RADON-INDUCED LUNG CANCER RISK AT ENVIRONMENTAL DOSE LEVELS

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ABSTRACT

A non-linear lung cancer risk model has been developed, in which both the functional form of the dose-response relationship and its parameter values arise from radio- biological observations at the cellular and organ level. Depending on the effectiveness of ionizing radiation as either promoter and/or initiator, different dose-effect curves will be obtained in the low dose region, which are generally lower than the linear risk estimate.

INTRODUCTION

Because of the inevitable interaction of confounding factors, any estimate of lung cancer risk at low, environmental exposures to radon progeny must be based on some form of extrapolation from high radon levels. Current radiation protection regulations are based on the philosophy that the excess risk is linearly related to the cumulative exposure. Here, we contrast the linear hypothesis with theoretical predictions based on a non-linear cancer risk model. This model is based on radiobiological mechanisms at the cellular level. The intent is to provide a coherent understanding of in-vitro cellular transformation and in-vivo organ carcinogenesis. Such an approach requires a set of assumptions concerning cellular radiation effects of alpha particles relevant to radiation carcinogenesis. Predictions of the relative lung cancer risk are compared with epidemiological findings in U.S. uranium miners (1).

CELLULAR RADIATION EFFECTS

In line with radiobiological observations, our predictive model of lung cancer induction is based on three properties of radiation: (i) transformation of cells, (ii) inactivation of cells, and (iii) stimulated cellular division in a stem cell population. This model has been used to estimate the carcinogenic risk of beta-emitting hot particles in lung tissue (2). Here, an additional assumption has been incorporated, namely (iv) the need of a cell to be released from contact inhibition in order to express its full potential as a transformed cell (3).

In the present lung cancer induction model we assume five states in the development of a cell from the initial unirradiated

level (state 1) to a fully transformed one (state 5) (3). The intermediate steps are: production of a specific DNA damage (state 1 to 2), production of a less specific DNA damage (state 2 to 3), cellular division (state 3 to 4) and release from contact inhibition (state 4 to 5). Competing with these mechanisms at each transition is radiation-induced cell death. Lung cancer risk is then assumed to be proportional to the number of transformed cells.

According to the common terminology of "initiation" and "promotion" in carcinogenesis, movement from state 1 to 3 may be identified as the initiating event and the two subsequent transitions as promotion events. Radiation, like all carcinogens, has properties of both initiation and promotion.

LUNG CANCER RISK PREDICTIONS

Cumulative doses for a given exposure category are calculated assuming a median length of exposure of 4 years in all exposure categories (1) and a dose-exposure conversion factor of 3.9 mGy WLM^{-1}. Multiplication of the risk for a sensitive cell in bronchial epithelium, receiving a given cumulative dose, by the number of cells in a given generation (4) and summation over all bronchial generations (5) yields the carcinogenic risk for a defined exposure category.

First we assume that radiation acts both as initiator and promoter (IP-model). The in-vitro tranformation frequency per viable cell for alpha particle irradiation (6,7) already represents the total probability of reaching the final stage of uninhibited growth, comprising all initiation and promotion steps. Two modifications have been made to obtain the transformation probability per exposed cell and to simulate in-vivo tranformation under conditions of cellular replacement.

The relative lung cancer risk for the IP-model as a function of cumulative exposure is plotted in Fig. 1 together with the epidemiological data of Hornung and Meinhardt (1). Given the large statistical uncertainty of the epidemiological information, there is excellent agreement between predicted and observed lung cancer risks over the entire range of cumulative exposures. At low doses, our non-linear model predicts a slightly lower risk as has been observed in the epidemiological study. It should be noted, however, that such a sublinear shape with a rising slope is consistent with the lung cancer data reported by Samet et al. (8).

If we assume that cells have already been initiated by co-carcinogenic factors, such as cigarette smoke, then radiation can promote these initiated cells by stimulating cellular division and stopping contact inhibition (P-model). At the same time, however, it can also kill the cells. Lung cancer risk in the P-model is very similar to the predictions with the IP-model displayed in Fig. 1.

Based on the histopathological observations of smoke- induced hyperplasia of bronchial cells, we assume that the primary promotional role of cigarette smoke is through stimulation of cellular division (CSP-model). An increase in the efficiency of cigarette smoke promotion relative to that of radiological promotion produces a higher risk at low doses and a smaller risk at high doses when compared to pure radiological promotion. Thus the additional promotional effect of cigarette smoke yields an approximately linear dose-effect curve at low doses.

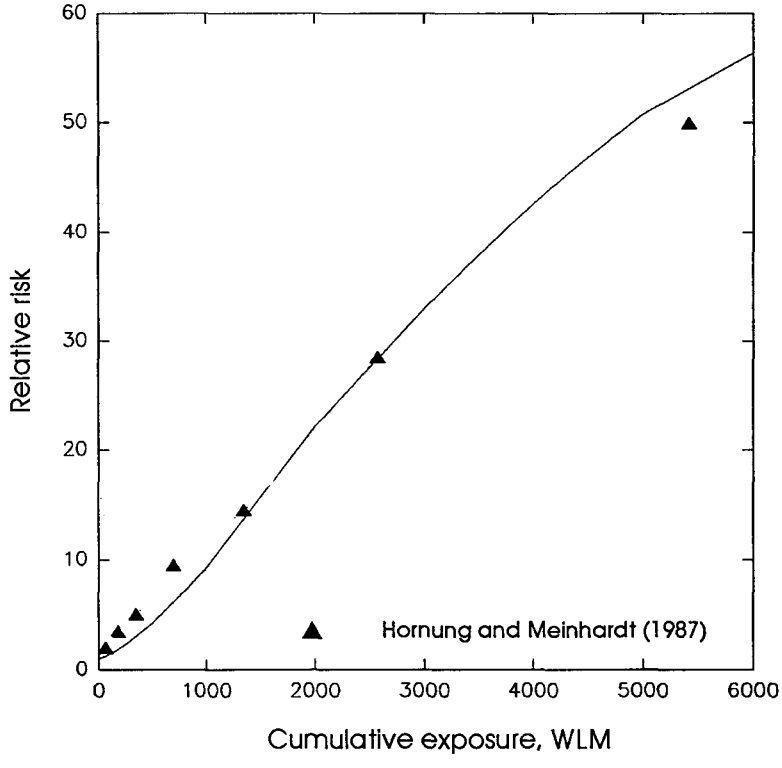

Fig. 1 Predictions of the relative lung cancer risk (radiation acts both as initiator and promoter) as a function of cumulative radon progeny exposure and comparison with epidemiological data.

CONCLUSIONS

If radiation is assumed to act as initiator and promoter (IP-model) or only as promotor (P-model), then the predicted lung cancer risk in the low dose regime is smaller than that based on the linear hypothesis. If radiation is effective primarily as an initiator (with cigarette smoke being the main promoter), then the

predicted incidence at low doses approaches the linear estimate.

While these models use mean doses, explicit incorporation of variability in cellular doses modifies the above risk predictions. Assuming lognormal cellular dose distributions, a larger variability increases the risk at high doses, but reduces the incidence at low doses (9). On the other hand, if enhanced deposition and reduced mucociliary clearance at bronchial bifurcations is factored into our risk analysis, then lung cancer risk is increased at low exposures relative to the current assumption of a uniform airway dose distribution used in the above models (10).

Considering the uncertainties of each modeling approach, a realistic combination of all factors discussed above suggests that the linear hypothesis represents a realistic upper boundary in the low doses region, thus being a viable compromise for radiation protection purposes.

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