

# Modifiers of Exposure–Response Estimates for Lung Cancer among Miners Exposed to Radon Progeny

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The association between lung cancer and exposure to radon decay products has been well established. Despite agreement on this point, there is still some degree of uncertainty regarding characteristics of the exposure–response relationship. The use of studies of underground miners to estimate lung cancer risks due to residential radon exposure depends upon a better understanding of factors potentially modifying the exposure–response relationship. Given the diversity in study populations regarding smoking status, mining conditions, risk analysis methodology, and referent populations, the risk estimates across studies are quite similar. However, several factors partially contributing to differences in risk estimates are modified by attained age, time since last exposure, exposure rate, and cigarette smoking patterns. There is growing agreement across studies that relative risk decreases with attained age and time since last exposure. Several studies have also found an inverse exposure–rate effect, i.e., low exposure rates for protracted duration of exposure are more hazardous than equivalent cumulative exposures received at higher rates for shorter periods of time. Additionally, the interaction between radon exposure and cigarette smoking appears to be intermediate between additive and multiplicative in a growing number of studies. Quantitative estimates of these modifying factors are given using a new analysis of data from the latest update of the Colorado Plateau uranium miners cohort. — *Environ Health Perspect* 103(Suppl 2):49–53 (1995)

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## Introduction

The association between lung cancer and radon gas ( $^{222}\text{Rn}$ ) and its decay products (radon progeny) has been well documented (1–4). Despite the abundance of evidence that exposure to radon decay products causes lung cancer, there is still uncertainty concerning the characteristics of the exposure–response relationship. Among the issues still being debated are the appropriateness of using epidemiologic studies of miners for indoor radon risk estimates, the existence and nature of an exposure–rate effect, the form of the radon/smoking interaction, and modification of relative risk by a number of temporal factors. These issues must be addressed to provide a better understanding of lung cancer risks to both miners and the general public.

Next to cigarette smoking, radon exposure poses the greatest risk of lung cancer, with an estimated 6600 to 24,000 lung cancer deaths per year in the United States attributable to indoor radon and its decay

products (5). Even though extrapolation from miner populations to indoor environments is problematic, the miner-based risk models remain essential to our understanding of the radon/lung cancer relationship. A number of case–control studies of indoor radon have been initiated in recent years; but these studies often have serious methodologic problems, especially in accurately assessing historical indoor exposure levels. Because of the lack of accurate exposure data to characterize retrospective indoor radon levels, it is necessary to examine important determinants of the radon/lung cancer risk relationship in underground miners.

The purpose of this presentation is to provide an overview of current occupational epidemiologic studies of radon decay products, with particular attention to the nature of the exposure–response models and factors that may modify this relationship. The latest results of many international miners studies will be presented, with quantitative examples from a new update and analysis of uranium miners from the Colorado Plateau of the western United States. Since this presentation is directed at a broader view of exposure–response modifiers across several different studies, details of the new analysis of the Colorado Plateau study will not be provided. An article reporting an in-depth description of the latest analysis is in preparation.

## Form of the Exposure–Response Model

Most attempts to quantify the dose–response relationships in radon research have centered on the linear relative risk model (4,6). There are persuasive arguments for a linear relationship made by radiobiologists using the one-hit theory and other mechanistic models. Another advantage of the linear model is that its simplicity facilitates comparisons across various study populations.

This review of risk models across different epidemiologic studies of miners will focus on the linear model. In most studies relative risk models are the method of choice since they provide an adequate fit to most data and they are generally simpler in form than attributable risk models. The general form of the linear relative risk model is:

$$\lambda(t,z) = \lambda_0(t)(1 + \beta z)$$

where  $\lambda(t,z)$  is the lung cancer mortality rate at age  $t$  with exposure  $z$ ,  $\lambda_0(t)$  is background or unexposed lung cancer mortality rate at age  $t$ , and  $\beta$  is the linear risk coefficient to be estimated.

Table 1 summarizes the linear relative risk relationships in seven of the major studies of underground miners. With the exception of the Colorado Plateau data, the estimates range from 0.6 to 3.6% excess

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**Table 1.** Exposure–response relationship in seven miners studies.

Study	Excessive relative risk/WLM	Reference
Chinese tin miners	0.6%	Xuan et al. (12)
Czech uranium miners	1.5%	Sevc et al. (9)
Beaverlodge (Canada) uranium miners	3.3%	Howe et al. (10)
Ontario (Canada) uranium miners	1.3%	Muller et al. (24)
Newfoundland fluorspar miners	0.9%	Morrison et al. (7)
Swedish iron miners	3.6%	Radford and Renard (11)
Colorado Plateau (US) uranium miners	0.2–1.6% <sup>a</sup>	Hornung et al. (25)

<sup>a</sup>Reported as a range due to modification of relative risk by temporal factors, exposure rate, and cigarette smoking. Lowest risk is for older miners, longer time since last exposure, and higher exposure rates.

relative risk per unit exposure (working-level month [WLM]). A working-level month is defined as any combination of exposure time and exposure level equivalent to 170 hr at one working level (WL). One WL is the concentration of short-lived radon decay products per liter of air giving rise to  $1.3 \times 10^5$  MeV of  $\alpha$ -radiation. Given the wide difference in populations in these studies, smoking habits, type of mining conditions, and risk analysis methodology, these estimates are fairly homogeneous. However, there are several factors that may further explain much of the difference in these risk estimates.

Because of the existence of a number of such effect modifiers (interactions) in the Colorado Plateau data, Table 1 reports a range of relative risk coefficients rather than a single, possibly misleading, overall estimate of excess relative risk.

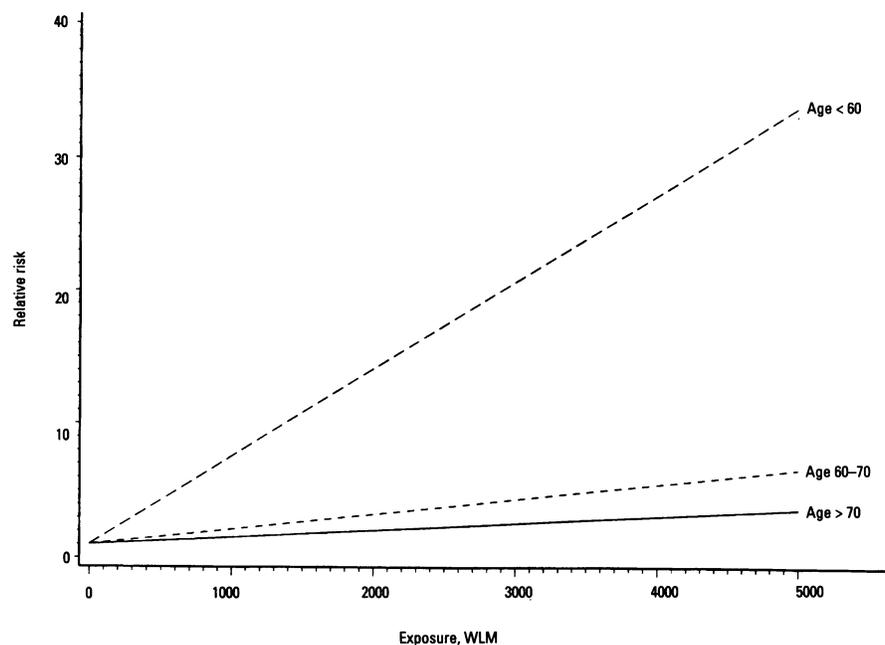
## Modifiers of Relative Risk Estimates

### Attained Age

The background risk of lung cancer rises rapidly after age 40, reaching a peak in the late 60s or early 70s. For linear relative risk estimates to be meaningful, they must remain stable over all age ranges. In many recent analyses of mining cohorts, there has been a discovery of a decrease in relative risk per WLM with increasing age at risk (3,4,7–9). One explanation for this phenomenon may be that the high relative risks estimated for large exposures would be difficult to maintain as background lung cancer risks rise in older age groups. This implies that the proportional hazards assumption for relative risk models, i.e., that excess risk is proportional to background at all ages, does not hold. If this is a general pattern in all radon-exposed cohorts, then it is misleading to cite an overall risk coefficient. Only age-specific risk coefficients would be meaningful. Comparison of results among several studies would require estimation of excess rela-

tive risk for each of several age intervals. Since most of the miners cohorts listed in Table 1 have quite different age distributions and each generally reports overall relative risk, this may partially account for differences in risk coefficients.

In our recent analysis of the Colorado Plateau uranium miners cohort, we quantitatively modeled the relative risk of lung cancer as a function of cumulative radon exposure for three different intervals of attained age: < 60, 60–70, and > 70. We chose a linear relative risk model versus the power function model used in an earlier analysis (3) because the linear model now produces slightly lower deviance in the updated follow-up through 1990 and is simpler to interpret. Plots of the three linear relationships are given in Figure 1. Table 2 contains relative risk estimates for several combinations of cumulative exposure and attained age.

**Figure 1.** Age-specific linear relative risks.

## Time since Last Exposure

Most of the miners in Table 1 worked for relatively short periods in underground mining compared to typical duration of employment in other occupational studies. The average duration of exposure ranged from approximately 2 years for the Beaverlodge study (10) to 18 years for the Swedish study (11). The mean duration of underground exposure among the Colorado Plateau miners was approximately 4 years. For this reason, much of the time of follow-up in these studies includes inactive person-years, i.e., person-years when no additional exposure to occupational radon progeny is occurring. It is of interest, therefore, to determine if relative risk estimates change with increasing time since last exposure.

Several studies have found that there is a statistically significant decline in relative risk with increasing time since last underground mining (3,4,9,12). Although time since last exposure is certainly correlated with age, these effects seem to be independent, at least in the Colorado Plateau study and the BEIR IV combined analysis of four cohorts. If this effect is applicable to other cohorts (some of which made no mention of having tested for it), we have a second temporal factor that could account for observed differences in risk coefficients across miners studies.

Our analysis of the Colorado Plateau data models the effect of time since last exposure as an exponential decay in relative risk. The half-life of age-specific relative

**Table 2.** Relative risk among Colorado Plateau miners, by exposure and age categories using the linear relative risk model for exposure and adjusting for smoking and time since last exposure.

Exposure	Age		
	< 60	60-70	> 70
50 WLM	1.33 [1.07,1.58]	1.06 [1.01,1.10]	1.03 [.99,1.05]
100 WLM	1.66 [1.13,2.18]	1.11 [1.03,1.20]	1.05 [.99,1.11]
500 WLM	4.28 [1.67,6.88]	1.56 [1.14,1.99]	1.27 [.99,1.55]
1000 WLM	7.56 [2.34,12.77]	2.13 [1.28,2.98]	1.53 [.98,2.09]
5000 WLM	33.79 [7.73,59.84]	6.64 [2.41,10.87]	3.67 [.89,6.45]

risk is approximately 15 years after the end of effective exposure (retirement from mining plus 5-year lag). This means that the relative risk for a given cumulative exposure is reduced by 50%, 15 years after effective exposure, compared to current miners and those within 5 years of last exposure. Figure 2 represents a plot of the proportional decline in relative risk as a function of years since last exposure.

### Exposure Rate

Most studies of the relationship between exposure to radon progeny and lung cancer utilize cumulative exposure as the primary causative agent. The use of cumulative exposure carries with it the implicit assumption that exposures to high levels for short periods are etiologically equivalent to long-term exposures to low levels of radon progeny. Animal and *in vitro* studies (13-15) have shown that the exposure rate or intensity is an important factor in addition to cumulative exposure. Specifically, these studies indicated that protracted

exposures at low levels of exposure were more carcinogenic than shorter term exposures to high levels of  $\alpha$ -radiation. A similar effect was observed for epidemiologic studies in earlier analyses of the Colorado Plateau uranium miners (3,16).

Since then, an inverse dose-rate effect has also been observed in several other studies of miners (9,17,18). Although similar effects have not been observed for low Linear Energy Transfer (LET) radiation, i.e.,  $\gamma$ -radiation, X-rays, etc., there have been at least two explanations offered for the presence of an inverse effect in  $\alpha$ -radiation studies. Brenner and Hall (19) suggest that one would expect an inverse dose-rate effect at higher dose rates due to the wasted dose from multiple traversals of individual lung epithelial cell nuclei when one traversal is sufficient to cause genetic alterations. Elkind (15) hypothesizes that cells are more sensitive to transformation during certain time windows near mitosis. This would make protracted exposures more hazardous since more cells would

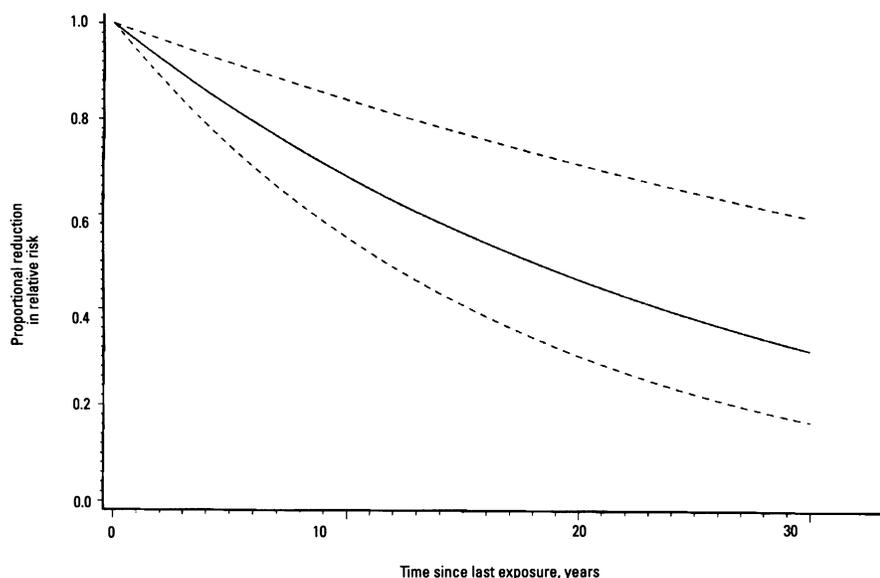
progress into the sensitive windows over a long period without a high probability of being killed.

We reestimated the dose-rate effect in our most recent analysis of the Colorado Plateau uranium miners study. We considered exposure rate both as an independent multiplicative effect on the linear cumulative exposure model and as an effect modifier by introducing an interaction term between cumulative exposure and exposure rate. The latter model was simplified by examining the interaction of exposure rate with a dichotomous variable for cumulative exposure indicating cumulative exposure above or below the mean for the cohort.

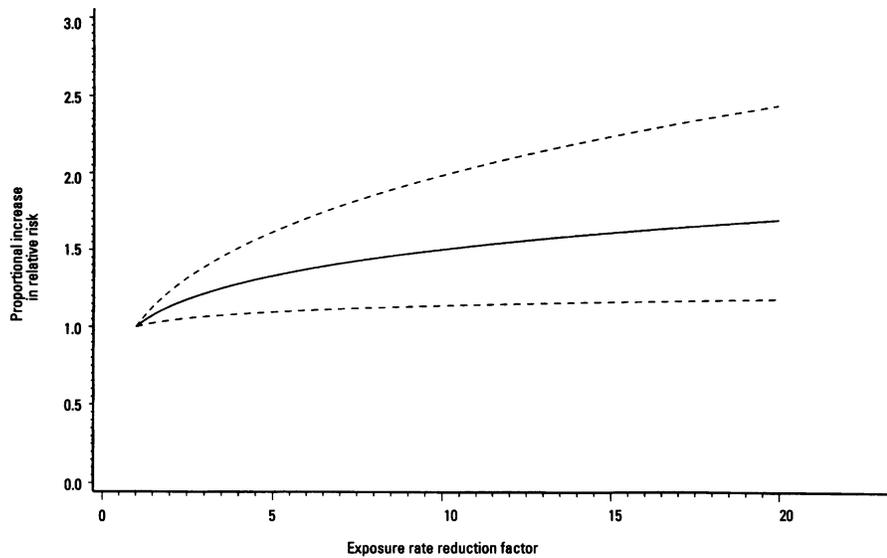
When exposure rate was introduced as an independent effect in the risk model, the regression parameter was negative ( $\beta = -0.18$ ,  $SE = 0.06$ ), indicating a higher risk for protracted exposures. The magnitude of the estimate was larger than previously estimated using vital status follow-up through 1982 (3). Our current analysis indicated that a 10-fold reduction in dose rate will increase the relative risk by 51%. Figure 3 illustrates the protraction effect as a function of exposure rates. When the interaction of exposure rate and cumulative exposure was introduced into the model, the result was not statistically significant ( $p = 0.06$ ), but suggestive of a stronger inverse effect at higher levels of exposure.

### Radon/Smoking Interaction

One of the most important issues regarding the lung cancer risk associated with radon exposure is the effect of cigarette smoking on this relationship. Conclusions as to the nature of this interaction have varied across different studies. Radford and Renard (11) reported that the interaction among Swedish iron miners was additive, i.e., the relative risk for a miner who smoked was roughly the sum of the relative risks for radon progeny exposure and cigarette smoking. A similar finding was reported by Sevc et al. (8) for the Czech uranium miners. An analysis by Samet (20) of a cohort of New Mexico uranium miners (largely distinct from the Colorado Plateau cohort) indicated that the interaction was essentially multiplicative. This would imply that the joint effect of exposure to radon decay products and cigarette smoking can be estimated as the product of their individual relative risks. The combined analysis of four cohorts (Colorado, Swedish, Ontario, and Beaverlodge) by the BEIR IV Committee (4) found an interaction intermediate between additive and multiplicative. A similar intermediate effect was reported in



**Figure 2.** Decline in relative risk as a function of time since last exposure; 95% confidence intervals denoted by broken lines.



**Figure 3.** Increase in relative risk as a function of an x-fold reduction in exposure rate; 95% confidence limits denoted by broken lines.

the most recent analysis of the Chinese tin miners cohort (12).

The analyses of the Colorado Plateau data benefited from the fact that it is the only miners cohort with smoking information on each member of the study. An earlier analysis of these data with vital status follow-up through 1977 indicated a multiplicative radon/smoking interaction (21,22). With an additional 5 years of follow-up (vital status through 1982), the relationship appeared to be intermediate between additive and multiplicative (3).

Since those analyses, NIOSH has conducted a smoking status survey of surviving miners and next of kin of deceased miners.

**Table 3.** Results of NIOSH smoking survey.

	Respondents	Nonrespondents
Total number	2205	1142
Alive	1330	304
Deceased	867	832
Unknown	8	6
Lung cancers	224	153
Median exposure	420	449
Prior smoking category, <sup>a</sup> percent		
Never	20	13
Current	69	79
Former	11	8
New smoking category, <sup>b</sup> percent		
Never	17	—
Current	32	—
Former	51	—

<sup>a</sup>Smoking status distribution based upon data collected prior to 1969. These data were used in all previous analyses of Colorado Plateau data. <sup>b</sup>Smoking status distribution reported by respondents to questionnaire mailed in 1986. Results from this questionnaire were used to update smoking data when appropriate.

Table 3 illustrates the reported changes in smoking status since the previous survey with smoking data through 1969 (23).

We used these new smoking data to more closely examine whether the radon/smoking interaction was continuing to move away from multiplicative toward additive. Results indicated that the interaction was still intermediate between additive and multiplicative and had not changed substantially since the 1982 follow-up, even though there were 8 additional years of mortality data. There is, however, a suggestion that the interaction is decreasing from multiplicative as follow-up lengthens and the cohort ages, although this trend is not statistically significant. Table 4 shows the nature of the radon/smoking interaction by length of follow-up for several miners cohorts.

### Discussion

There is no doubt as to the causative relationship between exposure to radon progeny and lung cancer. All of the studies of miners have demonstrated a strong exposure-response relationship. What remains as a matter for additional study is the accurate estimation of the excess risk per unit of

exposure and the identification and nature of factors that alter this relationship. Table 1 indicates that the differences in risk coefficients are not great given substantial differences in study populations, referent populations, and statistical methods of analysis. However, several factors have been identified in a number of studies which could further account for observed differences in excess relative risk. These factors include age, time since last exposure, exposure rate, and cigarette smoking. Since all studies of miners differ to some degree with respect to the distribution of these factors, it is important to consider their effects when comparing risk coefficients across studies.

Investigation of the effect of these modifying factors is especially important when considering the risk to the general population from indoor radon. The use of results from studies of underground miners to estimate risks from radon in the home environment is widely debated. However, the limitations in case-control studies of indoor radon, such as the lack of data on historical exposures and generally low statistical power, make the results from studies of miners our best source for current indoor risk estimates.

The effects of these modifying factors have important implications with regard to understanding the indoor radon problem. For example, if the interaction of cigarette smoking and radon exposure is multiplicative then there is enormous benefit to smoking cessation programs in high radon areas. However, if the effect is submultiplicative, the risk to nonsmokers may be substantial on a relative-risk scale. Similarly, if the inverse exposure-rate effect holds at the lower levels experienced in homes, then extrapolation from the higher exposed mining populations could actually underestimate risk to the public. A decrease in relative risk with the temporal effects of attained age and time since last exposure would emphasize the potential benefit of radon mitigation programs, especially for younger residents. We believe that further examination of these modifying factors is the key to a responsible public health response to the radon problem.

**Table 4.** Nature of radon/smoking interaction by length of follow-up.

Study	Length of follow-up	Joint effect	Reference
Colorado Plateau	30 years	Submultiplicative	Hornung et al. (25)
Swedish iron miners	44 years	Additive to submultiplicative	Radford and Renard (11)
Czech uranium miners	25–30 years	Additive to submultiplicative	Sevc et al. (9)
New Mexico uranium miners	18 years	Multiplicative	Samet (20)

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