A Simple Reductionist Model for Cancer Risk in Atom Bomb Survivors

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Abstract

1) In data from the atom bomb survivors of Hiroshima and Nagasaki, the roughly linear-quadratic radiation dose responses for chromosome aberration and leukemia correspond closely to each other, as do the linear dose responses for gene mutation and solid cancer incidence.

2) In view of the increasing evidence for multiple oncogene and suppressor gene changes in human cancer, as well as the evidence that human cancer rate is often proportional to age to the power of 6 or so, it is postulated that the radiation has contributed one and only one oncogenic mutational event to the radiation induced cancers.

3) The radiation induced cancers should therefore display a cancer rate versus age relationship that has a power of n−1, where n is the power for the corresponding background cancers.

4) It is shown that this is precisely what is happening in the collective solid cancer incidence of the atom bomb survivors.

Text

In a paper presented in Tokyo, June 1994, I gave the first rough description of a new way of thinking about human radiation carcinogenesis based on epidemiological and biodosimetric information obtained from the atom bomb survivors (1). Now, a half−year later I offer a progress report on how this thinking is evolving.

The approach begins with the recent dose-response data for the incidence of leukemia and solid tumors as described respectively by Preston et al.(2) and Thompson et al.(3). The two dose responses are combined in Figure 1 by plotting each as relative risk versus dose. The leukemia response is steeply curvilinear, approximating a linear-quadratic relationship. In striking contrast, the dose response for solid tumors is strictly linear and an order of magnitude lower in slope. It is well known that the leukemias tend to occur early after radiation and principally before adulthood, while the solid tumors progressively increase over the lifetime of the survivors.

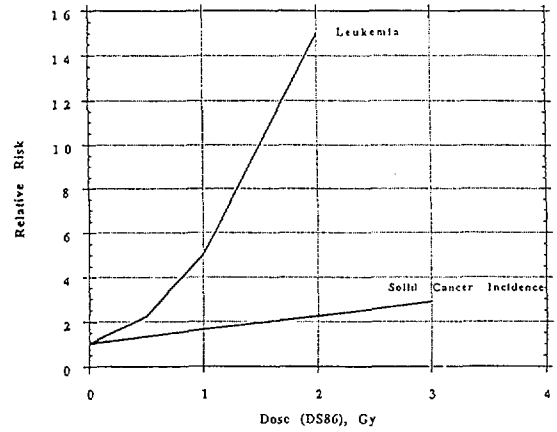

Fig. 1 Dose responses for the incidence of leukemia and solid cancer in atom bomb survivors. Solid cancer is all cancer except leukemia. The vertical axis is relative risk normalized to a background risk of 1. Note the dramatic difference in shape and magnitude for these two cancer endpoints.

Corresponding data have been accumulating at the Radiation Effects Research Foundation (RERF) for chromosome aberrations by Stram et al. (4) and gene mutations in somatic cells of the survivors by Akiyama et al. (5). The aberrations are balanced translocations in peripheral blood lymphocytes, and the gene mutations are of glycophorin A, a glycoprotein in the membrane of red blood cells. The two dose responses are shown in Figure 2, again in terms of relative risk versus dose. A similar contrast is observed in that chromosome aberrations are curvilinear and steeply rising, while the gene mutations are linear and much lower in slope. This dramatic difference strongly suggests that these two types of genetic damage operate through fundamentally different mechanisms. Thus, in spite of the large literature on radiation deletions as a cause of gene mutation, it is unlikely that these gene mutations are secondary to translocation-like two-hit aberrations.

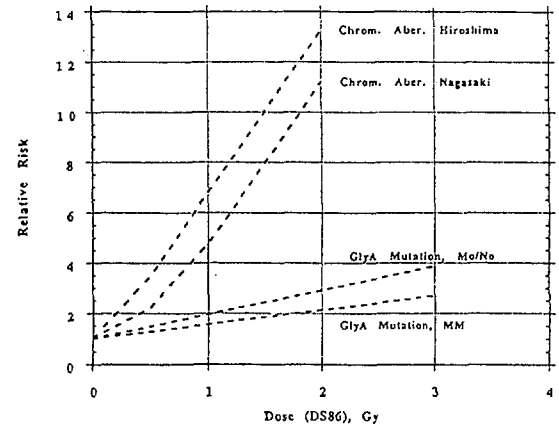

Fig. 2 Dose response for chromosome aberration and glycophorin A (GlyA) gene mutation. The vertical axis is relative risk; 1 is the background frequency for each endpoint. The aberrations are shown separately for Hiroshima and Nagasaki. Two related gene mutation responses are shown, one for gene inactivation (Mo/No), and one for reduction to homozygosity (MM). Note the dramatic difference in shape and magnitude for the chromosomal and gene-mutational biodosimeters.

Figure 3 combines these four data sets into a single plot, once more taking advantage of relative risk to put all of the responses on a similar scale. Surprisingly, the aberration response superimposes on the leukemia response, and the gene mutation response does the same for the solid cancer response. It was

in thinking about why this should happen that I chanced upon my simplified theory.

It is widely understood that chromosome aberration plays a pivotal role in human leukemia (6). In chronic myelogenous leukemia, we have known for 40 years that a specific translocation between chromosome 9 and 22 is involved in essentially every case. Similar, albeit less dramatic relationships exist for most other leukemias, making it reasonable to generalize that translocation is a central mechanism in the production of this group of diseases. Thus a correspondence between dose responses for leukemia and translocation should not be surprising, even though all of the kinetic details between these relationships have yet to be worked out.

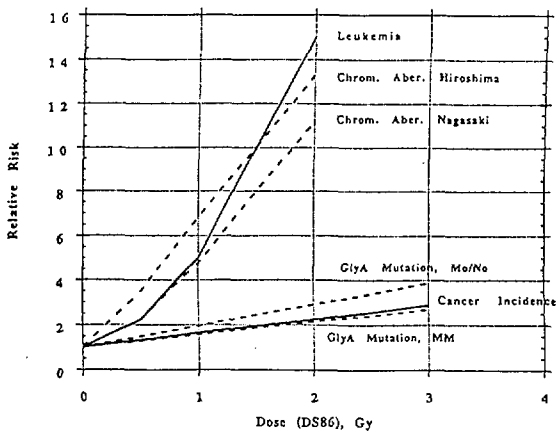

Fig. 3 Dose responses for cancer endpoints and biodosimetry. This figure combines the data in the two preceding figures, using relative risk on the ordinate to put all the responses in the same framework. Chromosome aberrations overlie the leukemia response, and gene mutations bracket the solid cancer response.

For the correspondence between solid cancer and the glycophorin A response, the parallel role for single－hit, kinetically linear, somatic gene mutation immediately comes to mind. However, the situation here is complicated by the rapidly increasing evidence that, as in the prototypic human colon cancer observed by Fearon and Vogelstein (7), solid cancers probably represent a series of seven or so independent gene changes in crucial oncogenes and suppressor genes. Such a 7－gene change would require responses involving the 7th power of dose. Thus for the dose response for a single gene mutation to overlie that for solid cancer, one must conjecture that exposures, such as those received by the atom bomb survivors, are affecting one and only one of such genes in the cascade toward a radiation－induced cancer. Further support for this argument in an acute radiation situation is the enormous unlikelihood of producing two mutations within the dozen or so candidate genes in a potential cancer cell. For example, given the mutation radiosensitivity of the glycophorin A gene, the probability of two such mutations in a single cell following a near lethal radiation dose is on the order of 10^{-10}. Even with chronic radiation, where mutations may be able to cumulate to higher levels than in acute exposures, the relative frequency of single versus multiple mutations is enormously in favor of the mutations being single.

At this point, the argument turns to the Armitage and Doll (8) model that relates cancer stages to the age distribution of cancer rates. Armitage and Doll were intrigued by reports that human cancer rates were often power functions of age. They confirmed this relationship for several human cancers, such as cancer of the stomach as shown in Figure 4. They reviewed the mathematics of such responses and their possible relationship to cancer staging, including mutation as one conceivable mechanism. With the proviso that each stage has roughly comparable sensitivity, they concluded that a power to the 6 relationship would involve a 7－stage process, i. e., having one more stage than the power. Of course

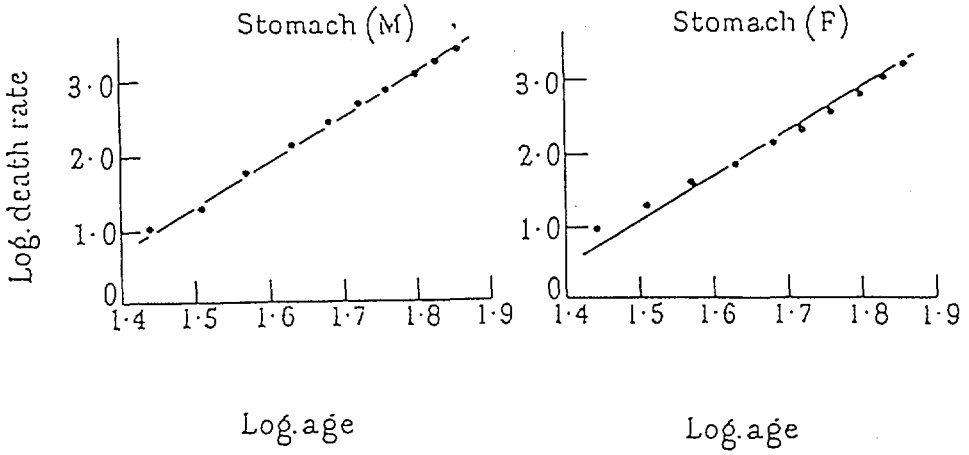

Fig. 4 Log death rate for stomach cancer versus log age, in males (M) and females (F), adapted from Armitage and Doll (8). The lines are drawn to have a slope of 6, indicating the reasonableness of fit of stomach cancer mortality to age to the 6th power.

they knew nothing of oncogene and suppressor gene changes in 1954. Viewing this situation today one must be struck by the coincidence of seven stages and the roughly comparable number of oncogene and suppressor gene changes that are now routinely found in almost every type of adult human cancer.

The final step in my June argument, then, is to contrast the difference between background and radiation-induced cancers by making the simplifying assumption that the background cancers require n independent somatic genetic events over the lifetime of the individual, while the radiation-induced cancers require only n-1 of such age-related events plus the single event caused by the radiation. To illustrate this concept further, Figure 5 shows the family of curves that describe cancer rate versus age for various powers of age ranging from 1 to 7. Figure 6 focuses on a cancer process which normally has 6 stages and follows age to the 5th power. After irradiation at age 60, there would be some probability based on a linear function of dose, that the single crucial radiation-induced mutational event had occur-

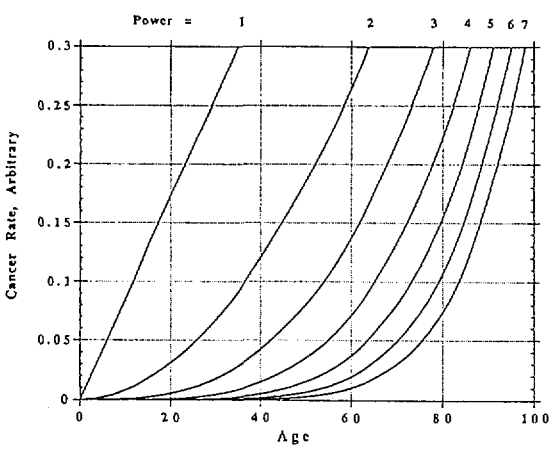

Fig. 5 Cancer rates at various powers of age, ranging in power from 1 to 7. The cancer rates are given an arbitrary scale. The number of stages implied by each of these curves is the power plus 1. The curve for power 6 would have the same shape as those shown logarithmically in Fig. 4.

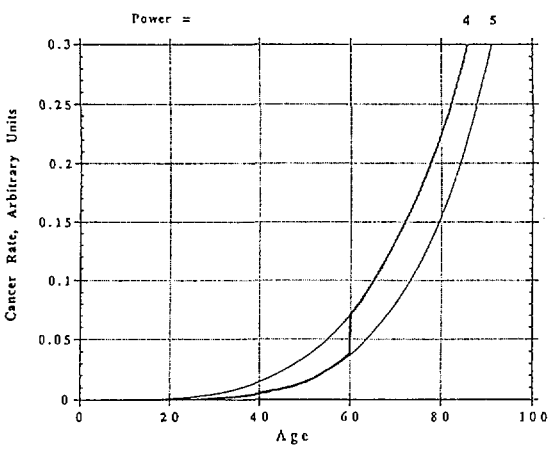

Fig. 6 Hypothetical effect of irradiation at age 60. The background response is power 5. Radiation reduces the age-based stages by 1, giving a response of power 4. The switch from power 5 to power 4 is driven by a linear function of dose, and ordinarily would have some latency of expression.

red. The occurrence of the event would shift the response down by one power of age, presumably with some latency which is not considered here. It then follows, based on the Armitage and Doll model, that radiation－induced cancers should show a slightly different age pattern than control cancers, i. e., should respond to an n－2 power function while the controls would be n－1.

In June, I had no evidence to support this conjecture about the age structure of radiation－induced versus background cancer. I only had the rough sense that such an effect would give relative induction dynamics not unlike what is actually seen with the survivors. I have since analyzed the age structure of cancer mortality and incidence in the atom－bomb survivors, with the help of D. Pierce and D. Preston of the Statistics Department of RERF. Since mortality and incidence give similar results, I will only show the incidence data here.

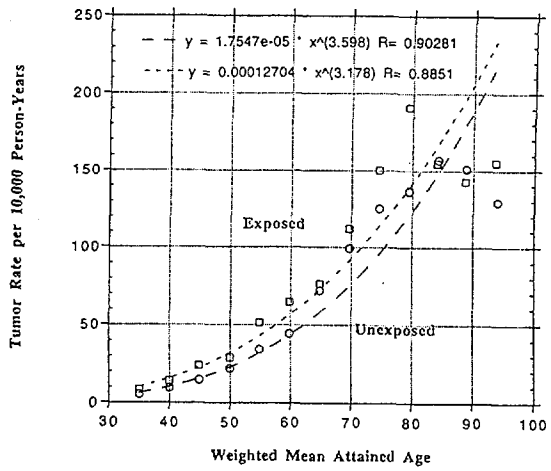

Fig. 7　Tumor rate versus attained age in unexposed and exposed atom bomb survivors. Shown are observed incidences of solid cancer for exposed and unexposed survivors, for tumors not involving sexual organs, and for ages truncated to 35. The two best－fitting power functions are shown as curved lines and equations. The unexposed survivors have a power of 3.598 and the exposed a power of 3.178. The exposed is a composite of background and induced solid cancer.

Figure 7 depicts the age response of cancer incidence rate for unexposed and exposed cases. Ages under 35 years have very few cases and were excluded from the analysis. I also eliminated the cancers

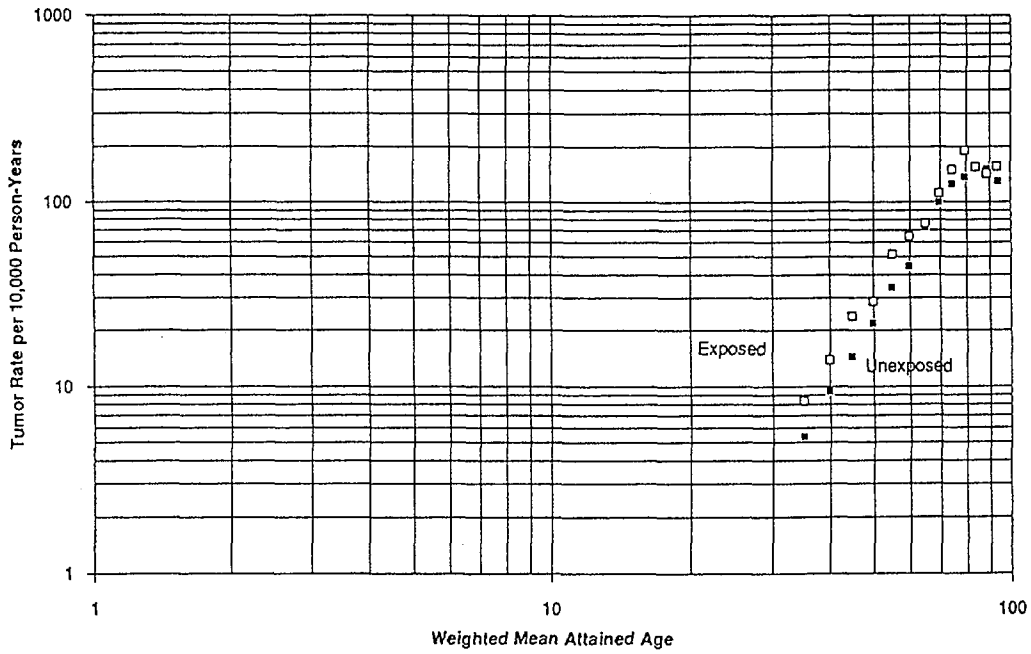

Fig. 8　Log tumor rate versus log attained age in unexposed and exposed atom bomb survivors. These are the same data as in Fig.7. The linearity of the data through most ages and the difference in slope for unexposed and exposed are well seen in this plot. The fall－off of tumor rate at the highest ages is commonly seen in such plots, and either represents a break－down in the model or ineffective diagnosis of tumor in the elderly.

of sexually related organs (breast, uterus, ovary, prostate and testis) from all solid cancers in order to equalize and then combine the results for males and females. Unexposed is defined as survivors in Nagasaki and Hiroshima who have Dosimetry System 86 doses from 0 to 0.01 Sv. The curving line fitted to the unexposed data points is a power function whose exponent is 3.598. The exposed survivors are those with doses between 0.1 and 4.0 Sv. The optimal power for the exposed group is 3.178. The same data are reshown in Figure 8 as log-log plots, to indicate directly the linearity and differences in slope of the responses. Slope in a log-log plot corresponds to power in a linear plot. Both the control and the exposed responses fit the general Armitage and Doll model, but differ in exponent, with the exposed having the lower value. That the difference in exponent is only 0.4 could be because the exposed group is expressing a mixture of radiation induced and background cancers.

The final stage of this analysis requires the full separation of the background and induced cancers. This is accomplished by using a multiple Poisson regression of survival data grouped by city, age, sex, dose and cancer information. D. Pierce has done this analysis for the incidence study, again omitting all sex-specific cancers and truncating the distribution to age 35. The AMFIT capability of the EPICURE package was used (9). Figure 9 shows the two resulting power-function-based age responses for the background rate and for the excess absolute rate (EAR) estimated for an exposure of 1 Sv. Both responses are consistent with the Armitage and Doll formulation. The exponents are 4.154 for background and 3.030 for the EAR response, a difference of 1.124, essentially in agreement with what is predicted by the n-1 formulation. Figure 10 shows the same data in log-log configuration.

The model clearly passes this one sensitive test of consistency regarding age structure of cancer risk.

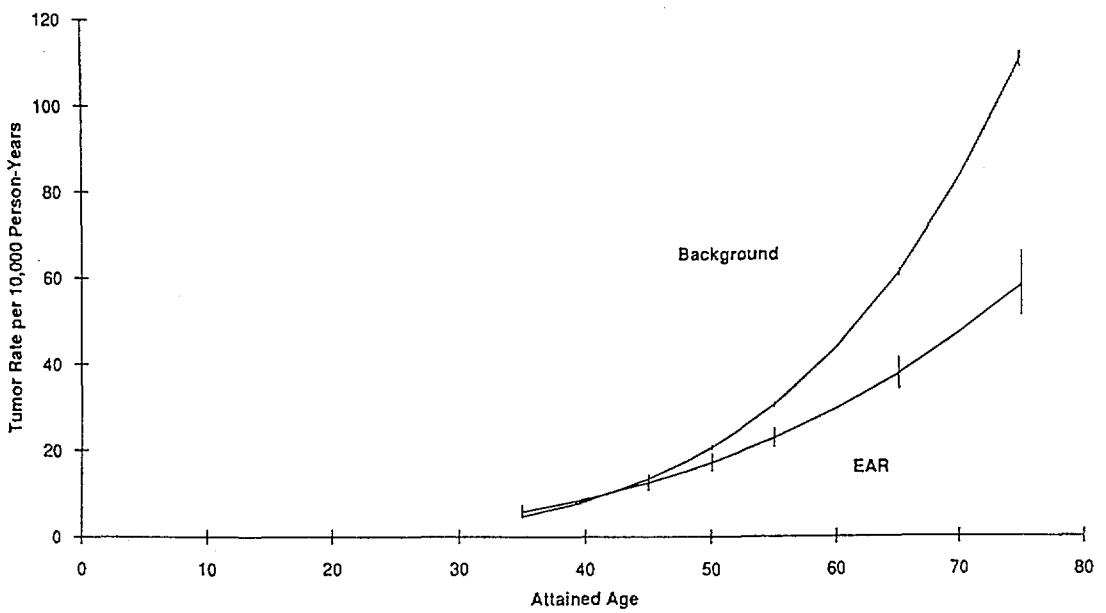

Fig. 9 Tumor rate versus attained age in background and excess absolute tumors of atom bomb survivors. These are the same data as in Fig. 7, but after calculation by AMFIT to extract the tumors induced by 1 Sv of radiation. The vertical bars represent standard error. The power of background is 4.154 and of the excess is 3.030, consistent with the prediction of the model.

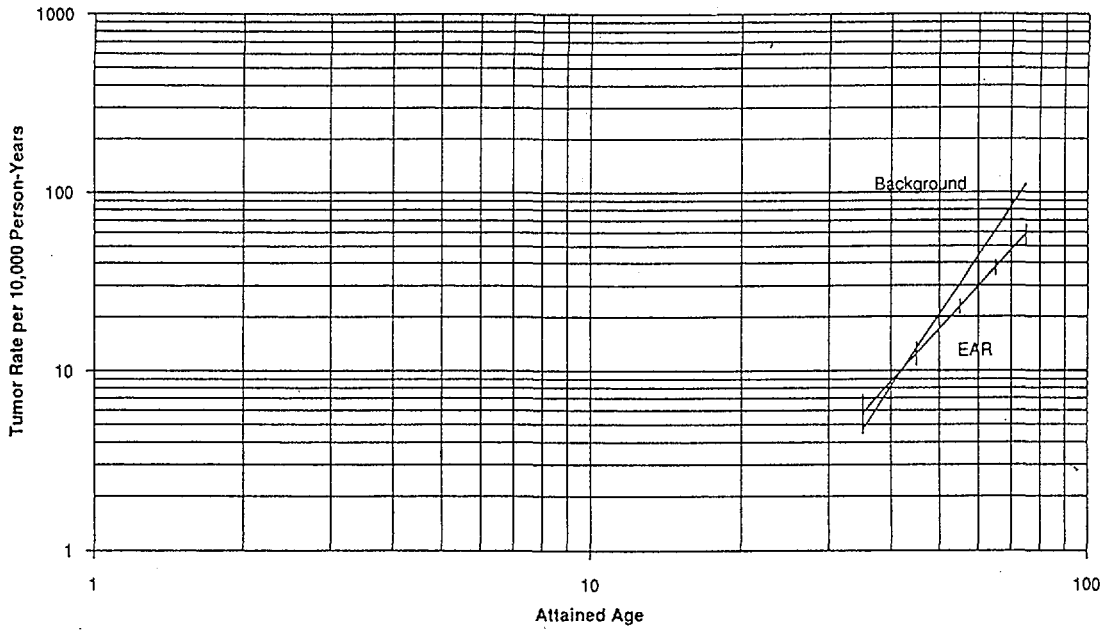

Fig. 10　Log tumor rate versus log attained age in background and excess absolute tumors of atom bomb survivors. These are the same data as Fig. 9. The standard errors are shown only for the excess. The linearity and differences of slope are readily seen in this log－log presentation.

It remains to be seen whether it agrees with other aspects of the cancer epidemiology and with the little that is known about human somatic mutation rates.

No doubt this is an overly simplified treatment of the highly complex process of human carcinogenesis. Essentially the model places all the complexity of human carcinogenesis in the background data. There it lumps the diversified effects of specific oncogenes, repair defects, initiation, promotion, progression, proliferation, time－varying properties, other carcinogens, sex, specific cancers, etc.. Its simplicity is in the argument that the radiation－induced cancers are mutational in origin, and are superimposed on the background mechanism in the form of one and only one somatic mutation in an oncogene or suppressor gene of the critical evolving cancer cell. It assumes that all solid cancers have similar multistage behavior, and that the stages are independent of order, representing gene mutations which have roughly identical sensitivity, rate over time, and hit number. The approach may not be compatible with the increasing evidence that the sequence of oncogenic gene changes is self－accelerating, unless the acceleration is neatly balanced by some other effect such as the progressive reduction in number of potential target－genes as the process progresses. Because of the likely linearity of somatic mutation, the model currently predicts linearity of low－dose carcinogenesis. How well this applies to low dose rate or fractionated exposure remains to be seen. It clearly fits the current non－thresholded appearance of the solid cancer incidence data at RERF. Conceivably, other patterns of exposure could modify the mutational dose－response, amd hence the model's prediction of carcinogenicity.

If this model succeeds as a reasonable approximation of human radiation carcinogenesis, one can then ask whether it will also apply to other species and other mutationally－based carcinogens? If so, this would provide the interesting option of being able to study carcinogenesis by studying mutagenesis. I would anticipate, however, that complications will arise. Regarding species, I suspect that we already

have a major discord in rodents because of their similar mutagenicity to humans and their dramatic difference in lifespan and time-course of carcinogenesis. Regarding other carcinogens, I suspect that chemical mutagens will be too influenced by host and organ factors such as metabolic activation and target-cell proliferation to follow the simple radiation model. Nevertheless, the enormous advantage of using mutagenesis as a surrogate for carcinogenesis might still be achievable provided one can sufficiently enrich the mutational input.

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