

The Role of Promotion in Carcinogenesis from Protracted High-LET Exposure

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Abstract

Recent analysis of epidemiological studies using the two-stage clonal expansion (TSCE) model has shown that radiation-induced promotion dominates radiation-induced initiation for protracted exposures to radon. This strong promotion effect (i.e. enhanced proliferation of already-initiated cells) causes a pronounced 'inverse dose-rate effect', but by a mechanism completely different from those usually discussed in this connection. This rather startling result is discussed along with implications to extended space missions that include a significant amount of high-LET radiation. It is suggested that the effect might be caused by a 'Bystander Effect' by which normal cells in the vicinity of initiated cells are hit by alpha particles and send out signals that modify the cell kinetics of the already-initiated clones.

KEYWORDS: Models of carcinogenesis, protracted exposure, high-LET, lung cancer risk.

1. Introduction

The two stage clonal expansion (TSCE) model has been used with some success to study trends in cancer mortality in several epidemiological data sets, for example, lung cancer mortality in Colorado Plateau miners, [1, 2] and radon-inhaling rats [3, 4], as well as for various cancers in other selected populations, such as the Japanese A-bomb survivors [5]. The conclusions of the studies involving radon inhalation are striking in that radiation-induced promotion appears to dominate radiation-induced initiation for the risk of protracted exposures of high-LET (alpha-particle) radiation. The model predicts that radiation-induced initiation is important only for short duration exposures (less than a day) and that the emergence of this importance at a given protraction interval depends on the exposure rate. The model predicts an 'inverse dose-rate effect' for the risk from protracted exposures that arises from an entirely different mechanism than has been measured in cellular studies and subsequently has been assumed to apply to the risk [6]. Thus, we refer to this effect as a *protraction effect* to distinguish it from effects due to other mechanisms, such as cellular repair/recovery and (perhaps) a 'sensitive stage in the cell cycle'. Although this protraction effect is dominant for high-LET radiation, it is not known how important a role it plays in low-LET radiation exposure. Presumably it is considerably less important, since many cellular and animal studies have shown that protraction of low-LET radiation decreases, not increases, tumor risk, (see e.g. [7]).

2. The Two Stage Clonal Expansion Model

The main hypotheses of the model are:

i) Two (or more) events must occur within a cell to produce a malignant cell. The events, presumably

mutational in nature, may be caused either spontaneously or by specific carcinogenic agents.

ii) At some point between the first and last event, a cell emerges that has altered net cell proliferation kinetics: the net average rate of growth of this population of cells is greater than that of the surrounding cells. The clone of these intermediate (or initiated) cells thus generated has a proliferative advantage over other cells in the tissue. The process of enhancing the growth of such clones is called *promotion*. The cell kinetic parameters of this population have been altered from those of the normal cell population.

iii) An initiated cell can sustain further spontaneous or induced genomic events that may lead to the appearance of a malignant cell, and ultimately to a malignant tumor.

Further details of this model can be found in [8] and [9]. A pictorial representation of the model is shown in Figure 1. In the following, we discuss the results of an analysis of an updated subset of Colorado

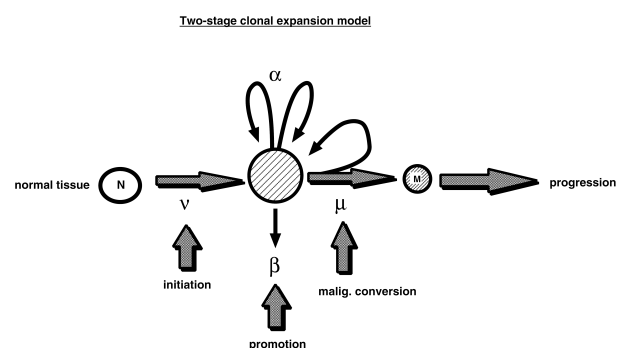


Fig. 1 – A pictorial representation of the Two Stage Clonal Expansion Model.

Plateau miners. The endpoint was lung cancer mortality. A maximum likelihood method was employed to obtain estimates for values of the model parameters that best fit the pattern of lung cancer induction in the miner population. The details of the analysis have recently been published [2].

3. Results

The best fits for the values of the parameters indicate that the risk, defined as the lifetime excess absolute risk of lung cancer mortality at age 70, shows a distinct increase for constant total exposure as the protraction interval (centered at a given attained age) increases, i.e. an ‘inverse dose-rate effect’ in conventional terms. In addition, whether there is a ‘direct’ or ‘inverse’ effect depends on the relative start times of the protraction intervals. Figure 2 shows that there is a conventional ‘direct dose-rate effect’ if exposures of 5 years and 20 years both start at age 42, and there is an ‘inverse dose-rate effect’ if they both end at age 42. This is a direct consequence of the domination of the

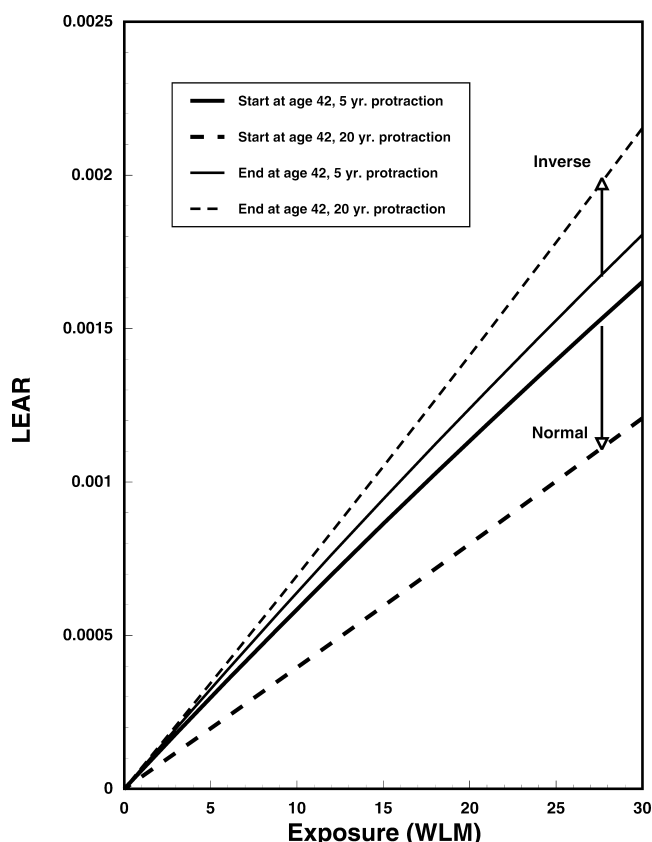


Fig. 2 – Lifetime excess absolute risk (at age 70) as a function of exposure in WLM plotted for two protraction schemes (5 years and 20 years) starting at age 42 and for the same schemes (5 years and 20 years) ending at age 42. The schemes starting at age 42 show a ‘direct dose-rate effect’ and the schemes ending at age 42 show an ‘inverse dose-rate effect’.

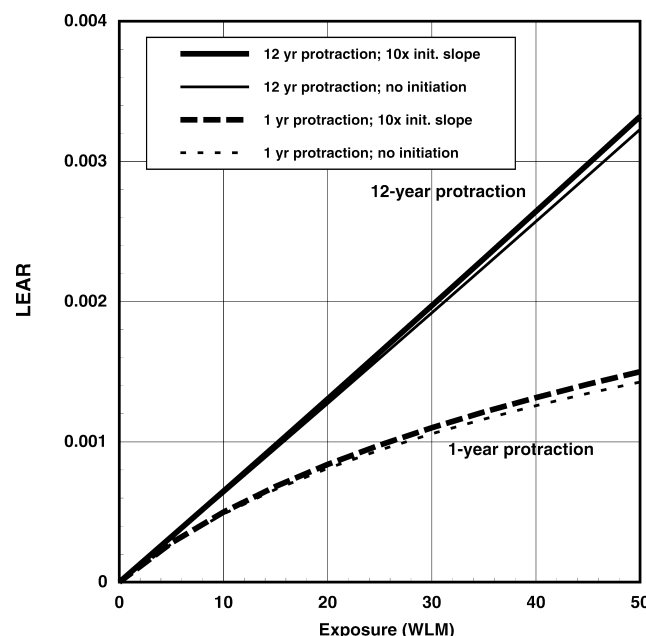


Fig. 3 – Lifetime excess absolute risk (at age 70) as a function of exposure in WLM plotted for one-year (dashed lines) and twelve-year (solid lines) protraction intervals. The thicker lines result from setting the radiation-initiation rate to 10 times the rate determined by the maximum likelihood method. The thinner lines result from setting the radiation-initiation rate to zero. Each exposure is centered on age 42.

promotion process, that is, a change in net cell proliferation rate of the intermediate cells. Since promotion (net rate of cell proliferation) occurs in an exponential term, and is integrated over the protraction interval, the length of the interval plays a strong role in determining the risk. Thus we call this effect a *protraction effect* to distinguish it clearly from other cellular processes which might also vary with dose-rate.

The large effect of promotion leads to the rather startling conclusion that radiation-induced initiation is negligible for such protracted exposures of high-LET radiation. This is shown in Figure 3. Here risk of lung cancer mortality at age 70 is plotted vs. total exposure for two protraction intervals (1 year and 12 years) centered at age 42, each showing two curves, one assuming *no* radiation-induced initiation and the other assuming *10 times* the radiation-induced initiation indicated by the maximum likelihood estimator. We note that there is very little difference between the two curves for either protraction interval, indicating that radiation-induced initiation plays a very small roll in the carcinogenic process for such long protraction intervals.

Finally in Figure 4, we show the lifetime excess absolute risk at age 70 as a function of protraction interval down to very short intervals (i.e. around 5 minutes) for two exposure levels, 2 and 200 WLM, which correspond to about 1 cGy and 1 Gy, respectively. The contribution to the risk from the promotion process alone is also indicated. We note that radiation-induced promotion dominates at long pro-

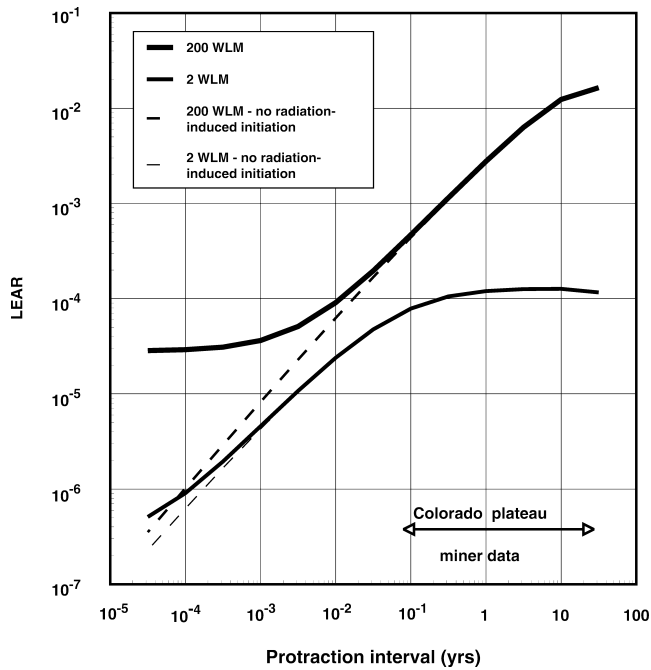


Fig. 4 – Lifetime excess absolute risk (at age 70) as a function of protraction interval for exposures of 2 and 200 WLM corresponding to doses of roughly 1 cGy and 1 Gy, respectively. In each case, the exposure was centered at 42 years of age. The dashed lines indicate the contribution of the promotion term for each exposure.

traction intervals for both exposure levels, and radiation-induced initiation becomes important only at very short intervals. Also the time intervals where it becomes important depends on the exposure level, with radiation-induced initiation becoming important at shorter intervals for the smaller exposure as the interval decreases.

4. Implications for Radiation Hazards in Space

The above analysis was done, of course, for a high LET radiation (alpha particles from radon and radon daughter decay). The quality (i.e. LET distribution) of the radiation experienced in space flight is extremely variable, from very low LETs produced by the high energy proton component up to very high LETs from the (secondary) neutron and the HZE components. Even if promotion dominates in protracted high-LET radiation, it may not dominate for low-LET radiation. Certainly the protraction effect ('inverse dose-rate effect') appears to be absent in animal studies of low-LET radiation carcinogenesis (see e.g. [7]). In any case, repair of damage or some other mechanism must become increasingly important at low LET in order to counteract any promotional pressure on the tissue due to the protraction process. It is up to further experimental research to determine the LET-dependence of this phenomenon and its importance at low LET.

One important implication that emerges is that, at

least for high-LET radiation, radiation-induced initiation (usually thought to be one or more mutations caused in the irradiated cells) may be unimportant compared to *radiation-induced modification of the cell proliferation kinetics of already initiated cells*. Thus, RBEs for mutation decrease in their importance and RBEs for cell kinetic modification assume a more important roll. Such a change in emphasis might change our ideas about the LET dependence of quality and radiation weighting factors when applied to protracted exposures of mixed high and low LET radiations.

The mechanism for the strong promotional effect is not known, but we make a conjecture that it is due to a 'Bystander Effect': a process in which normal cells hit by high-LET particles send out signals to cells surrounding them, inducing increased proliferation. Initiated cells nearby respond by increasing their proliferation rate, but since they are less controlled than are normal cells by the homeostatic process, they show a proliferative advantage, which ultimately leads to an increased probability of a malignant cell emerging.

5. Conclusions

- i. Alpha-particle-modified promotion (cell proliferation of *already initiated* cells) dominates alpha-particle-modified initiation in the induction of lung tumors for protracted exposure using the two-stage clonal expansion model.
- ii. An apparent 'inverse dose-rate' effect of the lifetime excess cancer risk can arise naturally due to this dominance of promotion. We call this a *protraction effect* to distinguish it from other effects which may be due to entirely different mechanisms. It occurs only for long protraction intervals and its magnitude depends on such details as the total exposure and when the exposure begins. The mechanism for this protraction effect is quite distinct from the mechanisms which have previously been postulated to underlie the 'dose-rate effect', cellular repair/recovery during the protraction interval.
- iii. This dominance of the promotion process results in a very weak dependence of the risk on radiation-induced initiation for protracted exposure. One suggestion for the strong promotion in already-initiated cells and/or clones is that signals are sent out by surrounding normal cells that are damaged by alpha-particle traversals, thus modifying the proliferation characteristics of unirradiated initiated cells. This could play an important role in the process of carcinogenesis from protracted exposure from high-LET radiation and modify our thinking about what quality and radiation weighting factors might be appropriate for high-LET radiation and mixtures of high and low LET radiation as found in the space radiation environment.

Acknowledgments

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