LUNG CANCER MORTALITY AMONG US URANIUM MINERS:
A REAPPRAISAL

ALICE S. WHITTEMORE
ALEX McMILLAN

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by

Alice S. Whittemore
and
Alex McMillan
Stanford University

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ABSTRACT--This report examines lung cancer mortality among a cohort of white underground uranium miners in the Colorado Plateau, based on mortality follow-up through December 31, 1977. The analytic methods represent a miner's annual age-specific lung cancer mortality rate as the (unspecified) rate among nonsmoking men born at the same time and with no mining history, multiplied by a relative risk factor $R$. This factor depends on the miner's total exposures to radon-daughters (in working level months (WLM)) and to cigarettes (in packs), accumulated from start of exposure until ten years before his current age. Among those examined, the relative risk function giving the highest likelihood of the data was:

$$R = (1 + 0.31 \times 10^{-2}\text{WLM})(1 + 0.51 \times 10^{-3}\text{packs}).$$

This multiplicative function specifies that ratios of mortality rates for miners vs nonminers with similar age and smoking characteristics do not depend on smoking status. By contrast, differences between miners' and nonminers' mortality rates are substantially higher for smokers than for nonsmokers. The data rejected (p=0.01) several additive functions for $R$ that specify relative risk as a sum of components due to radiation and to cigarette smoking. Cumulative exposures to both radiation and cigarettes gave better fits to the data than did average annual exposure rates. Age at start of underground mining had no effect on risk, after controlling for age at lung cancer death, year of birth, and cumulative radiation and smoking exposures.
INTRODUCTION

Men working underground in uranium mines in North America and Europe have experienced excess cancers of the lung that cannot be attributed to excessive cigarette smoking (1-3). Experimental evidence suggests that the excess is largely due to irradiation of the tracheobronchial epithelium by alpha particles emitted during the radioactive decay of radon and its daughter products. Little is known about the mechanisms by which these alpha particles induce malignancy, or about the role played by cigarette smoke in the carcinogenic process.

During the period from World War II until 1970, uranium miners in Colorado, Arizona, New Mexico, and Utah inhaled variable but generally high levels of radon daughters. Some miners accumulated lifetime exposures more than three orders of magnitude higher than those typically obtained from background sources. Starting in 1950, the United States Public Health Service (USPHS) initiated extensive collection of data on individual miners' exposures to radiation and tobacco, and mortality follow-up. The cohort is a valuable resource for the study of human hazards associated with alpha-irradiation in combination with exposures to cigarette smoke. Published analyses of these data (e.g., 1, 4-7) have motivated legislation on maximum permissible occupational and environmental exposures to radon-daughters (3). It is therefore important to follow the cohort through the lifetimes of all its members, and to reexamine exposure-response relationships as new deaths occur.

This report describes an analysis based on 194 lung cancer deaths among white miners in the cohort, using statistical methods developed within the last decade. Prior analyses of these data (e.g., (6)) included fewer than 150 such deaths, observed through September 30, 1974. The period since 1974 has seen the development of promising new methods for analyzing occupational
cohort studies. The methods are based on a proportional hazards model for mortality rates proposed by Cox (8). They permit estimation of associations between cause-specific mortality and exposures via internal comparisons within the cohort. Thus they avoid incomparability problems encountered with the use of mortality rates among control groups that may differ from the study group in important determinants of disease (9). The methods also permit study of the separate and combined effects of radiation and cigarette smoking, while controlling for age at death, year of birth, and other potential confounding variables. A preliminary analysis of these data using proportional hazards methods has been described by Hornung and Samuels (10). The analysis presented here compares the radiation and smoking histories of white lung cancer decedents with those of a sample of the surviving white miners, matched to the decedents on year of birth.

MATERIALS AND METHODS

Study subjects.--The cohort consists of a total of 3362 white and 780 nonwhite miners who were examined medically between 1950 and 1960, and who had worked underground in uranium mines in the Colorado Plateau for at least one month prior to January 1, 1964. The National Institute of Occupational Safety and Health (NIOSH) has followed the subcohort of white miners through December 31, 1977 (11); its vital status in 1974 and its status in 1977 are shown in table 1. Death certificates have been coded according to rules operative at the time of death, using the Seventh Revision of the International Classification of Diseases (ICD). The analysis presented here involves 185 white miners whose death certificates stated a diagnosis of cancer of the trachea, bronchus or lung, either primary (ICD code 162) or unspecified as to whether primary or secondary (ICD code 163), hereafter called lung cancer decedents or cases. The analysis also includes an additional nine white lung
cancer decedents who died after December 31, 1977, yielding a total of 194 cases. For each case four control subjects were randomly selected from among those white miners born within eight months of the case and known to survive him. (Controls matched to the nine cases dying since end of follow-up in 1977 could also have died since that time and slightly before their cases.)

**Estimated exposures to radiation and tobacco smoke.**—To estimate radiation exposures, the USPHS and state officials made nearly 43,000 radon-daughter measurements on 2,500 mines during the period from 1951 through 1968. The unit of measurement is a working level (WL), which equals any combination of radon-daughters in one liter of air that will result in the emission of $1.3 \times 10^5$ MeV of potential alpha energy. When no radon-daughter samples were recorded for a mine during a given year, a value was estimated by interpolation from measurements for that mine during adjacent years or from data from nearby mines or regional averages. Nearly 50% of the annual estimates were obtained in this way. Radon-daughter exposures accrued in hard rock mines other than uranium mines were not included in this analysis. Estimated exposure levels for this type of work are very low (<1WL) in comparison with average levels in uranium mines during the study period.

Detailed mine employment and smoking histories were obtained from the initial medical examinations, from annual uranium miner censuses, and from mail questionnaires. Cumulative radiation exposures were estimated in units of working level months (WLM), i.e., the cumulative product of length of underground exposure in working months (roughly equivalent to 170 hours) and concentration of radon-daughters in working levels specific for mine and calendar year. The USPHS has summarized radiation exposure histories on a computer tape containing for each miner the dates of underground uranium mining employment in each mine and the proportion of time employed underground. The tape also provides dates when the miner's estimated
cumulative radon-daughter exposure successively entered the seven categories shown in table 2, provided such dates were before 1969. Exposure histories were not estimated after this date. In order to avoid bias due to exposure underestimation for those subjects who died with lung cancer after 1969, cumulative radon-daughter and cigarette smoking exposures were evaluated for all lung cancer decedents and their controls at a date 10 years before the decedent's death, hereafter called the exposure cut-off date. This ten-year lag insures uniformly cumulated exposure estimates for all cases and controls. Some lag is appropriate, assuming that radon-daughters and cigarette smoke contribute nothing to the malignant process in the last years before death. A ten-year lag is consistent with estimates of Geddes (12), who noted that if all the human lung cancer doubling times in the literature are pooled, then the time from malignant cell transformation to diagnosis is about 10 years, and following diagnosis, the average time to death is about 18 months. When an individual's exposure cut-off date fell between the dates he entered or left one of the categories shown in table 2, his total exposure to the cut-off date was estimated by linear interpolation, taking into account any periods when he was not working underground.

Possible errors in work histories and in estimated mine working levels both contribute to potentially large errors in cumulative exposure estimates. There is some evidence that actual exposures may have been overestimated (1,4). Further discussion of exposure calculation and evaluation of errors can be found in (1,4).

Cigarette smoking histories, consisting of the date smoking started and subsequent smoking rates in packs/day, were obtained from each subject on from one to four occasions between 1950-1960, and on other occasions between 1963 and 1969. These histories were used to estimate total packs of cigarettes smoked until the exposure cut-off date. When necessary, we extrapolated
forward in time by assuming the miner continued smoking at his last reported rate. Pipe and cigar smoking was not considered.

Some of the analyses below assume that study subjects were exposed to "background" levels of radon-daughters and cigarette smoke at constant rates of 0.2 WLM/year and 0.1 cigarette/day. The first value was obtained from the 1980 BEIR III Report (3). It has also been proposed as the average indoor background rate in the US (13), and as the average outdoor background rate in Grand Junction, Colorado (14). We have ignored the small additional radon-daughter exposure associated with cigarette smoke (15) in all radiation exposure estimates. The value for background exposures to cigarette smoke was based on the estimates of Hinds and First (16). The range of background smoking rates proposed in the literature is large (16-19). However, modification of assumed values within this range produced negligible changes in risk estimates. Both background rates were cumulated from a miner's birth until his exposure cut-off date.

Statistical Methods.—We explored relationships between lung cancer mortality and exposures to radon-daughters and cigarette smoke using proportional hazards models and maximum likelihood methods applied to matched case-control studies (20-23). To do so, we represent the age-specific mortality rate $\lambda$ for lung cancer of given ICD code (162 or 163) among white miners as an unspecified underlying rate $\lambda_0$ among nonsmoking white males born at the same time and with no mining history, multiplied by a relative risk factor $R$. In symbols, this proportional hazards assumption is

$$\lambda(x;z) = \lambda_0(x)R(z,\beta).$$

(1)

Here $\lambda(x;z)$ is the mortality rate for a white male aged $x$, with smoking and radiation exposures expressed as a vector $z=(z_1,\ldots,z_p)$. The symbol $\lambda_0(x)$ denotes the age-specific mortality rate for a nonsmoking white male with no mining exposures. The relative risk factor $R$ is a specified function of
exposures $z$ that depends on unknown parameters $\beta$. These parameters measure the influence of exposures on mortality. They are estimated from the data by maximum likelihood (23). The mortality rates and $\lambda$ and $\lambda_0$ and the relative risk factor $R$ may also depend upon year of birth and lung cancer ICD code. For simplicity, our notation suppresses these dependencies.

We did not estimate the baseline mortality rate $\lambda_0$, and therefore we cannot estimate the miners' age-specific mortality rates $\lambda$. However, we assumed several different functional forms for $R$, and examined how well these functions describe the data. By using assumption (1), the information obtained about $R$ permits us to make inferences concerning how the mortality rates $\lambda$ vary with exposure.

We discriminated between two competing functional forms (i.e., models) for $R$ by choosing the one with the larger maximized likelihood. When convenient, we also assumed a more general model that includes both competing ones as special cases, and used likelihood ratio statistics to examine goodness-of-fit (21). The details of this procedure are described in the next section. Confidence intervals for $R$ were obtained by assuming that estimates for its parameters are normally distributed with covariance matrix given by the inverse of an expected information matrix (22).

The matched design and matched analysis ensure that all results are adjusted for age and birth cohort, two factors known to be associated both with lung cancer risk and with magnitude of radiation exposure (1).

RESULTS

Descriptive statistics.--Text-figure 1 gives the distribution of age-at-death for the 194 cases. The median age was 56, with 14 deaths occurring before age 45. These data suggest that the cohort experienced lung cancer at relatively young ages. However, this impression may be due to incomplete
follow-up. Its verification would require comparison of age-specific lung
cancer death rates for the cohort with those for say, US white males. Such a
comparison is beyond the scope of this report.

Text-figure 2, showing the joint distribution of cumulative radon-
daughters and cigarette smoking exposures for cases and controls, indicates
the very high radiation doses experienced by the cohort. Indeed one case and
one control accumulated approximately 10,000 WLM. The means are 1358.2 WLM
(cases) and 626.7 WLM (controls). By contrast, the average life-time exposure
due to background sources is estimated at 10-15 WLM. Those cases and controls
with zero radon-daughter exposures began underground mining subsequent to
their exposure cut-off date.

Like their radiation exposures, the miners' smoking totals are high; the
means for cases and controls are 29.0 and 20.5 pack-years of cigarettes. (One
pack-year equals 365 packs of cigarettes.)

Joint effects of radiation and smoking.--Table 2 shows estimates of lung
cancer relative risk obtained by partitioning the joint radiation and smoking
exposure data for cases and controls into 6 x 4 = 24 categories. The highest
two radiation categories were combined for this analysis because there were no
cases in the category specified by 3720 or more WLM and less than 10 pack-
years of smoking. To obtain these estimates, we let the variables "WLM" and
"PKS" represent cumulative radiation and smoking exposures in units of WLM and
packs, respectively. We took the relative risk function function \( R \) of (1) to be

\[
R(\text{WLM}, \text{PKS}, \beta) = 1 + \beta_{ij}
\]  

(2)

if a miner's WLM and PKS fell in the joint category \((i,j)\) of table 2, \(i = 1, \ldots , 6\), \(j = 1, \ldots , 4\). The relative risk for a miner in category \((i,j)\) is
therefore \(R_{ij} = 1 + \beta_{ij}\). We force \(R_{11} = 1\) by taking \(\beta_{11} = 0\). The relative risk
estimates for miners in the remaining categories give their risks relative to

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men in this baseline category. The resulting estimates are somewhat unstable
due to small numbers of cases and/or controls. Except for the category
represented by 22-119 WLM and 0-10 pack-years, all relative risks exceed unity
at a 0.05 (two-tailed) level of statistical significance.

The last row and column of table 2 present summary risk estimates for the
pooled smoking and radiation groups relative to risk in the lowest such group.
Each of these sets of relative risk estimates has been adjusted for the
effects of the other exposure, using the relative risk function

$$R(\text{WLM}, \text{PKS}, \beta) = (1 + \beta_i^{(r)})(1 + \beta_j^{(s)})$$  \hspace{1cm} (3)

for miners whose WLM and PKS fall in radiation and smoking categories $i$ and
$j$ of table 2. The lowest of these categories are assigned a relative risk of
unity by setting the parameters $\beta_i^{(r)}$ and $\beta_j^{(s)}$ equal to zero. The summary
relative risk estimates $1 + \beta_i^{(r)}$ for radiation (final column) and $1 + \beta_j^{(s)}$ for
smoking (final row) indicate that both exposures have strong independent
effects which cannot be explained by the contribution of the other. Smoking-
adjusted radiation risks increase with cumulative radiation dose. However,
risk among those exposed to 22-119 WLM does not differ from baseline at the
0.05 level of statistical significance. By contrast, summary relative risk
estimates for all groups exposed to more than 10 pack-years of cigarette
smoking are significantly greater than one, although the risk for the 20-30
pack-year group is less than that of the 10-20 pack-year group.

Considerable interest has focused on whether the joint role of cigarette
smoke and radon-daughters can be described more accurately by a relative risk
function which is additive or multiplicative with respect to these two
exposures (3,24,25). Using the smoking and radiation categories of table 2,
we addressed this question by comparing the fit of the multiplicative function
(3) with that of the additive function

$$R(\text{WLM}, \text{PKS}, \beta) = 1 + \beta_i^{(r)} + \beta_j^{(s)}.$$  \hspace{1cm} (4)

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if a miner's WLM and PKS fall in categories i and j of table 2. In (4) $\beta_1^{(r)} = \beta_1^{(s)} = 0$. When substituted into text-equation (1), the additive function (4) specifies that the difference between age- and smoking-specific mortality rates for miners in radiation category i and such rates for miners in radiation category 1 is independent of smoking status. By contrast, function (3) stipulates such smoking independence for the ratio of these two rates.

Table 3 shows likelihood-ratio statistics corresponding to function (2) (Model 3.A), function (3) (Model 3.B), and function (4) (Model 3.C). If neither radiation nor smoking affected lung cancer risk, these statistics would have approximate chi-squared distributions with degrees of freedom equal to the number of parameters in the model. Their overwhelming statistical significance provides further evidence of the combined predictive strength of the two exposures. One tests the goodness-of-fit of, say, the multiplicative model (3.B) by subtracting its likelihood ratio statistic from that of the more general model (3.A). If model (3.B) gives an adequate description of the data, one would expect this difference to have an approximate chi-squared distribution, with degrees of freedom obtained by subtracting the number of parameters in model (3.B) from those in model (3.A). Table 3 indicates that the additive model fits poorly by this criterion ($p = 0.01$), while the multiplicative model cannot be rejected.

Further evidence for multiplicative joint effects can be seen in table 4. This table presents goodness-of-fit statistics for a multiplicative linear relative risk model

$$R = (1 + \beta_1^{\text{WLM}})(1 + \beta_2^{\text{PKS}})$$

(5)

and an additive linear model

$$R = 1 + \beta_1^{\text{WLM}} + \beta_2^{\text{PKS}}$$

(6)

relative to a "mixture" model (22) which contains both of them as special cases. When the mixing parameter $\beta_3 = 1$, the mixture model reduces to the
multiplicative model, and when $\beta_3 = 0$, the mixture model becomes the additive model. Table 4 shows significantly poor fit for the additive linear model ($p=0.01$) and no indication of inadequacy for the multiplicative linear model. The maximum likelihood estimate for $\beta_3$ was 0.94. Therefore we shall assume hereafter that relative risk can be expressed as the product of some function of radiation exposure times some function of cigarette smoking. The issue of whether cigarette smoking hastens the appearance of radiation-induced lung cancer (25) will be discussed in a later section. We next explore alternatives to the linear exposure functions given in text equation (5).

Dose-response functions for radiation and smoking.--Table 5 shows likelihood ratio statistics and estimated regression coefficients corresponding to three forms for relative risk as a product of functions of smoking and radiation exposures. The three forms represent a subset of nine possibilities corresponding to three dose-response curves for each of the two exposures. Although all nine possibilities were examined, for brevity we report only the results for those shown in table 5.

The dose-response curves in model (5.A) are concave upward, with relative risk per unit dose increasing with dose. This model is used extensively in the analysis of epidemiological data because of its mathematically convenient properties (20). When applied to these data it predicts that lung cancer risk for a miner who has accumulated one WLM of radon-daughter exposure relative to a nonminer born at the same time and with the same smoking history is $e^{0.55 \times 10^{-3}} = 1.0005$, giving an excess relative risk of 0.05% per WLM. It also predicts the risk of smoking 20 pack-years of cigarettes to be $\exp(0.95 \times 10^{-4} \times 20 \times 365) = 2.00$ times that of a nonsmoker with the same age and work history, a relative risk considerably lower than values reported in the literature (26).
The functional form used in model (5.B) specifies that lung cancer mortality at a given age is proportional to a power of cumulative exposure. The function is similar to one used by Kneale et al (27) to analyze deaths due to cancers of radiosensitive tissues among Hanford employees exposed to plutonium. To avoid zero mortality rates at zero exposures, we augmented radiation and smoking exposures by "background" exposures at rates of 0.2 WLM/year and 0.005 packs/day, respectively, each accumulated until the miner's exposure cut-off date. Thus risk is proportional to a power of total dose, including background. The power exponents are estimated from the data. The exponents 0.4342 and 0.4113 indicate that risk varies roughly as the square root of each exposure, and that estimated exposure-response curves are concave downward, with relative risk per unit exposure decreasing with increasing exposure level. According to model (5.B), a miner who doubles his lifetime background radiation exposure experiences a lung cancer relative risk of $2^{0.4342} = 1.35$ relative to a nonminer of his age and with his smoking habits. The smoking exponent of 0.4113 suggests that a 50-year-old miner who smokes 20 pack-years of cigarettes by age 40 increases his risk by a factor of $1 + 20/(0.005 \times 365 \times 40) 0.4113 = 6.67$ relative to a nonsmoker born in the same year and with the same mining history.

The linear model (5.C) (also given by text equation (5)) predicts that among smokers and nonsmokers, excess relative risk due to radiation is proportional to total radiation exposure level. Thus relative risk per unit exposure is independent of exposure level, with estimated excess relative risk equal to 0.31% per WLM. Similarly, for fixed radiation exposure the excess risk due to cigarette smoking is proportional to total packs smoked and to risk among nonsmokers. The relative risk associated with 20 pack-years of smoking is $1 + (0.51 \times 10^{-3} \times 20 \times 365) = 4.72$. 

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Since we have not examined a general model containing (5.A)-(5.C) as special cases, we cannot compute goodness-of-fit statistics such as those presented in tables 3 and 4. However, comparison of likelihood-ratio statistics in table 5 shows that the likelihood of the data was largest for the simple linear model (5.C). None of the remaining six possible models obtained by combining different functional forms for radiation and smoking produced a larger likelihood than did (5.C).

Models (5.A)-(5.C) were also examined by embedding each in a more general model containing additional indicator variables for various radiation and smoking categories. Goodness-of-fit statistics, similar to those presented in tables 3 and 4, were used to test for improved fit. This procedure, described in (21), searches for departures from the postulated exposure-response curves that may occur in specific exposure categories. Addition of 23 indicator variables for the highest joint exposure categories in table 2 did not add significantly to any of the models (5.A)-(5.C), nor did addition of indicators for the three highest summary smoking groups in table 2. However, while indicator variables for the five highest radiation groups contributed significantly to models (5.A) and (5.B) (p<0.05) they did not do so for model (5.C) (p=0.45). This suggests that the exponential and power functions (5.A) and (5.B) provide less adequate quantitative descriptions of the relationship between lung cancer mortality and radon-daughters than does the linear function in (5.C). The absence of departures from the linear model in specific exposure categories implies that proportionality between radiation induced risk and low cumulative exposure levels cannot be rejected by these data, despite the lack of significantly elevated risk among those exposed to less than 120 WLM shown in table 2.
The curvature of the dose-response functions in fitted model (5.8) suggests that one might improve model (5.9) by adding quadratic terms in WLM and in PKS. As expected, the estimate for $\beta_2$ in the more general model

$$R = (1 + \beta_1 WLM + \beta_2 (WLM)^2)(1 + \beta_3 PKS)$$

(7)

was negative, indicating downward curvature in the graph of $R$ vs WLM. However, this model provided nonsignificant increase in likelihood over (5.9), as did the corresponding generalization obtained from text equation (7) by interchanging WLM and PKS.

The models in table 5 were also augmented by the inclusion of factors representing functions of average exposure rate, defined as total exposure in WLM (or packs) to exposure cut-off date divided by total time in years from start of underground uranium mining or (smoking) to exposure cut-off date. Nonsmokers were assigned average smoking rates of zero. Augmentation of model (5.9) by including average exposure rates did not significantly raise the likelihood of the data, regardless of the functional form in which these rates were included. By contrast, the likelihood ratio statistics of table 6 illustrate the general phenomenon that relative risk functions involving cumulative exposure performed significantly better than did their counterparts involving average exposure rate.

Other determinants of lung cancer mortality.---Text-figure 3 displays the distributions of age at start of underground uranium mining for cases and controls. This variable was negatively correlated with cumulative WLM in the group as a whole ($r=-0.32$). While cases began such work at younger ages (mean = 36.9 years) than did controls (mean = 39.5 years), age at start of mining had no effect on age-specific lung cancer mortality rates ($p=0.30$) after adjustment for total radiation exposure and total amount of cigarettes smoked. This was true regardless of the functional forms used for cumulative exposures and for age at start of mining.
We examined the effect of time since termination of underground uranium mining by adding a variable "TST" to each of the models in table 5. A miner's TST was defined to be the time in years from the date of his last underground employment until his exposure cut-off date, provided this was greater than zero; otherwise his TST was set equal to zero. Cases had smaller TST values than did their matched controls (p<0.001). However TST was zero for 138 (77%) of the 194 cases, indicating that these men stopped mining within ten years of their lung cancer death, while TST = 0 for only 56% of controls. Thus a possible tendency for miners with lung cancer to leave the industry because of their illness may explain the significance of this variable. Its inclusion in the regressions had negligible effect on the relative risk estimates for radiation and smoking. Therefore we shall not consider it further in this report.

A previous report of these data based on fewer lung cancer deaths found a positive relationship between a miner's risk and his height (28). To test this hypothesis, we augmented the models in table 5 by indicator variables for the largest two of the three height categories specified by the breakpoints 60 inches and 70 inches. However, we found no statistically significant differences in risk between the height categories.

Interactions between exposures and other factors.--There has been speculation that cigarette smoke may accelerate the clinical appearance of radiation-induced lung tumors (3,24,25). In particular, investigators have hypothesized that age-specific mortality rates for heavy smokers are more skewed toward young ages than are such rates for light smokers or nonsmokers. One can obtain indirect evidence concerning this hypothesis by checking whether relative risks due to smoking decrease with age. To do so, we augmented the relative risk model (5.C) by replacing the factor 1 + \( \beta_2 \)PKS with the factor 1 +\( \beta_2 \)PKS +\( \beta_3 \)PKSxAGE, where a case's AGE equals his age at death,
and a control's AGE equals his matched case's age at death. If relative risks due to smoking decreased with age, one would expect a negative estimate for $\beta_3$ with significantly increased likelihood over that of model (5.5). However, while the coefficient for $\beta_3$ was negative, there was virtually no improvement in likelihood.

For completeness, we repeated the above analysis with PKS replaced by WLM. As expected, the results provided no suggestion that radiation-induced relative risks vary with age at death. Similarly, augmentation of model (5.5) by inclusion of the product variables WLM x (AGE START MINING) and PKS x (AGE START MINING) provided no evidence that excess relative risk due to radiation or smoking differed by age at start of underground mining.

To check whether radiation-induced risks vary by birth cohort, we expanded model (5.5) by replacing the factor $1 + \beta_1WLM$ with the term $1 + \beta_1WLM + \beta_3WLMxBYR$, where the variable BYR represents year of birth. The likelihood ratio statistic for this expanded model relative to model (5.5) was 4.07 on 1 degree of freedom, with an approximate p-value of 0.04. The estimate for $\beta_3$ was positive, suggesting that men in recent birth cohorts experience higher radiation-induced risk per WLM than do their colleagues born earlier. By contrast, a similar analysis with WLM and PKS interchanged provided no evidence that smoking-induced risk per pack varies with birth cohort.

Eighty-nine (46%) of the lung cancer cases were classified as primary (ICD = 162) while the remaining 105 cases were unspecified as to whether primary or secondary (ICD = 163). To determine whether relative risks differ by ICD code, we added product variables of the form WLM x I and PKS x I to the functions in table 5. Here I is an indicator variable assuming the value 1 for a miner if his case's lung cancer was primary and 0 otherwise. None of these analyses gave any evidence for differences in risk by ICD code.
DISCUSSION

The preceding results provide strong and consistent support for a description of lung cancer risk as the product of components due to radiation and to cigarette smoke. The multiplicative model (5.5) implies that risk ratios for miners relative to nonminers with the same smoking history do not depend on this smoking history. It is contrary to earlier interpretations of these data (1), that argued against such a nonadditive effect. However, it is consistent with experimental results for radon-222 and cigarette smoke exposures in rats (29). We have made the basic assumption that age-specific radiation-induced lung cancer mortality rates among white miners are proportional to the corresponding rates among those unexposed. This assumption implies that the radiation-induced rates depend strongly on age. The relative risk model (5.5) further stipulates that these rates depend strongly on smoking status, with smokers experiencing substantially higher radiation-induced risk. The data suggest, for example, that men who have smoked 20 pack-years of cigarettes (excluding tobacco use within the past ten years) experience radiation-induced lung cancer rates per WLM that are roughly five times those of nonsmokers. This strong synergistic effect also prevails among cigarette smokers who are exposed to asbestos fibers (30).

The multiplicative model (5.5) assumes that age-specific lung cancer mortality rates for heavy and light smokers are simple multiples of each other. The data provide no evidence against this assumption, e.g., that heavy smokers experience lung cancer at younger ages than do light smokers. Proportionality between age-specific rates for smokers of differing amounts also provide an adequate description of lung cancer mortality among British physicians (26). Further, the present data do not support the hypothesis that heavy radiation doses shift the age distribution of lung cancer to younger ages.
A linear relationship between lung cancer mortality rates and cumulative radiation exposure provided a good fit to these data. The fit was not significantly improved by adding a quadratic term to allow curvature in the relationship. A concave-downward dose-response relationship (in which risk per WLM decreases with increasing dose) has been noted in earlier analyses of these data (1,3), in findings of Kneale et al for cancers of radiosensitive tissues among Hanford employees exposed to plutonium (27), and in published results concerning respiratory cancer mortality among uranium miners in Czechoslovakia (31). This downward concavity is consistent with power estimates obtained here using model (5.B). However, there were suggestions of poor fit for model (5.B), and a higher likelihood value was produced by the simpler linear model in which excess relative risk is proportional to cumulative radiation exposure. The maximum likelihood estimate for this risk is approximately 0.31% per WLM. This estimate is slightly lower than the 0.45% per WLM figure obtained from previous analyses of these data that did not control for cigarette smoking, and that included fewer lung cancer deaths (3). However, both of these figures are apt to underestimate risk for reasons discussed below.

These data clearly demonstrate the limitations of epidemiologic observations as bases for inferring risks due to low levels of ionizing radiation. On the one hand, the data fail to reject the notion of "threshold" levels, below which radiation induced lung cancer risks are zero. The lack of statistically elevated risk among those exposed to less than 120 WLM illustrates this failure. On the other hand, the data also fail to reject proportionality between risk and low level exposures, as illustrated by lack of departures from the linear model in low radiation exposure categories. This dilemma implies that low dose risk estimation cannot rely entirely on
epidemiological evidence, but instead requires additional scientific and judgmental components.

Average working levels in uranium mines of the Colorado Plateau decreased substantially over the period from 1940 to 1970 (1). Thus radiation exposure rates for many US uranium miners have changed appreciably over time. The variable "average exposure rate" defined in this report is a crude summary measure of these changing exposure intensities. Therefore the absence of an exposure-rate effect in this analysis provides only limited information about risk from protracted exposures at low rates, relative to risk from brief exposures at high rates. The absence of a dose-rate effect for radiation exposure is consistent with earlier analyses of these data (1 (Table 39), 4). It could be due to lack of variation in average exposure rates, as many of the miners were exposed at very high rates.

The present finding of proportionality between total radiation exposure and lung cancer mortality rates has also been noted for the relationship between asbestos and lung cancer (32). While the importance of total asbestos dose may arise simply from accumulation of fibers in the lung, such a buildup cannot explain the role of cumulative exposure to inhaled radioactive aerosols, because the half-lives of radon-daughters are very brief. More plausibly, inhaled radon-daughters may initiate a series of changes in stem cells in the tracheobronchial epithelium; initiated cells then accumulate in the lung in proportion to total radiation exposure and undergo risk of further transformation to malignancy.

These data fail to indicate a relationship between age-specific lung cancer mortality rates and age at first underground uranium mining exposure, after controlling for total WLM of exposure. A positive association with age at start of mining was found among Czechoslovakian uranium miners (2); however, these findings were not controlled for age at followup. A negative
association between lung cancer mortality rates and age at (first) exposure has been noted among atomic bomb survivors (33) and among asbestos workers (34). The broad distributions of this variable shown in text-fig. 3 suggest that the absence of an effect cannot be explained by lack of variation among the miners. The absence is consistent with the predictions of a theory in which alpha particles initiate changes in normal stem cells that lead to malignancy, rather than further transforming cells partially damaged by cigarette smoke or other carcinogens (35,36). In the latter case miners first employed at older ages would have accumulated more previously damaged cells and thus would experience greater radiation-induced risk. Such inferences must be made cautiously however, because some miners received low radiation exposures in other hard rock mines prior to work in the uranium industry.

The lung cancer risks due to cigarette smoking are lower than those found by other investigators (e.g., 26). This discrepancy may be due to bias caused by random reporting errors, described below. The proportionality between excess relative risk and total packs described by model (5.C), and the downward convexity described by model (5.B), are inconsistent with the quadratic dependence on smoking rate and quartic dependence on smoking duration found among British physicians (26). Two factors, however, mitigate against detailed comparison of these two data sets. The first is the relatively large errors in smoking estimates for the uranium miners. Secondly, age and smoking duration are highly confounded, and we have estimated the miners' mortality rates only up to the age-specific mortality rates among white males who neither mine nor smoke.

Several aspects of the present data set limit its relevance to risk estimates for low radiation exposures. These aspects include the miners' extremely high exposures and exposure rates, and their increased ventilation rates during hard physical labor. Furthermore, errors in both radiation and
smoking exposures are probably very large. There are two sources of error in the radiation exposure measurements: errors in the miners' work histories, and errors in the estimated mine working levels. The first source is probably small in comparison with the second, since less than half the working level estimates were based on actual mine measurements (1). Variations in mine ventilation and in the chemical composition of mine aerosols also contribute to errors in estimated lung dose. Recent work (37) indicates that random exposure errors can spuriously reduce the estimated regression coefficients in model (5.C). When such errors are large, the bias can be substantial. It may explain the reduced risk per WLM experienced by men in early birth cohorts, since their exposure estimates contain larger errors than do the estimates for later cohorts (1).

Other investigators have suggested that radiation exposures for this cohort may have been overestimated (1). Such systematic overestimation would also reduce relative risk estimates. It would explain why risk estimates obtained from these data are lower than those obtained from other uranium mining data (3).

The preceding analyses assume that environmental exposures act multiplicatively on the underlying age-, race-, cohort-, and sex-specific mortality rates among nonsmokers not employed in underground mining. This approach enjoys several advantages over traditional methods involving classification of deaths and person-years into age and exposure categories and calculation of category-specific relative and excess risks. First, it provides relative risk estimates from internal comparisons within the cohort, thus avoiding problems of incomparability between cohort and comparison group, such as differences in general health, smoking habits, and socioeconomic status. Second, it allows close control of important risk correlates such as age and year of birth. Third, it permits multivariate examination of several
risk factors, as well as of interactions among risk factors and between risk factors and other decedent characteristics. If histology data were available, for example, one might examine whether smoking or radiation relative risks differ among those with different cell types of bronchial carcinoma.

The relative computational ease of the case-control approach makes it an ideal tool for exploratory analysis. The loss in power suffered by omitting some of the cohort is not serious, unless a small fraction of the cohort is exposed to a factor inducing very large relative risk (21,38). A full cohort analysis stratified on year of birth (say in five-year cohorts) is computationally feasible, and would differ little from the present approach. Miners born in cohorts containing no lung cancer decedents would be excluded from the analysis. Investigators at NIOSH (10) are currently undertaking such an analysis of the US uranium miner data, for comparison with the findings of this report.

ACKNOWLEDGMENTS

The authors are grateful to Duncan Thomas for the use of computer programs that facilitated the analyses, and to Victor Archer, Richard Hornung, Frank Lundin, Robert Roscoe, Langon Swent, and Richard Waxweiler for helpful discussions. The reviewers' comments greatly improved an earlier version of this report.
REFERENCES


(3) NATIONAL ACADEMY OF SCIENCES. Effects on populations of exposures to low levels of ionizing radiation. Washington DC: National Academy of Sciences, 1980. (Referred to as BEIR III)


(10) HORNUNG RW, SAMUELS S. Survivorship models for lung cancer mortality in uranium miners. In: Gomez M, ed. Radiation hazards in mining: control,
measurement, and medical aspects. New York Soc Mining Engineers of Amer

(11) WAXWEILER RJ, ROSCOE RJ, ARCHER VE, THUN MJ, WAGONER JK, LUNDIN FE.
Mortality follow-up through 1977 of the white underground uranium mines
cohort examined by the US Public Health Service. In: Gomez M, ed.
Radiation hazards in mining: control, measurement, and medical aspects.
New York Soc Mining Engineers of Amer Inst Mining, Metallurgical and

(12) GEDDES DM. The natural history of lung cancer: a review based on rates of

(13) GEORGE AC, BRESLIN AJ. The distribution of ambient radon and radon
daughters in residential buildings in the New Jersey-New York area.

(14) HANCHEY LA. Uranium mill tailings and radon. Sandia Natl Labs Report No.
SAND 80-2141, 1981.

(15) COHEN BS, EISENBUDD M, HARLEY NH. Alpha radioactivity in cigarette smoke.
Radiation Research 1980; 83:190-196.

(16) HINDS WC, FIRST MW. Concentrations of nicotine and tobacco smoke in

(17) REPACE JL, LOWREY AH. Indoor air pollution, tobacco smoke and public

(18) HOEgg US. Cigarette smoke in closed spaces. Env Health Persp 1972; 2:117.

(19) WEBER A, JERMINI C, GRANDJEAN E. Irritating effects on man of air

(20) KALBFLEISCH, PRENTICE RL. The statistical analysis of failure time data.


(29) CHAMEAUD J, COGEMA RP, CHRETIEN J, MASSE R, LAFUMA J. Etude experimentale
de l'action combinee de la fumee de cigarettes et du depot actif du
radon-222. In: Late biological effects of ionizing radiation. Vol. II.

(30) SARRACCI R. Asbestos and lung cancer: an analysis of the epidemiological
evidence on the asbestos-smoking interaction. Int J Cancer 1977; 20:323-
331.

(31) WALSH PJ. Dose conversion factors for radon daughters. Health Physics

(32) PETO J. The establishment of industrial hygiene standards: an example.

(33) KATO H, SCHULL WJ. Studies of the mortality of A-bomb survivors, 7,

(34) SEIDMAN H, SELIKOFF IJ, HAMMOND EC. Short-term asbestos work exposure and

(35) DAY NE, BROWN CC. Multistage models and primary prevention of cancer. J

(36) WHITTEMORE AS. The age distribution of human cancer for carcinogenic

(37) PRENTICE RL. Covariate measurement errors and parameter estimation in

(38) BRESLOW NE, LUBIN JH, MAREK P. Multiplicative models and the analysis of
cohort data. Tech Rep No 50. Department of Biostatistics, School of
Table 1. Vital Status of White Uranium Miners in Cohort

<table>
<thead>
<tr>
<th></th>
<th>September 30, 1974</th>
<th>December 31, 1977</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number</td>
<td>Percent</td>
</tr>
<tr>
<td>Alive</td>
<td>2621</td>
<td>78</td>
</tr>
<tr>
<td>Deceased</td>
<td>745</td>
<td>22</td>
</tr>
<tr>
<td>With Lung Cancer(^a)</td>
<td>144</td>
<td>19</td>
</tr>
<tr>
<td>Without Lung Cancer</td>
<td>592</td>
<td>80</td>
</tr>
<tr>
<td>Certificate Outstanding</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Lost to Follow-up</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>3366</td>
<td>100</td>
</tr>
</tbody>
</table>

\(^a\)Seventh Revision ICD Nos. 162, 163, listed either as underlying or contributory cause of death.

\(^b\)Cohort total for 1977 is less than that for 1974 because four members had duplicate records in 1974.

Source: (6, 11)
Table 2. Numbers of Cases and Controls and Lung Cancer Relative Risk by Radiation and Smoking Status

<table>
<thead>
<tr>
<th>WLMa</th>
<th>Cases</th>
<th>Controls</th>
<th>Rb</th>
<th>Cases</th>
<th>Controls</th>
<th>R</th>
<th>Cases</th>
<th>Controls</th>
<th>R</th>
<th>Cases</th>
<th>Controls</th>
<th>R</th>
<th>Cases</th>
<th>Controls</th>
<th>R</th>
<th>Total e</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-21</td>
<td>1</td>
<td>55</td>
<td>1.00</td>
<td>9</td>
<td>45</td>
<td>9.12</td>
<td>3</td>
<td>38</td>
<td>4.18</td>
<td>5</td>
<td>7.66</td>
<td>18</td>
<td>177</td>
<td>1.00</td>
<td></td>
<td></td>
</tr>
<tr>
<td>22-119</td>
<td>1</td>
<td>45</td>
<td>1.12c</td>
<td>4</td>
<td>21</td>
<td>13.63</td>
<td>3</td>
<td>30</td>
<td>6.45</td>
<td>8</td>
<td>18.96</td>
<td>16</td>
<td>131</td>
<td>1.67c</td>
<td></td>
<td></td>
</tr>
<tr>
<td>120-359</td>
<td>3</td>
<td>50</td>
<td>3.56</td>
<td>7</td>
<td>27</td>
<td>15.96</td>
<td>4</td>
<td>28</td>
<td>8.78</td>
<td>8</td>
<td>23.07</td>
<td>22</td>
<td>138</td>
<td>2.38</td>
<td></td>
<td></td>
</tr>
<tr>
<td>360-839</td>
<td>4</td>
<td>33</td>
<td>7.76</td>
<td>3</td>
<td>35</td>
<td>5.19</td>
<td>7</td>
<td>30</td>
<td>16.22</td>
<td>24</td>
<td>44.62</td>
<td>38</td>
<td>142</td>
<td>3.44</td>
<td></td>
<td></td>
</tr>
<tr>
<td>840-1799</td>
<td>3</td>
<td>33</td>
<td>5.24</td>
<td>8</td>
<td>23</td>
<td>17.60</td>
<td>9</td>
<td>23</td>
<td>27.37</td>
<td>18</td>
<td>42.74</td>
<td>38</td>
<td>116</td>
<td>4.24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1800-3719</td>
<td>6</td>
<td>23</td>
<td>18.18</td>
<td>13</td>
<td>6</td>
<td>137.56</td>
<td>20</td>
<td>28</td>
<td>52.57</td>
<td>23</td>
<td>146.75</td>
<td>62</td>
<td>72</td>
<td>13.98</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3720+</td>
<td>6</td>
<td>23</td>
<td>18.18</td>
<td>13</td>
<td>6</td>
<td>137.56</td>
<td>20</td>
<td>28</td>
<td>52.57</td>
<td>23</td>
<td>146.75</td>
<td>62</td>
<td>72</td>
<td>13.98</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total d</td>
<td>18</td>
<td>239</td>
<td>1.00</td>
<td>44</td>
<td>157</td>
<td>4.20</td>
<td>46</td>
<td>177</td>
<td>3.17</td>
<td>86</td>
<td>203</td>
<td>7.53</td>
<td>194</td>
<td>776</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

a From start of exposure to cut-off date, excluding exposures from background sources; one pack-year equals 365 packs of cigarettes
b Risk relative to lowest category, adjusted for age and birth-cohort
c 95% confidence interval includes R = 1
d Relative risks adjusted for radiation, assuming smoking and radiation interact multiplicatively as in eq. (3)
e Relative risks adjusted for smoking, assuming smoking and radiation interact multiplicatively as in eq. (3)
Table 3. Additive and Multiplicative Models for Joint Effects of Smoking and Radiation

<table>
<thead>
<tr>
<th>Relative Risk Model</th>
<th>No. of Parameters</th>
<th>Likelihood Ratio Statistic(^b) df (p-value)</th>
<th>Goodness-of-Fit Statistic(^c) df (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. ( R_{ij}^a = 1 + \beta_i; \beta_{ij} = 0 )</td>
<td>23</td>
<td>151.19; 23 (&lt;0.001)</td>
<td>-</td>
</tr>
<tr>
<td>B. ( R_{ij} = (1 + \beta_i^{(r)})(1 + \beta_j^{(s)}); \beta_i^{(r)} = \beta_i^{(s)} = 0 )</td>
<td>8</td>
<td>137.78; 8 (&lt;0.001)</td>
<td>13.41; 11 (0.57)</td>
</tr>
<tr>
<td>C. ( R_{ij} = 1 + \beta_i^{(r)} + \beta_j^{(s)} )</td>
<td>8</td>
<td>120.92 8 (&lt;0.001)</td>
<td>30.27; 11 (0.01)</td>
</tr>
</tbody>
</table>

\(^a\)\( R_{ij} \) denotes the age- and birth-cohort-specific mortality rate for miners in joint radiation-smoking category \((i,j)\) of Table 2, divided the rate for miners in category \((1,1)\), \(i=1,\ldots,6, j=1,\ldots,4\).

\(^b\)Minus twice the difference in maximized log-likelihoods between given model and one in which risk is independent of both smoking and radiation. Under the null hypothesis of no effect for either exposure, this statistic has an asymptotic chi-squared distribution with degrees of freedom equal to the number of parameters in the model.

\(^c\)Difference between likelihood ratio statistics for model A and given model. If given model is correct, this difference has an asymptotic chi-squared distribution on 23-8=11 degrees of freedom.
Table 4. Additive and Multiplicative Linear Models for Joint Effects of Smoking and Radiation

<table>
<thead>
<tr>
<th>Relative Risk Model</th>
<th>No. of Parameters</th>
<th>Likelihood Ratio Statistic; df</th>
<th>Goodness-of-Fit Statistic Relative to Model A; df</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. ( \left[ \left( 1 + \beta_1 \text{WLM} \right) \left( 1 + \beta_2 \text{PKS} \right) \right] \beta_3 \left( 1 + \beta_1 \text{WLM} + \beta_2 \text{PKS} \right)^{1-\beta_3} )</td>
<td>3</td>
<td>132.62; 3</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(p-value)</td>
<td>(p-value)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(&lt;0.001)</td>
<td></td>
</tr>
<tr>
<td>B. ( (1 + \beta_1 \text{WLM})(1 + \beta_2 \text{PKS}) )</td>
<td>2</td>
<td>132.60; 2</td>
<td>0.02; 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(p-value)</td>
<td>(p-value)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(&lt;0.001)</td>
<td>(0.99)</td>
</tr>
<tr>
<td>C. ( 1 + \beta_1 \text{WLM} + \beta_2 \text{PKS} )</td>
<td>2</td>
<td>115.62; 2</td>
<td>17.00; 1</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(p-value)</td>
<td>(p-value)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>(&lt;0.001)</td>
<td>&lt;0.01</td>
</tr>
</tbody>
</table>

\(^a\) Minus twice the difference in maximized log-likelihoods between given model and one in which risk is independent of both smoking and radiation. Under the null hypothesis of no effect for either exposure, this statistic has an asymptotic chi-squared distribution with degrees of freedom equal to the number of parameters in the model.

\(^b\) Difference between likelihood ratio statistics for model A and given model. If given model is correct, this difference has an asymptotic chi-squared distribution on 3-2=1 degree of freedom (df).
Table 5. Exposure-response Models for Relative Risk vs. Radiation and Smoking

<table>
<thead>
<tr>
<th>Relative Risk Model</th>
<th>No. of Parameters</th>
<th>Likelihood Ratio Statistic&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Parameter Estimates (Standard Errors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. ( \exp(\beta_1 \text{WLM}) \exp(\beta_2 \text{PKS}) )&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2</td>
<td>99.46 (&lt;0.001)</td>
<td>( 0.55 \times 10^{-3} \quad 0.95 \times 10^{-4} )&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>B. ((\text{WLM} + \text{BGR})^{\beta_1} (\text{PKS} + \text{BGS})^{\beta_2})&lt;sup&gt;c&lt;/sup&gt;</td>
<td>2</td>
<td>120.86 (&lt;0.001)</td>
<td>( 0.4342 \quad 0.4113 )&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>C. ((1 + \beta_1 \text{WLM})(1 + \beta_2 \text{PKS}))</td>
<td>2</td>
<td>132.60 (&lt;0.001)</td>
<td>( 0.31 \times 10^{-2} \quad 0.51 \times 10^{-3} )&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup>Minus twice the difference in maximized log-likelihoods between given model and one in which risk is independent of both smoking and radiation. Under the null hypothesis of no effect for either exposure, this statistic has an asymptotic chi-squared distribution with degrees of freedom equal to the number of parameters in the model.

<sup>b</sup>WLM = cumulative radiation exposure in WLM at exposure cut-off date; PKS = cumulative cigarettes smoked in packs at exposure cut-off date.

<sup>c</sup>BGR = background radon-daughter exposure accumulated at rate of 0.2 WLM/year from birth to cut-off date.

BGS = background cigarette smoke exposure accumulated at rate of 0.005 PKS/day from birth to cut-off date.
<table>
<thead>
<tr>
<th>Relative Risk Model</th>
<th>No. of Parameters</th>
<th>Likelihood Ratio Statistic; df (p-value)</th>
<th>Goodness-of-Fit Statistic Relative to Model A; df (p-value)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A. $(1+\beta_1 WLM)(1+\beta_2 PKS)(1+\beta_3 PKS/\text{YR})$</td>
<td>3</td>
<td>$134.44; 3$ (&lt;0.001)</td>
<td>-</td>
</tr>
<tr>
<td>B. $(1+\beta_1 WLM)(1+\beta_2 PKS)$</td>
<td>2</td>
<td>$132.60; 2$ (&lt;0.001)</td>
<td>$1.84; 1$ (0.40)</td>
</tr>
<tr>
<td>C. $(1+\beta_1 WLM)(1+\beta_3 PKS/\text{YR})$</td>
<td>2</td>
<td>$120.22; 2$ (&lt;0.001)</td>
<td>$12.22; 1$ (&lt;0.001)</td>
</tr>
</tbody>
</table>

\(a\) See Table 4

\(b\) See Table 4
Text-figure captions

Text-figure 1. Distribution of age at death for 194 white underground uranium miners who died with lung cancer (7th Revision ICD 162-163).

Text-figure 2. Joint distribution of cumulative exposures to radon-daughters (WLM/1000) and cigarettes (packs/1000) for a) 194 white lung cancer decedents; b) 776 white miners (controls) who were matched to the lung cancer decedents in the ratio 4:1. A decedent's exposures were accumulated until ten years before his death. A control's exposures were accumulated until ten years before his matched decedent's death. The symbol "A" denotes one data point, "B" denotes two data points, etc.

Text-figure 3. Distribution of age at start of underground uranium mining for a) 194 white lung cancer decedents; b) 776 white miners (controls) who were matched to the lung cancer decedents in the ratio 4:1.