

RADON EXPOSURE AND LUNG CANCER RISK

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ABSTRACT

As information on indoor air quality accumulated, it became apparent that radon and its progeny are invariably present in indoor environments and that concentrations may reach unacceptably high levels. The lung cancer excess among miners exposed to radon progeny raised concern that exposure to radon progeny might also cause lung cancer in the general population. This presentation first provides an overview of radon daughter carcinogenesis, and then reviews the recent BEIR IV report. The report described a statistical model, based on analysis of data from four studies of miners, for estimating the lung cancer risk associated with exposure to radon progeny. The analyses showed that the risk of radon exposure declines with time since exposure and with increasing age. The BEIR IV committee concluded that radon progeny and cigarette smoking interact in a multiplicative fashion and that exposure-dose relationships are similar for exposure in homes and in mines.

INTRODUCTION

Radon decays with a half-life of 3.82 days into a series of solid, short-lived radioisotopes that are collectively referred to as radon daughters or radon progeny. Two of these isotopes, polonium-218 and polonium-214, emit alpha particles, high energy and high mass particles consisting of two protons and two neutrons. When these emissions take place within the lung as inhaled radon progeny decay, the genetic material of the cells lining the airways may be damaged and lung cancer may result.

The mining of radioactive ores that release radon was the first occupation associated with an increased risk of lung cancer. Over 100 years ago, Harting and Hesse described autopsy findings in eastern European miners

that documented an occupational lung cancer hazard. Excess lung cancer occurrence has subsequently been found in uranium miners in the United States, Czechoslovakia, France, and Canada; and in other underground miners exposed to radon progeny including Newfoundland fluorspar miners, Swedish and U.S. metal miners, British and French iron miners, and Chinese and British tin miners (1). Exposure of animals to radon and its progeny has confirmed that radon progeny cause lung cancer and the association between lung cancer in miners and radon exposure is generally accepted as causal (1).

As information on air quality in indoor environments accumulated, it became apparent that radon and its decay products are invariably present in indoor environments and that concentrations may reach unacceptably high levels in some dwellings. The well documented lung cancer excess among underground miners exposed to radon progeny raised concern that exposure to radon progeny might also be a cause of lung cancer in smokers and nonsmokers in the general population. In response to the recognition of widespread radon exposure in indoor environments, substantial research programs have been implemented. This research addresses not only biological aspects of radon exposure, but also geological aspects of the problem, the movement of radon into homes, and control measures. Epidemiological studies to directly measure the risk of radon exposure in indoor environments have been initiated; computer models have been used to more fully evaluate the comparative dosimetry of radon progeny in homes and in mines; and animal studies have been designed to refine understanding of carcinogenesis by radon progeny. To date, risk assessment methods have been used for the purposes of describing the magnitude of the lung cancer problem associated with radon and of establishing guidelines for exposure. This presentation will describe the risk model recently published by the BEIR IV committee of the National Research Council. This model will likely be preferred for risk assessment until new data become available from studies of radon exposure in the domestic environment.

RESPIRATORY DOSIMETRY OF RADON PROGENY

For historical reasons, the concentration of radon progeny is generally expressed as Working Levels (WL), where one WL is any combination of radon progeny in one liter of air that ultimately releases 1.3×10^5 MeV of alpha energy during decay (2). Concentrations of radon are also frequently expressed as picocuries (pci) per liter; a concentration of 1 pci/l translates to about 0.005 WL under usual conditions in a home. Exposure to one WL for 170 hours equals one Working Level Month (WLM) of exposure. The WLM was developed to describe exposure sustained during the average number of hours spent underground by miners. Because most persons spend much more than 170 hours in their home each month, a concentration of one WL in a residence results in an exposure much greater than one WLM on a monthly basis.

These units are now frequently replaced by SI-units. In SI-units, the concentration of radon in air is expressed as Becquerels per cubic meter (Bq/m^3); at radioactive equilibrium between radon and its progeny, one WL corresponds to $3.7 \times 10^3 \text{ Bq}/\text{m}^3$. Cumulative exposure in SI-units is expressed in Joule-hours per cubic meter (Jh/m^3) and 1 WLM is $3.5 \times 10^{-3} \text{ Jh}/\text{m}^3$.

The relationship between exposure to radon progeny, measured as WLM, and dose to target tissues in the respiratory tract is extremely complex and dependent on both biological and nonbiological factors (3, 4). The risks of exposure to radon progeny in indoor environments must be considered in the context of the relationship between exposure and dose. Furthermore, the risks of exposure indoors have been widely estimated on the basis of studies of underground miners. Because of differences in the circumstances of exposure in the mining and indoor environments, it cannot be assumed that exposures to one WLM in a mine and in a home lead to the same dose of alpha radiation to target cells in the lung. Factors influencing the dosimetry of radon progeny include physical characteristics of the inhaled air, the amount of air inhaled, breathing patterns, and the biological characteristics of the lung (Table 1). Computer models have been developed to describe the effects of these factors.

Radon is an inert gas but its decay products are solid, charged particles. While most of the progeny attach to aerosols immediately after formation, a variable proportion remain unattached and are referred to as the unattached fraction. The fraction of unattached radon progeny in inhaled air is an important determinant of the dose received by target cells at a particular concentration in inhaled air; as the unattached fraction increases, the dose also increases because of the efficient deposition of the unattached progeny in the larger airways. The particle size distribution in the inhaled air also influences the dose to the airways because particles of different sizes deposit preferentially in different generations of airways. The specific mixture of radon progeny also affects the dose to target cells, although to a lesser extent.

7 The amount of inhaled radon progeny varies directly with the minute ventilation, the total volume of air inhaled each minute. The deposition of radon progeny within the lung, however, does not depend in a simple fashion on the minute ventilation but varies with the flow rates in each airway generation. These flow rates depend on both tidal volume and breathing frequency. The proportions of oral and of nasal breathing also influence the relationship between exposure and dose. A substantial proportion of the unattached radon daughters deposits in the nose with nasal breathing whereas unattached daughters do not deposit in the mouth with oral breathing but rather on the bronchial epithelium where target cells are located.

Characteristics of the lung also influence the relationship between exposure and dose (Table 1). The sizes and branching patterns of the airways affect deposition and these aspects of airway configuration may

differ between children and adults, and between males and females. The rate of mucociliary clearance and the thickness of the mucous layer in the airways also enter into dose calculations, as does the presumed location of the target cells in the bronchial epithelium. Dose increases as mucociliary clearance slows and diminishes with increasing thickness of the mucous layer. Cigarette smoking tends to reduce the rate of clearance and to increase the thickness of the mucociliary layer.

RADON AND LUNG CANCER

INTRODUCTION

The causal association of exposure to radon progeny with lung cancer has been amply documented through epidemiological investigations of underground miners (1). Studies of miners have shown rising lung cancer risk as cumulative exposure to radon progeny increases and provided some insights into the combined effects of cigarette smoking and radon progeny exposure. These studies have been less informative concerning the temporal expression of the excess risk and the effect of varying exposure rate. Animal experiments have also provided data on exposure-response relationships and on the modifying effects of exposure rate and the physical characteristics of the inhaled radon progeny (1). Animal models have proved less useful for studying the interaction of radon daughters with cigarette smoking because of the difficulties of replicating smoking patterns of humans with animals.

Because cigarette smoking predominates as the cause of lung cancer, the risk of radon progeny exposure must be addressed separately for smokers and for nonsmokers. When one agent, cigarette smoke, for example, modifies the effect of another, radon progeny, for example, interaction is present. Interactions between two agents may be either synergistic or antagonistic; synergism refers to an increased effect of the independent exposures when both are present, whereas antagonism refers to a reduced effect. Synergism is considered to be present if the joint effect of the two exposures exceeds the sum of the independent effects. If the combined effect equals the product of the independent risks, then the interaction is considered to be multiplicative; the interaction is considered additive if the combined effect equals the sum of the independent risks.

EPIDEMIOLOGICAL STUDIES OF LUNG CANCER AND ENVIRONMENTAL RADON

To date, epidemiological investigations of indoor exposure to radon progeny as a risk factor for lung cancer have been limited by the methodological difficulties of studying this exposure (5). Both descriptive and analytical approaches have been used to examine the association between exposure to radon progeny in the home and lung cancer. Techniques for accurately estimating lifetime exposure of individuals to radon progeny in

indoor air are not yet available, and surrogates for exposure based on residence type, geology, or on limited measurements have of necessity been used in the case-control and cohort studies.

In the descriptive studies, incidence or mortality rates for lung cancer within geographic units have been correlated with measures of exposure for inhabitants of these units. These descriptive studies, which do not consider the exposures of individuals to radon progeny and other agents, can provide only suggestive evidence that radon progeny exposure in the home increases lung cancer risk. The association of exposure and lung cancer has been more directly tested in case-control and cohort studies involving subjects drawn from the general population. To date, these studies have not provided risk estimates suitable for quantitative risk assessment.

RISK ASSESSMENT

INTRODUCTION

Because only scant epidemiological data on environmental exposure to radon and lung cancer are available, the hazard posed by radon progeny exposure in indoor air has been primarily addressed with risk estimation procedures. Information on the population distribution of exposure in dwellings is used in a risk projection equation or "model" that describes the increment in lung cancer occurrence per unit exposure. For the United States, however, the needed data on the concentrations of radon progeny in a large, representative sample of homes have not yet been collected. The selection of risk coefficients for exposure to radon progeny is also problematic; the studies of miners include only males, much of the exposure of miners was at concentrations higher than generally occur in homes, and none of the study populations have yet been followed for the full lifetime of the subjects. Furthermore, the various factors that affect the dosimetry of radon progeny may differ substantially in homes and in mines (Table 1).

To accomplish the risk estimation, a mathematical model is used to project the occurrence of lung cancer cases caused by exposure. These risk projection models require assumptions concerning the temporal pattern of occurrence of lung cancer after exposure and the effects of such potentially important cofactors as age at exposure, age at risk, and cigarette smoking. The two most widely applied are the relative risk and attributable risk models; the relative risk model assumes that the background risk is multiplied by the risk of radon progeny, whereas the attributable risk model assumes that the excess risk is additive to the background risk. Some models describe the risk as varying with time since exposure (1, 3).

The manner in which radon progeny exposure and cigarette smoking are assumed to interact strongly influences the results of risk estimation models for radon progeny. If a multiplicative interaction is assumed, then the risks for smokers, already much greater than for nonsmokers, are

multiplied by the risk from exposure to radon progeny. If an additive interaction is assumed, then the same excess risk is added to the background rates for smokers and for nonsmokers. The interaction between the two agents might plausibly take some form other than purely additive or purely multiplicative. The epidemiological evidence indicates interaction between cigarette smoking and radon progeny exposure that is more than additive, although the data are not consistent (1).

THE BEIR IV REPORT

Introduction--

In 1988, the National Research Council published the report entitled "Health risks of radon and other internally deposited alpha-emitters. BEIR IV" (1). This report was prepared by the National Research Council's Committee on the Biological Effects of Ionizing Radiation. The committee, the fourth in a series that began in 1969, was charged with addressing the risks of internally deposited alpha-emitters. It began its work in 1985 when the extent of exposure to radon in the indoor environment was becoming widely recognized and a source of substantial public concern; consequently, health risks of radon were emphasized in the committee's deliberations and in its final report. The committee was asked to review the risks of radon in mining and in indoor environments, and was charged with developing estimates of the lung cancer risk associated with radon exposure in both the occupational and environmental settings. The committee also reviewed risk estimates for lung cancer prepared by other groups, and evidence on health effects other than respiratory cancer.

After initial review of the available risk models for radon, the committee concluded that a new model should be developed to overcome limitations and uncertainties of previous risk models. The committee elected to develop the risk model on the basis of data from epidemiological studies of underground miners exposed to radon. The committee concluded that scientific understanding was not sufficient for developing a risk model solely on a biological basis, and the committee also considered the available studies of lung cancer and environmental radon to be inadequate for risk assessment. To develop its risk model, the committee obtained data from four studies of underground miners exposed to radon: U.S. uranium miners in the Colorado region studied by the Public Health Service; underground uranium miners in Saskatchewan and in Ontario, Canada; and underground metal miners in Sweden.

The BEIR IV Risk Model--

With the cooperation of the investigative groups that had generated the four data sets from the underground-miner studies, the BEIR IV committee was able to obtain data in a form that permitted a unified analysis. The committee first carried out separate but parallel analyses of the four data

sets that were followed by a formal analysis of the combined data. The analysis used relative risk models for the age-specific lung cancer mortality rates of the following form:

$$r(a) = r_0(a)[1 + \beta\gamma(\nu)W],$$

where $r(a)$ is the lung-cancer mortality rate for a particular age and calendar time, $r_0(a)$ is the baseline lung cancer mortality rate in a population, W is the cumulative exposure up to five years before age (a) , β is the slope of the dose-response relation, and $\gamma(\nu)$ is a term for the modifying effects of other factors (ν) . This model implies that the background rate of lung cancer is multiplicatively increased by exposure to radon. Because cigarette smoking is one of the principal determinants of $r_0(a)$, the model implicitly assumes that cigarette smoking and radon exposure are synergistic in a multiplicative fashion. The modifiers (ν) might be such factors as age at first exposure and age at observation.

Statistical models of this type were fitted to the individual studies and then to the combined data set. The technique of Poisson regression was used to fit the models. In analyzing the data sets, the committee used a form of relative risk model which was termed the time-since-exposure model. Rather than considering cumulative exposure prior to age at observation, this model estimates the effects of exposures received in distinct time windows before the age at risk. The version of the model used by the committee estimated the effects during three time windows: exposures received from the fifth through the ninth year before age at risk, from the tenth through the fourteenth year, and the fifteenth year or earlier. The general form of this model is shown below.

$$r(a) = r_0(a)[1 + \beta\gamma(a)(d_1 + \theta_2d_2 + \theta_3d_3)],$$

Where d_1 , d_2 , d_3 are the exposures received during the three windows and θ_2 and θ_3 represent variation in the effects of exposure among the windows. This model was applied to each of the four data sets. The effects of the exposures were estimated, and the importance of various aspects of exposure including age at first exposure, age at risk, and duration of exposure were examined. The analyses showed reasonable consistency among the cohorts; the final model is given below.

$$r(a) = r_0(a)[1 + 0.025\gamma(a)(W_1 + 0.5W_2)],$$

$r_0(a)$ is the age-specific baseline rate; $\gamma(a)$ is 1.2 for (a) less than 55 years, 1.0 for (a) 55-64 years, and 0.4 for (a) 65 years or more; W_1 is Working Level Months (WLM) of exposure received 5 to 15 years before age (a) , and W_2 is WLM received 15 years or more before age (a) . This model departs from the widely used constant relative risk model, in which the increase in relative risk associated with a given exposure is constant over time after exposure. The BEIR IV time-since-exposure model implies that the effect of exposure wanes as the interval since exposure lengthens.

Uncertainties in the BEIR IV approach--

The BEIR IV report provides an extensive discussion of uncertainties in these analyses, and estimates the statistical uncertainties associated with the model. The lung cancer risk estimates have a multiplicative standard error of about 30%, which reflects only the consequences of sampling variation. The committee emphasized that errors in the exposure data were of substantial concern as a source of uncertainty. The errors in exposure estimates do not lend themselves to ready quantitation; the report does, however, provide a careful description of the procedures used to calculate exposure in each study. The committee judged that the exposure estimates were likely to be affected by both random and systematic errors. Random errors would tend to reduce the magnitude of the estimated risk, and systematic errors might bias exposure estimates either upwards or downwards. Error in classification of the cause of death was judged to be a lesser concern.

Cigarette smoking was not directly considered in the statistical analyses. The committee's final risk model assumes that the risk from radon exposure multiplies that of cigarette smoking, which is incorporated in the baseline rates. Based on literature review and its own data analysis, the committee concluded that cigarette smoking and radon exposure act in a combined fashion that is multiplicative, or close to multiplicative, on the relative risk scale.

Finally, the report addresses the limitations of the mathematical approach used to develop the model. The model may not correctly represent underlying biological phenomena, and probably does simplify an extremely complex process. Other factors, in addition to those in the model, may also affect the risk from radon exposure. The committee did not attempt to combine all the various sources of uncertainty into a single quantitative estimate of uncertainty.

The BEIR IV risk projections--

The committee used the time-since-exposure model to project the risk of lung cancer associated with radon-daughter exposure. The committee calculated the lifetime risks of lung-cancer mortality, and the years of life lost, for various patterns of exposure, age at risk, and cigarette smoking. For these calculations, the committee assumed the age-specific lung cancer rates observed in the U.S. population from 1980 through 1984. The report provides tables and graphs that give the resulting risk projections.

These risk projections must be used with awareness of the associated uncertainties. In the in-depth discussion in the report, the committee addresses the uncertainties related to gender, age at exposure, cigarette smoking, temporal expression of risk, and extrapolation from the mining environment to the indoor environment.

With regard to gender, the committee's model was based only on data from studies of males. In extending the model to females, the committee assumed that baseline risks would be multiplied by the excess associated with radon exposure, as in males. This assumption was viewed as biologically plausible, although data from the Japanese atomic bomb survivors have suggested that the radiogenic excess for lung cancer is additive to the background rates for males and females.

The committee did not find an effect of age at first exposure in its analyses. Dosimetric considerations suggest that exposure at an early age might have a greater effect than exposure during adulthood. Unfortunately, data on exposure during childhood were not available to the committee.

Cigarette smoking, the predominant cause of lung cancer, represents an important source of uncertainty. The committee did not directly consider cigarette smoking in its analyses, but selected a multiplicative model for the interaction between smoking and exposure to radon, largely on the basis of data from the study of Colorado Plateau uranium miners. However, the committee's analysis did show that a submultiplicative model provided the best mathematical fit to the Colorado Plateau data. If the submultiplicative, rather than the multiplicative, model is more appropriate, then the time-since-exposure model overestimates the risk associated with exposure to radon for smokers, and underestimates the risk for nonsmokers.

In making projections of lifetime risk with the time-since-exposure model, the model is being extrapolated beyond the period over which the miners were observed. None of the four cohorts of miners have yet been followed across their entire lifetimes. Accordingly, assumptions are necessary concerning the lifetime expression of risk. Additionally, the committee did not have sufficient data for a detailed examination of the decline of risk following exposure. The time-since-exposure model lumps together all exposure received 15 years or more before age at risk. Variation of risk as the time since exposure lengthens was not described.

Conditions of exposure to radon differ substantially in mines and in homes. Breathing pattern, ventilation pattern, fraction of unattached radon daughters in inhaled air, particle size distribution in inhaled air, and equilibrium of radon with its daughters are likely to differ in the two environments. The committee considered the probable range of variation in these factors in the two environments, and the results of dosimetric models that have been used to assess the effects of varying these parameters. The committee concluded that exposure to one WLM in a home provides the same dose to target cells as one WLM in a mine.

The report provides risk projections for sustained exposure at exposure rates from background to 10 WLM per year above background, for

exposure to radon across varying age intervals, and the lifetime effects conditional on survival to particular ages. The tables are extensive, and can only be illustrated in this presentation.

Table 2 provides representative risk projections for male nonsmokers and smokers receiving radon exposure at a constant rate throughout the lifetime. At low levels of exposure, the increments and risks are comparable for smokers and nonsmokers, as would be anticipated from the multiplicative interaction between cigarette smoking and radon exposure assumed in the model. At higher exposure rates, the relative risks fall for smokers because of lifespan shortening. While the relative risks for smokers and nonsmokers are comparable at lower exposures, the background lung cancer risk is much greater in smokers than in nonsmokers. For the reference category of no additional exposure, the lifetime risk of lung cancer for a male nonsmoker is 1.1 percent, whereas that for a male smoker is 12.3 percent. Radon's effects on lung cancer mortality are similar for females.

Exposure to radon generally takes place in a variable fashion across a lifetime. The exposure rate may change with a move from one home to another or following the mitigation of a high level of exposure. In the occupational setting, a miner's exposure generally begins in early adulthood and ends after a variable period of employment. The BEIR IV report provides tables for males and females showing lifetime risks at varying exposure rates for varying age intervals. Several patterns emerge from review of these tables. Because the time-since-exposure model is used, exposures in early life have less effect on lifetime risks than exposures during young adulthood and middle ages. Exposures received later in life have less effect because the time available before death for expression of the risk is limited. Representative projections are provided in Table 3 for males at an exposure rate of 4 WLM per year.

Other Risk Projection Models--

Other risk projection models have recently been published for lung cancer risk associated with radon exposure. The model developed by the National Council for Radiation Protection and Measurements (NCRP) projects the risk from radon as additive to the background risk (3). The model assumes that the excess associated with radon exposure declines as time since exposure lengthens. Cigarette smoking is assumed to interact in an additive fashion with radon exposure. The International Commission on Radiation Protection (ICRP) has prepared a constant relative risk model which assumes a multiplicative interaction between cigarette smoking and radon exposure (6).

Risk projections from the ICRP, NCRP, BEIR IV models differ substantially for some exposure scenarios (7), even though the risk

coefficients in each of the models are based on the epidemiological studies of miners. The choice of risk projection model will have important implications for determining acceptable levels for radon exposure.

CONCLUSIONS

The BEIR IV report provides a comprehensive summary of the information available on radon and lung cancer, and on other potential health effects of radon exposure. The committee has developed a new risk model based on analysis of data from four investigations of underground miners. The model describes the risk as decreasing with increasing time since exposure, and thus departs from the constant relative risk models that have been widely used for describing effects of radiation exposure on cancer occurrence. The committee also concluded that cigarette smoking and radon exposure interact synergistically, although the magnitude of the synergism could not be precisely described. The committee further concluded that comparable exposures in a home and in a mine lead to comparable doses of alpha radiation to target cells in the respiratory tract.

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TABLE 1. FACTORS INFLUENCING THE DOSE TO TARGET CELLS IN THE
RESPIRATORY TRACT FROM RADON EXPOSURE

Physical Factors

Fraction of daughters unattached to particles

Aerosol size distribution

Equilibrium of radon with its progeny

Biological Factors

Tidal volume and respiratory frequency

Partitioning of breathing between the oral and nasal routes

Bronchial morphometry

Mucociliary clearance rate

Mucus thickness

Location of target cells

TABLE 2. LUNG CANCER RELATIVE RISKS FOR MALES
CONSTANT RADON EXPOSURE

Exposure Rate (WLM/yr)	Non Smokers	Smokers
0	1.0	1.0
0.2	1.19	1.16
0.5	1.46	1.40
1.0	1.91	1.76
2.0	2.81	2.39
5.0	5.41	3.74
10.0	9.48	4.96

TABLE 3. LUNG CANCER RELATIVE RISKS FOR EXPOSURE AT 4 WLM/YR
ACROSS VARYING AGE INTERVALS FOR MALES

Age (yr) Started	Age (yr) Exposure Ends				
	20	40	60	80	110
0	1.59	2.17	2.72	2.89	2.90
20		1.61	2.20	2.38	2.39
40			1.62	1.81	1.82
60				1.20	1.21