Paper

RADON-EXPOSED UNDERGROUND MINERS AND INVERSE DOSE-RATE (PROTRACTION ENHANCEMENT) EFFECTS

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Abstract—**Recent models for radon-induced lung cancer assume that at high levels of cumulative exposure, as experienced historically by many underground miners of uranium and other ores, the risk of lung cancer follows an inverse dose-rate (protraction enhancement) pattern. That is, for equal total dose, a greater risk is incurred by those whose total dose is accumulated at a lower rate over a longer duration than at a higher rate over a shorter duration. This inverse dose-rate effect is hypothesized to be the consequence of multiple traversals of the nucleus of a target cell by alpha particles. It has recently been concluded, however, that for low total doses, as in most residential settings, the inverse dose-rate effect should diminish and perhaps even disappear, since at very low doses the probability that more than one alpha particle would traverse a cell is small and there would be no possibility for interactions from multiple hits. Pooling original data from 11 cohort studies of underground miners, including nearly 1.2 million person-y of observation and 2,701 lung cancer deaths, we evaluate the presence of an inverse dose-rate effect and its modification by total dose. An inverse dose-rate effect was confirmed in each cohort, except one, and overall in the pooled data. There also appears to be a diminution of the inverse dose-rate effect below 50 Working Level Months (WLM), although analyses were necessarily hampered by a limited range of exposure rates at low total WLM. These data support both the presence of an inverse dose-rate effect, as well as its diminution at low total dose. As a consequence, assessment of risks of radon progeny exposure in homes (on average 15–20 WLM for a lifetime) using miner-based models should not assume an ever-increasing risk per unit dose. Rather, it is more appropriate to apply risk models that take into account protraction enhancement and its diminution.**

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Key words: radon; cancer; lungs, human; epidemiology

INTRODUCTION

Studies of miners show that high levels of cumulative exposure to radon progeny can cause lung cancer and that the increase in the relative risk (RR) is approximately linear in exposure, as estimated by cumulative Working Level Months[##] (WLM) (Lubin et al. 1994; NRC 1988; Samet 1989). In miners, the dose-response relationship is modified by several factors. (WLM is not a measure of dose, but exposure; however, we use dose and dose-response as synonymous with exposure and exposure-response.) The excess RR per WLM (ERR/WLM) declines with increasing age at observation and time since exposure, and increases with increasing duration or, equivalently, decreasing dose rate (Lubin et al. 1994). This latter pattern, sometimes called a protraction enhancement effect, is consistent with biophysical models

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[##] One Working Level (WL) equals any combination of radon progeny in 1 L of air which results in the emission of 1.3 MeV of energy from alpha particles. WLM is the product of time, in units of 170 h, and WL. One WLM equals a lung dose of approximately 0.5 rad or about 5 to 10 rem (NRC 1991). Indoor radon is measured in Becquerel per cubic meter, Bq m^{-3} (or picocuries per liter, pCi L^{-1}), the number of atomic decays per liter of air. In an average home, radon concentration is about 48 Bq m^{-3} (1.3 pCi L^{-1}), or a radon progeny level of 0.007 WL. With 70 percent occupancy, one year of residence at 37 Bq m^{-3} results in approximately 0.2 WLM.

which postulate that lung cancer induction from high-LET radiation follows an inverse dose-rate effect, i.e., for a fixed total dose the highest risk is experienced by those exposed for a longer duration and a lower dose rate (Brenner and Hall 1990; Brenner et al. 1993; Dennis and Dennis 1991; Elkind 1991; Rossi and Kellerer 1986). The miner studies provide consistent evidence of an inverse dose-rate pattern, as do experimental animal studies (Chameaud et al. 1984; Cross 1992; Morlier et al. 1992) and *in vitro* studies (Miller et al. 1993).

As outlined by Brenner (1994), an inverse dose-rate effect is postulated to result from cell cycling, whereby cells in a particular period of their cycle are more sensitive to radiation than at other times. With an acute dose, only a fraction of the pool of cells is in the sensitive phase and has the potential for oncogenic transformation. With protracted exposure for the same total dose, a greater proportion of cells is exposed during the sensitive phase (albeit at a smaller dose rate). If even at low dose rates energy deposition from alpha particles is sufficient to produce oncogenic change, then an inverse dose-rate effect will result. Finally, multiple traversals of a cell by alpha particles are necessary for an inverse dose-rate effect. If at most only one alpha particle is likely to pass through a cell nucleus, changing the "rate" can have no effect. Thus, at low total dose the effect would diminish, since extreme protraction results in a low probability of multiple traversals.

An inverse dose-rate effect has been shown in cohort studies of radon-exposed underground miners (Hornung and Meinhardt 1987; Ševc et al. 1988; Xuan et al. 1993), and also proposed by Darby and Doll (1990). In the 1988 Report of the National Academy of Sciences' Committee on the Biological Effects of Ionizing Radiations (BEIR) IV, no conclusive inference could be drawn from the pooled analyses of four miner cohorts (NRC 1988). In a more extensive pooled analysis of 11 miner studies, an inverse dose-rate effect was seen consistently in individual cohorts and overall (Lubin et al. 1994).

A recent note by Brenner compared risks from several miner cohort studies by exposure rate and suggested such a diminution (Brenner 1994). However, data from only a few studies were available and no firm conclusion was reached. In this note, we revisit the pooled data from 11 miner studies and consider two issues: (1) the existence of the inverse dose-rate effect; and (2) the diminution of the effect at low total dose.

As described in Lubin et al. (1994), data were obtained from all published cohort studies of underground radon-exposed miners which met two criteria: at least 40 lung cancer deaths, and available estimates of exposure in WLM for individual workers. In the pooled data, there were 2,701 lung cancer deaths and 1.2 million person-y of observation. The studies are listed in Table 1. Data were cross-classified into multi-way person-years tables and analyzed using relative risk regression methods (Lubin et al. 1994; NRC 1988).

Table 1. Numbers of lung cancer cases, estimates of the ERR/WLM and its modification by continuous exposure rate in WL.[a]

Study cohort	Cases[b]	$\beta \times 100$	γ	P[c]
China tin miners	980	0.59	−0.79	<0.001
Czechoslovakia[d] uranium miners	661	5.84	−0.78	<0.001
Colorado Plateau uranium miners	294	14.5	−0.79	<0.001
Ontario uranium miners	291	2.40	−0.55	0.002
Newfoundland fluorspar	118	5.14	−0.53	<0.001
Sweden iron miners	79	1.55	−1.02	0.03
New Mexico uranium miners	69	6.56	−0.30	0.17
Beaverlodge uranium miners	65	7.42	−0.67	0.001
Port Radium uranium miners	57	1.15	−0.42	0.24
Radium Hill uranium miners	54	5.68	−0.63	0.30
France uranium miners	45	1.92	0.57	0.57

[a] Background lung cancer rates are adjusted for attained age (all studies), other mine exposures (China, Colorado, Ontario, New Mexico, France), and indicator of radon progeny exposure (Beaverlodge), and ethnicity (New Mexico). Colorado data restricted to exposures under 3,200 WLM. The RR is modeled by the form $RR = 1 + \beta \times WLM \times (WL)^{\gamma}$.

[b] Total number of cases is 2,701 and omits 12 cases which were included in both the New Mexico and Colorado studies.

[c] P-value for test of significance of continuous variation of ERR/WLM by WL.

[d] For historical reasons, the study is referenced as the Czechoslovakia cohort, although Czechoslovakia is now two independent countries, the Czech Republic and Slovakia. About 25% of the miners were of Slovak origin and many later returned to Slovakia.

INVERSE DOSE-RATE EFFECTS

A direct approach to evaluating an inverse dose-rate effect computes relative risks (RR) of lung cancer for categories of mean exposure rate, measured in WL, stratifying on categories of attained age, other concomitant factors (see Table 1 footnote [a]) and cumulative WLM. For the pooled analysis, in seven cohorts (China, Colorado, Ontario, Newfoundland, Beaverlodge, Port Radium, and Radium Hill) WL for each worker for each year of follow-up was computed using cumulative WLM and either cumulative duration of exposure or mean WL for the year. For the remaining four cohorts, precise information on exposure rate was not available for the data pooling and WL was computed from cumulative WLM and cumulative exposure, assuming 2,000 h of exposure for years in which some exposure occurred. Fig. 1 shows RRs by WL category for each of the 11 cohorts, plotted at the mean of each category. Except for the French miners cohort (middle panel), RR patterns are consistent and show decreasing RRs with increasing WL, indicative of an inverse dose-rate effect. A test of trend is provided in Table 1. For all data combined and with additional stratification by cohort, RRs decline with increasing WL (Fig. 2), although as suggested by the wide confidence limits there is substantial uncertainty at the lowest WL categories. Categories are <0.1, 0.1–0.29, 0.3–0.49, 0.5–0.99, 1.0–1.9, 2.0–2.9, 3.0–4.9, 5.0–9.9, 10.0–14.9, ≥15.0 WL and include 17, 106, 128, 216, 873, 608, 227, 148, 114, and 148 lung cancer cases, respectively; 116 cases were not exposed.

To provide a simple summary of cohort-specific dose-rate effects, we fit a linear ERR risk model in WLM, with a power variation in dose rate, namely,

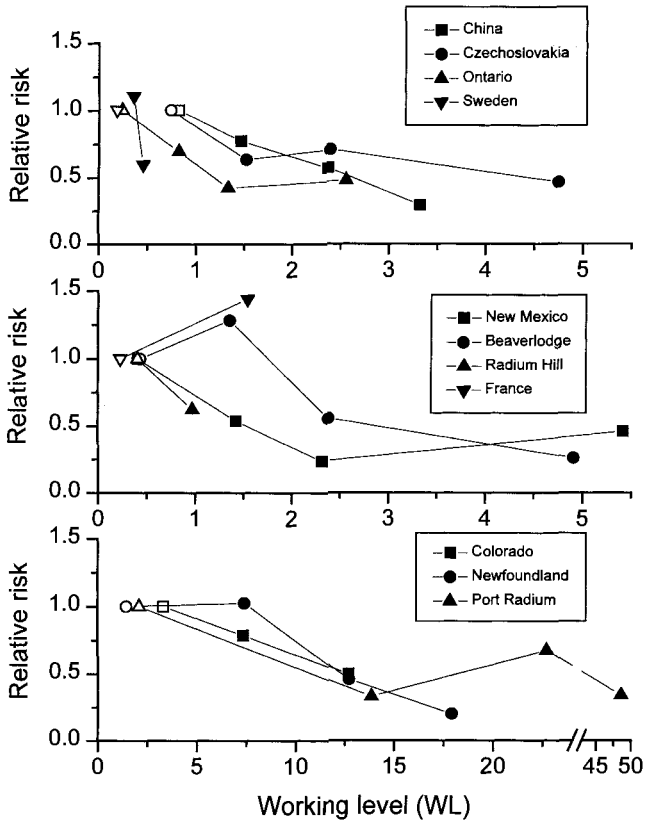

Fig. 1. Relative risk (RR) of lung cancer for categories of WL, adjusted for attained age, other concomitant factors and WLM. Open symbols denote referent category for RR.

$$RR(WLM, W) = 1 + \beta \times WLM \times (WL)^{\gamma}, \quad (1)$$

where β is the ERR/WLM (dose-response) parameter and γ represents a power modification by WL to the ERR/WLM. Table 1 shows estimates of β and γ and a test of no dose-response variation ($\gamma = 0$) for each cohort. The estimates of γ were negative for all cohorts, except the French miners, and indicate a decreasing dose-response with increasing WL; formal tests of $\gamma = 0$ were significant in the six studies with the largest number of cases and in seven of the largest eight studies.

Related patterns of RRs are seen for categories of duration of exposure; RRs increased with increasing duration of exposure. With duration of exposure replacing WL in eqn (1), estimates of γ exceeded zero for all cohorts except France (not shown), again indicating a protraction enhancement effect.

DIMINUTION OF THE INVERSE DOSE-RATE EFFECT

Brenner (1994) argues that an inverse dose-rate effect depends on total dose. Fig. 2 shows a decline in the RRs for categories of increasing WL; however, RR patterns at low exposure rates are difficult to interpret, because the data cover the entire range of WLM exposures. Fig. 3 shows adjusted RRs by WL within six categories of total exposure, 1–49, 50–99, 100–199, 200–399, 400–799, and ≥800 WLM. For each WLM category, the Figure also shows the fit of the model $(WL)^{\gamma}$, adjusted to pass through the mean of the referent RR category. RRs for WL do not appear to vary for exposures under 50 WLM, while RRs exhibit a decreasing pattern with increasing WL in the higher WLM categories. Table 2 shows that estimates of γ for the WL effect generally decrease with greater WLM exposure; the (5 degree-of-freedom) test of homogeneity of the estimates is significant ($p < 0.001$). For exposures under 50 WLM, the γ estimate is not significantly different from zero. The pattern of the estimates of γ are consistent with no protraction enhancement at low total exposure.

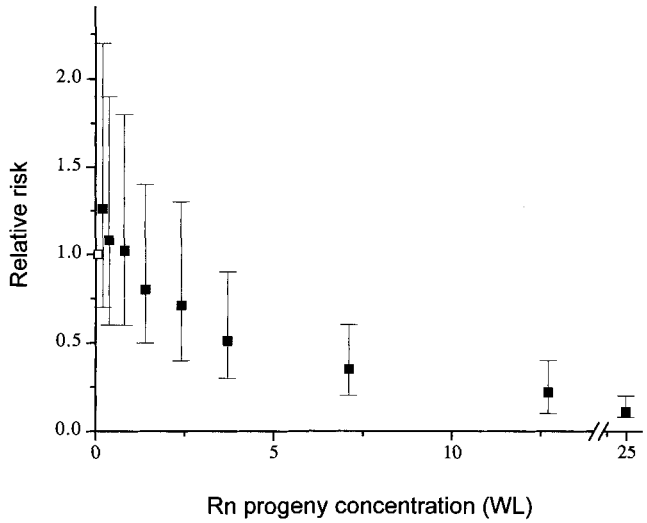

Fig. 2. Relative risk (RR) of lung cancer and 95% CIs for all miner data by WL categories, adjusted for attained age, other concomitant factors, WLM and cohort. Open square denotes referent category.

The diminution of the inverse dose-rate effect is also evaluated by computing RRs for categories of duration of exposure, adjusting for WLM, attained age, concomitant factors (see Table 1 footnote [a]) and cohort. Fig. 4 show RRs for duration of exposure by categories of cumulative WLM and the best fitting power model in duration, $(DUR)^{\gamma}$. The inverse dose-rate effect is again apparent, with increasing RRs with increasing duration. For total exposure under 50 WLM, there is minimal increase in the RRs with duration, again indicating a lessening of the inverse dose-rate effect at low total doses. Parameter estimates of γ for the duration of exposure effect are given in Table 2 and again illustrate the diminution, with the γ estimates for duration of exposure significantly different from 0 for all WLM categories, except under 50 WLM.

DISCUSSION

Over a broad range of cumulative exposures to radon progeny, studies of underground miners (Hornung

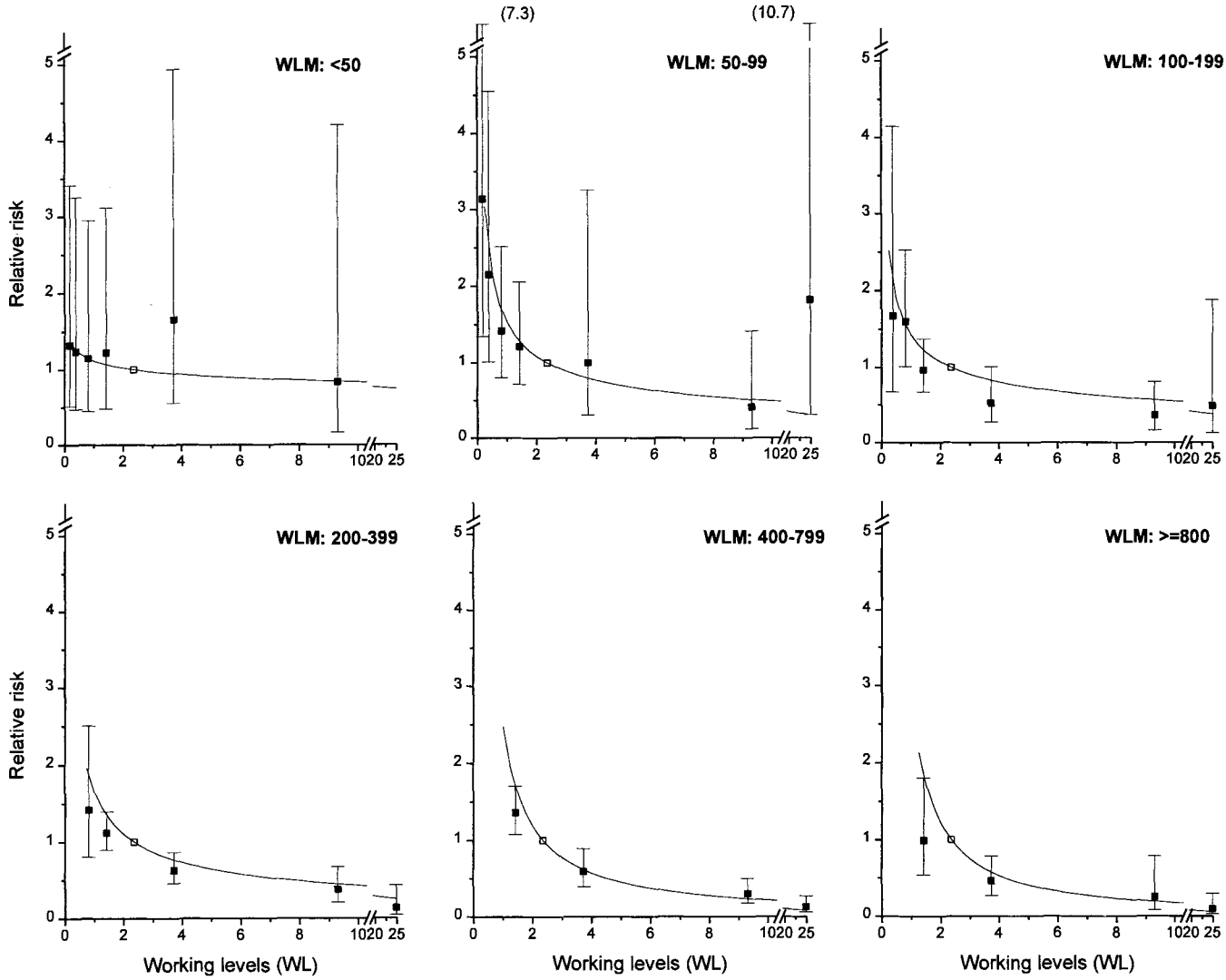

Fig. 3. Relative risk (RR) of lung cancer and 95% CIs by categories WL within WLM groups and fitted power curve $(WL)^{\gamma}$, adjusted to referent category for RR (open square).

and Meinhardt 1987; Lubin et al. 1994; Ševc et al. 1988; Xuan et al. 1993) provide evidence for an inverse dose-rate effect (protraction enhancement effect) for high-LET radiation. Our analyses suggest, however, that this effect diminishes, and possibly disappears, for cumulative exposures under 50 WLM. There are several plausible explanations. At doses common in mines, lung epithelial cells may experience multiple traversals by alpha particles. Reducing dose rate may allow proliferation of initiated cells, more exposure at critical stages of the cell cycle, or both, resulting in an enhanced transformation rate. At the low doses common in homes, traversal of a cell by more than a single alpha particle is unlikely. Thus, at such doses, there is no mechanism for interactions of multiple hits by alpha particles to occur and protraction enhancement should approach zero.

Brenner (1994) suggests that for miners 50 WLM is a reasonable demarcation between high and low expo-

Table 2. Parameter estimates and 95% confidence intervals (CI) from fitting power models to the relative risk[a] of radon progeny exposure rate $(WL)^{\gamma}$ and exposure duration $(DUR)^{\gamma}$ within categories of total cumulative WLM.

		Exposure rate		Exposure duration	
WLM	Cases[b]	γ	95% CI	γ	95% CI
1–49	358	−0.13	(−0.3,0.0)	0.13	(0.0,0.2)
50–99	213	−0.46	(−0.8,−0.2)	0.46	(0.2,0.7)
100–199	461	−0.41	(−0.7,−0.2)	0.45	(0.2,0.7)
200–399	508	−0.59	(−0.8,−0.4)	0.59	(0.4,0.8)
400–799	613	−1.07	(−1.4,−0.8)	0.78	(0.8,1.4)
≥800	432	−1.21	(−1.6,−0.9)	0.82	(1.1,1.8)

[a] Background lung cancer rates are adjusted for attained age (all studies), other mine exposures (China, Colorado, Ontario, New Mexico, France), and indicator of radon progeny exposure (Beaverlodge), and ethnicity (New Mexico). Colorado data restricted to exposures under 3,200 WLM. Models were also adjusted by additional categories of WLM.

[b] Among cases, 116 have no WLM exposure.

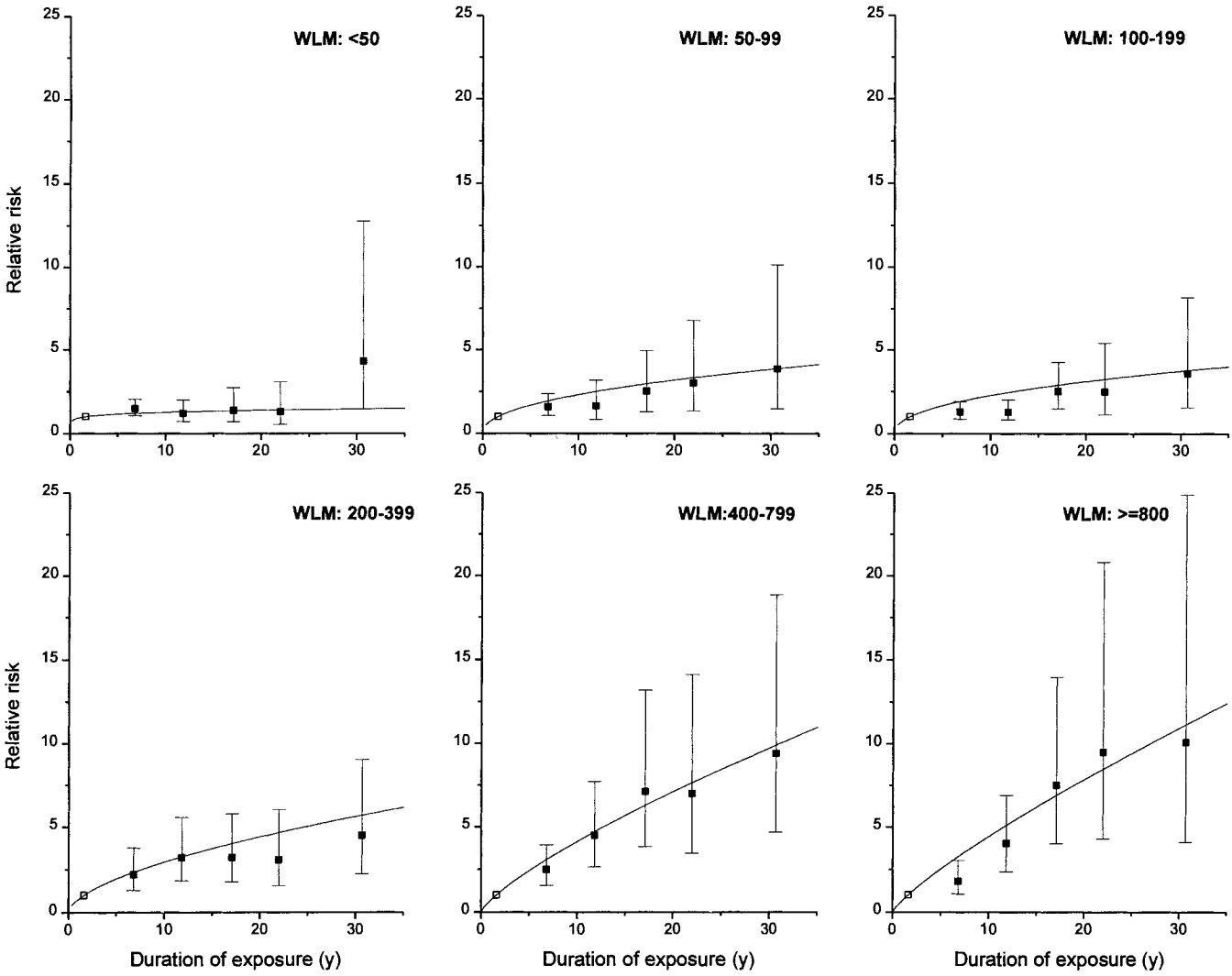

Fig. 4. Relative risk (RR) of lung cancer and 95% CIs by duration of exposure within WLM groups and fitted curve $(DUR)^{\gamma}$, adjusted to referent category (open square).

sures and that below this level the probability of multiple traversals of a cell nucleus by an alpha particle is likely small. Still, without detailed knowledge of stem cells in the lung and since the diminution of an inverse dose-rate effect is likely a continuous process, the choice of 50 WLM must be considered somewhat arbitrary. In addition, exposure assessments in miner data are subject to great uncertainty, and misspecification of exposure and exposure rate will have uncertain consequences for any analysis of inverse dose-rate effects and their diminution.

In residential settings cumulative exposures are on average about 10-fold lower than in the miner data, while durations of exposure are much longer and radon progeny concentrations are typically much lower (Nero et al. 1986; Marcinowski et al. 1994). For example, the radon level in an average U.S. home is about (48 Bq m^{-3}) (1.3 pCi L^{-1}) corresponding under standard equilibrium assumptions to a radon progeny concentration of about 0.007 WL; the vast majority of homes have radon levels under 370–555 Bq m^{-3} (10–15 pCi L^{-1}) or under 0.05–0.08 WL. This range contrasts with miner data in which mean radon progeny level is 2.8 WL, about 400 times the mean residential exposure rate, and ranges from 0.1 WL to over 30 WL.

Our findings on protraction enhancement are an important source of uncertainty in applying models developed from miner data for risk assessments in residential settings where total dose and dose rate are typically low. Moreover, risk estimates for the general population using miner-based models that do not incorporate effects of protraction enhancement or that fail to account for their diminution at low total dose may overestimate risk.

To illustrate the consequences of the inverse dose-rate effect and its diminution on extrapolation of risk to low dose rates, consider three miner-based, relative risk

models presented in Lubin et al. (1994). Fig. 5 plots the values of the slope parameter for a linear ERR model (ERR/WLM) by WL for three different models for an individual 60 years of age with 5–14 years since exposure. (1) The TSE/AGE/WL-cat model consists of a linear dose-response in cumulative WLM that varies by categories of time since exposure, attained age and WL. The ERR/WLM parameter for various WL categories is shown by the solid line, while the square symbols identify mean WL for the categories <0.5, 0.5–0.9, 1.0–2.9, 3.0–4.9, 5.0–14.9, and ≥15.0 WL. This model was selected as a "final" model by Lubin et al. (1994). (2) The TSE/AGE/WL-ctn model consists of a linear dose-response in cumulative WLM that varies by categories of time since exposure, and by an exponential of attained age and a power of WL. The ERR/WLM parameter by WL is shown by the dashed line. (3) The TSE/AGE-cat model is similar to models (1) and (2), but does not include a factor for WL and the ERR/WLM estimates do not vary with WL. The dose-response parameter is shown by the dotted line. The TSE/AGE-cat model is similar in form to the BEIR IV model (NRC 1988), which for comparison is shown by the combined dotted-dashed line. Exposure rates in the miner data range from about 0.1 WL to over 30 WL. In this range, Fig. 5 indicates that the TSE/AGE/WL-cat and TSE/AGE/WL-ctn models estimate similar dose-response parameters.

Assuming the relevance of miner data to residential radon progeny exposure and the validity of the descriptive models, each of the three models described above could be used to estimate risks at exposure rates found in homes, generally below 0.1 WL. The TSE/AGE/WL-ctn model includes a single parameter to account for protraction enhancement and, since most miners experience high exposure rates, the model cannot effectively incorporate a diminution of the protraction effect to typical residential levels. Thus, use of this model likely overestimates residential risks. Conversely, the TSE/AGE-cat model omits all protraction effects and therefore likely underestimates residential risks. The ERR/WLM from the TSE/AGE/WL-cat model is modified by a parameter for rates below 0.5 WL and thereby accounts, at least partially, for a diminution of an inverse dose-rate effect. Thus, estimates of residential risk based on the TSE/AGE/WL-cat model are likely to be more realistic than either of the other models; however, because the model may not fully incorporate a diminution of the inverse dose-rate effect, the TSE/AGE/WL-cat model may also over-estimate risk. The BEIR IV model was developed from a pooled analysis of 4 cohort studies and 360 lung cancer cases (NRC 1988). Its ERR/WLM estimate is similar to the ERR/WLM estimate from the TSE/AGE/WL-cat model at low exposure rates, but the ERR/WLM estimate is substantially larger at higher exposure rates.

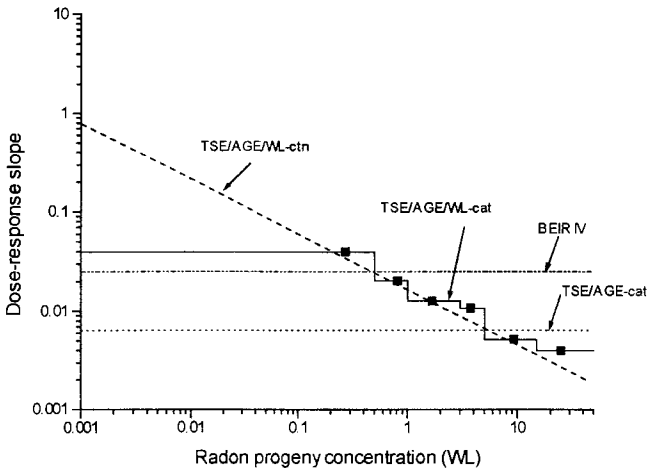

Fig. 5. Dose-response slope parameter based on three regression models (see text) for a subject 60 years old and 5–14 years since exposure.

In a recent analysis of updated data from the Czechoslovakian study, Tomášek et al. (1994) found an inverse dose-rate effect; however, they also found that the effect was not significant when the analysis was limited to miners never exposed at or above 10 WL. (The method of data restriction was unbiased, since the criterion for restriction of miners involved work experience prior to start of follow-up.) The reasons for these results are uncertain, since in the pooled miner data, the decline in the RR with increasing WL was observed over a broad range of concentrations, including those found in the Czechoslovakian study, in which the majority of miners had mean exposure rates under 3 WL. The Tomášek et al. results are not likely due to the diminution of the inverse dose-rate effect, since mean exposures were 219 WLM for the full cohort and 163 WLM for the restricted cohort, but could be the consequence of a particular pattern of exposure rates. Thus, the importance of their results are uncertain until similar examinations of exposure rate are conducted in other miner cohorts.

Error in the WL and WLM estimates also need to be considered in interpreting the dose-rate analysis. The highest exposure rates, which typically result in the highest cumulative exposures, occurred in the earliest years of mining, when the fewest measurements were made. Moreover, in the earliest years, concentrations of radon, rather than radon progeny, were measured in many studies, necessitating equilibrium assumptions in translating to WL. Errors in estimation of WL were therefore likely greatest in the earliest years of mining. This pattern of errors would tend to lessen the effects of high exposure rates, thereby inducing an apparent inverse dose-rate effect. Direct information on errors in WL data are not generally available. To partially address the issue, RRs for WL categories were computed by levels of calendar year of first exposure, calendar year of exposure, attained age or years since last exposure. RR patterns for WL and inference on the γ power parameter were unchanged when RRs were computed within levels of or after adjusting for these factors (Lubin et al. 1994). Thus, while inverse dose-rate patterns may have been influenced by WL measurement error, it appears unlikely

that such errors could be responsible for the entire exposure rate effect.

Animal studies using very high exposure rates have shown that longer duration of radon exposure at a lower rate induced more lung cancers than shorter duration at a higher rate (Cross 1992). In contrast, one study found no inverse dose-rate effect when animals were exposed at the low total exposure 25 WLM (Morlier et al. 1992). Based on the 2-stage initiation-progression model for carcinogenesis, Moolgavkar et al. (1990, 1993) suggest that extended duration allows time for proliferation of initiated cells and thus the higher disease occurrence rates.

In the analysis, no special "weighting" factors for the various studies, objective or subjective, were used. All of the miner studies were imperfect and any attempt to omit a study from analysis or to define a quality score would be problematic. Any factor proposed to confound results must have a substantial influence, and the influence must be distinct from attained age, calendar year, birth cohort, exposure, and exposure rate, which were included in analyses. Because data from 11 studies were pooled, it was unlikely that any single study drove results for the combined data. For example, all 11 studies contributed to the 358 lung cancer cases which occurred among exposed miners under 50 WLM.

In summary, for high-LET radiation at low total dose there is a low probability of more than one alpha particle traversing a cell, and thus the inverse dose-rate effect should diminish. Results of analyses of pooled miner data support this assertion for exposures under about 50 WLM. For estimating radon effects in homes, miner-based models should make provision for an inverse dose-rate effect and its diminution at low rates.

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