# Promoting Action of Radiation in the Atomic Bomb Survivor Cancer Incidence Data

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# LETTERS TO THE EDITOR

## Promoting Action of Radiation in the Atomic Bomb Survivor Cancer Incidence Data

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Heidenreich *et al.* have recently reported an analysis of the cancer incidence data for the atomic bomb survivors with mathematical models of carcinogenesis (*1*). The main result of the paper is, as expressed in the title, the suggestion of an evidence for a promoting radiation effect on carcinogenesis in several organs, i.e., of evidence for a radiation-induced growth of preneoplastic lesions. Such evidence was also found earlier for lung cancer incidence among the atomic bomb survivors (*2*). Heidenreich *et al.* (*1*) use the same assumed time $\Delta t$ for the promoting effect (1 week) as was used in ref. (*2*).

Consistent with earlier work (*3*), Heidenreich *et al.* hypothesize that the promotional effect of radiation might be due to a replacement of normal cells that were killed by radiation. An alternative possible explanation of the radiation exposure-related growth of preneoplastic lesions is a disturbance of the control of initiated cells by surrounding normal cells (*2, 4, 5*).

Heidenreich *et al.* (*1*) do not give any mechanistic explanation for using a logarithmic dose dependence of the promotion rate

$$\gamma(D) = \gamma_0 + \ln(1 + g_r D)/\Delta t. \quad (1)$$

In our earlier work on promotional effects in the lung cancer data of atomic bomb survivors (*2*), the promoting radiation effect was assumed to be proportional to the number of cells killed. Thus the radiation-related change in the division rate, $\alpha$, of initiated cells was modeled by

$$\Delta_r\alpha(D) = \alpha_r[1 - S(D)]/\Delta t, \quad (2)$$

where $S(D)$ is the survival curve of normal human lung epithelial cells (*6*). The resulting equation for the promotion rate was

$$\gamma(D) = \gamma_0 + (\alpha_r - 1)[1 - S(D)]/\Delta t. \quad (3)$$

For lung cancer among males, the optimized model parameters had the values $\gamma_0 = (0.16 \pm 0.12)$ year$^{-1}$ and $\alpha_r = 2.1 \pm 1.0$.

It is interesting to observe that the promotion rate for initiated cells in nine organs obtained by Heidenreich *et al.* (they do not give the results for lung cancer) and for initiated cells in the lung obtained by Jacob *et al.* (*2*) are quite similar in the dose range below 1 Gy (Fig. 1), although the nine sites include many sites other than the lung and although a different dose system and a different follow-up time were used. Both analyses are based on the TSCE model. They indicate that an acute exposure to $\gamma$ radiation with a dose of 0.5 Gy increases the number of initiated cells by about 30%.

Larger differences in the promotion rates in the two studies are observed for higher doses. This may be partly due to the different functional dependences used. For females, there are also larger differences, which may be due to the relatively small number of lung cancer cases among females and the related larger uncertainties of the model parameters.

Another point worth discussing in the study of Heidenreich *et al.* (*1*) is the assumption of a promotion rate that depends on dose while keeping the model parameter $q$ constant. Like the promotion rate $\gamma$, the parameter $q$ depends on the division and inactivation rates of initiated cells. It is very hard to imagine biological processes that change $\gamma$ while leaving $q$ constant. In our earlier work on the promotional effect in the lung cancer data for the atomic bomb survivors (*2*), changes in $\gamma$ and $q$ were consistently modeled through the cell survival function $S(D)$.

In summary, the functional dependence of model parameters used in a model of radiation carcinogenesis should be based on mechanistic considerations and should be derived in a consistent manner.

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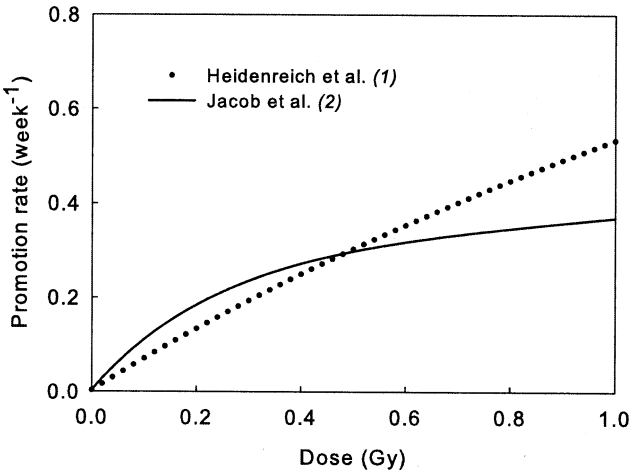


**FIG. 1.** Dose dependence of the promotion rate in TSCE model applications to cancer incidence data among male atomic bomb survivors by Heidenreich *et al.* (*1*) for nine sites [Eq. (1)] and by Jacob *et al.* (*2*) for the lungs [Eq. (3)].

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## Criteria for Testing Promoting Action of Radiation in the Atomic Bomb Survivors Data

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Carcinogenesis is a multistep process that until now has been too complicated for a solid quantitative understanding based on systems biology (*1*), and the same is unfortunately true for the wide spectrum of reversible and irreversible disturbances in the homeostasis of living objects produced by exposure to ionizing radiation. Therefore, in view of this lack of knowledge of the truth and the importance of this topic, it is no wonder that different scientists follow different routes in research to improve our knowledge about radiation carcinogenesis, and this is true even for scientists working in the same institute. For the benefit of scientific progress sensitive details of such routes, which are controversial, should be discussed openly as it is done here.

An earlier paper (*2*) that was coauthored by Jacob discussed a possible effect of radiation on the clonal expansion rate (promotion), but this was done only for the deterministic version of the two-step clonal expansion (TSCE) model. Later, in a paper presenting the results of a study using a stochastic version of the TSCE model (*3*), it was stated that ''[f]or several tumor sites and the two sexes, a model with radiation acting on initiation and promotion was fitted to the atomic bomb survivors data, which were made available at RERF in Hiroshima for this purpose. While for a pooled analysis with nine organs the signal seems sufficient for pointing to a promoting action of radiation, for individual tumor sites, it becomes weak. More work is needed before the question of a promoting action of acute radiation in the atomic bomb survivors can be answered with confidence. Any lengthening in follow-up will clarify the time since exposure pattern.'' The present work (*4*) uses such a longer follow-up, which is now available. However, in specifying the assumed underlying biological mechanisms in the TSCE model, the present authors have chosen not to use the particular experimental findings on the survivorship curves for human embryo lung cells (hypersensitivity of L132 cells) suggested by Jacob (*5*) to fix in part the parameters of the birth-death process of the TSCE model. One reason for our choice was that we question the relevance of such data for the present problem when we have adult lung epithelial cells in a living tissue. Also, the so-called death parameter of the TSCE model implicitly comprises both cell inactivation and cell differentiation, and we do not want to exclude the possibility that cell differentiation (or other tissue-level events) might be the dominating process.

Jacob asks for an explanation of our choice of 1 week as the period for the assumed duration of radiation action, whereas the actual duration during bombing was only of the order of 5 s, and of the chosen form of the dose dependence of promotion action. We want to respond to these two points in reverse order: The mathematical description of radiation action on initiation and on promotion can be separated in the TSCE model after acute irradiation, because they show different age-at-exposure and time-since-exposure patterns in cancer incidence. In principle, the dose-rate dependence of these radiation actions can be chosen arbitrarily in the model (*6*) if no separate experimental or theoretical data of direct relevance are available. As we have explained previously (*4*), the relevant parameter $g_r$ was chosen in such a way that the initial excess relative risk from promotion is roughly $g_r D$, i.e. linear in dose. In this way the relative importance of initiation and promotion should be influenced as little as possible by differences in the assumed dose dependences. Figure 5 of ref. (*4*) compares this choice with arbitrary, piecewise linear dose dependences, confirming this choice.

The assumed period of radiation action $\Delta t$ in Eqs. (2) and (3) of ref. (*4*) is only a technical, mathematical construction to calculate the predictions of the stochastic TSCE model with a promoting action for short exposures. For the parameters used, this time should be short compared to the inverse of the effective background growth rate of intermediate cells; this inverse rate is estimated to be about 6–10 years for the present situation. If $\Delta t$ is chosen as 1 min (which would be much closer to the actual circumstances) instead of 1 week, no difference in the calculated results is found within the line thickness in Fig. 3 of ref. (*4*). The calculated excess relative risks typically differ only in the fourth relevant digit. The value of 1 week was also used previously (*3*) in a related context, but we did not consider it necessary to give a citation for this uncritical choice.

Jacob suggests that the parameter $q$ should be made dose-dependent: This parameter was introduced to get identifiable parameters for the baseline TSCE model and to get a well-defined limit to the deterministic version of the model (*7*). We explained our reason for keeping it constant (*4*): ''Radiation could also modify the parameter $q$. Tests showed that this would influence the risk only very long after exposure and is not estimable from the present data set. Therefore it was not used in this study.'' The next follow-up of the RERF data set may allow us to get an estimate of radiation action on this quantity.

Jacob states that it is very hard to imagine biological processes that change the effective clonal expansion rate $\gamma$ but leave the parameter $q$ constant. In view of what is said above, this is not a very relevant point. Nevertheless, we do not agree completely with his statement: If, for example, the death rate of intermediate cells is much smaller than the growth rate, and if the rate for malignant conversion is not dose-dependent, then $q$ would also be independent of dose.

Jacob summarizes that the functional (dose?) dependence of model parameters should be motivated by mechanistic considerations: The major aim of our previous study (*4*) was to test whether there is consistency with the epidemiological data of an assumed effect of radiation on the effective clonal expansion rate of the TSCE model used. The estimated model parameters can then be compared with experimental evidence for such biological processes. We do so in the discussion section of our paper. Fixing parameters that do not change the hazard function sufficiently to be testable by the epidemiological data set may help to make the model look more appealing, but it would not help to clarify the issue. Fixing parameters that are estimable from the data set to values that are based on experimental evidence can be used to test the extent to which the assumptions made are compatible with the data. But this needs to be done with care: The better description of age at exposure and time since exposure due to a promotion term may give an improvement of the fit even for very non-linear dose dependences in risk. This in turn may lead to misinterpretations of the model predictions, especially in the low-dose region.

We are confused by Fig. 1 in the letter of Jacob and by the discussion derived from this figure: It gives the estimated radiation-induced effective clonal expansion rate $\gamma(D) - \gamma_0$ during the assumed period $\Delta t$ as a function of cumulative dose. This expression is dependent on the choice of the quantity $\Delta t$, which is principally unidentifiable in this framework. It would be better to plot e.g. the quantity $\exp(\gamma(D) - \gamma_0)\Delta t)$, which is the initial relative risk due to promotion. But what is most confusing is that according to table 2 of ref. (*5*), the model for males with a promoting action is not significantly better in fit quality than the one without (deviance change from 451 to 450 by one additional parameter; it is significant for females with a deviance change from 551 to 542). The similarity of the lines in the figure observed by Jacob is pure chance.

It is apparent from this discussion that much more research must be done before even medium-dose radiation carcinogenesis is understood in any mathematical way to an extent where the findings of radiobiological experiments should be included in biologically based models directly. If this is done nevertheless, at least side effects need to be tested carefully.

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