Paper

CORRECTING FOR EXPOSURE MEASUREMENT ERROR IN A REANALYSIS OF LUNG CANCER MORTALITY FOR THE COLORADO PLATEAU URANIUM MINERS COHORT

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Abstract—**The exposure estimates used to date for the analysis of lung cancer mortality in the Colorado Plateau Uranium Miners cohort were developed from radon progeny measurements taken in mines beginning in 1951. Since uranium miners were often exposed over long periods of time and since mines were not continuously monitored, much extrapolation and/or interpolation of measured dose-rates was needed in order to develop estimates of exposure for each of the miners in the cohort. We have recently re-examined the interpolation scheme used to create the histories in the light of the fit of a statistical model for the radon progeny measurements taken in mines within the Plateau, and we have computed revised exposure estimates for the large majority of miners in the cohort. This report describes the use of these new model-based revised exposure estimates in the analysis of lung cancer mortality, using follow-up data current through 1990. Specific issues addressed here are (1) the strength of the association between exposure and risk of lung cancer mortality; (2) effects of attained age and time since exposure upon risk of lung cancer mortality; and (3) exposure-rate effects upon risk. Results using the revised exposure estimates are compared to those obtained fitting the same models using the original Public Health Service (PHS) exposure estimates. We found evidence that the new exposure histories provide a better fit to the lung cancer mortality data than do the histories based upon the original PHS dose-rate estimates. In general, the new results show a stronger overall relationship (larger slope estimate) between lung cancer mortality and exposure per unit exposure compared to those obtained with the original estimates, while displaying similar age at exposure and time since exposure effects. In the reanalysis the impact of low dose-rate exposure is found to be relatively unchanged before and after exposure error correction, while the estimate of the effect of high dose-rate exposure is considerably increased. Even after applying our measurement error corrections, evidence of inverse dose-rate effects is found, since the estimate of the impact of high dose-rate exposure is still below that of the low dose-rates. The magnitude and statistical significance, however, of the dose-rate effect estimates are diminished when fit using the revised exposure estimates.**

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INTRODUCTION

THE COLORADO Plateau uranium miners cohort has been an important source of information concerning the relationship between lung cancer risk and extended exposure to high levels of radon (Lubin et al. 1994). Moreover, observations of the effect of these relatively high levels of exposure upon lung cancer risk are subsequently interpolated down to much lower levels in order to estimate the impact of low levels of exposure to large populations as done in the case of residential radon (NRC 1998).

As with all studies of human exposure to radiation and its effects, incomplete knowledge of the true exposures borne by the Colorado cohort members complicates the interpretation of risk estimates derived from the epidemiologic analysis of these data. Random exposure measurement error, particularly in complex exposure situations, can have a variety of effects upon risk estimates. Risk estimates, for example, may be too low, particularly if the estimated exposures are more variable than the true exposures; there may also be artifacts introduced into the data, such as apparent dose-rate effects, which would not be seen if true exposure was known. Some discussion of these issues is given in the Lubin et al. (1994) analysis of a large number of underground miners cohort studies. These effects of exposure errors, besides being important in the analysis of the relationship between lung cancer and the high exposures in the miners' cohorts, may have impact upon the extension of the results to the effects of low level exposure to large populations. Crucial to this low-dose interpolation has been an observation in many of the miners' studies that the effect of the same cumulative exposure extended over a long period of time is actually greater than when received over short time periods (Lubin et al. 1994). This observation is known as the inverse dose-rate effect. The inverse dose-rate effect is

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especially important in the assessment of the importance of low dose residential exposure to radon progeny since these are typically accumulated over very long periods of time (NRC 1998). While a biophysical basis for an inverse dose-rate effect of extended exposure to alpha particle radiation has been described (Brenner et al. 1993), exposure errors in the miners studies may be a source of bias in the estimation of these effects. This is true because in most models for errors in radiation exposure assessment that have been applied to epidemiological studies (Pierce et al. 1990) it is presumed that high instantaneous exposures are estimated with less accuracy (on the additive scale) than low instantaneous exposures. Indeed, for the Colorado Plateau Lundin et al. (1969) concluded that measurements from individual mines exhibited a relatively constant coefficient of variation across a wide range of average dose. Thus, lengthy accumulation of exposure to radiation may be ascertained more accurately than short term exposures to the same total dose.

The focus in this report is upon the effect upon risk estimates and other aspects of the relationship between exposure and lung cancer of measurement error correction in the Colorado Plateau cohort. We compare the results of fitting a variety of models to the lung cancer data from the cohort, before and after measurement error correction. Particular interest is placed upon the magnitude of risk estimates, age at exposure, time since exposure (latency) and dose-rate effects.

The derivation of the exposure estimates that have been used for the Colorado Plateau cohort in all analyses to date may be described as follows. All exposures were estimated at the level of the mine-year, meaning that exposure rates in each mine in which cohort members worked were estimated on a yearly basis. Mine-year exposure rate estimation involved two aspects—first the averaging of measured exposure rates for each mine-year in which there were measurements, and second the extrapolation of these average measured exposure rates to years and mines in which there were no measurements. These measured and extrapolated mine-year estimates were then combined with each miner's history of employment in the industry to produce dates at which the cumulative exposure reached specific levels. These estimates have subsequently been used in a large number of analyses of the relationship between lung cancer risk and radon exposure in this cohort.

A crucial aspect of this exposure-estimation procedure is the extrapolation of measured dose-rates to years and mines without measurements, since, in fact, 63% of mine-years of interest do not have any measurements (see below). This extrapolation procedure is described in Lundin et al. (1971) and relied upon a hierarchical classification of mines into mining localities and mining districts. The analysis here utilizes an approach towards measurement error correction of lung cancer risk estimates based upon fitting a multi-level statistical model for all actual mine-year measurements, within this same hierarchy of mine, locality, and district. We replace the imputation process that was used by the PHS to provide dose estimates for mine-years for which there were no measurements, with an imputation scheme which gives "best-estimates" under the multi-level model that we fit to the actual measurements. In imputing estimates for mine-years without data the model explicitly allows for measurement error in exposure rates for all mine-years with data. These resulting imputations are used to create revised exposure-history estimates for the miners, and used in the epidemiologic analysis.

MATERIALS AND METHODS

Subjects and data

The cohort consists of 3,347 white miners who were employed at least 1 y during 1950–1960. Lung cancer mortality data current to 1990 is used in the reanalysis (Roscoe 1997). For the purposes of these analyses, we consider two smaller sets of data. The first, the 1950 cohort, is restricted to 2,704 white miners, with 263 lung cancer deaths, who had initial uranium mining exposure beginning only in 1950 or later. Similarly, we defined a 1952 cohort, consisting of miners with first exposure in 1952 or later, which had 2,388 subjects and 209 lung cancer deaths. The reason for focusing on these subgroups is that measurements of radon levels in the mines did not begin until 1951, and were not systematic until 1952.

Mine-year dose-rate information (levels of radon progeny in working levels, WL) for 1,706 mines in the Colorado Plateau for the years 1950–1969 (the "mine-year file") was also made available to us. This mine-year information was categorized into two types of data records—those of actual measurements, and the interpolations based on the PHS method referred to above. The 2,704 miners who make up the 1950 cohort reported work in a total of 937 of the mines, for a total of 5,274 distinct mine-years. Of these mines, 567 had at least one actual measurement, but the measurements only covered a total of 1,959 (37%) of the mine-years with cohort members at work. Moreover, the measurements were not distributed evenly over the time period in which significant exposures occurred. In 1950–1954 only 13% of the mine-years in which cohort members worked had measurements, compared to 71% in 1965–1969.

The work history file also included the original exposure histories as developed by PHS for the Lundin et al. analysis (Lundin et al. 1971). Upon examination we found that there were a large number of mines referred to on the work history file, for which no records appeared on the mine-year file. A former PHS investigator, Victor Archer, provided us with additional data regarding these missing mines. The mine codes on the work history file refer to conglomerations or summaries of mines that were used when a miner was unable to recall exactly which mine he had worked in during specific periods. For example, a miner may have remembered the company, or the general locality where he was working, but not the specific mine. For each such group of mines a

distinct identifying mine number had been assigned. We refer to these conglomerations as "pseudo-mines." The data from Archer included information on the geographical location of most of these pseudo-mines as well as the dose-rates believed to have been used by the PHS in constructing the original exposure histories.

Statistical methods

The mine-year dose-rate data are used, in conjunction with the miners' work histories from 1950–1969, to develop exposure histories for each miner in the analysis. To facilitate the analysis of these data, a nested case-control study from each cohort was formed. Each lung cancer case was matched by age and five year calendar period of the case's death to 40 controls. Analyses of the dose-response relationships using models for the excess relative risk (ERR) of death from lung cancer due to exposure to radon progeny were performed by conditional relative risk regression analysis. This analysis is very close to a partial likelihood analysis (Cox regression) of the full cohort. The nested case-control samples formation and model fitting were done with the statistical package Epicure (Preston et al. 1993). Each model for ERR was fit twice: once before and once after measurement error correction.

Correction for measurement error

The measurement error correction method was based on the calculation of imputations of mine-year dose-rates for each mine and year of interest by combining a multi-level model for true average dose-rate, X_{klmt} at year t, in mine m, in locality l, and district k, with a multiplicative measurement error model, for the errors in the actual measurements, Z_{klmt}, of dose-rate in that mine-year (if any were taken). Imputations for each mine-year, (m', t') in which at least one cohort member was represented were calculated as the conditional expectations,

$$E(X_{kl'm't'}|\text{all } Z_{klmt} \text{ data in district } k).$$

Considerable further information regarding the fit of the model and calculation of imputations is available in technical report form (Stram et al. 1998).

The model for true dose. Denoting the log of X_{klmt} as x_{klmt} we fit a random slope and intercept model on the log scale

$$x_{klmt} = \alpha + a^D_k + a^L_{l(k)} + a^M_{m(kl)} + (\beta + b^D_k + b^L_{l(k)} + b^M_{m(kl)})t + e_{klmt}. \quad (1)$$

Here α and β give the intercept and slope of an overall linear change in log(WL) levels by year from 1950 to the end of 1969, over which time dramatic reductions in measured exposure rates were indeed observed. The α and β parameters specify random intercepts and slopes at each level of a hierarchy, i.e., district, locality, and mine, as mean zero random variables with variances to be estimated in the course of the fitting of the model. At each level it is assumed that the slope and intercept parameters are uncorrelated with the slope and intercept parameters at the other levels and are uncorrelated with the e_{klmt}. Note that while eqn (1) may seem complicated, if we restrict our consideration to data from just one mine, we see that the model merely hypothesizes an exponential decline in dose-rates over the period 1950–1969 (i.e., a linear decline in the log dose-rates). The complexity in the model arises because each mine is allowed to have its own slope and intercept, and these terms are allowed to cluster together at each higher level of the hierarchy.

The measurement error model. Each measurement Z_{klmt} is given (in the mine-year data set available to us) as the mean of n_{mt} measurements taken in that mine for that year. Data on the variability of the mine year estimates is described in Lundin et al. (1971) who indicate that a constant coefficient of variability (SD/Mean) of approximately 50% reasonably characterizes the variability of measurements within a mine-year. Therefore we assume that the expectation of each mine-year measurement is equal to X_{klmt} with variance equal to $0.25 \times X_{klmt}/n_{mt}$.

The multi-level model for the mine-year data was fit to a total of 2,896 mine-years with measurements for 768 mines within 125 localities and 36 mining districts, using the MLn program (Rashbash and Woodhouse 1995). The first year with measurements is 1951; however, it was not until 1952 that a systematic program of measurements was implemented, and data for 1950 consists only of a total of 340 "guesstimated values." These guesstimates were based upon expert opinion as well as a summary of very early radon (rather than radon progeny) measurements taken in the plateau (Lundin et al. 1971). In our analysis we treated the guesstimates as equivalent to a single measurement in a mine. The results of the fitting, and general considerations of the adequacy of the model in representing the mine-year measurements is discussed in the technical report (Stram et al. 1998).

Record linkage

Measurement error adjusted exposure histories are computed from the imputations combined with the work histories. Pseudo-mines were handled as a special case in calculating the mine-year imputations, using the same model and techniques as for all the other imputations. Each pseudo-mine was categorized according to the mining locality, or if this was not possible, the mining district that contained the conglomeration of mines referred to by the pseudo-mine, based on Archer's records. Imputations for the pseudo-mine were performed as if a pseudo-mine was equivalent to a mine in that locality or district for which no measurements were available.

As a check on the record linkage of mine-year dose-rates to form exposure histories, we attempted to recalculate the original exposure histories as they appeared on the work history file. This effort was not always successful, even after incorporating the additional

information from Archer. First, there were still miners (n = 283) who reported some work in pseudo-mines which remained unidentified in Archer's data. Even after excluding these miners, there remained a considerable fraction of miners for whom we were unable to recreate the original exposure histories. Fig. 1 graphs our "recomputed" total WLM exposures (by record linkage) against the original total exposures appearing on the work history file.

All of the models for lung cancer mortality described below are fitted both before and after applying our measurement error correction method. In each case the "uncorrected" results are based upon our recomputed exposure histories, based on record linkage, rather than on the exposure history appearing in the work history file. In some of the analyses given below, we check our results by restricting analyses to include subjects for whom the original and recomputed total exposure estimates shown in Fig. 1 do not differ by more than 100 WLM.

Models for lung cancer mortality

In order to understand the effect of our imputation and measurement error correction compared to the use of the unadjusted exposures, we fitted a range of models. In each model, the effect of radon exposure on rates of lung cancer is taken to have an excess relative risk (ERR) form as has been done in previous analyses (Thomas et al. 1994). It was assumed in all models that only exposures taking place at least 2 y in the past had any effect on current lung cancer mortality risk (Thomas et al. 1994). Thus, we accumulate exposures up to this reference time. Table 1 lists the models fitted to these data. The first model, Model A, is a simple linear excess relative risk model with β the excess relative risk per 100 WLM of cumulative exposure. Model B adds both a multiplicative term for cumulative smoking per 1,000 packs of cigarettes up to the reference time, and an interaction term between smoking and radon. The parameters specify the excess relative risk for cumulative radon and smoking adjusting for correlation in smoking and radon levels, the interaction term allows for a submultiplicative combined effect of these two exposures. In model C, a separate excess relative risk slope for cumulative exposure is assigned by categories of attained age <50, 50–59, 60–69, 70+ y. Model D is a simple latency model in which separate slopes β_1, β_2, and β_3 are assigned to exposure accumulated 5–14, 15–24, and 25 or more years in the past (prior to the reference time), respectively.

Models E and F explore effect modification of cumulative exposure with dose-rate. Model E is a simple descriptive model in which dose-rate is computed as the average rate of exposure, over time intervals that the miner was working in uranium mines, up to the reference time. This dose-rate was categorized into ≤14 and 15+ WL so that in the model β is the excess risk slope for cumulative exposure for exposure accumulated at a rate up to 14 WL and the parameter ϕ_{15+} quantifies the relative difference in slope, relative to β, for the high dose-rate category. Model F is a "mechanistic" dose-rate model similar to that proposed by Brenner et al. (1993). In this model the term $\alpha x(t)$ is the mean number of traversals of a cell by an alpha particle during some

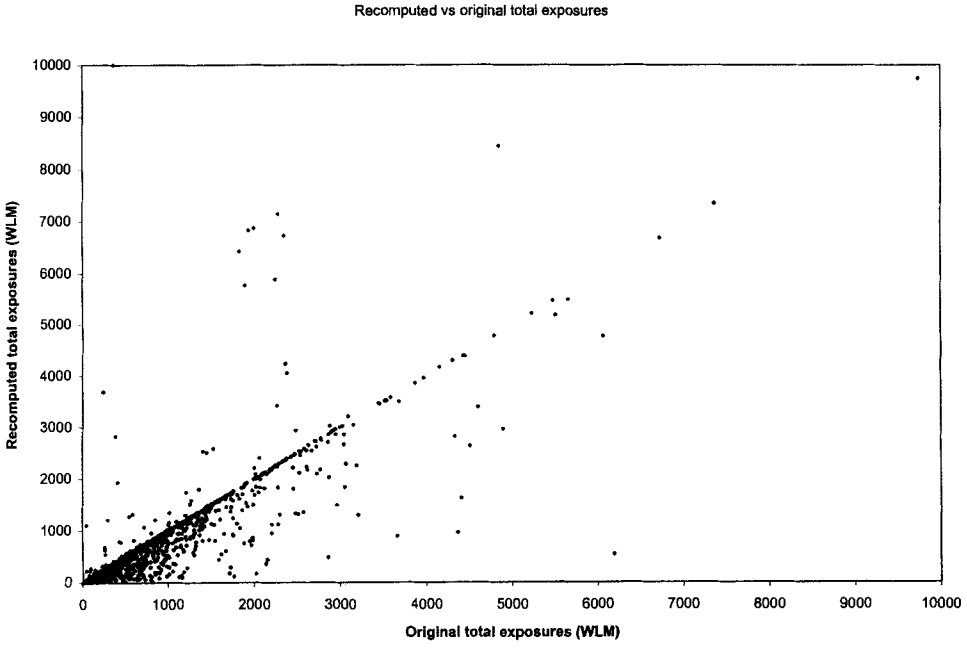

Fig. 1. Comparison of total exposure calculated from the original exposure histories as developed by the Public Health Service, with the recomputed exposure histories based on the mine-year data and work histories made available by NIOSH.

Table 1. Models for risk of lung cancer mortality.

Model	Description	Form of the relative risk model	Comments
A	Simple linear model	$1 + \beta X(t)$.	$X(t)$ is cumulative radon exposure up to 2 y before attained age t.
B	Models including smoking	$[1 + \beta X(t)][1 + \alpha S(t)][1 + \gamma X(t)S(t)]$	$S(t)$ is cumulative smoking to $t - 2$ y.
C	Models including effects of attained age	$1 + \beta_{Age}X(t)$	Risk is estimated separately by categories of attained age.
D	Models including time since exposure	$1 + \beta_1 X(t)_{5-14} + \beta_2 X(t)_{15-24} + \beta_3 X(t)_{25+}$	$X(t)_{5-14}$ is exposure accumulated 5–14 y in past, etc.
E	Empirical dose-rate model	$1 + \beta X(t)\phi_{\text{dose-rate}}$	Similar to model of Lubin et al.
F	"Mechanistic" dose-rate model	$1 + \beta/\alpha\int[1 - \exp - \alpha x(u)]du$	$x(u)$ is the exposure rate at time u, integral is from $u = 0$ to $t - 2$ y.
G	Simplified BEIR-VI model	$1 + [\beta_1 X(t)_{5-14} + \beta_2 X(t)_{15-24} + \beta_3 X(t)_{25+}]\phi_{\text{dose-rate}}\phi_{\text{Age}}$	Includes attained age, time since exposure, and dose rate effects.

critical part of the cell cycle. It is assumed that the DNA damage caused by either one or more than one traversals during the critical phase is equivalent. The integrand, $1-\exp[-\alpha x(t)]$, is the Poisson probability of at least one such traversal at time t so that this probability is integrated over the time periods of exposure. If α approaches zero then $1-\exp[-\alpha x(t)]$ becomes equivalent to $\alpha x(t)$ so that the model reduces to the simple linear model, with β being the ERR per unit dose as in model A. Thus, an inverse dose-rate effect is detected if the estimate of α is significantly greater than zero.

Finally, model G is a simplified version of the BEIR-VI model which simultaneously incorporates latency adjusted exposure, dose-rate, and attained age. The latency and dose-rate components are as in models D and E. Attained age was categorized as <55, 55–64, 65+ y of age and treated in the model as an "effect modifier" analogous to dose-rate in model E. The β parameters are latency interval specific slopes for <5 WL dose-rate, <55 y of age. The $\phi_{\text{dose-rate}}$ and ϕ_{age} parameters are the relative difference that multiplies all of the latency specific slopes according to the dose-rate and age category. Tests of statistical significance were based on the difference of deviances (the deviance is defined as -2 times the log-likelihood) of nested models. Under the null hypothesis that the additional parameters do not better explain the variation in lung cancer rates in the cohort, these differences have a Chi-square distribution with degrees of freedom equal to the difference in the number of parameters. We note that comparison of deviances over the different analysis data sets is not valid because the basic data is not the same.

Analyses presented

For each model above we present two analyses, before and after measurement error correction. In addition, we note that imputations for 1950 and 1951 are highly dependent upon the guesstimated values for 1950. Because of this we performed a second full set of analyses restricting the cohort to the 2,388 members who began working in uranium mines only in 1952 or later.

RESULTS

Multi-level model for measurement error correction

The fit of the multi-level model gives an overall estimate of decline in mine-year exposures of approximately 11% per year over the time period of interest (1950–1969). Significant variability at each level of the hierarchy (mine, locality, and district) was found for either the random slopes, intercepts or both. Imputations were calculated for each mine-year in which miners from the cohort reported work.

Lung cancer risk estimates

Table 2 presents results for each model fit both before and after error correction for all miners starting work in uranium mines in 1950 or later. Table 3 presents similar results restricting the cohort to those beginning exposure in 1952 or later. Comparisons of Tables 2 (1950 cohort) and 3 (1952 cohort) are quite consistent in most respects. For model A (radon only) measurement error correction increases the ERR/WLM estimate by 58% for the 1950 cohort and 64% for the 1952 cohort. Model B (smoking and radon) shows similar increases in the radon ERR/WLM, due to measurement error correction, while leaving the ERR/Pack Year (PKYR) estimate essentially unchanged. The interaction estimate indicates a sub-multiplicative relationship between radon exposure and smoking, both before and after measurement error correction.

Time since exposure and attained age

In other models similar increases in ERR/WLM for radon are also noted. For example, the effects of radon received in each of the time since exposure categories (5–14, 14–25, and 25+ y) are increased, as are the effects of radon according to the various attained age categories. This holds true for both the 1950 (Table 2) and 1952 (Table 3) cohorts. The measurement error correction has small or moderate impact upon the estimates and/or statistical significance of the influence of latency on risk. For example, in model D in Table 2, the estimate of the impact on risk of exposure received 5–14 y in the past is 8 fold higher than for exposure received

Table 2. Model parameter estimates using corrected and uncorrected doses. All miners beginning exposure in 1950 or later (N = 2,704, total lung cancer deaths = 263).

ERR model	Parameter type	Parameter estimate using unadjusted doses		P-value	Deviance	Parameter estimate using adjusted doses		P-value	Deviance
A. Radon only	ERR/100 WLM	.28[a]	.075[b]	<.0001[c]	1815.7[d]	.44	.14	<.0001	1801.1
B. Radon and smoking	ERR/100 WLM	.55	.20	<.0001	1763.3	.82	.35	<.0001	1749.9
	ERR/1000 PKS	.178	.050	<.0001		.174	.050	<.0001	
	Interaction	−.00086	.00030	.004		−.00094	.00038	.004	
C. Attained age	ERR/100 WLM								
	0–54 y	.78	.54	.006	1804.2	3.26	8.09	.012	1790.1
	55–64 y	.53	.30			1.69	1.64		
	65+ y	.084	.039			.20	.11		
D. Time since exposure	ERR/100 WLM								
	5–14 y in past	.73	.29	.006	1805.6	1.68	1.80	.013	1792.3
	14–24 y	.42	.14			.80	.54		
	25+ y	.092	.046			.14	.067		
E. Empirical dose rate	ERR/100 WLM	.59	.21	<.0001	1792.7	.60	.22	.02	1795.9
	Avg. dose rate (Modification of ERR)[e]								
	0–15 WL	0	fixed			0	fixed		
	15+ WL	−.96	.21			−.48	.21		
F. Mechanistic dose rate model	α	.0060	.0031	<.0001	1789.1	.0038	.0021	<.0001	1785.6
	β	1.25	.53			1.07	.46		
G. BEIR-VI model	Time since exposure × Radon (ERR/100 WLM)								
	5–14 y	2.46	2.18		1781.2	2.84	2.75		1783.7
	14–24 y	1.75	1.53			1.74	1.67		
	25+ y	.88	.83			.92	.93		
	Attained age (Modification of ERR)[e]								
	0–54 y	0	fixed	.18[f]		0	fixed	.14	
	55–64 y	−.53	1.07			−.44	1.18		
	65+ y	−1.91	.99			−1.88	1.07		
	Avg. dose rate (Modification of ERR)[e]								
	0–15 WL	0	Fixed	<.0001[g]		0	fixed	.04	
	15+ WL	−.91	.21			−.44	.22		

[a] Parameter estimate.
[b] Standard error.
[c] Likelihood ratio p-value based on changes in deviance.
[d] Deviance statistic.
[e] Effect modifier estimates given on log scale.
[f] For adding attained age to latency.
[g] For adding dose rate to latency and age.

Table 3. Model parameter estimates using corrected and uncorrected doses. All miners beginning exposure in 1952 or later (N = 2,388, total lung cancer deaths = 209).

ERR model	Parameter type	Parameter estimate using uncorrected doses		P-value	Deviance	Parameter estimate using corrected doses		P-value	Deviance
A. Radon only	ERR/100 WLM	.33[a]	.10[b]	<.0001[c]	1448.3[d]	.54	.20	<.0001	1435.2
B. Radon and smoking	ERR/100 WLM	.51	.20	<.0001	1410.3	.68	.32	<.0001	1399.8
	ERR/100 PKS	.16	.05	<.0001		.14	.05	<.0001	
	Interaction	−.00089	.00045	.004		−.00069	.00068	.004	
C. Attained age	ERR/100 WLM								
	0–54 y	.80	.60	.038	1441.7	2.08	2.73	.035	1428.5
	54–64 y	.52	.30			1.02	.82		
	65+ y	.15	.10			.17	.096		
D. Time since exposure	ERR/100 WLM								
	5–14 y in past	.65	.29	.11	1443.8	.93	.46	.18	1431.7
	14–24 y	.42	.16			.67	.28		
	25+ y	.15	.08			.29	.16		
E. Empirical dose rate	ERR/100 WLM	.62	.24	.0002	1434.2	.63	.26	.31	1434.1
	Avg. dose rate (Modification of ERR)[e]								
	0–15 WL	0	fixed			0	fixed		
	15+ WL	−.92	.26			−.27	.27		
F. Mechanistic dose rate model	α	.0058	.0027	.0002	1434.0	.0035	.0020	.04	1431.1
	β	1.12	.50			.99	.45		
G. BEIR-VI model	Time since exposure × Radon (ERR/100 WLM)								
	5–14 y	1.63	1.48	.001	1428.0	1.78	1.80	.15	1427.1
	14–24 y	1.19	1.06			1.28	1.26		
	25+ y	.79	.75			.99	1.02		
	Attained age (Modification of ERR)								
	0–54 y	0	fixed	.26[f]		0	fixed	.16	
	55–64 y	−.098	1.13			−.046	1.26		
	65+ y	−1.55	1.04			−1.73	1.12		
	Avg. dose rate (Modification of ERR)								
	0–15 WL	0	fixed	.0003[g]		0	fixed	.33	
	15+ WL	−.89	.26			−.27	.28		

[a] Parameter estimate.
[b] Standard error.
[c] Likelihood ratio p-value based on changes in deviance.
[d] Deviance statistic.
[e] Effect modifier estimates given on log scale.
[f] For adding attained age to latency.
[g] For adding dose rate to latency and age.

25 or more years ago, before, and 12 fold higher, after, measurement error correction. In contrast to the 1950 cohort, the effect of latency is not statistically significant in the 1952 cohort with either adjusted or unadjusted measurements. This is likely to be a consequence of the smaller sample size in the latter cohort and should not be overinterpreted.

The impact of attained age on the ERR is also moderately increased after measurement error correction. For example, in model C of Table 2 the ERR is 9 fold larger for miners aged 0–54 y than for miners aged 65+ y before and 16 fold higher after measurement error correction.

Dose-rate effects

Three models in Tables 2 and 3 include dose-rate terms. In each of the models, both before and after measurement error correction, the parameter estimates are indicative of the existence of inverse dose-rate effects in which protracted exposures to the same total exposure have greater effect than does shorter term exposure. The dose-rate parameters are generally reduced in size, however, after measurement error correction. For example, the parameter α in the mechanistic model F is reduced by approximately 40% in both Table 2 (1950 cohort) and Table 3 (1952 cohort). In the 1950 cohort data, the inverse dose-rate effect, while smaller, remains strongly statistically significant in both the empirical and mechanistic models (E and F) after measurement error correction (Table 1). However, in Model G (the simplified BEIR model), which simultaneously includes dose-rate, time since exposure, and attained age in the model, the inverse dose-rate effect is less statistically significant ($p = 0.04$) after measurement error correction than before ($p < 0.0001$). For the 1952 cohort (where we assume the imputations are more accurate) the effect of measurement error correction upon the statistical significance of the inverse dose-rate effect is quite pronounced. All three models (empirical, mechanistic, and simplified BEIR) show significant inverse dose-rates effects before measurement error correction (p-values from 0.002 to 0.003 for the 3 models). After correction only the mechanistic dose-rate model is significant with p-values for the 3 models ranging from 0.04 to 0.33). The point estimates, however, for the dose-rate terms in the measurement error corrected models are quite consistent from Table 1 (1950 cohort) to Table 2 (1952 cohort). For example the fit of the mechanistic model gives virtually the same dose-rate parameter estimate, α, after measurement error correction in the 1950 and 1952 cohorts. Thus, the dose-rate findings must be interpreted with caution; in particular, we should avoid the temptation of concluding that there is no dose-rate effect in the 1952 cohort. Because we are starting with fewer lung cancer deaths in the 1952 cohort, the power of detecting these effects is reduced enough so that essentially the same dose-rate effects seen after measurement error correction using the full data are not significant.

Fit of the model

An important observation is that, for models not including dose-rate effects (models A-D), the deviance of the model is smaller when the measurement-error adjusted exposures are used than for the unadjusted. For example, in model A (radon only) in Table 2, the difference in deviance before and after measurement error correction is $1815.7 - 1801.1 = 14.6$. We interpret this as indicating that the adjusted exposure histories fit the lung cancer mortality data better than do the unadjusted histories. This can be formalized as a likelihood ratio test by nesting the two models (unadjusted vs. adjusted exposure histories) within a larger model—in which the exposure histories are a mixture (i.e., a linear combination) of the adjusted and unadjusted—and estimating the mixing parameter by maximum likelihood. Doing so, in the case of model A, we find that we can reject the hypothesis that the unadjusted exposure histories provide as good a fit as does the mixture. In fact, the best fitting mixture is virtually identical to the use of the adjusted histories alone. An assessment of the significance of this change in deviance is obtained by comparison to a chi-square random variable with 1 degree of freedom ($p = .00013$). Fig. 2a illustrates that the ERR estimates are more linear in total radon exposure when the adjusted exposure histories rather than the unadjusted are used, indicating that model A fits better using the adjusted dose histories.

It is evident from the results shown for models E–G that the source of this improved fit using the adjusted exposure histories is directly related to the reduction of dose-rate effects in the data. Once dose-rate effects are incorporated the unadjusted and adjusted exposures provide a very similar fit to the lung cancer mortality, with a slightly better fit given by the unadjusted exposures in the empirical dose-rate model, and by the adjusted exposures in the mechanistic. Fig. 2 illustrates this point as well. A greater similarity of the effects of high and low dose-rate responses is shown in Fig. 2c (showing the adjusted histories) than in Fig. 2b (unadjusted).

DISCUSSION

The importance of data from uranium miners cohort studies has been highlighted recently by the publication of the BEIR-VI report, which estimates the number of lung cancer deaths due to residential exposure to radon. The basis for these estimates is further analysis of 11 miners cohorts (Lubin et al. 1994) including the Colorado Plateau cohort. There are two features of the reanalysis that has relevance for these analyses. First is the evidence that the dose-response relationship, i.e., ERR/WLM, in all previous analyses of this cohort may have been importantly attenuated by measurement errors. Our measurement error corrected estimates of risk generally are larger (by as much as 60%) than the uncorrected estimates. However, the real issue in understanding the effect of residential exposure is the impact of low-exposure rate exposures. We find that the inverse

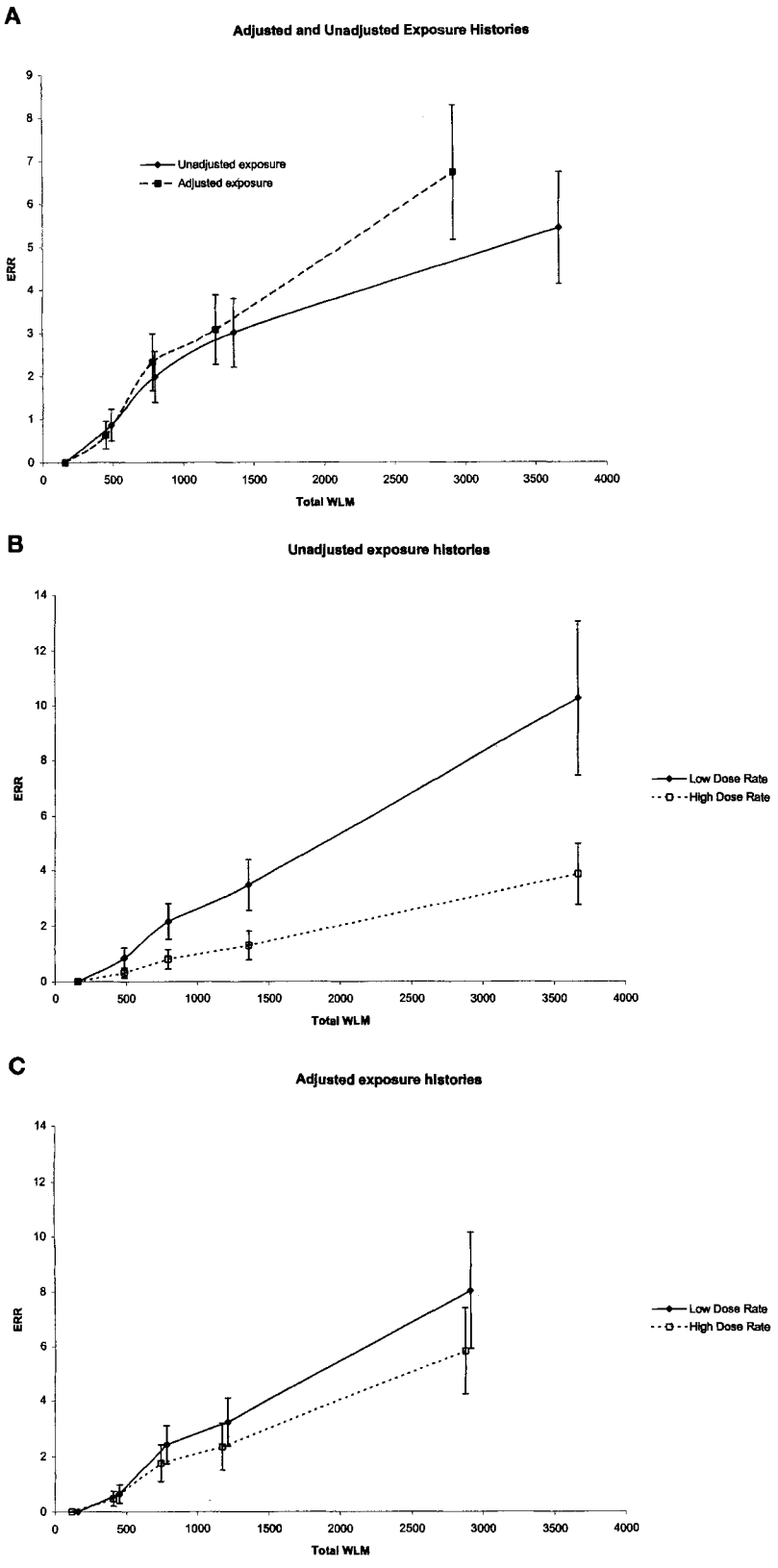

Fig. 2. Excess relative risk of lung cancer mortality; (A) Due to total radon exposure for adjusted and *unadjusted* exposure histories; (B) Using unadjusted exposure histories separating effects due to radon exposure accumulated at low (0–15 WL) and high (>15 WL) exposure rates; (C) using measurement-error adjusted exposure histories and separating low and high dose-rate effects. Fits are from a categorized version of models A and E of Table 1. One standard error bars are also shown for the excess relative risk estimates.

exposure-rate effect, which plays an important role in the way that risk estimates from the high exposures received by the miners are interpolated by BEIR-VI down to residential levels, is generally weakened after measurement error correction. These two effects (increase in risk/WLM at high exposures, and smaller-exposure rate effects) tend to cancel each other out at low exposure rates. In our simplified BEIR-VI model (model G) the impact of low dose-rate exposures (0–15 WL) is almost identical before and after measurement error correction. The estimate of the impact of high dose-rate exposures on the other hand are increased substantially by measurement error correction.

Our measurement error correction method is based upon the development of measurement-error adjusted dose-rate estimates for the mine-years of interest in the Colorado Plateau. The log-linear model for the decline in dose-rates over the years from 1950–1969 given in eqn (1) is, admittedly, a gross simplification of the effects of changes in ventilation practices which took place over these years in each of the mines in the Colorado Plateau region. In any given mine, major improvements in ventilation would have lead to abrupt discontinuities in exposure dose-rates rather than in the smooth declines over time predicted by the model. Without the benefit of historical records dating these ventilation changes, the inclusion of discontinuities in our models for the dose-rates is highly problematic. Even considering just those mines with good dose-rate measurement data from 1951 onwards, an attempt to empirically estimate the times when ventilation improved for each mine is difficult because of the large amount of random error for each measurement. For mines with few or no measurements this becomes impossible. If we believe that the true state of nature is a discontinuity at the time of installation of ventilation, but we do not know the date of the discontinuity then, by averaging over all possible dates, we get some sort of smooth decline over time, which appears to be reasonably loglinear. In those mine-years in which measurements are available the imputations we use may be regarded as a variance-weighted average of the measured values and the log-linear model prediction. Thus, in mines with data, if there is evidence for an abrupt discontinuity in measured levels, this will also be reflected in the imputations. It is only for the mines without any data that the pure loglinear decline would be used. Fig. 3 illustrates the relationship between the measurements and dose-rate imputations in a Colorado mine (M539) in which measurement data exists from 1959 onwards. Our overall impression, from viewing plots of all the measurement data on a mine by mine basis, is that the assumption of a loglinear model for declines over the 20-y period considered is reasonable for the large majority of mines.

Also at the basis of our approach is the presumption that the measurements taken provide unbiased estimates for a given mine year. It has been noted (Schiager 1989) that this may not have been the case for measurements

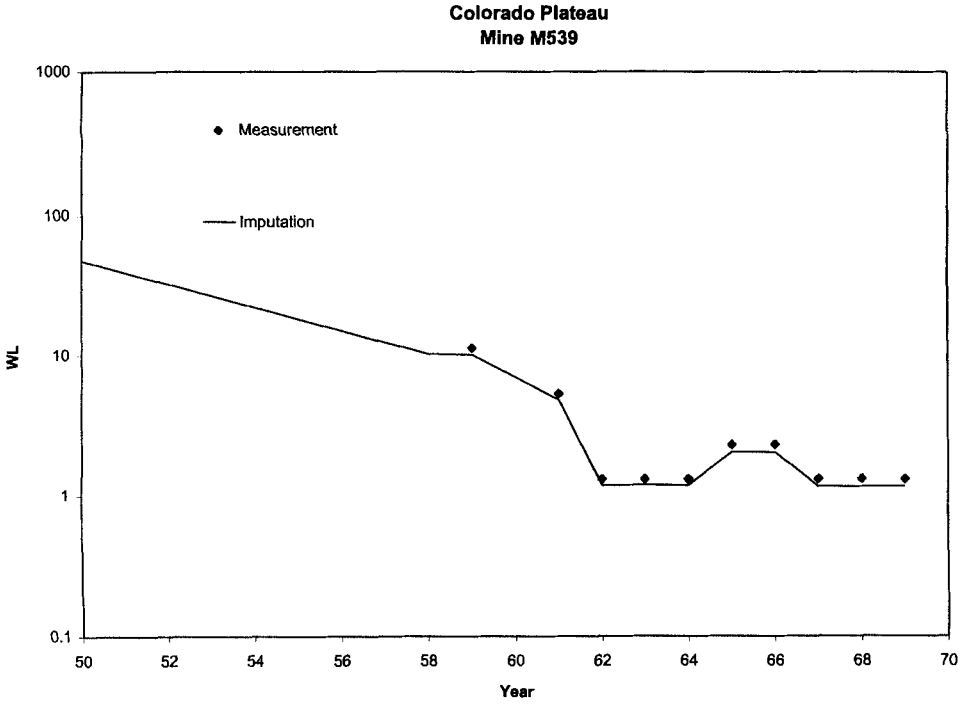

Fig. 3. Imputations of dose-rate in a mine with measurements. Mine M539 had between 4 and 57 measurements taken in each of the years 1959 and 1961–1969. The average of the measured values are plotted (diamonds) together with the imputations (solid line). This plot illustrates that the mine-specific log-linear decline is used as the imputation only for those years without measurements. Because of the large number of measurements for the later years in this mine, the model-derived imputations track the measured values very closely in those years.

taken from 1951–1953 which were made in the summer only, when natural ventilation would have been at its poorest, and dose-rates at their highest. As noted by Schiager, systematic over-estimation of dose-rate in the early years, due to sampling biases, would have resulted in further under-estimation of the cancer-causing effects of both total, and, in particular, high dose-rate exposure, in the epidemiologic analyses.

Fig. 1 illustrates that our analysis has not been able to completely reproduce the exposure histories that have been used in all previous analyses of this cohort starting with that of Lundin et al. (Lundin et al. 1971) in 1971. We believe that additional mine-year measurements were probably available to the PHS researchers that were not recorded in the mine-year file that we have received. We anticipate, however, that if it were possible to fully reconstruct all the exposure histories from the original measurements and interpolations, that the effect of our measurement error corrections on these histories would be similar to that reported here. To address this issue we performed additional analyses of the cohort data after excluding 595 miners (leaving 2,109 subjects with 193 cancer cases) whose total exposure could not be reproduced to within 100 WLM. In this restricted analysis the main features of Table 2 were again replicated. Measurement error correction increased the estimate of the effect of cumulative radon exposure by 52% and the dose-rate effect parameters in models E, F, and G were reduced by about half. The combination of these two effects meant, again, that the effect of dose cumulated at the lowest rate of exposure was relatively unchanged by measurement error correction. Moreover, the measurement error adjusted exposure histories again gave a significantly better fit to the lung cancer data than did the unadjusted histories in models A–D, and similar fits in the models (E–G), which included dose-rate effects (results not shown).

Exposure estimation for individual miners, especially those working in the early years, is extremely uncertain. One potential benefit of statistical approaches, such as the one that we have taken here toward exposure estimation, is that the mine-year dose-rate estimates from the model are also accompanied by numerical uncertainty estimates. Description of these is given in a technical report (Stram et al. 1998). The uncertainty in mine-year dose-rate estimates can be combined over years and locations to describe the uncertainty in exposure histories as well. Of course, that evidence that we do not have at our disposal all the mine-year measurement data that went into the developing the original PHS doses means that any such uncertainty calculations would be incomplete at this time.

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