Paper

DOMESTIC RADON RISKS MAY BE DOMINATED BY BYSTANDER EFFECTS—BUT THE RISKS ARE UNLIKELY TO BE GREATER THAN WE THOUGHT

D. J. Brenner* and R. K. Sachs†

Abstract—**Radon risks derive from exposure of bronchioepithelial cells to alpha particles. Alpha-particle exposure can result in bystander effects when irradiated cells emit signals resulting in damage to nearby unirradiated bystander cells. Bystander effects can cause downwardly-curving dose-response relations and inverse dose-rate effects. We have extended a quantitative mechanistic model of bystander effects to include protracted exposure, with inverse dose-rate effects attributed to replenishment, during exposure, of a subpopulation of cells which are hypersensitive to bystander signals. In this approach, bystander effects and the inverse dose-rate effect are manifestations of the same basic phenomenon. The model was fitted to dose- and dose-rate dependent radon-exposed miner data; the results suggest that one directly-hit target cell can send bystander signals to about 50 neighboring cells and that, in the case of domestic radon exposures, the risk could be dominated by bystander effects. The analysis concludes that a naive linear extrapolation of radon miner data to low doses, without accounting for dose rate/bystander effects, would result in an underestimation of domestic radon risks by about a factor of ~4. However, recent domestic radon risk estimates (BEIR VI) have already applied a phenomenological correction factor of ~4 for inverse dose-rate effects, and have thus already implicitly taken into account corrections which we here suggest are due to bystander effects. Thus current domestic radon risk estimates are unlikely to be underestimates as a result of bystander effects.**

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Key words: NCRP; radiation risk; radon; health effects

INTRODUCTION

More than half of the background effective radiation dose is from domestic radon exposure (NCRP 1987). Direct epidemiological assessment of the risks from domestic radon exposure is, however, difficult, resulting in risk estimates with wide confidence intervals. Consequently, domestic radon risk estimates are currently based on extrapolation of data from miner studies, largely at considerably higher radon exposures and exposure rates.

Domestic radon exposure results in a very small proportion of potential target cells in the bronchial epithelium of a home resident being struck or traversed by an alpha particle over the course of, say, 30 d (NRC 1999), a characteristic turnover time of the bronchoepithelial target cells (Adamson 1985), whereas, for miners, the proportion is much higher. This fact is of potential relevance to the radon problem because there is convincing evidence, at least in vitro, that irradiated cells can send out signals that can result in damage to nearby unirradiated "bystander" cells (reviews by Mothersill and Seymour 2001; Goldberg and Lehnert 2002). The evidence is particularly strong for high-LET radiation and for a broad variety of endpoints (summarized, for example, by Sawant et al. 2001) including chromosomal damage and oncogenic transformation.

As we will discuss, both experimental and theoretical considerations suggest that the dose-effect relationship typical of a bystander response is downwardly curving, i.e., increasing rapidly as the dose increases from zero, and then reaching a near plateau (Fig. 1). Such a downwardly-curving dose-response relation for an acute exposure leads to the expectation that protracting the dose will increase the response (Rossi et al. 1982; Brenner and Sachs 2000), as illustrated in Fig. 1. This is known as an "inverse dose rate effect," and we give quantitative mechanistic arguments below suggesting that the epidemiologically-observed inverse dose-rate effect for radon exposure is actually a manifestation of the bystander phenomenon.

Downwardly curving dose response effects have another important consequence. As illustrated in Fig. 2, a naive extrapolation from a higher dose point back to the origin will clearly underestimate the risk at lower doses. This has led to speculation that, because of the bystander

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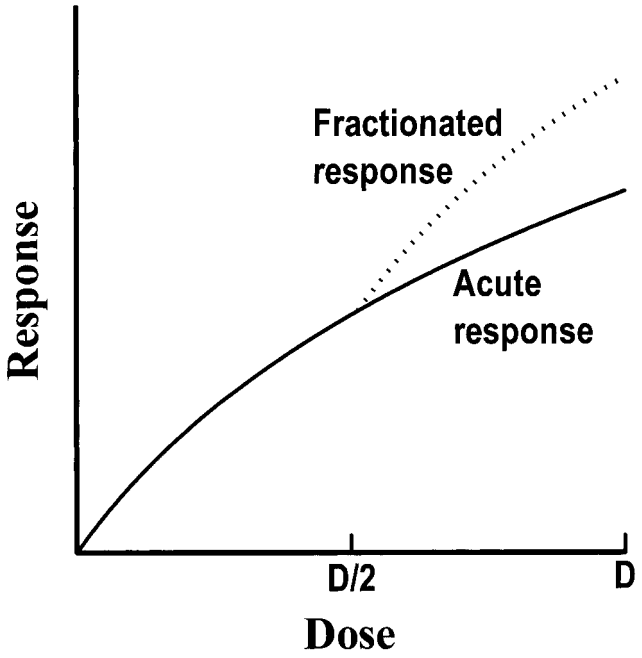

Fig. 1. Potential influence of the shape of an acute, downwardly-curving dose-response curve on the effect of protracting the dose, here by dividing the dose into two fractions (Rossi et al. 1982; Brenner and Sachs 2000). The dotted curve, for the second of two fractions, results from rigidly displacing the initial part of the solid curve; it illustrates how downwardly-curving acute dose-response relations can yield "inverse" dose-rate effects (increasing risk with increasing protraction).

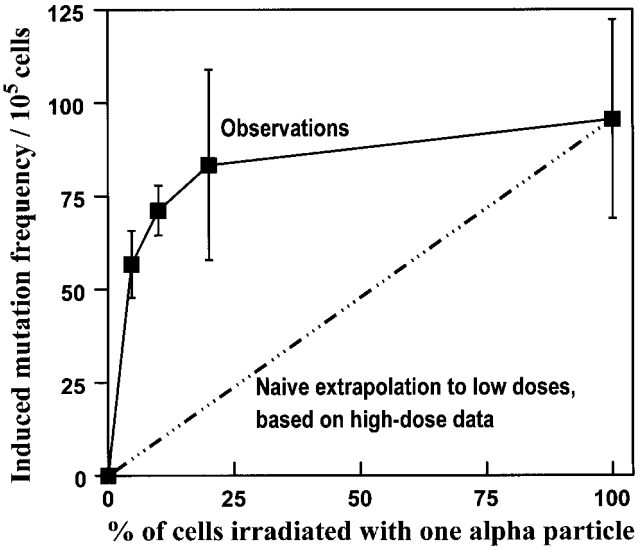

Fig. 2. Naive extrapolation to low doses, based on high-dose data, when the acute dose-response relation is downwardly curving (based on Zhou et al. 2001). The possibility of underestimating the low-dose risk is clearly present. For domestic radon exposure, however, the risks are unlikely to have been underestimated, as discussed in the text (and see Fig. 4).

effect, domestic radon risks (which are indeed extrapolated from higher doses, i.e., from uranium miner data), may be greater than currently estimated (Zhou et al. 2001; Goldberg and Lehnert 2002; Hall 2003). We shall argue that this is unlikely to be the case, primarily because (1) bystander effects are probably associated with inverse dose-rate effects and (2) inverse dose-rate effects are already phenomenologically taken into account in current radon risk estimates.

MATERIALS AND METHODS

A model of the bystander effect for acute exposure

A model has previously been suggested (Brenner et al. 2001) for acute exposure to high-LET particles, incorporating both bystander effects and the more classical "direct effects." It has come to be known as the $\mathcal{B}a\mathcal{D}$ (bystander and direct effects) model. The basic picture proposed was that

1. bystander signaling is an "all or nothing" phenomenon, in which a signal is sent out by cells whose nuclei are directly hit, but at high-LET more hits to a cell nucleus do not lead to an increased bystander response in its neighbors;
2. at any given time, the target cells population contains a subpopulation of cells which are hypersensitive in their response to the bystander signal; and
3. cells from this hypersensitive subpopulation are also very sensitive to direct radiation damage, such that an alpha-particle traversal of the nucleus generally results in cell death.

Predictions based on this approach were consistent with data from in vitro experiments designed to probe the bystander effect (Miller et al. 1999; Belyakov et al. 2001; Sawant et al. 2001). The model predicts dose-response curves for acute high-LET irradiation that rise rapidly (due to bystander effects) to a plateau at low doses and then show a further increase (due to "direct" effects) at higher doses. At low doses, then, the curve is downwardly curving (Fig. 1), a pattern apparent for lung-cancer incidence in animals acutely exposed to radon (Cross 1992; Gilbert et al. 1996; Monchaux et al. 1999). This downward curvature for acute exposure is of potential significance for dose-rate effects, as discussed above (and see Fig. 1).

Extension of the bystander model to include protracted exposure

The $\mathcal{B}a\mathcal{D}$ bystander model described above has been extended to high-LET exposure at lower dose rates (Brenner and Sachs 2002). We provide some validation of this extended model by comparing it with the data provided by Lubin et al. (1995) for lung-cancer mortality

in radon-exposed miners with data stratified both by exposure and by exposure time. Finally, we use this extended model to draw some conclusions regarding the basis for the complex interplay of dose and dose rate (Brenner 1994) in extrapolating radon risks from mines to homes, providing a mechanistic rationale for the phenomenologically-based dose-rate corrections adopted in the BEIR VI report (NRC 1999).

The extension to the $\mathcal{BaD}$ model focuses on how the number of bystander-signal-sensitive hypersensitive cells changes as a function of time during irradiation. It is assumed that, in the absence of irradiation, the number of hypersensitive cells is kept at a dynamic equilibrium value by a balance between cell production and cell loss. Production (e.g., from suitable progenitor cells, and/or by cells changing phenotype from normal to hypersensitive) is taken to be at a constant rate; endogenous losses (e.g., by cell death or by phenotypic change from hypersensitive to normal) are taken to occur at a rate proportional to the number of hypersensitive cells present at that time.

Two effects will tend to deplete the hypersensitive subpopulation during irradiation: killing and activation. As discussed above, an alpha particle traversal of a hypersensitive cell nucleus is expected to result in cell death. In addition, a hypersensitive cell may be activated through a bystander signal, i.e., the signal causes an increase in the probability that one of the cell's progeny will lead to cancer.

Implementing these observations quantitatively gives a model with four adjustable parameters, all with clear biophysical interpretations (Brenner and Sachs 2002).

RESULTS

The extended $\mathcal{BaD}$ model described above has been fitted (Brenner and Sachs 2002) to the data reported by Lubin et al. (1995) for lung-cancer mortality in multiple cohorts of radon-exposed miners, stratified by cumulative exposure and by duration of exposure, and adjusted for attained age, cohort, and other concomitant factors. The results are given in Fig. 3 and show reasonable agreement with the patterns present in the miner data—very little dose-rate effect at low doses, with an increasing inverse dose-rate effect as the dose increases.

Among the four $\mathcal{BaD}$ model parameters, the number of cells that can be affected in vivo by a bystander signal from a single cell was estimated from these data to be

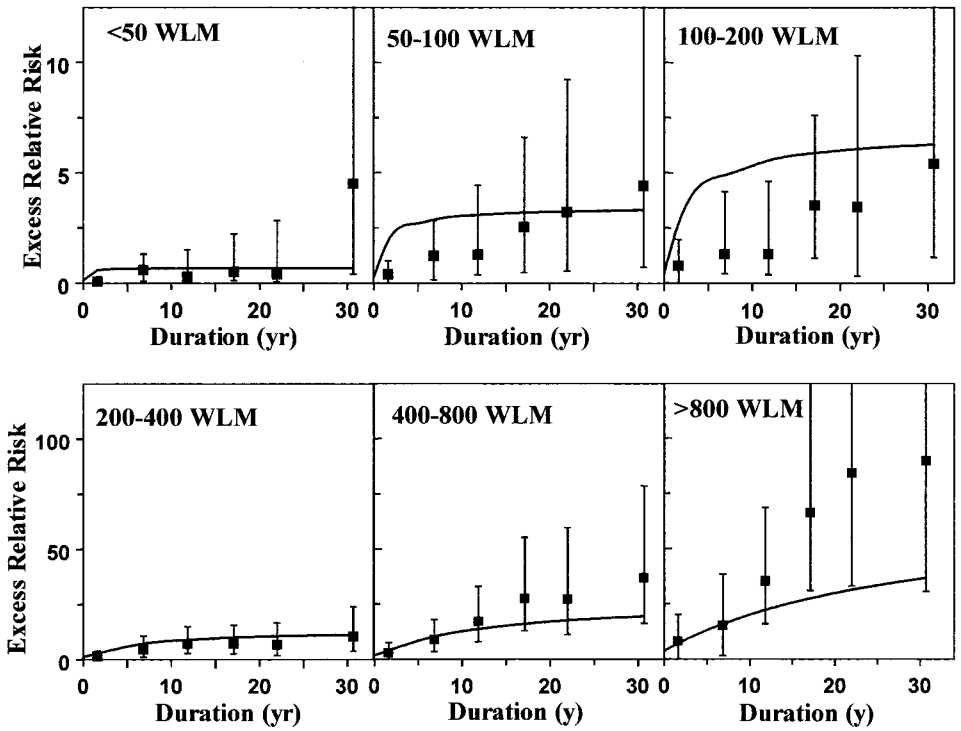

Fig. 3. Curves show extended $\mathcal{BaD}$ model fits (Brenner and Sachs 2002) to the data reported by Lubin et al. (1995) for lung-cancer mortality in eleven cohorts of radon-exposed miners, stratified both by duration of exposure and by cumulative exposure (in WLM). Data were adjusted for attained age, cohort, and other concomitant factors. Note the different vertical scales in the lower and upper panels. Both the data and the model show little dose rate (i.e., duration) effect at low WLM (cumulative exposure), but a significant inverse dose-rate effect at high WLM.

about 50; the replacement rate constant for hypersensitive cells was estimated to be about 2 per 30 d, comparable with the estimated 30 d turnover time for the target cells (Adamson 1985). However, these parameter estimates must be treated with caution, as the uncertainties are large.

Based on the estimated parameter values, the extended $\mathcal{B}a\mathcal{D}$ model was used to estimate risks from prolonged (60 y) low doses. The results are shown in Fig. 4. For the comparatively short miner exposures (solid curve; for illustrative purposes, we use a duration of 6 y, the average time of miner exposure in the data), the dose-response relation is linear at comparatively high doses (where the direct effect dominates). It can be seen, however, that at intermediate doses, where the bystander response starts to become important, the 6-y exposure (solid) curve becomes non linear. At these intermediate doses the risks from a 60-y exposure (dotted line) are larger than those for a 6-y exposure (solid line)—the inverse dose-rate effect. At still lower doses, dose rate effects become small so that, according to the model, the 6-y exposure and the 60-y exposure produce the same risk.

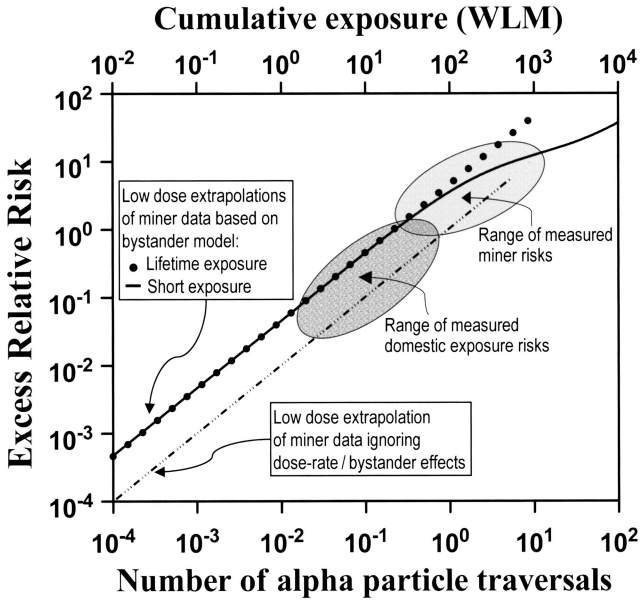

Fig. 4. Radon risk extrapolations to low doses and dose rates predicted by the extended $\mathcal{B}a\mathcal{D}$ model (Brenner and Sachs 2002), with parameters estimated from miner data fits (Fig. 3); In this log-log plot, any linear (no threshold) response appears as a straight line at 45°, with the response per unit dose specified by the height in the log-log plot (*not* by the slope). **Solid curve:** Excess relative risk computed with the parameters fixed by miner data (see Fig. 3) and assuming an exposure period of 6 y, typical for the miner data. **Dotted line:** Corresponding prediction for a 60-y exposure. Note the inverse dose-rate effect at high doses, relative to the 6-y exposure; at low doses there is no dose rate effect. **Dot-dashed line:** Linear (no threshold) extrapolation of miner data to low doses (Lubin et al. 1994) in which doses-rate effects are not accounted for (see Fig. 2). The results of this "naive" extrapolation are lower, by about a factor of ~4, than the low-dose risk extrapolation in which the bystander effect/inverse dose rate effect have been accounted for (dotted line).

Fig. 5 shows the proportion of the overall risk which, using our estimated parameters, can be attributed to bystander effects rather than direct effects. At low doses, bystander-induced damage dominates the risk. With increasing dose, the proportion of the risk due to bystander effects decreases, though more slowly for long compared with short exposure times, as long exposures allow for replenishment of cells which are hypersensitive to bystander signals. At very low doses, the fraction of the overall risk which is attributable to bystander effects becomes independent of dose and dose rate.

What would be the effect of the naive linear extrapolation from the miner data discussed above (and see Fig. 2)? Fig. 4 also shows a linear extrapolation of the miner data (Lubin et al. 1994) in which the effects of dose rate are ignored. It can be seen that ignoring dose-rate effects and simply using a linear extrapolation from the miner to the domestic situation would result (using our estimated parameters) in an underestimation of the low-dose radon risk by about a factor of 4.5. This underestimation is comparable to the corresponding empirically-estimated dose-rate correction factor in the BEIR VI report (NRC 1999) of ~3.7.

DISCUSSION

Alpha particles from radon-progeny exposure can result in bystander effects, where irradiated cells emit

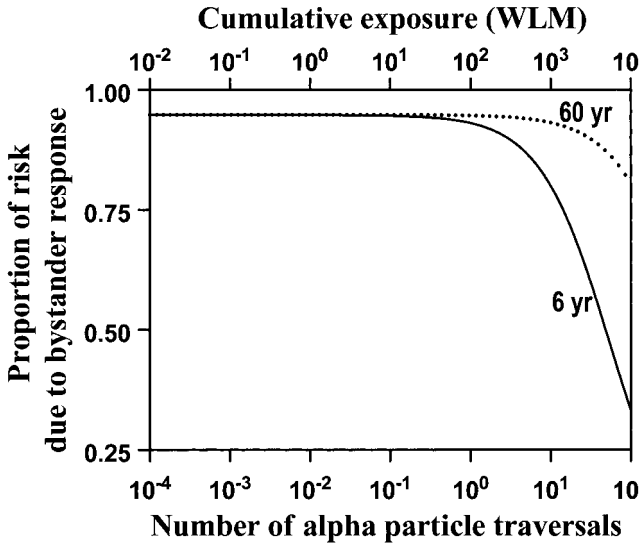

Fig. 5. Estimated proportion of the total radon risk which can be related to bystander effects. Results estimated using the same (best fit) extended $\mathcal{B}a\mathcal{D}$ model parameters as in Figs. 3–4.

signals resulting in damage to nearby unirradiated bystander cells. This can result in nonlinear dose-response relations and inverse dose-rate effects. Domestic radon risk estimates are currently extrapolated from miner data, which are at both higher doses and higher dose rates, so bystander effects on non-hit cells could play a large role the extrapolation of risks from mines to homes.

The $\mathcal{B}a\mathcal{D}$ model that we have discussed considers radiation response as a superposition of bystander and linear direct effects. Bystander effects are attributed to a small subpopulation of hypersensitive cells with the bystander contribution dominating the direct contribution at very low acute doses but saturating as the dose increases. Inverse dose-rate effects are attributed to replenishment of the hypersensitive subpopulation during prolonged irradiation. The implication here is that high-LET inverse dose-rate effects are manifestations of the bystander phenomenon.

The analysis concludes that a naive linear extrapolation of radon miner data to low doses, without accounting for dose-rate/bystander effects, would result in an underestimation of domestic radon risks by about a factor of ~4. However, the BEIR VI approach to extrapolation from miner to domestic risks (NRC 1999) uses an empirical exposure-time correction factor to take into account inverse dose-rate effects, which is also ~4. The model presented here thus provides a potential mechanistic underpinning for the empirical exposure-time correction factors applied in BEIR VI. It also implies that no further adjustment in low-dose risks for bystander effects is needed beyond that which has already been made to account for inverse dose-rate effects.

In conclusion, these results suggest that, at low radon exposures, the domestic radon risks could be dominated by bystander effects, but this analysis suggests that the domestic radon risk estimates in BEIR VI (NRC 1999) are unlikely to be underestimates.

It is emphasized that we have not definitively proven the relevance of bystander phenomena to low-dose radon risks; we have, however, described a mechanistic model which has few parameters (making the model highly testable) and which is consistent with a considerable body of epidemiological and laboratory data. Bystander effects represent a plausible quantitative and mechanistic explanation of inverse dose-rate effects by high-LET radiation.

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