Models for the Analysis of Radon-Exposed Populations

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Radon-222 is a radioactive decay product of radium-226 and uranium-238, which are found throughout the crust of the earth. Studies of underground miners clearly show that exposure to radon and its decay products increases the risk of developing lung cancer. Data on standardized mortality ratios from eight cohort studies indicate that the radon-lung cancer relationship is statistically homogeneous, even though cohorts are from different types of mines and from different countries.

Regression methods for cohort data based on a Poisson probability model permit a thorough consideration of risk patterns. In this report, we review these methods, wherein the disease rate in each cell of a multi-way table is modeled as a function of the cross-classifying variables. The National Academy of Sciences' Committee on the Biological Effects of Ionizing Radiation uses the Poisson regression approach to develop a model for age-specific lung cancer risk which depends on cumulative exposure, age at risk, and time since exposure. This model is reviewed and its implications discussed.

The most important determinant of lung cancer is cigarette smoking. This paper discusses relative risk models for analysis of joint exposure to radon and tobacco products. The review of available studies suggests that the joint relationship of radon and smoking with lung cancer is consistent with a multiplicative model, but a submultiplicative relationship is most likely. An additive model is rejected.

INTRODUCTION

Radon-222 is a radioactive gas which arises from the decay of radium-226, the fifth progeny of uranium-238. Radium-226 and uranium-238 are found throughout the earth's crust. Because of inadequate ventilation, radon gas can accumulate in mines and, as was recently discovered, in homes.

It is known that, at exposure levels historically found in underground mines, radon-222 and its decay products can cause lung cancer. Because of the potential public health effect, there is need to characterize precisely the degree and pattern of lung cancer risk due to radon exposure. Several populations are potentially at elevated risk: namely, active and retired underground miners who have been exposed in the past to high levels of radon, active underground miners who are exposed to radon levels at or near current work standards, and individuals who are exposed at home to relatively low levels, potentially for a lifetime.

In the past, investigators have usually approached the analysis of radon-exposed cohorts by computing standardized mortality ratios (SMRs) or relative risks (RRs) by categories of exposure and of other variables. This approach is useful in identifying the level of risk but has limitations for adequately characterizing an exposure-response

Abbreviations: BEIR IV: National Academy of Sciences' Committee on the Biological Effects of Ionizing Radiation  CWLM: cumulative working level months  RR: relative risk  SMR: standardized mortality ratio  WLM: working level months

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relationship, particularly in the presence of secondary variables such as age at risk, smoking, and so on. Since data are limited, simple analysis of SMRs broken down by categories of exposure and other variables quickly becomes inadequate for addressing many important questions. Thus, some type of regression modeling is required.

It should be noted that even simple epidemiologic analysis relies quite heavily on modeling assumptions. The SMR is the proportionality factor in an assumed multiplicative model between age-specific disease rates in an exposed cohort and a non-exposed referent population [1].

In this report, we present statistical models which can be used to analyze epidemiologic studies, with a particular emphasis on studies of radon-exposed populations. Recent methodologic advances in analysis of cohort and case-control data permit multivariate regression modeling, which incorporates complex time-varying relative-risk functions. These methods have been applied in a report by the National Academy of Sciences’ Committee on the Biological Effects of Ionizing Radiation (BEIR IV), which evaluated lung cancer risk in radon-exposed populations [2]. We review some of these methods and discuss the implications of resultant models.

In miner studies, exposure to radon is usually measured in units of cumulative working level months (CWLM). It is the product of time, in units of a working month, which is taken to be 170 hours, and working levels, a measure of radiation exposure. One working level equals any combination of radon daughters in one liter of air which results in the emission of 130,000 MeV of potential energy from alpha particles.

**Analytic Approaches**

The problem of defining patterns of risk with exposure to radon and with joint exposure to radon and the effects of other factors, such as age, sex, and cigarette use, can be addressed with models which derive from biologic and mechanistic considerations or from models which are primarily descriptive. Biology-based models postulate an effect of an agent or agents on cellular processes, which then induces a mathematical representation of disease risk. Models are then fit and parameters estimated. The multi-stage model [3–9] and the two-stage model [10] have been remarkably effective in predicting site-specific cancer disease rates in populations.

Epidemiologists have been slow in applying these models to analysis of individual exposures. The reason may relate to perceived limitations of currently available mechanistic models. Relationships between disease patterns and exposure to one or more agents can be extremely complex (for example, effects of the temporal sequence of exposures and possible inhibitive or stimulative effects of several agents acting together) and tend to preclude their use in a general exploratory way. There is also an inability to use available data to verify model assumptions independently. Thus, the result is that one needs to rely quite heavily on the validity of the underlying biologic assumptions.

Starting with a multi-stage model, several authors [5–9,11] have attempted to characterize patterns of excess disease risk and of relative risk which would be expected if an agent acted early or late in the carcinogenic process. For example, investigators have suggested that arsenic acts at the penultimate stage for lung cancer [5,6] and cigarette smoke is a lung carcinogen which acts at an early and a late stage, but primarily at a late stage [12]. (See Day and Brown [7] and Thomas and Whittemore [13] for additional examples.) There has been, however, relatively little
work on the reverse issue; that is, how a given pattern of excess risk or of excess relative risk relates to a specific stage of action. Indeed, equations in Day and Brown [7] suggest that using risk patterns to distinguish between a carcinogen which acts both early and late in a multi-stage process from an agent which acts at an intermediate stage would be dubious. The multi-stage models, therefore, have an element of non-identifiability, and may be most useful for clearly defined risk variables when there is a specific hypothesis regarding the biologic mode of action.

Descriptive models are developed under few a priori assumptions, or at least with assumptions which can be tested during analysis. The models are used primarily to describe concisely the underlying structure in the data, although descriptive models can often be used qualitatively to deduce aspects of mechanistic models [5–9,11]. Similarities of descriptive models across data sets offer reassurance that the model is characterizing some underlying commonality of the disease-exposure relationship. No biologic model is required. The descriptive approach is strongly data-dependent, however; sparse data severely limit flexibility in modeling and power to discriminate among alternative models. These limitations usually manifest themselves through nonsignificant results and instability of parameter estimates. These problems also, however, serve as signals to an investigator against over-interpretation of results. In addition, a few data points may have substantial influence on the model. (Note that these considerations also pertain to the application of biologic models.) Because of flexibility in the modeling and in the ability to test assumptions and because of uncertainty in the application of specific mechanistic models, we only consider the data-based descriptive approach, recognizing the possible biologic interpretations.

Data Structure

In epidemiologic cohort studies, follow-up and exposure data are obtained on individuals. Risk factors can be analyzed relative to external or internal referent rates [1,14–16]. This type of analysis is typically computer-intensive, particularly if exposures vary with follow-up, and may be cumbersome for general exploratory work.

Procedures are simplified greatly if background rates and exposure covariates are assumed to be approximately constant over age and year intervals. Data are cross-classified by age, calendar time, and categories of covariates of interest. In our context, covariates include categories of CWLM, duration of employment, age at first exposure, age at exposure, and time since cessation of employment. For each cell of a multi-way table, one counts the number of events of the cause of interest and the accumulated person-years, then computes mean values for each variable, weighting by person-years. For each cell, the observed number of disease events is assumed to be Poisson-distributed and is regressed on age, year, and the covariates [1,17–21]. If the piecewise constancy assumption is approximately correct, results will likely be quite similar to analyses on individuals. For any specific analysis, the potential number of cells may be quite large, although only non-empty cells are used. The large number of cells does not usually pose a problem, if the number of parameters in any model is small.

Let a, y, w, and x denote age, calendar year, radon exposure measured in CWLM, and another exposure (or vector of exposures), respectively. We let these variables denote category indices or cell means as needed; the meaning will be clear from context.
MODELS FOR ANALYSIS OF RADON

A frequent analytic approach to estimating an exposure-response relationship is to regress SMRs on category-specific mean CWLM exposures, weighting by person-years. Since the SMR is a summary measure over age and year, important time effects may be obscured, unless SMRs are stratified on age and other factors, which are then included in the regression equation. Second, person-year weights are not optimal, in the sense of minimum variance of the adjusted estimator. Inverse variances are optimal weights for a summary measure. Using the inverse variance results in less influence for stratum-specific SMRs with greater variance, and hence less precision, on the summary measure and in greater influence for SMRs with smaller variances. For combining SMRs, optimal weights are expected values. In practice, expected values, which depend on the unknown parameters, are computed by inserting estimates for unknown parameters. In contrast, weighting by person-years can result in greater variance for the regression and, for many occupational cohorts, a possible overemphasis on low-exposed and younger subjects.

Current approaches to the analysis of time to response data begin with a specific model for the age and year disease rate (hazard rate or incidence density) and then incorporate covariates through their effect on the underlying hazard. Estimators for the SMR and standard tests of hypothesis (null association, homogeneity, and trend over categories) can be derived as standard score tests, using time-to-response models [1].

Suppose \( r(a, y, w) \) is the age- and year-specific lung cancer disease rate at exposure \( w \), and \( r_0(a, y) = r(a, y, 0) \) is the baseline disease rate for a non-exposed individual \( w = 0 \). We can write the disease risk as:

\[
r(a, y, w) = r_0(a, y) + \rho(a, y, w)
\]

where \( \rho \) is the additional rate due to exposure. This model is frequently referred to as the excess risk model. The added term \( \rho \) describes the elevation in disease rate above background due to \( a, y, \) and \( w \). Equation (1) can be rewritten as an excess relative risk model, namely:

\[
r(a, y, w) = r(a, y)[1 + \eta(a, y, w)]
\]

by setting \( \eta = \rho / r_0 \). Since no restrictions have been placed on \( \rho \) or \( \eta \), models (1) and (2) are equivalent in specifying added risk due to \( w \), and so there is no distinction between them. The two models are merely different ways of describing the age-specific disease rate.

Two important special cases arise if \( \rho \) or \( \eta \) does not depend on \( a \) and \( y \); namely, \( r(a, y, w) = \rho(w) \) or \( r(a, y, w) = \eta(w) \). These models are, respectively, the constant (in time) excess risk model and the constant relative-risk model. Note that if the excess relative risk \( \eta(w) \) does not involve \( a \) and \( y \), then the excess risk depends on these quantities, \( \rho(a, y, w) = \eta(w)r_0(a, y) \). Similarly, if the excess risk does not involve \( a \) and \( y \), the excess relative risk does. If the excess risk \( \rho \) or the excess relative risk \( \eta \) is independent of time, then the model assumes a particularly simple form. In the absence of a specific alternative, this simplicity is a clear advantage for its use. Alternatively, if the data do not conform to one of these simple models, then neither the excess risk nor excess relative risk have an a priori advantage, since both models must accommodate a dependence on \( a \) and/or \( y \). In the multi-stage model for carcinogenesis, the excess risk
contains more qualitative information for assessing stage of action for an agent [7–9], implying greater usefulness of formulation (1). For many human cancers, however, excess risk due to exposure commonly increases with age or time since exposure. In such circumstances, the relative-risk approach, equation (2), frequently results in a simpler form for the age-specific rates.

Analyses of radon exposure data suggests that excess risk is not a constant excess above the background rate or proportional to the background rate, but that the relative-risk formulation is generally more convenient (2). We therefore restrict attention to (2). Previous descriptive, theoretical, and experimental work indicate a linear exposure-response pattern for radon exposure [2,22]. This pattern is characterized by the factorization \( \eta(a, y, w) = \gamma(a, y)f(w) \), where \( f(w) = \beta w \). The disease rate becomes:

\[
    r(a, y, w) = r_0(a, y)[1 + \gamma(a, y)\beta w] \tag{3}
\]

In equation (3), the \( \beta \) parameter is interpretable as the increase in relative excess risk per unit increase in \( w \) for fixed \( a \) and \( y \). Model (3) allows the dependence of the slope \( \beta \) on \( a \) and \( y \) through the function \( \gamma \). If \( \gamma \) does not vary by \( a \) and \( y \), then one gets the proportional hazards model, \( r(a, y, w) = r_0(a, y)(1 + \beta w) \).

Suppose that \( x \) is another exposure of interest (or a vector of exposures), and assume the effects of \( x \) and \( w \) jointly multiply the background rate \( r_0(a, y) \). We get as a result that \( r(a, y, x, w) = r_0(a, y)R(x, w) \), where \( R \) is the joint relative-risk function with \( R(0, 0) = 1 \). Since \( x \) may include \( a \) and/or \( y \), this characterization includes equation (3). The lung cancer disease rate is \( r_0(a, y)R(x, w) \).

Two strategies for analysis can be suggested [23]. Let \( R(x) \) and \( R(w) \) define relative-risk patterns for \( x \) and for \( w \), respectively, with \( R(0) = 1 \). Suppose combined exposure to \( x \) and \( w \) results in multiplicative relative risks; that is, \( R(x, w) = R(x)R(w) \), so that the disease rate is \( r_0(a, y)R(x)R(w) \). The adjusted relative risk for \( w \) within stratum defined by a fixed value for \( x \) is:

\[
    \frac{r(a, y, x, w)}{r(a, y, x, 0)} = \frac{r_0(a, y)R(x)R(w)}{r_0(a, y)R(x)} = R(w)
\]

This result suggests that one strategy for analysis stratifies on levels of \( x \) and fits \( R(w) \), adjusting for \( a \) and \( y \). If the estimated \( R(w) \) is homogeneous across \( x \), then data are consistent with the multiplicative model. If estimates are heterogeneous, then some alternative model is suggested. Note that one needs only the weaker assumption that \( R(w) \) multiplies the non-exposed rate \( r(a, y, x, w) = r(a, y, x, 0)R(w) \). This is what is meant by the terminology “constant relative-risk” model; that is, for fixed levels of \( x \), \( R(w) \) does not depend on time variables. For illustration, suppose \( x \) is a binary variable and \( R(w) = 1 + \beta w \). To test homogeneity, one fits \( R(w) = 1 + \gamma_w \beta w \), where \( \gamma_w = 1 \) if \( x = 0 \) and \( \gamma_w = \gamma \) if \( x = 1 \). (An equivalent formulation for the latter model is \( R(w) = 1 + \beta_w \), where \( \beta \) and \( \beta_w \) depend on stratum.) In the usual way, one can use a likelihood ratio test to obtain an approximate chi-square distribution with degrees of freedom equal to one less than the number of strata.

The BEIR IV report on radon effects applies this approach to the analysis of four miner cohorts to derive a model for radon-induced lung cancer risk [2]. They found significant departures from the constant relative-risk model \( R(w) = 1 + \beta w \). Their model is discussed later.

A second strategy directly models the joint relative-risk relationship for \( x \) and \( w \),
The mixing parameter $\lambda$ defines a smooth deformation in the relative risks from subadditive ($\lambda < 0$), through additive ($\lambda = 0$) and multiplicative ($\lambda = 1$) to supramultiplicative ($\lambda > 1$). The maximum likelihood estimate, $\hat{\lambda}$, is most easily obtained by fixing a sequence of $\lambda$ values and solving for the remaining parameters. The $\hat{\lambda}$ is the value for which the log-likelihood is maximized.

Using a likelihood ratio chi-square on one degree of freedom, one can test the fit of the multiplicative model $R(x, w; \lambda = 1)$ relative to the maximum likelihood model $R(x, w; \hat{\lambda})$; likewise one can test the additive model $R(x, w; \lambda = 0)$ relative to $R(x, w; \hat{\lambda})$. These comparisons test the null hypothesis that the additive model or the multiplicative model is consistent with the maximum likelihood fit with $\lambda$ unconstrained; they do not test whether the additive or multiplicative model is "better," since $R(x, w; \lambda = 0)$ and $R(x, w; \lambda = 1)$ are not nested in each other. It may happen that neither is preferred and both are consistent with the data. (Wahrendorf et al. have recently proposed a bootstrap procedure for comparing likelihoods from additive and from multiplicative models, in order to test whether either of these two models are "better," without specifying a richer family of models [26].

The strategies for evaluating joint exposures did not depend on particular forms for the relative-risk patterns for $R(w)$ and for $R(x)$. The characterization of joint relative risks as multiplicative or additive is distinct from the form of the relative risks of the individual factors [20]. Until recently, standard practice defined the risk pattern for exposure $x$ using the exponential function, $\exp(\beta x)$, where $\beta$ is the unknown logarithm of the relative risk. (If $x$ is a vector of exposures, then exposure effects enter through the inner product $\beta x = \sum \beta_i x_i$, where $\beta$ is now a vector of parameters. The joint relative-risk model is then the multiplicative, $\Pi_i \exp(\beta_i x_i)$. The exponential form is not always viable; for example, it is inappropriate for radon exposure, where the linear form $R(w) = 1 + \beta w$ is most consistent with available data. By introducing an additional parameter, several authors have proposed richer families of models, much in the spirit of (4). Three formulations are Breslow and Storer [27]:

$$R_{B-S}(x) = \begin{cases} \exp [(1 + \beta x)^\alpha - 1/\alpha] & \text{if } \alpha \neq 0 \\ 1 + \beta x & \text{if } \alpha = 0 \end{cases}$$

Thomas [25]:

$$R_T(x) = [\exp(\beta x)]^\alpha[1 + \beta x]^{1-\alpha}$$

Guerrero and Johnson [28]:

$$R_{G-J}(x) = \begin{cases} [(1 + (1 - \alpha)\beta x)]^{1/(1-\alpha)} & \text{if } \alpha \neq 1 \\ \exp (\beta x) & \text{if } \alpha = 1 \end{cases}$$
For a single exposure $x$, these models define a smooth transition from sublinear ($\alpha < 0$), through linear ($\alpha = 0$) and exponential ($\alpha = 1$) to supra-exponential ($\alpha > 1$). See Moolgavkar and Venzor for a critique of these models [29].

The above models were originally proposed for univariate $x$ or vector-valued $x$. With more than one exposure, however, the additional parameter $\alpha$ simultaneously constrains all covariate risk patterns, thus contradicting the concept that joint effects, for example, multiplicative and additive, should not depend on individual risk patterns. Therefore, use of $R_{a-S}$, $R_{T}$, and $R_{G-S}$ is more properly reserved for single exposures, relying on models such as equation (4) for joint patterns [20].

**INTERNAL VERSUS EXTERNAL COMPARISONS**

The previous section focused on models for the relative risk $R(x, w)$. We now consider models for baseline disease rates $r_{0}(a, y)$. Cox partial likelihood regression utilizes data on individuals and permits $r_{0}(a, y)$ to remain unspecified [15,16]. The estimation proceeds by comparing at each event time $(a$ and $y)$ exposures of the case with exposures of all cohort members at risk. In a related procedure, $r_{0}$ is replaced by rates from an external standard population [1]. These approaches are flexible but can be computer-intensive, particularly if exposures vary with follow-up.

In contrast, one may group the data, as suggested above, and carry out Poisson regression, using an internal or an external non-exposed referent population. In practice, the different approaches generally lead to quite similar results. Choice of a particular technique depends on any unique aspects of the particular set of data, type, and range of exposures, computer costs, availability, and ease of use of computer software. For example, if all subjects were exposed and the range of exposure was limited, then external comparisons may be useful. If a cohort has an unusual disease experience and there is no comparable standard population (second tumor after cancer treatment or healthy workers), then internal comparisons may be most appropriate.

Analysis of grouped data proceeds under an assumption that the number of observed lung cancer deaths in each cell is Poisson-distributed [1,17–21,30,31]. Suppose $d_{aywx}$ and $T_{aywx}$ are the observed events and total person-years in the cell designated by $a$, $y$, $x$, $w$. The Poisson mean, the expectation of $d_{aywx}$ is modeled as person-years times disease rate; that is,

$$E(d_{aywx}) = T_{aywx} r(a, y, x, w) = T_{aywx} r_{0}(a, y)R(x, w)$$  \hfill (5)

For an internal analysis, one models $r_{0}(a, y)$ and estimates parameters for $r_{0}$ and $R$ from the data. A particularly general parametrization for $r_{0}$ specifies a separate parameter for each age and year category, $r_{0}(a, y) = \delta_{ay}$. This representation is quite general, resulting in relative-risk estimates for $R(x, w)$ which are usually rather similar to estimates from Cox regression. Other parametrizations are possible, for example, a multiplicative main-effects model $r_{0}(a, y) = \delta_{a}\delta_{y}$. Alternatively, age (and year) rates can be modeled with a smooth parametric function.

For an external analysis, suppose $s_{ay}$ is the lung cancer rate for age $a$ and year $y$ in a referent population of nonsmoking and non-radon exposure individuals. If $s_{ay}$ replaces $r_{0}(a, y)$ in equation (5), then

$$E(d_{aywx}) = e_{aywx} R(x, w)$$  \hfill (6)

where $e_{aywx} = T_{aywx} s_{ay}$ is the expected number of deaths for the cell. The regression
model (6) is similar to (5), except that external baseline rates are used. Models for 
\( R(x, w) \) and their interpretations remain the same.

Model (6) postulates equivalent lung cancer rates in the standard population and in 
the cohort. Due to the "healthy worker effect" and other factors related to noncomparability, differences in the disease rate between the cohort and the standard population

### TABLE 1
Lung Cancer Standardized Mortality Ratios (SMR) from Several Cohorts of Radon-Exposed Miners

| Study/Site                        | Person-Years | Mean CWLM | No Lung Cancers Observed | SMR |
|-----------------------------------|--------------|-----------|--------------------------|-----|
| Colorado uranium miners [32,33]*  | 66,234       | 416       | 157                      | 3.6 |
| Malmberget, Sweden, iron miners [34]| 27,349       | 76        | 51                       | 3.4 |
| Ontario uranium miners [35–37]    | 217,806      | 25        | 82                       | 1.4 |
| Beaverlodge, Canada, uranium miners [38] | 114,159     | 10        | 65                       | 2.1 |
| Port Radium, Canada, uranium miners [39] | 34,673      | 183       | 48                       | 2.3 |
| Czech uranium miners [40,41]      | 56,955       | 273       | 212                      | 5.0 |
| Newfoundland fluor spar miners [42,43] | 2,414\(^b\) | 147       | 71                       | 4.5 |
| Chinese tin miners [44]           | 12,243\(^b\) | 457       | 558                      | 12.5|

*Data restricted to exposures less than 2,000 CWLM

*Number of workers, since person-years were not given
ANALYSIS OF RADON-EXPOSED POPULATIONS

FIG. 1. Observed excess standardized mortality ratios and 90 percent confidence limits and fitted regression lines for selected cohort studies of miners. A. Czechoslovakian uranium miners  B. Newfoundland fluorspar miners  C. Port Radium uranium miners  D. Chinese tin miners  E. Beaverlodge uranium miners  F. Ontario uranium miners  G. Malmberget, Sweden, iron miners  H. Colorado Plateau uranium miners

may occur. Model (6) can be generalized to account for these differences, namely:

\[ E(d_{gxyw}) = e_{gxyw} \exp(\xi)R(x, w) \]  \hspace{1cm} (7)

where \( \exp(\xi) \) estimates the proportional differences in the rates. If \( R(x, w) \) were excluded from model (7), then \( \exp(\xi) \) would just be the estimated lung cancer SMR. Modeling other differences between disease rates in the cohort and in the standard population is accommodated by allowing \( \xi \) to vary by age and/or year.

STUDIES OF MINERS

Table 1 summarizes several studies of radon-exposed miners. Study populations cover a wide variety of types of mining operations and of countries. All study populations have elevated SMRs and have mean CWLM values in excess of ambient levels. The SMRs range from 1.4 in Ontario uranium miners with mean exposure 25 CWLM, to 12.5 in Chinese tin miners with mean exposure 457 CWLM.

The SMRs in Table 1 are difficult to compare directly; because different standard populations were used, age profile and mean CWLM exposure levels differ. In addition, investigators used different techniques to estimate exposure levels. We can
make a crude comparison of exposure-response relationships, however, by using data on SMRs broken down by categories of CWLM. (See BEIR IV [2] and Thomas and McNeill [22].) For convenience, all exposures were restricted to less than 500 CWLM. For most cohorts, SMRs were approximately linear in mean CWLM, but the intercepts at zero exposure did not always equal one. This fact suggests that lung cancer mortality in several of the standard populations was different from the cohort, after adjustment for exposure. Any comparisons among cohorts must, therefore, account for this difference.

We fit the following model to each cohort,

$$\text{SMR} = \exp(\xi)(1 + \beta w)$$

where \( w \) is the CWLM value, \( \exp(\xi) \) is the intercept at \( w = 0 \), and \( \beta \) is the excess relative-risk parameter which specifies the exposure-response relationship. Figure 1 shows the excess relative risks, 90 percent confidence interval, and fitted exposure-response trend for each cohort. Graphs are plotted on a common scale. Estimates for \( \beta \) are shown in Table 2. There was no significant nonlinearity, although the Newfoundland data suggest some quadratic effect. Linear models in excess relative risk are adequate. A test of homogeneity for the \( \beta \) estimates is not rejected (\( p = 0.13 \)). (If the Newfoundland data are omitted, the \( p \)-value for the test of homogeneity is \( p = 0.16 \).) Thus, despite differences in type and location of the mines, the variation in radon effects is no more than would be expected by chance alone. The combined estimate of \( \beta \) is 0.015 with multiplicative standard error 1.2. In modeling, we replaced \( \beta \) by the exponential, \( \exp(\beta) \); with reparametrization, the estimate is more nearly symmetric and its distribution is better approximated by the normal distribution. The 90 percent confidence interval is \((0.015/1.2^{1.64}, 0.015 \times 1.2^{1.64}) = (0.011, 0.020)\). SMRs are summary measures over age and calendar year. An analysis in greater depth of risk patterns with age and other factors requires detailed cross-classifications or actual data on individuals.

### RADON RISK MODEL FROM BEIR IV

The BEIR IV committee obtained raw data on cohorts from Sweden [34], Ontario [35–37], and Eldorado Beaverlodge [38], and detailed cross-classifications from the
Colorado Plateau cohort [32,33]. Table 3 summarizes the experience of the cohorts. A total of 360 lung cancer deaths and 425,614 person-years of follow-up were available [2]. Parallel analyses for each cohort were carried out, using the basic model:

\[ r(a, y, w, x) = r_0(a, y) \left[ 1 + \gamma(a, x)\beta w \right] \]  

(8)

Several factors were evaluated for their effect on the slope estimate for CWLM exposure. Factors which exhibited consistent patterns across cohorts were then included in a joint analysis of all cohorts. In the combined analysis, the committee fit a separate \( \beta \) parameter in equation (8) for each cohort in order to account for cohort differences. Significant modifiers to the slope parameter were observed for age at risk and time since cessation of employment. In the presence of these factors, no significant model improvement was found for age at first exposure, age at exposure, or duration of exposure [2]. Since CWLM was included in the model, any residual variation of \( \beta \) by duration is an assessment of exposure rate.

The declining risk with time since last employment was noteworthy, but interpretation is obscure when exposure occurs over long periods of time. A more meaningful variable was defined by considering exposure during a fixed length of time prior to age \( a \). At each age \( a \), an individual’s cumulative exposure is the sum of exposure increments over time. Specifically, suppose time before age \( a \) is divided into \( K + 1 \) intervals with end-points \( a - t_0, a - t_1, \ldots, a - t_K \), where \( t_K \) is in years. Total exposure \( w \) is the sum of the cumulative exposure from each “window,” \( w = w_1 + w_2 + \cdots + w_K \), where \( w_K \) is the cumulative exposure from \( a - t_{K-1} \) to \( a - t_K \); that is, from \( t_{K-1} \) to \( t_K \) years prior to \( a \). The first interval, from \( a \) to \( a - t_0 \), is the lag time and exposure \( w_0 \) is ignored. The relative effects of the increments are estimated by replacing \( w \) in model (8) by “effective” exposure \( w^* \), where \( w^* = w_1 + \theta_2 w_2 + \cdots + \theta_K w_K \). The parameters, \( \theta_k, k = 2, \ldots, K \), measure effects relative to \( \theta_1 = 1 \).

The model accepted by the committee, the time-since-exposure model, is:

\[ r(a, w_1, w_2) = r_0(a) \left[ 1 + \gamma(a)\beta w^* \right] \]  

(9)

with \( \beta = 0.025 \) and

\[ \gamma(a) = \begin{cases} 
1.2 & \text{for } a < 55 \\
1.0 & \text{for } 55 \leq a < 65 \\
0.4 & \text{for } a \geq 65 
\end{cases} \]

where \( w^* = w_1 + 0.5 w_2 \), with \( w_1 \) CWLM exposure 5–15 years before age \( a \) and \( w_2 \) CWLM exposure 15 or more years before age \( a \).
Model (9) is a synthesis of the four cohort data sets. The model is not a "constant" relative-risk model but postulates that the effect of an exposure declines with age and time since exposure. This change is a departure from previous models [45,46]. Lundin et al. [33] and Harley and Pasternack [47] have also proposed models where excess risk declines with time, although these were not based on any systematic evaluation of human data. The strength of model (9) is that it was developed directly from human data.

Important consequences result from the form of model (9). Radon effects decline with time since exposure, so that exposures 15 or more years prior to attained age have half the influence on the excess relative risk than do exposures 5–15 years prior to attained age. (Exposures within five years are assumed unrelated to lung cancer risk.)

It is important to note that the time-since-exposure effect in the model does not decline to zero but remains elevated. The eventual disposition of the decline is unknown and not estimable from current miner cohorts, since follow-up beyond 30–40 years has not yet occurred. Thus, for lifetime projection of risk, it is not known whether \( w_2 \) should be cumulative exposure 15 or more years prior to attained age or limited, say, to cumulative exposure 15–40 years prior to attained age. A time limitation on the effectiveness of an increment of exposure affects estimates of lifetime risk.

The relative risk for exposure declines with age. Further analysis indicated that the magnitude of the decline was not sufficient to induce a decline in the absolute excess risk [2].

Model (9) is noteworthy for the variables which were not included. After controlling for age and cumulative radon exposure, there were no residual effects of age at exposure or age at first exposure. Age at first exposure has a limited range in most occupational groups, and, hence, there is little power to assess effects. An argument could be advanced that the effectiveness of exposure is enhanced at young ages, because of the dynamics of lung tissue development. Such inference, however, is not currently supportable in human epidemiologic data for radon. In any case, since background rates for lung cancer are low and since the radon exposure effect declines with time, early exposures have little consequence on lifetime risk of lung cancer from radon exposure.

Duration of exposure is not included in equation (9). Animal studies have shown that, for fixed CWLM, long duration of exposure (low exposure rate) is more deleterious than short duration of exposure (high exposure rate) [48,49]. In human data, results are ambiguous. A report from a cohort study among Czech miners suggests an increased risk of lung cancer with long duration of exposure [41]. In the data analyzed by the BEIR IV committee, there was a significant effect of duration in the Colorado cohort, but, in general, no consistent effect emerged. Thus, the possible role of duration of radon exposure has not yet been clarified. Assessment of this important variable must wait for continued follow-up of available cohorts and for additional study populations.

In equation (9), the relative-risk function shows discrete jumps at ages 55 and 65 years and at five and 15 years before attained age. Clearly, these jumps are only approximations of some "true" relationship, which undoubtedly is characterized by a smooth functional form. With limited data, the categorizations must be crude, unless a specific function is imposed. (An interim model defined three time-since-exposure categories, but estimates of the \( \theta \) parameters for five to ten years and for 10–15 years were not significantly different, and categories were merged [2].) Age-specific rates
using equation (9) are estimated with great uncertainty, and many functional relationships could be applied. Retaining the limited categorizations in the modeling is consistent with the descriptive approach which was taken by the committee throughout the analysis. Lifetime risk projection, which is a summation over a lifetime of age-specific risk times the probability of survival, is not grossly affected by the discrete nature of equation (9) and is smoothly increasing with exposure.

**COMBINED EFFECTS OF SMOKING AND RADON EXPOSURE**

Any discussion of the etiologic effects of radon would be incomplete without consideration of tobacco use, the major cause of lung cancer. Table 4 is adapted from [2], where a detailed critique of each study is given. Among the four cohorts which were analyzed, only the Colorado cohort has smoking data for all individuals.

Several important features emerge from Table 4. In general, the amount of data which is available for the study of joint effects is quite limited. The largest number of cases of lung cancer (256) occurs in the Colorado miner cohort. The next largest study includes 60 cases. Thus, apart from the Colorado data, other studies have little power to discriminate among various models. The amount of information is further limited, since the studies in Uranium City, Saskatchewan, Canada, and Grand Junction, Colorado, are of moderate or more severe cell atypia, as determined from sputum cytology screenings, and are related to the joint-risk effects of smoking and radon only insofar as abnormal cytology is predictive of lung cancer.

A formal assessment of the joint effects of smoking and radon using model (4) and a variant which allows R(w) to vary with age has been carried out for the Colorado cohort [2,20] and for a case-control study of New Mexico uranium miners [2]. The Colorado analysis rejects the additive model (\( \lambda = 0 \)) and indicates that the multiplicative model (\( \lambda = 1 \)) is consistent with the data. In an analysis of the New Mexico data, the best-fitting model was supramultiplicative (\( \lambda > 1 \)); however, the number of lung cancers was limited, and both the multiplicative and additive models were consistent. These analyses generally agree with the results of others (Table 4).

There appear to be two exceptions in Table 4. The study in Hammar, Sweden [52], reports a seemingly protective effect of smoking (subadditive), which may be due to smokers having a thickened mucous layer in critical bronchial regions. The study, however, was small (29 cases) and results may be biased because of design constraints. In addition, no information was available on smoking status for non-miners (non-exposed), and mine foremen were the source of smoking status for miners. Also, controls were drawn from death records and matched on time of death. Thus, it is difficult to draw conclusions from this study, since controls may have included persons who died with tobacco-related causes, company records which were used to determine exposure (miner/non-miner) status may be incomplete, foremen may not have accurately recalled smoking status, and nonsmokers may have spent more time underground than smokers (no quantitative data on exposure or duration of employment were reported) [2].

The conclusion in Table 4 for the Swedish study differs from that of the authors. It has been shown that if smoking and radon are additive, if smoking is unrelated to radon exposure, and if the deleterious affects of radon are similar in smokers and nonsmokers, then relative risks for exposure of 10.0 among nonsmokers and of 2.9 among smokers result in a relative risk for smoking of 4.7, which is smaller than expected [23].
| Study Area                        | Design                                                                 | Results                                      | Comments                                                                                           |
|----------------------------------|------------------------------------------------------------------------|----------------------------------------------|----------------------------------------------------------------------------------------------------|
| Kiruna and Gallivare, Sweden [50]| Cases (60) from death register 1972–1982; two types of controls, alive from general population (60) and deceased from death register (67) | Underground Miner                              | Smoking data from interviews of subjects or next-of-kin; results consistent with multiplicative RR model, although formal testing not presented |
|                                  |                                                                        | Cigarette Use<sup>a</sup>                   |                                                                                                    |
|                                  |                                                                        | 0                                            |                                                                                                    |
|                                  |                                                                        | <150                                         |                                                                                                    |
|                                  |                                                                        | >150                                         |                                                                                                    |
|                                  |                                                                        | No                                           |                                                                                                    |
|                                  |                                                                        | 1.0                                          |                                                                                                    |
|                                  |                                                                        | 2.4                                          |                                                                                                    |
|                                  |                                                                        | 8.4                                          |                                                                                                    |
|                                  |                                                                        | Yes                                          |                                                                                                    |
|                                  |                                                                        | 5.4                                          |                                                                                                    |
|                                  |                                                                        | 21.7                                         |                                                                                                    |
|                                  |                                                                        | 69.7                                         |                                                                                                    |
| Malmberget, Sweden [34]          | Cohort study of 1,415 miners with 50 lung cancers                       | Nonsmoker                                    | Results suggestive of greater than additive model; calculation of RR models not precisely described; formal model fitting not presented |
|                                  |                                                                        | Smoker                                       |                                                                                                    |
|                                  |                                                                        | Non-miner                                    |                                                                                                    |
|                                  |                                                                        | 1.0                                          |                                                                                                    |
|                                  |                                                                        | 1.0                                          |                                                                                                    |
|                                  |                                                                        | Miner                                        |                                                                                                    |
|                                  |                                                                        | 10.0                                         |                                                                                                    |
|                                  |                                                                        | 2.9                                          |                                                                                                    |
| Oeland, Sweden [51]              | Cases (22) and controls (178) drawn from death registry 1960–1978; smoking habits obtained from next-of-kin using mail questionnaire | Housing Type<sup>b</sup>                     | Data sparse and no formal models fitted but RR models suggest multiplicative interaction, or at least greater than additive |
|                                  |                                                                        | Cigarette Use                                |                                                                                                    |
|                                  |                                                                        | No                                           |                                                                                                    |
|                                  |                                                                        | 1.0                                          |                                                                                                    |
|                                  |                                                                        | 2.7                                          |                                                                                                    |
|                                  |                                                                        | Yes                                          |                                                                                                    |
|                                  |                                                                        | 1.3                                          |                                                                                                    |
|                                  |                                                                        | 3.6                                          |                                                                                                    |
|                                  |                                                                        | 2                                            |                                                                                                    |
|                                  |                                                                        | 4.4                                          |                                                                                                    |
|                                  |                                                                        | 9.3                                          |                                                                                                    |
| Hammar, Sweden [52]              | Cases (29) listed in death register 1957–1976; controls (174) also from register, matched on year of death | RR for smoking 16.6 (90 percent CI 7.8–35.3); RR for smoking among miners 0.5 (90 percent CI 0.1–2.2) | Suggestive of a protective effect of smoking among miners; results subject to biases (see text) |
| Colorado, U.S.A. [53]            | Cohort study of uranium miners examined through 1960; follow-up from 1964–1967 with 39 lung cancers | Lung Cancer Rate × 10<sup>b</sup>            | Multiplicative combination suggested                                                                 |
|                                  |                                                                        | Cigarette Use                                |                                                                                                    |
|                                  |                                                                        | No                                           |                                                                                                    |
|                                  |                                                                        | 7.1                                          |                                                                                                    |
|                                  |                                                                        | 42.2                                         |                                                                                                    |
|                                  |                                                                        | Yes                                          |                                                                                                    |
|                                  |                                                                        | 1.1                                          |                                                                                                    |
|                                  |                                                                        | 4.4                                          |                                                                                                    |
| Location                                      | Description                                                                                                           | Cigarettes (No./Day) | Cigarette Use (Pack-Years) | Cigarette Use (No./Day) | Cigarette Use             |
|-----------------------------------------------|-----------------------------------------------------------------------------------------------------------------------|----------------------|---------------------------|--------------------------|---------------------------|
| Colorado, U.S.A. [24]                         | Cohort study of 3,362 miners followed through 1982, with 256 observed lung cancers; exposures lagged five years         |                      |                           |                          |                           |
|                                               | WLM 0-4 5-19 20-29 30+                                                                                                 |                      |                           |                          |                           |
|                                               | 0-59 1.0 2.7 7.8 2.9                                                                                                    |                      |                           |                          |                           |
|                                               | 60-119 0.0 0.0 5.6 26.6                                                                                                  |                      |                           |                          |                           |
|                                               | 120-239 2.4 9.1 15.3 9.8                                                                                                 |                      |                           |                          |                           |
|                                               | 240-479 8.4 3.5 14.6 25.8                                                                                               |                      |                           |                          |                           |
|                                               | 480-959 17.8 12.6 32.0 34.0                                                                                             |                      |                           |                          |                           |
|                                               | 960+ 27.6 36.0 63.6 90.3                                                                                                |                      |                           |                          |                           |
| Grand Junction, Colorado, U.S.A. [54]         | Cases (489) and controls (992) drawn from cohort of 9,817 miners followed from 1960–1980 for whom                     |                      |                           |                          |                           |
|                                               | sputum specimens regularly obtained; cases defined as moderate or worst cell atypia                                      |                      |                           |                          |                           |
|                                               | Years Underground 0 1-20 21+                                                                                             |                      |                           |                          |                           |
|                                               | 0 1.0 0.3 2.9                                                                                                           |                      |                           |                          |                           |
|                                               | 1-10 7.3 4.1 18.2                                                                                                      |                      |                           |                          |                           |
|                                               | 11+ 9.6 9.8 26.0                                                                                                       |                      |                           |                          |                           |
| New Mexico, U.S.A. [2]                        | Cases (52) and controls (222) extracted from cohort of uranium miners                                                   |                      |                           |                          |                           |
|                                               | Years Mining Underground <5 5-14 15-24 25+                                                                               |                      |                           |                          |                           |
|                                               | <10 1.0 5.1 7.0 8.2                                                                                                     |                      |                           |                          |                           |
|                                               | 10-14 1.0 12.0 6.7 6.2                                                                                                  |                      |                           |                          |                           |
|                                               | 15-19 3.7 4.2 17.5 0.0                                                                                                  |                      |                           |                          |                           |
|                                               | 20+ 0.0 39.9 24.0 30.1                                                                                                  |                      |                           |                          |                           |
| Uranium City, Saskatchewan, Canada [55]       | Follow-up for three years of underground miners (249) and controls (123) who participated in lung cancer screening    |                      |                           |                          |                           |
|                                               | program; cases defined as moderate or worst cell atypia                                                                  |                      |                           |                          |                           |
|                                               | WLM No Yes                                                                                                             |                      |                           |                          |                           |
|                                               | 0 1.0 2.7                                                                                                              |                      |                           |                          |                           |
|                                               | 120 2.6 3.7                                                                                                            |                      |                           |                          |                           |
|                                               | >120 1.2 12.6                                                                                                          |                      |                           |                          |                           |

Data fit well with multiplicative model \( (p = 0.53) \), while additive was rejected \( (p = 0.03) \); although data consistent with multiplicative model, best-fitting power model submultiplicative.

Study of cell atypia; suggests multiplicative effects, although statistical testing not presented.

Both multiplicative and additive RR models consistent with data, although former exhibits better fit.

Study is of cell atypia; few events among non-smokers; data and analysis insufficient to assess interaction of exposures.
| Study Area                  | Design                                                                 | Results               | Cigarette Use | Comments                                                                 |
|-----------------------------|-------------------------------------------------------------------------|-----------------------|----------------|--------------------------------------------------------------------------|
| Port Hope, Ontario, Canada  | Cases (27) from cancer registry 1969–1979; controls (49) from cancer  | WLM                   | No             | Study has few cases, but suggestive of multiplicative RR model           |
|                              | registry or family physicians; all subjects residing 7+ years in area;  |          | Yes            |                                                                          |
|                              | WLM exposure since 1933 estimated from homes                            | 0                    | 1.0            |                                                                          |
|                              |                                                                         | >0                   | 1.9            |                                                                          |
|                              |                                                                         |                      | 25.6           |                                                                          |

*Lifetime number $\times 10^3$

*See text for category definitions.

*Incidence based on rates in mountain states

*Baseline category had zero observed cases replaced by expected ($= 0.7$).
Thus, the observed relative risks appear compatible with a joint model which is greater than additive, and thus generally consistent with other studies.

In summary, results which are currently available on the issue of joint effects of radon and smoking suggest that an additive model is unlikely and that a multiplicative model is consistent, although a wide range of models from submultiplicative to supramultiplicative is also possible.

**DISCUSSION**

In this report, we have discussed strategies and models for the analysis of epidemiologic cohort data, with emphasis on radon-exposed groups. The regression techniques based on the various models for radon exposure and for radon and smoking offer powerful methods for general exploration of data and for evaluation of specific exposure-response relationships.

Although the methods are quite flexible, one must use caution against over-interpreting specific models, particularly in observational studies. Table 5 lists some of the uncertainties and limitations in the use of analytic models with miner and non-miner populations. The points are presented in the context of risk models for radon exposure but are applicable in general. A discussion of some of these issues is found in the BEIR IV report [2].

The regression models produce parameter estimates and estimates of their asymptotic variance. The variance measures the statistical variation in the data and arises in the context of repeated sampling of data. This variance estimate is probably the only quantifiable measure of uncertainty. The other sources of uncertainty cannot usually be measured and may be of equal or greater importance. The estimated parameters and their variances depend on the fitted model and are affected by model misspecification. Random errors in exposure attenuate the slope estimate for the exposure-response relationship [57,58]. The precise extent of nonrandom error is unknown, but its effects could be substantial. Thus, the overall direction and magnitude of the effects of errors are not easily evaluated.
Model (9) will probably be used for projecting lifetime lung cancer risk due to radon for mine-exposed populations. It was developed from data which have limited follow-up, and which include mostly males, nearly all of whom were above the age of 25 at first hire. The applicability of model (9) beyond the range of the data from which it was developed adds great uncertainty in specific projections.

For home-exposed populations, model (9) offers no guidance on the inclusion of effects of gender or of very young ages at exposure. Use of model (9) is further complicated by an inability to quantify accurately exposures in the home. Radon exposure is a function of occupancy time, location within the home, season of the year, and degree of ventilation. Thus, estimates of exposure are necessarily imprecise. Applying model (9) also requires relating working level months (WLM) exposure in a mine to WLM exposure in a home. The relationship is complex and depends on breathing rate, percentage of nasal versus oral breathing, the amount and size of aerosols and other pollutants, fraction of unattached radon ions, and the proportions of the various radon progeny [2].

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