4,604.6		
Model 1	Z_1 = ln(WLM + K_r)	0.613	0.046	4,405.4	199.2	<.001
Model 2	Z_1 = ln(WLM + K_r)	0.617	0.047			
	Z_2 = ln(PKYRS + K_s)	0.292	0.042	4,338.9	66.5	<.001
Model 3	Z_1 = ln(WLM + K_r)	0.576	0.048			
	Z_2 = ln(PKYRS + K_s)	0.299	0.042			
	Z_3 = TSLE	−0.049	0.010	4,313.7	25.2	<.001
Model 4	Z_1 = ln(WLM + K_r)	0.656	0.056			
	Z_2 = ln(PKYRS + K_s)	0.294	0.042			
	Z_3 = TSLE	−0.042	0.011			
	Z_4 = RATE	−0.011	0.004	4,302.3	11.4	<.001

[a] WLM = Working Level Months.
PKYRS = Total packs of cigarettes smoked/365.
TSLE = Time since last exposure (years).
RATE = WLM/number of months in uranium mining.
K_r = Background radon exposure (0.4 WLM/year) × (age − 5).
K_s = Background smoking [(0.005 packs/day) × (Age in days − 5 (365))]/365.
[b] Change in deviance between models can be interpreted as a chi-square test for inclusion of additional terms to the model. Degrees of freedom are equal to number of additional terms.

a restricted range (0–600 WLM), however, a linear model and the power function model provided nearly identical fits to the data from the 1982 vital status follow-up.

In most recent analyses of underground miner data from other studies as well as pooled analyses, a linear excess relative risk (ERR) model has been used (Samet et al. 1991; Lubin et al. 1994; Tomasek et al. 1994). The current update of the Colorado Plateau cohort produced 121 additional lung cancer deaths as well as additional smoking data. Since a linear exposure-response model provides a better way of comparing the recent Colorado Plateau cohort to the BEIR IV model and the recent combined analysis of 11 international cohorts, we decided to investigate the reason for the non-linearity found in earlier analyses of this data.

Table 4 contains the results of models used to explore the linearity of the exposure-response relationship. Inspection of Table 4 indicates that a linear relative risk function provides a good fit to the full range of exposure data when a term representing average exposure rate is added to the model. The quadratic term in cumulative exposure represents a test for non-linearity, which results in no significant improvement in the linear Model ($\chi^2 = 0.0$, $p = 0.99$). We conclude that the better fit of the power function model vs. the linear model in earlier analyses was due to inadequate accounting for the effect of exposure rate. The results in Table 4 showed a significant non-linearity ($\chi^2 = 7.4$, $p = .007$) when the quadratic term was added to the model where exposure rate was not considered. As a final check on the linearity of the dose-response when adjusting for exposure rate, we fit a restricted cubic spline function to cumulative exposure. This approach provides a general picture of the exposure-response relationship free of any assumptions concerning the functional form of the model (Harrell et al. 1988). Fig. 1 shows the shape of the dose-response relationship as estimated by the restricted cubic spline function both adjusted and unadjusted for exposure rate. Examination of this plot clearly shows the relationship is close to linear when exposure rate is considered. All subsequent models included exposure rate and a linear relative risk function to estimate the effect of cumulative exposure to radon decay products.

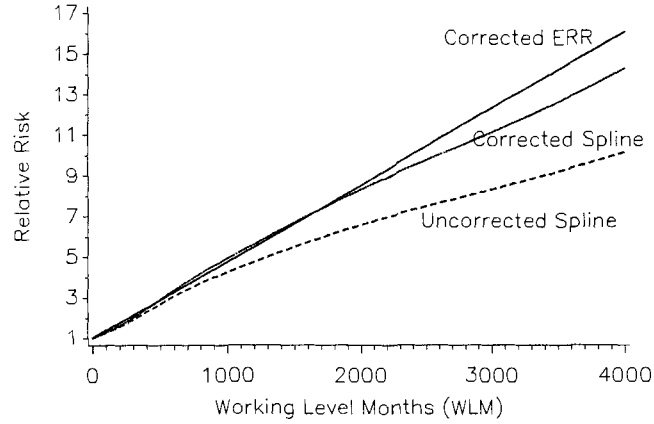

Fig. 1. ERR Model and restricted cubic spline corrected for exposure rate effect vs. Restricted cubic spline uncorrected for exposure rate.

Table 4. Linearity of exposure-response and the effect of exposure rate.
Model: $(1 + \beta_1 \text{ WLM/100}) \exp(\Sigma \beta_i Z_i)$

Model	Variable[a]	Estimate	(Std. Error)	Deviance	χ^2 [b]	p-value
Model 1	WLM/100	0.226	(0.049)	4,317.9		
	Z_1 = ln (PKYRS + K_s)	0.306	(0.042)			
	Z_2 = TSLE	−0.051	(0.010)			
Model 2	WLM/100	0.359	(0.096)	4,310.5	7.4	0.007
	(WLM/100)^2	−0.003	(0.001)			
	Z_1 = ln (PKYRS + K_s)	0.302	(0.042)			
	Z_2 = TSLE	−0.048	(0.010)			
Model 3	WLM/100	0.377	(0.100)	4,296.9		
	Z_1 = ln (PKYRS + K_s)	0.299	(0.042)			
	Z_2 = TSLE	−0.038	(0.010)			
	Z_3 = Rate	−0.013	(0.004)			
Model 4	WLM/100	0.388	(0.118)	4,296.9	0.0	0.99
	(WLM/100)^2	−0.0004	(0.002)			
	Z_1 = ln (PKYRS + K_s)	0.298	(0.042)			
	Z_2 = TSLE	−0.038	(0.010)			
	Z_3 = Rate	−0.013	(0.004)			

[a] WLM = Cumulative exposure in working level months.
PKYRS = Total packs of cigarettes smoked/365.
TSLE = Time since last exposure in years.
RATE = Average exposure rate = WLM/months underground.
K_s = [0.005 packs/day × (Age in days − 5 (365))]/365.
[b] Change in deviance between models can be interpreted as a chi-square test for inclusion of additional terms to the model. Degrees of freedom are equal to number of additional terms.

Effect modification (interaction)

Several risk factors were investigated to ascertain whether the magnitude of the risk coefficient for radon exposure was dependent upon levels of these factors. Attained age showed a strong interaction with cumulative exposure. Since age represented the time dimension over which the changes in the miners cohort were tracked, this interaction indicates a departure from the proportional hazards assumption, i.e., the assumption that relative risk for a given level of radon is constant over time. Both continuous and categorical models indicated a substantial decline in relative risk with increasing age. We chose the model that categorized attained age at <60, 60–70, and >70 for ease of interpretation. The categorical model indicated that a miner under 60 y of age had more than 10 times the excess relative risk per unit exposure than a miner with the same cumulative exposure who was over 70 y of age (1.107 vs. 0.097). Fig. 2 illustrates the striking difference in linear relative risk models for the three age groups. The figure also includes relative risk estimates and 95% confidence intervals for WLM categories corresponding to intervals 0–400, 400–1,000, 1,000–2,000, and >2,000 WLM.

Since the current data include updates of the smoking histories for 66% of the cohort through 1986, we were especially interested in examining the potential interaction of smoking and radon exposure. An analysis of the smoking-radon interaction using follow-up through 1977 concluded that the relationship between these two lung carcinogens was multiplicative (Whittemore and McMillan 1983; Hornung 1985). With an additional 5 y of follow-up through 1982, the interaction appeared to be sub-multiplicative but greater than additive (Hornung and Meinhardt 1987). Since the current data involve an additional 8 y of follow-up and results of the 1986 smoking survey, we hypothesized that the relationship might continue to move closer to additive.

Since the most important potential confounder was cigarette smoking measured in cumulative pack years, we first attempted to find the best function describing the relationship between pack years and lung cancer risk.

Fig. 2. ERR models stratified by three age intervals.

Examination of several functional forms (linear, log-linear, and power function) indicated that the linear function produced the best fit in terms of lower deviance.

We first examined the multiplicative relationship between the linear ERR model for radon and the linear ERR for pack years of smoking. As seen in Table 5, when a term for interaction of these terms was added to the model, the coefficient was negative but not statistically significant ($\chi^2 = 3.2$, $p = .07$). Since the radon ERR was significantly different for the three strata of attained age, we also examined the radon smoking interaction in an age-specific fashion. Again the two-way interaction of radon and smoking in the presence of the age-specific ERR's showed an indication of a sub-multiplicative relationship, although a multiplicative relationship could not be rejected. In an effort to investigate whether the interaction was moving away from multiplicative and closer to additive as the cohort ages, we also examined the three-way interaction of radon, smoking and attained age. As seen in Table 5, the three terms describing the cumulative radon/smoking interaction by age interval result in a significant reduction in the model deviance ($\chi^2 = 8.2$, d.f. = 3, $p = 0.04$). Further inspection of the results in Table 5 indicates that the ERR due to cigarette smoking alone is not age dependent ($\chi^2 = 0.3$, d.f. = 3, $p = 0.86$). In order to determine whether the updated smoking data may have been responsible for the change in radon/smoking interaction across age intervals, we fit the same three-way interaction model to the original smoking data. This analysis did not show any change in the radon/smoking interaction with attained age ($\chi^2 = 1.96$, d.f. = 3, $p = 0.42$). The nature of the overall interaction was submultiplicative, although the multiplicative relationship could not be rejected.

As an additional check on the nature of the radon/smoking interaction, we fit mixed models consisting of an additive and multiplicative contribution to the joint risk. These models were of the form:

$$\lambda(t,z) = [(1 + \beta_1 \mathrm{WLM})(1 + \beta_2 \mathrm{PKYRS})]^{\lambda} \times (1 + \beta_3 \mathrm{WLM} + \beta_4 \mathrm{PKYRS})^{1-\lambda}. \quad (2)$$

This analysis also indicated a submultiplicative relationship, with λ in the 0.3 to 0.4 range, i.e., $\lambda = 1$ implies fully multiplicative, $\lambda = 0$ implies fully additive. Results were consistent with a similar analysis of the Colorado Plateau data using the 1982 follow-up in the study of 11 cohorts of miners (Lubin et al. 1994).

To further explore the potential for modification of the ERR attributed to radon by smoking status, we examined the risk estimates by category of current smoker (as of 1986), former smoker, and never smoker. The results shown in Table 6 agree closely with the results obtained when using quantitative measures of cumulative smoking history. Again the results indicate a sub-multiplicative relationship but a multiplicative interaction cannot be rejected. When fitting a main effects model including cumulative exposure to radon decay products, time since last exposure and exposure rate to the subcohort of miners who never smoked, the ERR

Table 5. Interaction of radon and smoking.
Model: $(1 + \beta_1$ WLM/100$)(1 + \beta_2$ PKYRS$)$ exp $(\beta_3$ TSLE $+ \beta_4$ RATE$)$

Model[a]	Variable	Coefficient	(Std Error)	Deviance	χ^2 [b]	p-value
Main effects	WLM/100	0.382	(0.101)	4,295.2		
	PKYRS	0.057	(0.014)			
Radon/age interaction	WLM (<60)	1.135	(0.590)	4,276.7	18.5	<0.001
	WLM (60–70)	0.194	(0.079)			
	WLM (>70)	0.093	(0.047)			
	PKYRS	0.055	(0.014)			
Radon/age and smoking/age interactions	WLM (<60)	1.134	(0.587)	4,276.4	0.3	0.86
	WLM (60–70)	0.194	(0.079)			
	WLM (>70)	0.094	(0.047)			
	PKYRS (<60)	0.051	(0.019)			
	PKYRS (60–70)	0.051	(0.023)			
	PKYRS (>70)	0.067	(0.067)			
Interaction model: $(1 + \beta_1$ WLM/100$)(1 + \beta_2$ PKYRS$)(1 + \beta_3$ WLM/100×PKYRS$)$ exp $(\beta_4$ TSLE $+ \beta_4$ RATE$)$						
Radon/smoking interaction	WLM/100	0.420	(0.120)	4,293.7		
	PKYRS	0.063	(0.141)			
	WLM×PKYRS	−0.00008	(0.0008)			
Radon/age/PKYRS interaction	WLM (<60)	1.577	(0.759)	4,268.2	8.2	0.04
	WLM (60–70)	0.254	(0.107)			
	WLM (>70)	0.161	(0.070)			
	PKYRS (<60)	0.106	(0.038)			
	PKYRS (60–70)	0.079	(0.042)			
	PKYRS (>70)	0.114	(0.059)			
	WLM×PKYRS (<60)	−0.014	(0.007)			
	WLM×PKYRS (60–70)	−0.002	(0.001)			
	WLM×PKYRS (>70)	−0.0014	(0.00006)			

[a] *All models include* time since last exposure (TSLE) and average exposure rate (RATE).
[b] Change in deviance between models can be interpreted as a chi-square test for inclusion of additional terms to the model. Degrees of freedom are equal to number of additional terms.

coefficient is more than three times the magnitude of the smoking-corrected ERR for all miners (1.268 vs. 0.396). However, this estimate is imprecisely estimated and not significantly different from the overall ERR estimate.

DISCUSSION

The continuing followup of the Colorado Plateau uranium miners cohort makes this the longest-running study that NIOSH has ever done and one of the few examples of a true prospective occupational epidemiologic study. Since the last followup (with vital status through 1982) reported by Hornung and Meinhardt in 1987, there have been 121 additional lung cancer deaths (as of 31 December 1990) and smoking data have been updated to 1986 from 1969. These additional data have further clarified and solidified previous findings as well as providing some new insights concerning the relationship between exposure to radon decay products and lung cancer.

Several temporal factors have strong effects upon estimates of relative risk of lung cancer due to radon exposure. The strongest temporal effect is the interaction of attained age with cumulative exposure. Current analyses indicate that the relative risk of lung cancer drops dramatically with increasing age. These results were generally consistent with a recent joint analysis of 11 miners cohorts (Lubin et al. 1994) that estimated that miners reaching 75 y of age had approximately 22% of the excess relative risk of a similarly exposed miner who was less than 55 y.

Another temporal factor having a strong effect on risk estimates is time since last exposure. We chose to model this risk factor as an exponential function with a continuous variable measured in years since last known underground exposure. Since the coefficient was negative ($\beta = -0.038$) the impact on relative risk was an exponential decay with risk reduced 50% for miners surviving 18 y after last underground mining compared to miners with the same exposure less than 5 y since last underground exposure. Time since last exposure was also examined as an effect modifier, i.e., as an interaction with cumulative radon exposure. This model would make the relative risk coefficient for exposure to radon decay products dependent upon the amount of time since retiring from uranium mining. This effect was not statistically significant when added to a model already including the age interaction (likelihood ratio $\chi^2 = 0.98$, $p = .322$). This may be due to the fact that time since last exposure is strongly correlated with attained age. Since we have already estimated a strong reduction in the strength of the linear relationship between relative risk and radon exposure as the mining population ages, the independent effect of time since last exposure is espe-

Table 6. Radon risk by smoking status.

Model[a]	Variable	Coefficient	(Std Error)	Deviance
Model 1	WLM (<600)	1.194	(0.634)	4,299.4
	WLM (60–70)	0.200	(0.081)	
	WLM (>70)	0.095	(0.047)	
	TSLE	−0.037	(0.010)	
	RATE	−0.014	(0.004)	
	Current smoker	1.169	(0.207)	
	Former smoker	0.797	(0.236)	
Model 2	WLM	1.148	(0.557)	4,295.8
	WLM (60–70)	−0.864	(0.543)	
	WLM (>70)	−0.998	(0.546)	
	TSLE	−0.037	(0.010)	
	RATE	−0.014	(0.004)	
	Current smoker	1.297	(0.340)	
	Former smoker	1.206	(0.367)	
	Current×WLM	−0.050	(0.122)	χ^2 = 3.60, d.f. = 2, p = 0.308
	Former×WLM	−0.150	(0.125)	
	Err model restricted to never smokers			
	TSLE	−0.055	(0.036)	
	RATE	−0.019	(0.016)	
	WLM	1.268	(2.295)	

[a] All models include TSLE and RATE.

cially noteworthy. These findings suggest that there is an incremental reduction in risk with increasing time outside the mines even for older miners with already reduced relative risk. However, the effect does not seem to depend upon different levels of radon exposure as reported in the analysis of 11 miner cohorts (Lubin et al. 1994). Rather, it seems to be related to the general experience of miners exposed to high levels of radon decay products.

The nature of the interaction between cigarette smoking and exposure to radon decay products plays an important role in both risk estimation and public health policy. Results reported in recent analyses of several miners cohorts have ranged from approximately additive (Radford and Renard 1984) to fully multiplicative (Samet et al. 1991). More recent analyses of the 1982 vital status data from the Colorado plateau indicate a sub-multiplicative relationship (Lubin and Steindorf 1995).

Since there is an age difference in many of these cohorts, we attempted to examine the dependence of the radon/smoking interaction on age. In our current analyses, the three-way interaction of radon, smoking, and age was statistically significant, indicating that the radon/smoking interaction changed with attained age. The strong decrease in the ERR for radon with increasing age makes this three-way interaction difficult to interpret. However, our analyses indicate a sub-multiplicative radon/smoking interaction that may depend upon attained age. This three-way interaction was not significant when the older, non-updated smoking data were used. Therefore, the interpretation of the current age interaction is dependent upon the accuracy of the new smoking data. We believe the updated smoking data are a definite improvement over the older data, but there may have been a tendency for some miners to underestimate their smoking habits because of compensation issues. If this age dependency is a general phenomenon, it may partially explain why analyses of individual cohorts with different age distributions often disagree on the nature of the radon/smoking interaction. It also points to the importance of using combined analyses across cohorts to gain a better understanding of this important relationship.

Recent pooled analyses of six of the 11 miner cohorts containing at least some smoking data indicated that the combined effect was sub-multiplicative, with never smokers having almost three times the risk per WLM as smokers (Lubin et al. 1994). The current analysis of the Colorado Plateau data supports this estimate. Examination of the smoking/radon interaction using the most recent data on smoking is consistent with a sub-multiplicative effect whether using a quantitative measure of smoking (pack years) or a categorical separation of miners into never, former and current smokers. The excess relative risk per WLM is more than 3 times higher in never smokers compared to those miners who ever smoked cigarettes. This estimate is also supported by a study of the non-smoking Colorado Plateau miners that found a much larger Standardized Mortality Ratio (SMR = 12.7) than for the entire cohort (SMR = 5.8) (Roscoe et al. 1989). Although not examined in our analyses, another possible explanation for a submultiplicative interaction of radon and smoking is the temporal relationship of the joint exposures. Thomas et al. (1994) showed that smoking that started prior to beginning uranium mining produced a sub-multiplicative interaction, while mining before beginning to smoke produced a greater than multiplicative interaction. Since the large majority of miners began smoking before mining, these results are consistent with our sub-multiplicative estimate.

In addition to the effect of smoking, another factor that has substantial relevance to the estimation of risk to indoor radon is the exposure rate effect. The nature of this effect has been more closely examined in this analysis. However, the result that cumulative exposure received at lower average levels of radon produces higher risk of lung cancer has not changed substantially since it was first reported in 1981 (Hornung and Samuels 1981). In the current analysis, the negative exposure rate effect was actually shown to be an important factor in producing the concave downward dose response reported in the last analysis of the Colorado Plateau data (Hornung and Meinhardt 1987). When the model is corrected for the exposure rate effect, the exposure-response is linear in all age strata. This is consistent with the linearity found by Lubin et al. (1994) when the Colorado data was restricted to lower cumulative exposures (<3,200 WLM). In addition, the current data suggest that the negative exposure rate effect may diminish or disappear at lower levels of cumulative exposure. In this sense, the results are consistent with the recent findings of Tomasek et al. (1994), which indicated that miners in West Bohemia never exposed above 10 WL showed no evidence of an exposure rate effect. The Colorado Plateau miners also

showed no significant exposure rate effect below 10 WL. When miners exposed below the mean cumulative exposure (834 WLM) were compared to miners exposed above 834 WLM, the exposure rate effect was three times lower. This is also consistent with the analysis of 11 miner cohorts (Lubin et al. 1995a), which showed a diminution of the exposure-rate effect below 50 WLM. In addition, animal studies have also shown a reduction in the inverse exposure-rate effect at lower cumulative exposures (Gilbert et al. 1996). These results support the theory proposed by Brenner et al. (1993) that the negative exposure rate effect is only seen at higher radon levels due to multiple traversals of target cells which result in redundant exposure. However, another theory proposed by Elkind holds that the negative exposure rate effect in protracted exposures can be explained by the timing of exposure at the time of cell mitosis (Elkind 1992). This theory would predict negative exposure rate effects down to indoor radon levels. The current data appear to indicate that the exposure rate effect substantially diminishes at environmental levels. Whatever theory is correct, it is clear that the most accurate current estimates of excess relative risk attributed to indoor radon will be produced by correcting miners data for the exposure rate effect. This may be accomplished by reporting ERR estimates after stratification of dose response analyses at the lower exposure rates (<10 WL) or cumulative exposures (<800 WLM), although examination of risk estimates at reduced exposure levels in WL is the most direct way of investigating the exposure-rate effect.

A final word is necessary on the potential for errors in measuring exposure factors to affect the results of these analyses. Measures of cumulative exposure to radon decay products are subject to both random errors and systematic bias. Random errors are those associated with using area measurements in fixed locations in the mines to assign exposures to all miners working in that mine during the years when measurements were done. There are also errors associated with interpolating and extrapolating exposure estimates when no measurements were made in a given year. The combined effect of these sources of random error has been estimated as a relative standard deviation of 97% (Hornung 1985). Systematic bias in estimated exposures may have occurred due to the use of mine inspector data before 1960. Mine inspectors may have measured the highest areas of the mines rather than a true cross-section of exposures typically experienced by workers (Lundin et al. 1971).

The effect of both of these types of errors generally results in an underestimation of the true relative risk. Newer statistical methodology has been developed to correct biases in risk estimates for exposure measurement error (Prentice 1982). However, the error distributions necessary for implementation of this methodology are not well-estimated for the Colorado Plateau data. Another possible effect of such errors, particularly in the estimation of exposure levels in the early years, may be to induce curvilinearity in the exposure-response models (Stefanski and Carroll 1985). This may be a partial explanation of the result that correction for the exposure-rate effect removes non-linearity in the exposure-response function. Although the magnitude of any potential bias due to random or systematic errors is difficult to estimate, the nature of these errors would appear to reduce risk estimates in analyses of these data.

In summary, the most recent update of vital status and smoking history of the Colorado Plateau uranium miners cohort suggests that summary estimates of lung cancer risk as a function of level of exposure to radon decay products should not be reported. The results obtained in this current analysis are consistent with the findings reported in a combined analysis of 11 miner cohorts (Lubin et al. 1994). This analysis, as well as several other recent publications, indicates that ERR estimates are strongly age-dependent and must also be corrected for exposure rate, time since last exposure and cigarette smoking history. The age dependence of the radon/smoking interaction found in this analysis may explain apparent disagreements in estimates of the nature of this interaction reported in cohorts with different age distributions.

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