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Biologically Based Analysis of the Data for the Colorado Uranium Miners Cohort: Age, Dose and Dose-Rate Effects

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This study is a comprehensive analysis of the latest follow-up of the Colorado uranium miners cohort using the two-stage clonal expansion model with particular emphasis on effects related to age and exposure. The model provides a framework in which the hazard function for lung cancer mortality incorporates detailed information on exposure to radon and radon progeny from hard rock and uranium mining together with information on cigarette smoking. Even though the effect of smoking on lung cancer risk is explicitly modeled, a significant birth cohort effect is found which shows a linear increase in the baseline lung cancer risk with birth year of the miners in the cohort. The analysis based on the two-stage clonal expansion model suggests that exposure to radon affects both the rate of initiation of intermediate cells in the pathway to cancer and the rate of proliferation of intermediate cells. However, in contrast to the promotional effect of radon, which is highly significant, the effect of radon on the rate of initiation is found to be not significant. The model is also used to study the inverse dose-rate effect. This effect is evident for radon exposures typical for mines but is predicted to be attenuated, and for longer exposures even reversed, for the more protracted and lower radon exposures in homes. The model also predicts the drop in risk with time after exposure ceases. For residential exposures, lung cancer risks are compared with the estimates from the BEIR VI report. While the risk estimates are in agreement with those derived from residential studies, they are about two- to fourfold lower than those reported in the BEIR VI report. © 1999 by Radiation Research Society

INTRODUCTION

Residential radon exposure has been recognized as a risk factor for lung cancer in humans for well over 20 years (*1–3*). However, there are few epidemiological studies that directly address the association of residential radon with lung cancer. These studies are at best only broadly consistent with the risk estimates extrapolated from the studies of various underground miner cohorts (*4–6*), probably because of the large uncertainties in ascertaining individual lifetime radon exposures in homes. Consequently, the Committee on Health Risks of Exposure to Radon in its BEIR IV and VI reports (*1, 3*) based its risk estimates for lung cancer from environmental radon on extrapolation from the studies of miners.

In extrapolating lung cancer risk from the mining environment to the home environment, it must be remembered that the radon exposures received by miners are typically 10- to 100-fold higher than those received by individuals in their homes. On the other hand, the time miners spend underground is generally much shorter than the time spent in residences. These differences in exposure patterns are difficult to address with common methods of risk analysis that merely provide empirical descriptions of the data in various strata of cumulative exposure. For example, the rather detailed temporal information on radon exposures and cigarette smoking available in the data for the Colorado uranium miners cohort has hitherto not been fully considered in the mostly empirical analyses of that cohort (*7–10*).

Our analysis is based on the two-stage clonal expansion model of carcinogenesis that has been shown to be consistent with many epidemiological and experimental data sets as outlined below. The model considers explicitly the effects of a carcinogenic agent on the initiation, transformation and proliferation of intermediate cells on the pathway to cancer (*11–13*). It is this feature of the two-stage clonal expansion model that sets it apart from other more empirical models and allows the results to be interpreted in terms of key biological events. The model has also been shown to predict an inverse dose-rate effect: Protraction of a given cumulative dose of radon results in a higher lifetime tumor probability (*14*). Within the framework of the two-stage clonal expansion model, the inverse dose-rate effect can be attributed to the existence of a promotional effect of radon on the intermediate cell pool. While the existence of an inverse dose-rate effect at moderate and high radon levels is widely accepted, it has been called into question at lower rates of exposure (*5*), say below 10 WLM/month. Here we use the two-stage clonal expansion model to investigate the

TABLE 1
Quartile Ranges for Various Covariates of Interest (whites and nonwhites)

	1	2	3	4
Birth year	1877–1913	1913–1923	1923–1932	1932–1944
Age at start of smoking	4–16	16–18	18–21	21–71
Smoking (pack-years)	0–1.2	1.2–23.9	23.9–43.5	43.5–196.6
Age at first job in mine	8–23	23–29	29–40	40–73
Radon (WLM) uranium mines only	0.3–154	154–430	430–1034	1034–10000
Radon (WLM) uranium mines and hard rock	1–170	170–444	444–1039	1039–10000
Radon mean exposure rate (WLM/month) uranium mining only	0.03–5.2	5.2–10	10–17.4	17.4–998

low-dose and dose-rate behavior of the lung cancer risks from radon exposures in mines to predict the lung cancer risk from typical exposures in homes. Because the model incorporates explicitly detailed patterns of exposure in individual miners, this extrapolation directly addresses the different exposure patterns in the two environments.

In a previous analysis of the Colorado uranium miners cohort (*14*) (1984 follow-up), we were able to show that the two-stage clonal expansion model fit the data adequately and was consistent with previous findings (*7, 9*). However, in that analysis we did not fully consider the individual patterns of radon exposure and cigarette smoking available in the data set released by the National Institute for Occupational Safety and Health (NIOSH), but used single periods of radon exposure and cigarette smoking (for smokers) averaging the respective exposures. Thus, for each miner in the cohort, we computed an average radon dose rate (in WLM/month) by dividing the cumulative exposure experienced in the mines (in WLM) by the cumulative time on the job (in months).

Compared to the first two-stage model analysis of the miners cohort, we have 6 more years of follow-up with updated information on cigarette smoking (see ref. *10* for details). Moreover, we use a fully identifiable parameterization of the model that does not require the assumption of equality of the first and second mutation rates and does not require knowledge of the number of susceptible stem cells in the human lung. The use of this new parameterization in conjunction with recently developed algorithms for efficient computation of the hazard function for piecewise constant parameters also makes it possible to include all the available covariate information, including detailed patterns of exposure for both radon and cigarette smoke, in the likelihood-based analysis of these data (see refs. *15, 16*). Finally, we also improve on previous analyses of the data for the miners by explicitly including the radon exposures from prior hard rock mining.

THE COLORADO URANIUM MINERS DATA

The U.S. Public Health Service (USPHS) established a database on 3,347 white and 756 nonwhite male uranium miners working in the Colorado Plateau (located within the states of Colorado, Utah, New Mexico and Arizona) between 1950 and 1964. Recently, the database was updated to include vital status follow-up until at least December 31, 1990, with a large fraction of miners that were still alive actually being followed up until 1995. Also, additional information on smoking was ascertained by a questionnaire survey by mail or telephone in 1986 (for details, see refs. *9, 10*). The data, as compiled by NIOSH, provide individual covariate information on smoking patterns and on radon exposure from hard rock and uranium mining. Radon exposures are given in terms of up to nine times during the working history of a miner, when the cumulative exposure crossed the thresholds of 60, 120, 360, 600, 840, 1800 and 3720 WLM. About 40% of the miners were also exposed to radon while mining hard rock prior to uranium mining. For these miners, the number of years mining hard rock and the respective cumulative radon exposure are also given. For cigarette smoking, up to five times are listed when smoking levels (in packs/day) changed.

For each miner in the cohort, we computed a piecewise constant pattern of radon exposure based on the times when changes in the cumulative radon exposure occurred. Thus, for the interval defined by two adjacent times, we derive a radon dose rate (in WLM/month) by dividing the incremental exposure (in WLM) by the length of the interval (in months). To account for hard rock mining, an additional interval was defined for those miners that also worked in hard rock mines. This interval was inserted prior to the start of uranium mining, reflecting the time spent in hard rock mines and the average radon exposure received during that time. Note that for the purposes of our analyses all age-specific risk functions were effectively truncated at a lag time $t - t_{lag}$, reflecting the assumption that the disease status at age t could not be affected by exposures after the lagged time.

From the total of 3,347 white miners we excluded 109 miners (3.3%) from our analyses because of unknown vital status, missing ICD code when deceased, or inconsistencies in the covariates. We also excluded pipe smokers from the analysis.

For each individual birth year, age at entry into the study (first medical examination), attained age, and vital status are given. If the miner died before the end of follow-up, the listed ICD code (*17*) indicates his cause of death. Only miners with ICD code 162 (malignant neoplasms of trachea, bronchus and lung) were chosen by us to represent lung cancer cases. ICD code 163 (referring to pleura as of the 8th revision of the ICD code in 1965) was not used. A summary of important properties and indicators of the data is given in Table 1. All age- and time-related variables are expressed in terms of years.

THE TWO-STAGE CLONAL EXPANSION MODEL

The two-stage clonal expansion model provides a stochastic description of carcinogenesis that explicitly acknowledges the effects of initiation and promotion of cells. The model has been applied to several experimental and epidemiological data sets (*18–27*), including an analysis of the Colorado uranium miners cohort with follow-up until 1984 (*14*).

In a recent reanalysis of the data from the Pacific Northwest Laboratory study of rats (*20*) using the two-stage clonal expansion model, the model predicted an inverse dose-rate effect of the radon progeny/ore dust mixture. It is noteworthy that the predicted protraction effects were based entirely on the interplay between initiation and promotion of intermediate cells, without invoking the hypothesis of a sensitive window in the cell cycle (*28, 29*).

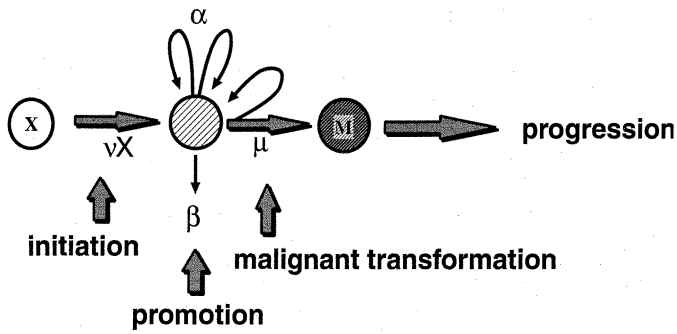

FIG. 1. Pictorial representation of the two-stage clonal expansion model.

The two-stage clonal expansion model constitutes a mathematical framework in which specific covariate information (e.g. exposure patterns) can be incorporated explicitly into parameters for cell proliferation and mutation rates. The mathematical and statistical properties of this and similar models have been discussed in considerable detail in the literature and will not be repeated here (e.g. see refs. *13, 15, 30–34*). Heidenreich *et al.* (*16*) address the problem of parameter identifiability and provide simple iterative algorithms for the computation of the exact hazard and tumor probability functions for piecewise constant parameters. For completeness, a brief description of the basic model assumptions relevant to radon- and smoking-induced lung cancer follows.

In the tissue of interest there exist cells—in the lung thought to be the basal or secretory cells lining the bronchial tubes—that are susceptible to malignant transformation. Mutational events that are required for the initiation of premalignant cells may be caused either spontaneously or by specific carcinogenic agents including α-particle radiation from radon and its decay products. A cell that has sustained such events is called an initiated cell. A primary initiated cell together with its daughter cells is called a clone of initiated cells. The process of clonal growth of initiated cells is called promotion, leading to the appearance of premalignant lesions. Promotion may be enhanced by nongenotoxic effects of the carcinogen in question or by concomitant exposures to promoting agents such as cigarette smoke or uranium ore dust.

Eventually, premalignant clones, unless they become extinct, sustain further genomic damage that may lead to one or more malignant cells, and ultimately to a malignant tumor.

To be specific, let $X(s)$ represent the number of normal susceptible cells in the tissue of interest at time (age) s, and suppose that initiated cells, that is cells that have sustained the first rate-limiting event in the pathway to malignancy, arise from normal cells as a nonhomogeneous Poisson process with intensity $\nu(s)X(s)$, where ν is a parameter defining the rate of critical genomic events involved in initiation. Note that ν and X are not separately identifiable. However, information on one or the other may be available from independent sources. In a small interval at time s, an initiated cell divides into two intermediate cells with rate $\alpha(s)$; it dies or differentiates with rate $\beta(s)$ (note that death and differentiation are equivalent events for carcinogenesis, because both events remove the cell from the pool of susceptible cells); it divides into one intermediate cell and one cell that has sustained the second event (malignant cell) with rate $\mu(s)$. A pictorial representation of the two-stage clonal expansion model is shown in Fig. 1.

In many applications, the parameters are assumed to be constant or piecewise constant, in which case exact expressions of the hazard function and the probability of tumor are available (see refs. *13, 15, 16*). Because not all biological parameters are identifiable when analyzing data on tumor incidence, either suitable constraints or identifiable parameter combinations have to be chosen.

In the earlier analysis by Moolgavkar *et al.* (*14*), the two-stage clonal expansion model was employed with the constraint of equality of the spontaneous rates of the first and second mutation. In addition, that approach required that the number of susceptible stem cells X be fixed. In the present approach, we use a parameterization that is strictly identifiable without making any assumptions regarding the number of stem cells or the equality of mutation rates.

When parameters are constant, there are three identifiable parameters which are related to the biological parameters α, β, νX and μ as follows:

$$y = \nu X\mu;$$

$$g = \alpha - \beta - \mu;$$

$$q = \alpha(B - 1).$$

Here B is the upper root of the quadratic $\alpha x^2 - (\alpha + \beta + \mu)x + \beta$. As is shown by Heidenreich *et al.* (*26*), when parameters are piecewise constant, we can also identify the second mutation rate, up to a constant. Without loss of generality, we choose this constant as the background rate of the second rate-limiting step, μ_o, and define the additional parameter

$$m = \mu/\mu_o.$$

Note that the parameter y can then be redefined and written simply as $y = \nu X\mu_o$ which is the form of y used here.

Biologically, the parameter g measures the net proliferation of intermediate cells, and the parameter y measures the rate of initiation among normal cells times the background rate μ_o, which is assumed to be constant. The parameter q is related to the asymptote of the hazard function; i.e., the hazard approaches the value y/q as $t \to \infty$, and the parameter m follows the changes in the rate of the second rate-limiting step relative to its background.

Using the recursive algorithms we have developed (*16*), the exact hazard function $h(t)$ and the survival function $P(t)$ can be computed and the likelihood function constructed for the data.

Now, let d_r (in WLM/month) be the rate of radon exposure, and let d_s (in cigarettes/day) be the rate of smoking. Using a systematic model selection procedure (see the Appendix), the data were best described by the following nine-parameter dose–response model:

$$\begin{aligned} y(d_s, d_r) &= y_1(\text{birth year} - 1877)(1 + y_2[1 - \exp(-y_3 d_s^2)] + y_4 d_r) \\ g(d_s, d_r) &= g_0\left[1 + g_1\begin{Bmatrix} 0 & \text{if not smoking} \\ 1 & \text{if smoking} \end{Bmatrix} + g_2\log(1 + g_3 d_r)\right] \\ q(d_s, d_r) &= q_o \\ m(d_s, d_r) &= 1. \end{aligned} \tag{1}$$

According to preliminary analyses, only the parameter y is affected substantially by birth cohort. The best data fits were obtained with y as a linear function of birth year (see the Appendix for details). Note that among white miners the birth years range from 1877 to 1944. Our results also show that radon exposure affects both the initiation parameter y and the promotion parameter g, but not the rate for the second rate-limiting step, i.e. $m = 1$, consistent with previous findings (*14*). These findings, especially the possibility that α particles may exert a promotional effect on the growth of intermediate cells, will be discussed later. The promotional effect of smoking is adequately described by an indicator function. We refer the reader to the Appendix for a more detailed discussion of this model and the model selection process.

Likelihood Construction

Each subject j in the cohort contributes to the total likelihood as follows: Let $s'_j = s_j + t_{lag}$ be the age at which subject j enters the study. For the miners, the age at entry into the study is given by the age at the time of the first medical examination. Let $t'_j = t_j + t_{lag}$ be the time of observation at which the subject j dies (from lung cancer or from other causes), or is lost to follow-up. Here we assume that lung cancer, or more precisely the appearance of a malignant lung tumor that starts with a single malignant cell, causes death after the lapse of a fixed time t_{lag} which is estimated from the data. Then the total likelihood of the data consists of the product of all individual contributions; i.e. $\mathcal{L} = \Pi\mathcal{L}_j(t_j, s_j)$, where

TABLE 2
Maximum Likelihood Estimates of the Model Parameters with Their Respective 95% Wald-based CIs

	Maximum likelihood	
Parameter	Estimate	95% CI
$y_1 \times 10^7$ (year^{-2})	0.077	0.026–0.226 (0.030–0.237)
y_2	5.642	2.652–11.60 (2.479–11.12)
y_3 [cigarettes/day)$^{-2}$]	0.013	0.005–0.034 (0.006–0.116)
y_4 [(WLM/month)$^{-1}$]	0.101	0.013–0.811 (0–0.324)
g_0 (year^{-1})	0.091	0.066–0.127 (0.062–0.119)
g_1	0.485	0.248–0.944 (0.228–0.922)
g_2	1.292	0.778–2.071 (0.795–2.449)
g_3 [(WLM/month)$^{-1}$]	0.897	0.293–2.434 (0.256–2.818)
$q_0 \times 10^4$ (year^{-1})	0.5	0.19–1.4 (0.20–1.3)

Notes. All parameters were constrained to be positive and log-transformed for the CI computations. For comparison, 95% CIs based on a 10,000-cycle Markov chain Monte Carlo calculation are also shown in parentheses.

$$\mathcal{L}_j(t_j) = \begin{cases} h(t_j)S(t_j)/S(s_j) & \text{if death from lung cancer} \\ S(t_j)/S(s_j) & \text{otherwise} \end{cases}$$

is the likelihood contribution of subject j conditional on surviving lung cancer up to the time of entry into the study (adjustment for left truncation). Here h is the two-stage clonal expansion model hazard function and S is the corresponding survival function.

RESULTS

Table 2 shows the maximum likelihood estimates with their 95% Wald-based confidence intervals (CIs). For comparison we also show 95% CIs based on a 10,000-cycle Markov chain Monte Carlo simulation using uniform priors for the parameters used in the likelihood (*35*). The Markov chain therefore represents samples generated directly from the likelihood.

From the maximum likelihood estimates in Table 2 and the form of the model presented in Eq. (1), we see that the rate of initiation depends linearly on the radon dose rate and its background value is doubled by a dose rate of 10 WLM/month, the median rate of exposure for the miners. It should be noted, however, that the "initiation parameter" y_4 is not significantly different from zero ($P = 0.22$). In comparison, the background value of initiation is already doubled by a smoking rate of about 4 cigarettes/day. No significant effect of radon or cigarette smoking on the rate of malignant transformation was found, i.e. $m = 1$. However, we find a strong cell proliferation response with radon exposure. The background value of the parameter g, which measures the rate of spontaneous net cell proliferation, is doubled in response to an exposure of 1.3 WLM/month increasing from 0.09 per year to 0.18 per year. For comparison, the model predicts that smoking increases the background value of g by about 0.044 per year, independent of smoking level. In view of the fact that clonal expansion is roughly exponential, the strong promotional response of intermediate cells to radon exposures leads to hazard functions whose shape is determined mainly by promotion and to a lesser degree by initiation.

The maximum likelihood estimates are used to compute the expected number of lung cancer deaths in each of four groups defined by the exposure quartiles in Table 1, which are further subdivided into groups by attained age. Table 3A shows observed and predicted lung cancer deaths among whites for total radon progeny exposure (in WLM) from underground mining (uranium and hard rock combined), and Table 3B shows observed and predicted lung

TABLE 3
Predicted and (in Parentheses) Observed Lung Cancer Deaths among Whites Together with the Number of Individuals at Risk Stratified by Age and Quartiles of Total Exposure to (A) Radon Progeny (Uranium and Hard Rock Mining Combined) and (B) Total Exposure to Cigarette Smoke

	Age	Quartiles of cumulative exposure to radon			
		1	2	3	4
A.					
	<20	0.03 (0/1)	0.03 (0/0)	0.02 (0/0)	0.02 (0/1)
	20–29	0.14 (0/6)	0.14 (0/11)	0.14 (0/4)	0.15 (0/3)
	30–39	0.74 (0/21)	0.96 (1/20)	1.37 (0/16)	3.08 (5/21)
	40–49	3.16 (1/44)	4.90 (5/38)	8.91 (2/51)	29.57 (31/91)
	50–59	9.22 (6/227)	15.03 (19/236)	28.77 (37/220)	68.39 (62/203)
	60–69	12.95 (8/290)	20.36 (13/286)	34.17 (39/303)	53.76 (51/264)
	70+	9.18 (8/218)	13.43 (15/215)	17.71 (25/230)	20.19 (26/218)
B.		Quartiles of cumulative exposure to cigarette smoke			
	<20	0.02 (0/1)	0.02 (0/1)	0.03 (0/0)	0.03 (0/0)
	20–29	0.07 (0/4)	0.13 (0/20)	0.18 (0/0)	0.19 (0/0)
	30–39	0.48 (0/7)	1.35 (3/59)	2.18 (2/9)	2.16 (1/3)
	40–49	2.59 (3/24)	8.49 (11/59)	17.86 (21/120)	17.61 (4/21)
	50–59	5.26 (5/133)	19.03 (27/183)	42.02 (56/357)	55.10 (36/213)
	60–69	5.05 (6/171)	16.17 (13/257)	35.70 (35/301)	64.31 (57/414)
	70+	3.33 (4/162)	7.19 (9/161)	16.05 (17/204)	33.93 (44/354)

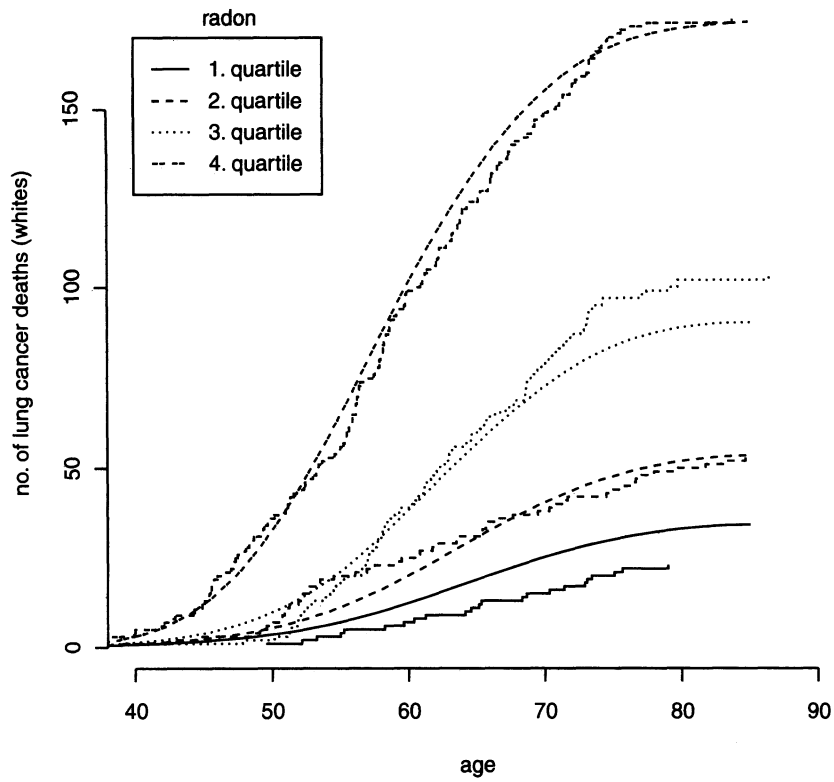

FIG. 2. Observed and predicted (cumulative) number of lung cancer deaths (whites) as a function of age in the four quartiles for total exposure in the uranium mines.

cancer deaths among whites for total exposure to cigarette smoke (in pack-years). For any group of interest, the predicted number of cases that occur in a given interval from time t_1 to t_2 is computed by summing the cumulative hazards of all individuals that are present in the risk set of that group at time t_1; i.e., for group j the number of expected lung cancer deaths is given by $\sum i \epsilon R_j(t_1) \int_{t_1}^{\min(t_1,t_2)} h_{ij}(u)\, du$, where $h_{ij}(u)$ is the hazard function for individual i in group j. We also compute the predicted lung cancer deaths among whites as a function of age in each quartile of total radon and compare them with the observed number of failures. These results are presented in Fig. 2. Age-specific hazard functions for lung cancer mortality for various rates of exposure to radon and various durations are shown in Fig. 3a–d.

Finally, we investigate the inverse dose-rate effect. Typically, this effect is defined by the observation that protraction or fractionation of a given total dose confers a higher relative risk at some specified age. Another definition, one that we will adopt here, is that protraction or fractionation of dose leads to a higher lifetime probability of tumor. Figure 4 demonstrates the inverse dose-rate effect as predicted by the model for various total exposures to radon in the absence (Fig. 4a) and presence (Fig. 4b) of cigarette smoking. Exposures from 1 to 1000 WLM were protracted evenly and symmetrically (centered at age 40) up to 50 years in duration. The lifetime excess absolute risk (EAR) per WLM is then computed as a function of exposure duration. Here we define lifetime EAR as the excess probability of dying from lung cancer at age 70, given the specific exposure pattern, symbolically: lifetime EAR = $P(t = 70,d_r) - P(t = 70,0)$. For the particular example in Fig. 4, the inverse dose-rate effect is most pronounced for larger total radon exposures. With increasing duration (decreasing exposure rates), the computed lifetime EAR/WLM curves reach maxima that are shifted toward shorter durations for smaller total exposures. For total exposures less than 10 WLM, the inverse dose-rate effect is strongly attenuated and exhibits a weak direct dose-rate effect for durations longer than 10 years. An interesting characteristic of the curves, shown in Fig. 4a, is that they all yield approximately the same lifetime EAR/WLM value for exposures between 10 and 15 years in duration (nonsmokers). The curves are qualitatively similar for smokers (Fig. 4b). The inverse dose-rate effect will be discussed in more detail in the following section.

DISCUSSION

The determination of lung cancer risk associated with radon in homes is based chiefly on the analyses of miner data using empirical relative risk models [BEIR IV (*1*) and BEIR VI (*3*)]. While these models do consider cumulative exposures and average exposure rates of radon and smoking as covariates (e.g. ref. *10*), they do not fully use all available information on exposure rate from birth until death or end of follow-up. Attained age, ages at start and stop of all exposures, and time since last exposure are all implicit cov-

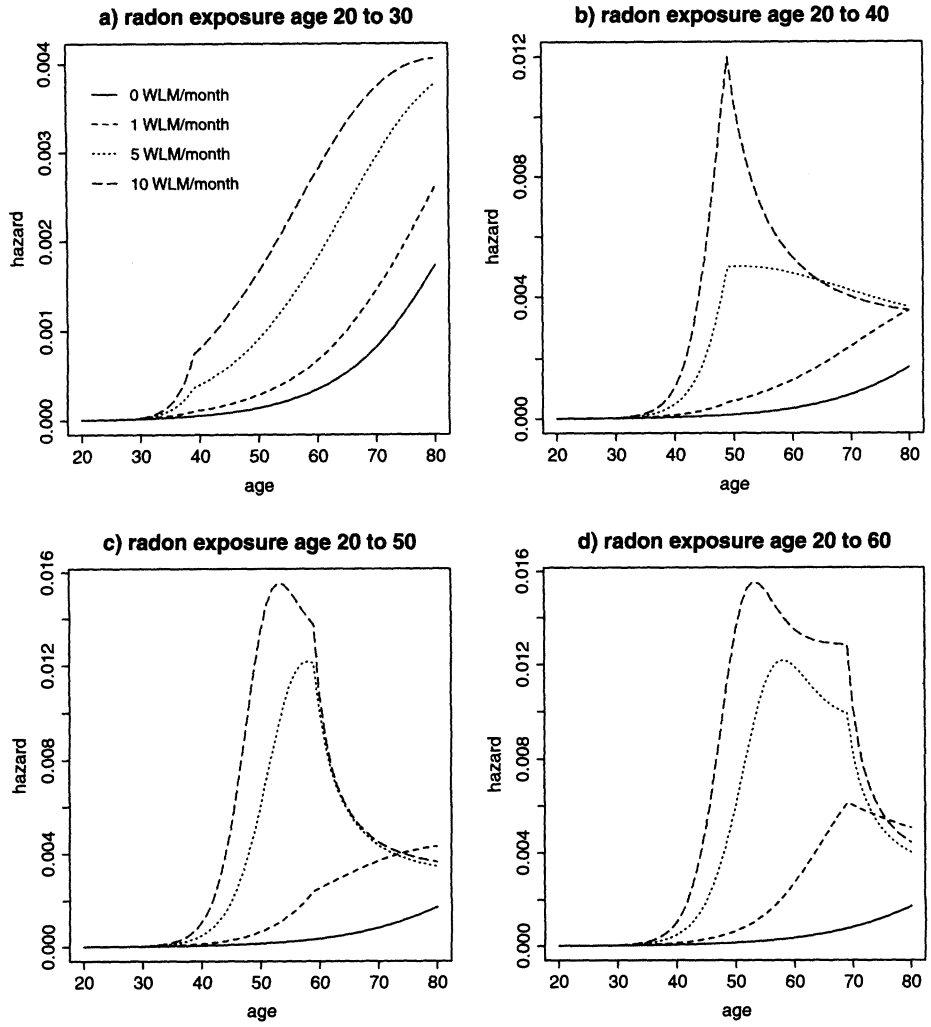

FIG. 3. Age-specific hazard functions for lung cancer mortality (for individuals born in 1920) for various durations and rates of exposure to radon. Exposures start at age 20.

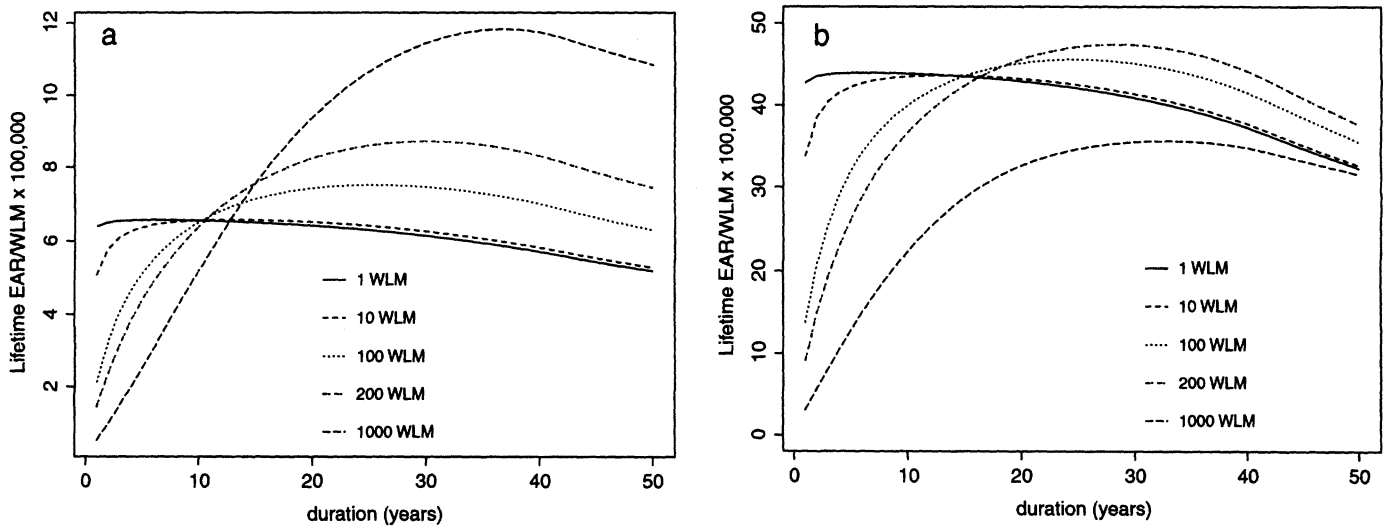

FIG. 4. Lifetime EAR per WLM at age 70 as a function of the duration of exposure (in years) for various total exposures. The exposures were centered at age 40 for (panel a) nonsmokers and (panel b) smokers smoking 10 cigarettes/day starting at age 15.

ariates in the two-stage clonal expansion model and need not be explicitly modeled. Variations in exposures to radon and cigarette smoke over time are reflected in the time dependence of the relevant cellular parameters (see description of the model above). It is important, however, to realize that there is considerable uncertainty associated with the reconstruction of individual levels of exposure to radon progeny. Various sources of uncertainty are identified and their potential effects on risk estimates discussed in the BEIR IV (*1*) and VI reports (*3*). No evaluation of the robustness of the two-stage clonal expansion risk estimates in the presence of such measurement errors is carried out here.

Although the analysis of the 1984 follow-up data by Moolgavkar *et al.* (*14*) employed the two-stage clonal expansion model, their analysis made use only of total radon and cigarette smoking exposures. Exposure rates were computed by averaging the entire exposure received over the period from first to last employment in the mine for radon, and by averaging cumulative cigarette smoking over all years a miner smoked. Thus much less information was used in that analysis. Furthermore, the analysis made no adjustment for birth cohort and age at entry in the study; i.e., the analysis did not adjust for left truncation. The earlier two-stage clonal expansion model analysis, however, was strengthened by the inclusion of additional data on smoking from the British Doctors cohort (*36*). This was necessary to obtain convergence in the estimation of the maximum likelihood estimates and to obtain stable estimates of background lung cancer risks. Because all available information on exposure, including radon exposure from hard rock mining prior to uranium mining, is used in our present analysis producing stable maximum likelihood estimates and acceptable smoking-related lung cancer risks, we chose not to include the British Doctors data in the present analyses.

The model on which our results are based has 9 (nonzero) parameters (see the Appendix). Three of these parameters are needed to estimate the baseline hazard of lung cancer mortality. Note that the empirical relative risk model used by Hornung *et al.* (*10*) uses up to 11 parameters in the attempt to model the interaction between radon and smoking.

The lag time t_{lag} was estimated from the data and is close to 9 years, while previous analyses have either assumed or arrived at a shorter lag time of 4–6 years (*9, 10*). Note, however, that t_{lag} has a definite meaning in the two-stage clonal expansion model: It refers to the time from the occurrence of the first malignant lung cancer cell to death from lung cancer. Clearly, the commonly made assumption of a constant lag time is an oversimplification that is difficult to improve upon.

The following points of discussion underscore the predictive power of the two-stage clonal expansion model.

Birth Cohort Effect

It is generally believed that smoking and associated trends in lifestyle factors are responsible for the observed increase in lung cancer mortality with birth year. It is therefore important to include accurate information on smoking to adjust for the effect of smoking on lung cancer, or in the absence of such information to adjust for the effects of birth cohort in these analyses (see ref. *23*, for example). Although all available information on smoking was included in our analyses, the results still show a strong dependence of lung cancer mortality on birth year. Note, however, that the data on smoking were self-reported and that these data are not considered to be reliable (*10*). Indeed, the pattern of failures, if categorized in terms of cumulative smoking quartiles, show anomalies that are difficult to explain. For instance, miners below age 70 have fewer lung cancer cases in the highest smoking quartile compared to miners belonging to the third smoking quartile (e.g. see Table 3b).

To understand better the contribution of cigarette smoking to the cohort effect, we have also estimated the parameters of the model without using the information on cigarette smoking, that is, by setting y_2 and g_1 to zero and estimating the other parameters. We then compared the cohort-specific baseline lung cancer mortality rates in the miners (age 72.5), with and without adjustment for cigarette smoking, with the lung cancer mortality rates in the U.S. white male population (ages 70–74). It can be seen (Fig. 5) that the predicted baseline hazard for the miners, when fitted with a model that ignores the available information on smoking, follows closely the observed lung cancer mortality rate from the earliest birth years onward. After adjusting for smoking, that is, fitting the data for the miners with the final model and including all available information on smoking, the observed birth cohort effect is strongly reduced (Fig. 5), but a residual secular trend remains that is not explained by the information on smoking in the data, although it is possible that this residual trend is due to under-reporting of the numbers of cigarettes smoked among miners born at later years. A log-likelihood ratio test (setting $y_o \neq 0$ and $y_1 = 0$; see the Appendix) shows that this residual effect remains highly significant ($P < 10^{-5}$).

Dose-Rate Effects

An important question for extrapolating lung cancer risks from radon exposures in the mine to indoor radon is the role of the inverse dose-rate effect, especially at lower exposures and exposure rates. It has been suggested (ref. *3*) that the inverse dose-rate effect diminishes or disappears at radon levels below 10 WLM/month. This conclusion has also been drawn by Lubin *et al.* (*5*) and Hornung *et al.* (*10*) using relative risk models.

To investigate this effect here, the predicted lifetime EAR per WLM, as defined above, is computed for various total exposures and exposure durations (Fig. 4). Our results show that, depending on total radon exposure, the lifetime

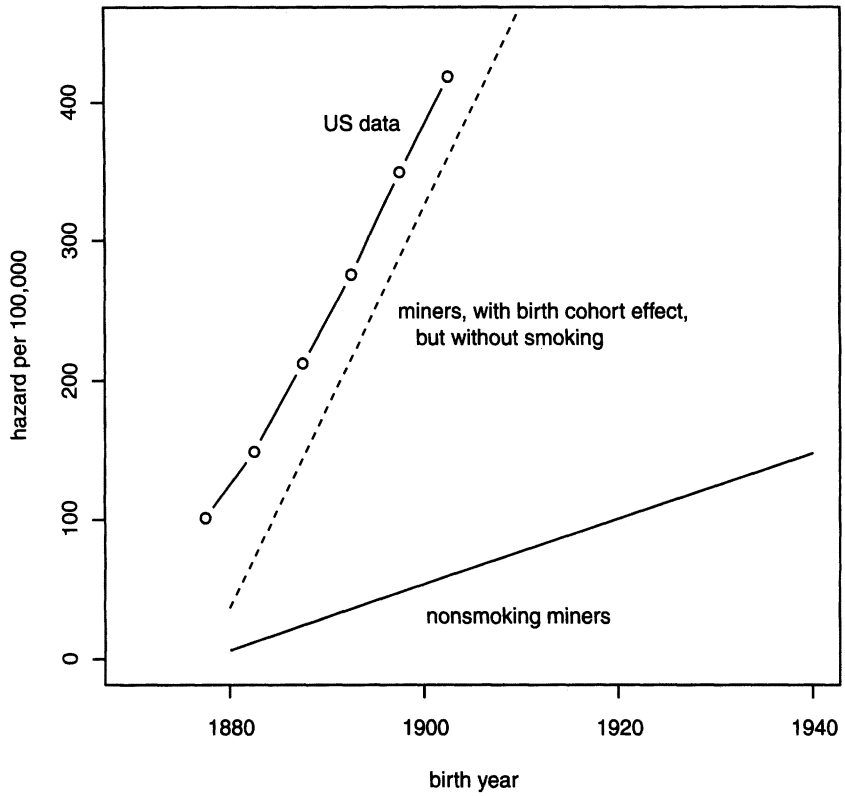

FIG. 5. Comparison of observed lung cancer mortality rate in the white male U.S. population (age 72.5) as a function of birth cohort with predicted baseline rates in the miners: with birth cohort effect, but using the model (Eq. 1) with smoking information ignored, that is, with parameters y_2 and g_1 set to zero (dashed line), and for nonsmoking miners using the same model with information on smoking incorporated (solid line). Note that smoking explains much of the effect of birth cohort, but that there is a residual effect of birth cohort even after smoking is accounted for. The U.S. data are taken from NCI Monograph 59, *Cancer Mortality in the U.S.: 1950–1977.*

EAR/WLM first increases with duration, reaches a maximum and then declines; that is, with increasing protraction, the inverse dose-rate effect is replaced by a direct (albeit weak) dose-rate effect. The lower the total exposure, the weaker the inverse dose-rate effect and the sooner the direct dose-rate effect sets in. From Fig. 4 we see that nonsmoking miners who are exposed to radon for 10 years have approximately the same risk per WLM (as measured by lifetime EAR/WLM) as a nonsmoking individual who spends 10 to 20 years in a residence with very low levels of radon. Beyond 20 years of duration, the risk declines slightly. Obviously, if the inverse dose-rate effect observed in miners at much higher total doses were extrapolated naively to durations (and exposure rates) more typical for homes, the risk (lifetime EAR/WLM) would be grossly overestimated.

It is important to point out that the predicted dose-rate effects do depend on the definition of dose protraction. In general, the computed risks depend on age at start of exposure, age at end of exposure, and time since last exposure. Because the hazard function may change drastically after exposures stop (see Fig. 3), we use lifetime risk to measure the inverse dose-rate effect. Lifetime risk is a monotonically increasing function of age regardless of the pattern of exposure.

The inverse dose-rate effect that is predicted for exposures typical for mining persists even if all miners who were ever exposed to more than 20 WLM/month are removed from the analysis (excluding 1165 white miners). Inspecting Fig. 4a, it can be seen that the inverse dose-rate effect holds up for exposure rates that are well under 10 WLM/month. It can be shown that in the two-stage clonal expansion model the inverse dose-rate effect is caused by the promotional dose response, i.e. the parameter function $g(d_r)$. If radon were solely an initiator, the inverse dose-rate effect would not manifest itself. However, a model without a radon-sensitive promotion term (i.e. with g_2 set to zero) fits the data very poorly. The log-likelihood ratio test for setting the promotion term $g_2 = 0$ for $d_r < 5$ WLM/month yields $2\Delta\log L = 60$.

Whether or not the promotional response is due to ambient cocarcinogens (uranium ore dust, fossil fuel exhausts) in the mines or is due to a direct promotional effect in premalignant lesions exposed to α particles and to resulting cellular damages cannot be decided on the basis of these data. Recent analyses of the data from the PNL rat study (*20*) suggest that the uranium ore dust may play a promotional role in the development of malignant lung tumors in rats. This hypothesis is also supported by the Zirkonotrast/quartz dust studies in rats (*37*) in which an excess of malignant lung tumors is seen only after concomitant exposure

to quartz dust, and by studies of Thorotrast-associated lung cancers in humans. In Thorotrast patients, Ishikawa *et al.* (*38*) found that the lung cancer risks are smaller than expected from risks derived from studies of miners, pointing to a possible role of promotion by dust in the mining environment. It is also possible that α particles trigger "bystander" effects (*39*) that cause increased cell proliferation through changes in gene expression and/or disruption in cell-to-cell communication. In this context, it is of interest that our results are consistent with a model that shows only a modest increase in initiation from radon exposure, but a strong promotional effect.

In summary, within the framework of the two-stage clonal expansion model, a definite inverse dose-rate effect is predicted for the Colorado uranium miners. However, at lower total exposures (<100 WLM) and for exposures lasting more than 10 years, the inverse dose-rate effect is neutralized and may even show a weak direct dose-rate effect.

Recently, the two-stage clonal expansion model has also been shown to predict a direct dose-rate effect for low-LET radiation consistent with other radiobiological findings (*18, 40*). For any model of carcinogenesis that considers the temporal progression of initiated cells toward a malignant state, protraction of an acute initiating dose received at age t_{acute} spread over times $t > t_{acute}$ will reduce cancer risk. In general, this direct dose-rate effect is also dependent on the age at the start of exposure and the duration of exposure.

Whether a direct or an inverse dose-rate effect is more important for residential radon exposures depends on the interplay between initiation and promotion. In general, within the context of the model, radiation-induced initiation predicts a direct dose-rate effect (*40*), while radiation-induced promotion predicts an inverse dose-rate effect. Because clonal expansion of initiated cells is approximately exponential, for any dose rate, promotion will dominate when exposures are long enough. Obviously, exposures beyond the human life span are not relevant. With our estimated parameters, the inverse dose-rate effect is not seen with levels of exposure typical of those seen in residences.

For nonsmokers, the predicted lifetime EAR per WLM is about 6.4×10^{-5} [95% CI = $(2.8, 15.3) \times 10^{-5}$], and the excess relative risk (ERR) per WLM about 7.8×10^{-3} [95% CI = $(3.6, 16.5) \times 10^{-3}$] for 25 years of residential radon exposure at a level of 150 Bq/m^3. Confidence bounds are computed through Markov chain Monte Carlo simulation and reflect the uncertainty in the estimates of the parameters of the model. Interestingly, the ERR/WLM estimate is consistent with the ERR estimates from a meta-analysis of eight epidemiological studies of residential radon by Lubin and Boice (*41*). In that study, an ERR of 0.14 at 150 Bq/m^3 is derived, which translates into an ERR/WLM of 8.75×10^{-3}, also assuming 25 years of residential radon exposure resulting in a total exposure of approximately 16 WLM. However, the risks reported in the BEIR VI report (*3*) although expressed as lifetime relative risks, are two- to fourfold higher.

Dependence of Risks on Age and Time since Last Exposure

The estimated parameters of the two-stage clonal expansion model can be used to construct the hazard function after exposure ceases. The model can therefore be used to predict an (attained) age dependence of lung cancer risk on time since last radon exposure. This dependence is depicted schematically in Figs. 3 and 6. Figure 3 shows that for sufficiently long and sufficiently high exposures the hazard function may drop precipitously after the exposure stops. This rather strong dependence on attained age was also found by Hornung *et al.* (*10*) who categorized the miners by attained age. For instance, for the scenario depicted in Fig. 6, the relative risk decreases about sixfold from age 50 to age 80. Note, however, that this drop in risk after the exposure stops is predicted quite generally by stochastic multistage models (e.g. discussed in refs. *13, 16* and *25*).

The hazard functions in Fig. 3c and d also exhibit maxima during exposure that are shifted toward earlier ages for higher exposure rates. Within the context of the two-stage clonal expansion model, the occurrence of such a maximum in the hazard can be explained by a stochastic effect linked to the clonal expansion of the pool of spontaneously initiated cells that were initiated prior to the exposure.

Figure 7 shows the observed and predicted number of lung cancer cases in the white subcohort as a function of time since last (radon) exposure. The observed numbers are well described by the model. Note that such a comparison is impossible within the framework of a relative risk model.

Interaction of Radon and Smoking

In contrast to the empirical models used by others (e.g. see refs. *10* and *42*), no assumptions are necessary with regard to the specific form of the risk model for describing the interaction of radon and smoking. However, our final model does make the assumption that at the cellular level there is no biological interaction of radon and cigarette smoke; that is, radon and cigarette smoke affect the initiation and promotion parameters independently. Yet our model describes an age-specific relative risk that is somewhere between additive and multiplicative as shown in Fig. 6 (curve labeled *RS*). The situation depicted in Fig. 6 also suggests that for current smokers an empirically construed relative risk model would likely be multiplicative or submultiplicative after exposure to radon stops. For ex-smokers (results not shown), we find that the relative risk gradually approaches the multiplicative risk with increasing time since last exposure to radon and cigarette smoke. These observations are in qualitative agreement with the findings of Hornung *et al.* (*10*).

To arrive at these findings, Hornung and colleagues categorize the miners according to their smoking status (current, former and never-smokers). Using the two-stage clonal expansion model, no categorization is needed, as this model incorporates the smoking pattern of each miner explicitly,

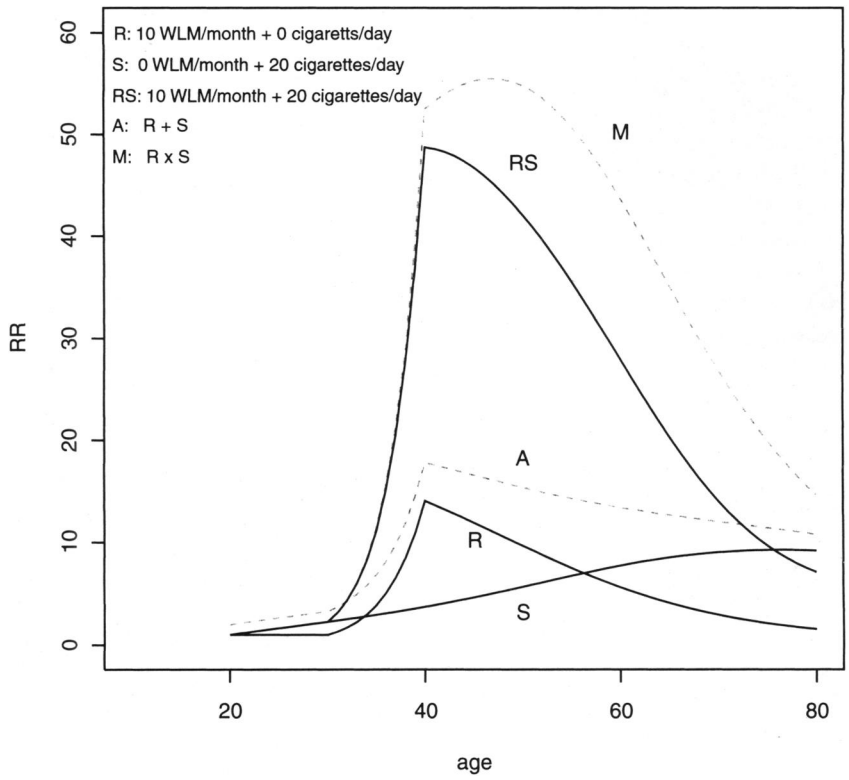

FIG. 6. Comparison of age-specific relative risk generated from the two-stage clonal expansion model for single exposures [smoking (S): 20 cigarettes/day starting age 20; radon (R): 10 WLM/month between ages 30 and 40] with the relative risk from the combined exposure (RS). Dashed lines (A and M) show strictly additive and multiplicative models, respectively.

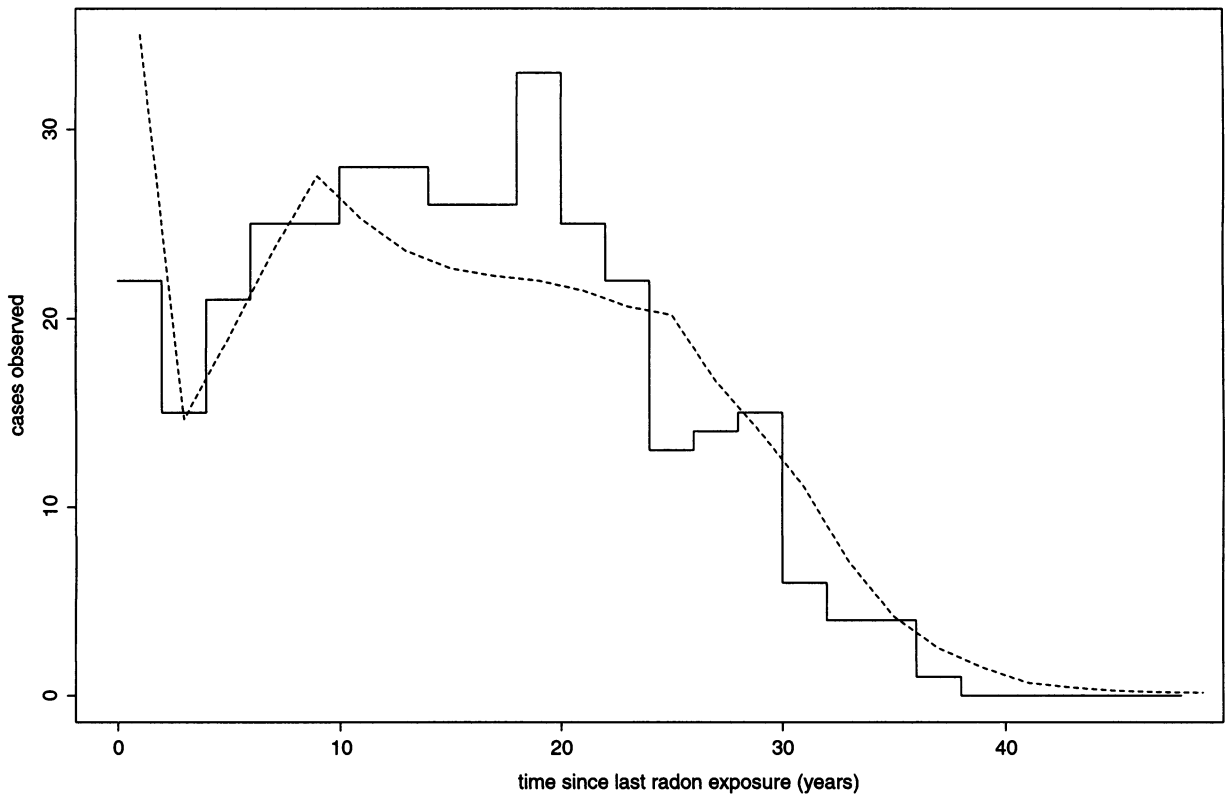

FIG. 7. Observed (solid line) and model-predicted (dashed line) numbers of lung cancer cases as a function of time since last radon exposure (among whites) and computed on 2-year intervals.

TABLE 4
Comparison of Computed Lifetime Relative Risks (Age 70) of Indoor Radon Exposures with the Respective BEIR VI Estimates Taken from Table ES-1 of the Executive Summary Report (3)

Radon exposure (WLM/year)	LRR (our model)		LRR (BEIR VI)[a]	
	Nonsmoker	Smoker[b]	Nonsmoker	Ever-smoker
0.19	1.065	1.050	1.259	1.108
0.78	1.289	1.212	2.033	1.420
3.12	2.503	1.921	5.058	2.507

[a] BEIR VI estimates from the exposure-age-duration model (males).
[b] Ten cigarettes/day starting at age 15.

giving rise to a mostly sub-multiplicative relative risk function. Finally, for the scenario shown in Fig. 6, the relative risk associated with radon exposure is higher for the smoking miner than the nonsmoking miner, but depends on attained age. At age 40 the relative risk for miners who smoke 20 cigarettes/day starting at age 20 is four times higher, and at ages 60–70 it is almost five times higher compared to the relative risk for nonsmoking miners. Similar results were found by Lubin *et al.* (*4*) and Hornung *et al.* (*10*).

Radon in Homes

Using the BEIR VI estimates for indoor radon levels, which are adjusted for the conversion from radon in mines to radon in homes (assuming 70% home occupancy and a 40% equilibrium between radon and its progeny), we also compute the lifetime relative risks (LRR) at age 70 and compare our estimates with the BEIR VI estimates [Table 4, and Table ES-1 in the executive summary of the BEIR VI report (*3*)]. Here we define LRR as the ratio of the lifetime tumor probabilities for exposed and unexposed individuals. For smokers, we assume that smoking started at age 15 and continued until the end of life at a level of 10 cigarettes/day. The comparison reveals that the two-stage clonal expansion model predicts substantially lower LRRs at low dose rate. For continuous exposure at the level of 0.19 WLM/year (see Table 4), the excess LRR is approximately fourfold lower than the BEIR VI estimate for nonsmokers, and a factor of 2 lower for smokers. Note that the LRR is lower among smokers (or ever-smokers) compared to nonsmokers. However, if the lifetime risk of lung cancer among exposed smokers were to be compared to unexposed nonsmoking miners, then their LRR would be higher.

For the same lifetime exposure (0.19 WLM/year), we compute a corresponding ERR (age 70) of about 0.08 for nonsmokers. This estimate is consistent with the value of the ERR/WLM reported above (0.0078). At the level of 0.19 WLM/year (50 Bq/m^3), we derive a total effective lifetime (including t_{lag} 61 years) exposure of 11.6 WLM. Hence the ERR would extrapolate to $0.0078 \times 11.6 = 0.09$, in good agreement with the explicitly computed value.

While we have been using risk estimates in terms of ERR/WLM for comparison of our results with those from other radon studies, we do not think that this measure is always the most useful for summarizing the risks associated with protracted exposures to carcinogens. In our opinion, excess absolute risk, which is simply the difference between the probability of lung cancer in populations exposed to radon and those not exposed, would be a better choice and is readily computed within the framework of the two-stage clonal expansion model. The excess absolute risk is an integral measure of lifetime risk and is usually less sensitive to variations in background cancer rates.

APPENDIX

Here we describe the model selection process in more detail. In principle, all parameters of the model may be assumed to be functions of time, either explicitly or implicitly through time-dependent covariates (here smoking and radon exposure rates). A practical approach is to first identify those parameters that show a significant radon or smoking dose response and then select suitable dose–response functions for them.

Preliminary analyses showed a strong dependence on birth cohort, i.e. birth year. The effect is strongest (as measured by the likelihood) when the birth cohort effect is assumed to modify the background rates of the parameter y. For a definition of the parameters, see the description of the two-stage clonal expansion model in the text. For simplicity, a linear function of the general form $bce(y_o, y_1) = y_o + y_1 \times$ (birth year $-$ 1877) is assumed to describe the birth cohort effect. The year 1877 is the earliest birth year present in the white subcohort. This choice imposes the simple constraint that y_o be positive. We also modeled the birth cohort effect as a linear-quadratic function in birth year. However, this did not improve the fit significantly.

To facilitate the analysis of this data set in which each miner has one or more underground mining experiences with different radon exposure-rate levels, and in which many miners smoke cigarettes at different levels in their life, we break up the time line into k intervals (thus $0 = t_0 < t_1 \ldots < t_k = t$) and assume that the biological parameters α, β and μ are piecewise constant; i.e., on (t_i, t_{i+1}), the parameters are α_i, β_i and μ_i.

Further, let A_i and B_i be the two roots of the polynomial $\alpha_i x^2 - [\alpha_i + \beta_i + \mu_i]x + \beta_i$. Then the following set of identifiable parameters can be derived:

$$y_i = (\nu X)_i \mu_o;$$

$$g_i = (\alpha - \beta - \mu)_i;$$

$$q_i = \alpha_i(B_i - 1);$$

and the $k - 1$ ratios

$$m_i = \mu_i/\mu_o, \qquad i = 1, \ldots, k-1, \tag{A1}$$

where μ_o can be chosen to be the background rate of the second rate-limiting step. The parameters g_i, y_i and q_i are related to the ones used by Kai *et al.* (18) by

$$y_i = -\tilde{A}_i \tilde{B}_i \tilde{C}_i / m_i$$

$$g_i = -(\tilde{A}_i + \tilde{B}_i)$$

$$q_i = \tilde{B}_i \tag{A2}$$

where $\tilde{A}_i = \alpha_i(A_i - 1)$, $\tilde{B}_i = \alpha_i(B_i - 1)$ and $\tilde{C}_i = (\nu X)_i/\alpha_i$.

Let $\theta_i = \{y_i, g_i, q_i, m_i\}$ denote the piecewise constant parameter vector ($m_o = 1$). Then the components θ_{ij} $j = 1, \ldots, 4$ are assumed to depend jointly on smoking rate d_s and radon rate d_r; i.e., $\theta_{ij} = \theta_{ij}(d_s, d_r)$. Hence the parameters depend on time implicitly through their relationship to the time-dependent covariates so that the index i is redundant and is dropped for convenience.

To construct appropriate dose–response functions $\theta_j(d_s, d_r)$, we adopt

a hierarchical approach that starts off with a simple baseline model with parameters that either are constant or depend linearly on d_s or d_r. The baseline model was obtained as follows: First, all parameters are assumed to be linear functions in both d_s and d_r; then, one by one and independently, the significance of a nonzero linear dose response is tested against the null hypothesis (no dose response in that particular parameter). If significant ($P < 0.05$), a linear dose response is adopted after all parameters have been tested. Otherwise the parameter remains constant. With the exception of the parameter $g(d_s)$, which shows a stepwise increase for $d_s > 0$ and is much better described by an indicator function, the following baseline model is obtained:

$$\begin{aligned} y(d_s, d_r) &= bce(y_o, y_1)(1 + y_2 d_s + y_3 d_r) \\ g(d_s, d_r) &= g_0\left[1 + g_1\begin{Bmatrix} 0 & \text{if not smoking} \\ 1 & \text{if smoking} \end{Bmatrix} + g_2 d_r\right] \\ q(d_s, d_r) &= q_o(1 + q_1 d_r) \\ m(d_s, d_r) &= 1. \end{aligned} \tag{A3}$$

Thus the baseline model shows no significant dose response of the second mutation rate with smoking or radon exposures, a result which is consistent with earlier findings (*14*). The final model was then built from the baseline model by replacing each smoking- or radon-related linear dose response in the model with one of the following three two-parameter dose–response curves:

$$\begin{aligned} \theta_L(d; a_0, a_1) &= a_o \log(1 + a_1 d) \\ \theta_{E1}(d; a_0, a_1) &= a_o[1 - \exp(-a_1 d)] \\ \theta_{E2}(d; a_0, a_1) &= a_o[1 - \exp(-a_1 d^2)] \end{aligned} \tag{A4}$$

where $d = d_{s(r)}$. These forms were applied to each parameter in turn, keeping all the others unchanged. Thus a total of 3×5 models were fitted to the data. If any one of the three forms provided a better fit (as measured in terms of the overall likelihood), then that model was adopted for the final model; otherwise, the linear form (or the indicator for g_1) was retained. Because the parameters are correlated, this procedure may not result in the best-fitting model. An exhaustive search using the functional forms in Eq. (A4) would require 3^5 model fits. Our strategy, however, does afford a systematic approach to the model-building process. Note that the selected dose–response forms either are logarithmic or are exponentially growing (when $a_1 < 0$) or saturating with dose rate (when $a_1 > 0$). We also use an exponential model that is quadratic in dose rate. A simple linear-quadratic dose response form was used in preliminary analyses but was not used in the systematic exploration because it frequently led to nonconvergent results.

The analyses led to the following 11-parameter model (excluding t_{lag}):

$$\begin{aligned} y(d_s, d_r) &= bce(y_o, y_1)[1 + \theta_{E2}(d_s; y_2, y_3) + y_4 d_r] \\ g(d_s, d_r) &= g_0\left[1 + g_1\begin{Bmatrix} 0 & \text{if not smoking} \\ 1 & \text{if smoking} \end{Bmatrix} + \theta_L(d_r; g_2, g_3)\right] \\ q(d_s, d_r) &= q_o(1 + q_1 d_r) \\ m(d_s, d_r) &= 1. \end{aligned} \tag{A5}$$

In this model, the maximum likelihood estimate of the intercept parameter y_0 (assumed to be positive) approaches zero and is therefore dropped from the model. The parameter q_1 also approaches zero and is not needed in the final model; that is, it does not improve the fit significantly. Fixing the lag time t_{lag} near the maximum likelihood estimate of approximately 9 years improves the convergence of the maximum likelihood estimates in terms of the numerical stability of the Hessian which is used to compute the 95% CIs. Thus the final model has 9 parameters which are determined by maximizing the total likelihood $\mathcal{L}$ over the 9 parameters. We use the Davidon-Fletcher-Powell algorithm (*43*). Stability of the maximum likelihood estimates is determined by running a modified Newton-Raphson method after convergence with the Davidon-Fletcher-Powell algorithm and by checking for "positive definiteness" of the Hessian. The CIs in Table 2 are 95% CIs based on the information matrix of the log-transforms of the parameters. We also use a Markov chain Monte Carlo sampler (*19*) to sample the likelihood function (assuming uniform priors for the parameters) to construct the CIs for the parameters of the model and also the CIs for the risk functions referred to in the Discussion.

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REFERENCES

1. National Research Council, Committee on the Biological Effects of Ionizing Radiation, *Health Effects of Radon and Other Internally Deposited Alpha Emitters (BEIR IV).* National Academy Press, Washington, DC, 1988.
2. J. M. Samet, Radon and lung cancer. *J. Natl. Cancer Inst.* **81**, 745–757 (1989).
3. National Research Council, Committee on the Biological Effects of Ionizing Radiation, *Health Effects of Exposure to Radon (BEIR VI).* National Academy Press, Washington, DC, 1998.
4. J. H. Lubin, J. D. Boice, Jr., C. Edling, R. W. Hornung, G. Howe, E. Kunz, R. A. Kusiak, H. I. Morrison, E. P. Radford and D. A. Pierce, *Lung Cancer and Radon: A Joint Analysis of 11 Underground Miners Studies.* Publication No. 94–3644, U.S. National Institutes of Health, Bethesda, MD, 1994.
5. J. H. Lubin, J. D. Boice, Jr., C. Edling, R. W. Hornung, G. Howe, E. Kunz, R. A. Kusiak, H. I. Morrison, E. P. Radford and S. X. Yao, Radon exposed underground miners and inverse exposure-rate (protraction enhancement) effects. *Health Phys.* **69**, 494–500 (1995).
6. J. H. Lubin, J. D. Boice, Jr. and J. M. Samet, Errors in exposure assessment, statistical power and the interpretation of residential radon studies. *Radiat. Res.* **144**, 329–341 (1995).
7. A. S. Whittemore and A. McMillan, Lung cancer mortality among U.S. uranium miners: A reappraisal. *J. Natl. Cancer Inst.* **71**, 489–499 (1983).
8. D. C. Thomas, K. G. McNeill and C. Dougherty, Estimates of lifetime lung cancer risks resulting from Rn progeny exposure. *Health Phys.* **49**, 825–846 (1985).
9. R. W. Hornung and T. J. Meinhardt, Quantitative risk assessment of lung cancer in US uranium miners. *Health Phys.* **52**, 417–430 (1987).
10. R. W. Hornung, J. A. Deddens and R. J. Roscoe, Modifiers of lung cancer risk in uranium miners from the Colorado plateau. *Health Phys.* **74**, 12–21 (1998).
11. S. H. Moolgavkar and A. G. Knudson, Mutation and cancer: A model for human carcinogenesis. *J. Natl. Cancer Inst.* **66**, 1037–1052 (1981).
12. S. H. Moolgavkar, Model for human carcinogenesis: Action of environmental agents. *Environ. Health Perspect.* **50**, 285–291 (1983).
13. S. H. Moolgavkar and E. G. Luebeck, Two-event model for carcinogenesis: Biological, mathematical and statistical considerations. *Risk Anal.* **10**, 323–341 (1990).
14. S. H. Moolgavkar, E. G. Luebeck, D. Krewski and J. M. Zielinski, Radon, cigarette smoke and lung cancer: A re-analysis of the Colorado Plateau uranium miners' data. *Epidemiology* **4**, 204–217 (1993).
15. W. F. Heidenreich, On the parameters of the clonal expansion model. *Radiat. Environ. Biophys.* **35**, 127–129 (1996).
16. W. F. Heidenreich, E. G. Luebeck and S. H. Moolgavkar, Some properties of the hazard function of the two-mutation clonal expansion model. *Risk Anal.* **17**, 391–399 (1997).

17. *International Classification of Diseases, 8th Revision (ICD 8).* WHO, Geneva, 1967.
18. M. Kai, E. G. Luebeck and S. H. Moolgavkar, Analysis of the incidence of solid cancer among atomic bomb survivors using a two-stage model of carcinogenesis. *Radiat. Res.* **148**, 348–358 (1997).
19. S. H. Moolgavkar, F. T. Cross, E. G. Luebeck and G. E. Dagle, A two-mutation model for radon-induced lung tumors in rats. *Radiat. Res.* **121**, 28–37 (1990).
20. E. G. Luebeck, S. B. Curtis, F. T. Cross and S. H. Moolgavkar, Two-stage model of radon-induced malignant lung tumors in rats: Effects of cell killing. *Radiat. Res.* **145**, 163–173 (1996).
21. A. Kopp-Schneider and C. J. Portier, Birth and death/differentiation rates of papillomas in mouse skin. *Carcinogenesis* **13**, 973–978 (1992).
22. S. H. Moolgavkar and E. G. Luebeck, Multistage carcinogenesis: Population-based model for colon cancer. *J. Natl. Cancer Inst.* **84**, 610–618 (1992).
23. S. H. Moolgavkar, E. G. Luebeck and E. L. Anderson, Estimation of unit risk for coke oven emissions. *Risk Anal.* **18**, 813–825 (1998).
24. M. P. Little, Are two mutations sufficient to cause cancer? Some generalization to the two-mutation model of carcinogenesis of Moolgavkar, Venzon and Knudson, and of the multistage model of Armitage and Doll. *Biometrics* **51**, 1278–1291 (1995).
25. M. P. Little, Generalization of the two-mutation and classical multistage models of carcinogenesis fitted to the Japanese atomic bomb survivor data. *J. Radiol. Prot.* **16**, 7–24 (1996).
26. W. F. Heidenreich, P. Jacob and H. G. Paretzke, Exact solutions of the clonal expansion model and their application to the incidence of solid tumors of atomic bomb survivors. *Radiat. Environ. Biophys.* **36**, 45–58 (1997).
27. W. F. Heidenreich, P. Jacob, H. G. Paretzke, F. T. Cross and G. E. Dagle, Two-step model for fatal and incidental lung tumor risk of rats exposed to radon. *Radiat. Res.* **151**, 209–217 (1999).
28. H. H. Rossi and A. M. Kellerer, The dose rate dependence of oncogenic transformation by neutrons may be due to variation of response during the cell cycle. *Int. J. Radiat. Biol.* **50**, 589–598 (1988). [letter to the Editor]
29. D. J. Brenner and E. J. Hall, The inverse dose rate effect for oncogenic transformation by neutrons and charged particles. A plausible interpretation consistent with published data. *Int. Radiat. Biol.* **58**, 745–758 (1990).
30. D. G. Kendall, Birth-and-death processes, and the theory of carcinogenesis. *Biometrika* **47**, 13–21 (1960).
31. J. Neyman and E. Scott, Statistical aspects of the problem of carcinogenesis. In *Fifth Berkeley Symposium on Mathematical Statistics and Probability*, pp. 55–77. University of California Press, Berkeley, 1967.
32. Q. Zheng, On the exact hazard and survival functions of the MVK stochastic carcinogenesis model. *Risk Anal.* **14**, 1081–1084 (1994).
33. A. Kopp-Schneider, C. J. Portier and C. D. Sherman, The exact formula for tumor incidence in the two-stage model. *Risk Anal.* **14**, 1079–1080 (1994).
34. J. Denes and D. Krewski, An exact representation for the generating function for the Moolgavkar-Venzon-Knudson two-stage model of carcinogenesis with stochastic stem cell growth. *Math. Biosci.* **131**, 185–204 (1996).
35. W. R. Gilks, D. J. Spiegelhalter and S. Richardson, *Practical Markov Chain Monte Carlo.* Chapman and Hall, London, 1995.
36. R. Doll and R. Peto, Cigarette smoking and bronchial carcinoma: Dose and time relationships among regular smokers and life-long non-smokers. *J. Epidemiol. Community Health* **32**, 303–313 (1978).
37. A. Spiethoff, H. Wesch, K. Wegener and H. J. Klimisch, The effects of Thorotrast and quartz on the induction of lung tumors in rats. *Health Phys.* **63**, 101–110 (1992).
38. Y. Ishikawa, T. Mon, Y. Kato, E. Tsuchiya, R. Machinami, H. Sugano and T. Kitagawa, Lung cancers associated with Thorotrast exposure: High incidence of small-cell carcinoma and implications for estimation of radon risk. *Int. J. Cancer* **52**, 570–574 (1992).
39. J. B. Little, Commentary: What are the risks of low-level exposure to α-particle radiation from radon? *Proc. Natl. Acad. Sci. USA* **94**, 5996–5997 (1997).
40. S. H. Moolgavkar, Stochastic cancer models: Application to analyses of solid cancer incidence in the cohort of A-bomb survivors. *Nucl. Energy* **36**, 447–451 (1997).
41. J. H. Lubin and J. D. Boice, Lung cancer risk from residential radon: Meta-analysis of eight epidemiological studies. *J. Natl. Cancer Inst.* **89**, 49–57 (1997).
42. X-Z. Xuan, J. H. Lubin, J-L. Li, L-F. Yang, L. Q. Sheng, Y. Lan, J-Z. Wang and W. J. Blot, A cohort study in Southern China of tin miners exposed to radon and radon decay products. *Health Phys.* **64**, 120–131 (1993).
43. W. H. Press, B. P. Flammery, S. A. Teukolsky and W. T. Vetterling, *Numerical Recipes: The Art of Scientific Computing.* Cambridge University Press, Cambridge, 1986.