Response to the Commentary of Donald A. Pierce (*Radiat. Res.* 160, 718–723, 2003)

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Source: Radiation Research, 161(3):369-370.
Published By: Radiation Research Society
DOI: http://dx.doi.org/10.1667/RR3139
URL: http://www.bioone.org/doi/full/10.1667/RR3139

RADIATION RESEARCH **161**, 369–371 (2004)
0033-7587/04 $15.00

LETTERS TO THE EDITOR

Response to the Commentary of Donald A. Pierce (*Radiat. Res.* 160, 718–723, 2003)

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We tend to agree with many of the positions expressed by Pierce (*1*) in his optimistic views about modeling and his more general comments. Biologically based mathematical models necessarily are and will always be far from giving a true picture of all the details of the carcinogenic process, but they can be a useful tool to connect quantitatively various hypotheses about the rate-limiting processes with epidemiological and experimental data. They are indispensable to obtain scientifically based, more reliable extrapolations from large, directly observable risks to the area of small risks which need to be quantified for the rational protection of humans and their environment against low doses of ionizing radiation (and other carcinogens).

We agree with Pierce that the goals of our respective modeling efforts might be different. The TSCE model was developed to provide a general framework for analyses of data on different biological end points related to cancer, not just incidence data. Thus we are interested not only in the hazard function but also in the number and size distribution of intermediate lesions on the pathway to cancer. We have in fact used the model for analysis of data on intermediate lesions (*2, 3*).

We want to point out that some of us considered multiple stages in carcinogenesis much before Pierce thinks we did, starting in a paper on colon cancer published in 1992 (*4*). However, we are convinced that any model that does not accommodate clonal expansion of intermediate cell populations is unrealistic. Pierce's attempt to incorporate clonal expansion in their idealized version of the multistage model is only an approximation with very different properties.

SPECIFIC REPLIES

A few comments on detailed points raised by Pierce may help to clarify some of the issues:

a. Pooling: It is well known that the background rates (absolutely and their age dependence) are different between sites and sexes. It may well be that the effect of radiation in some of these is similar, but this is a conclusion that should be drawn from the analysis, not an assumption made before analysis.

b. Background: We believe the data should be analyzed *in toto* (holistically). Excess risks cannot be viewed in isolation from background risks, particularly when using biologically based or mechanistic models. Attempts by one of us—mentioned by Pierce—to strengthen the relative risk component by adding a Cox likelihood to the usual binomial one are nonstandard and did not give substantial changes in the estimated parameter values when applying the TSCE model to the atomic bomb data (unpublished).

c. Leveling of risk at high age: We offered several possible alternative hypotheses in ref. (*5*) in addition to the stochasticity effect in the mathematically exact formulation of the various models. If any of these is believed to be the dominant effect, it should be quantified explicitly and incorporated in the model [as was done for heterogeneity of the cohort with respect to smoking in the analysis of radon-induced lung cancer (*6*)]. We do believe that the mathematical cancer models should be used in their exact mathematical form or in an approximation that does not alter any of its features. At least for the clonal expansion models, the so-called deterministic approximation leads to very different age patterns of risk [see e.g. Fig. 1 in ref. (*7*)]. The additional cost in model development and computer time is minor compared to the previous costs of collecting the precious data sets.

d. Age trends in excess risk: The age trends observed in the data of RERF for the excess risk are of great interest to us, but the estimation of the model parameters should be done from the raw data (grouped data for Poisson regression) not from derived quantities. In ref. (*5*), equation A40 in that paper was used as stated (and as in earlier publications), and no additional terms were added in this work. It represents the conventional notion that radiation acts through its mutagenic potential at an early stage. The TSCE model does allow for other radiation actions [see e.g. our work on radon effects in miners, where apparently a promoting action dominates (*6*)] with other age patterns. Indeed, work is under way to add a promoting action in the TSCE model for acute exposure, in addition to the initiating one. The age patterns in such models are much closer to those of the Pierce-Mendelsohn model, as we described in ref. (*7*). Unfortunately, the statistical power without pooling is barely sufficient to distinguish between the possibilities.

e. ''Clonal expansion'' compared to ''more stages'': Pierce suggests that the idea of promotion by radiation may arise if clonal expansion was compensating for the assumption of too few required mutations. This is not true. Some of us tested this claim by sensitivity analyses with models with varying numbers of stages. The estimates of the clonal expansion rates (including their dependence on dose) remain very stable (*8*).

f. Large growth and death rates: The misleading statement made in ref. (*9*) unfortunately is repeated by Pierce and requires a comment: Neither the growth nor the death rate parameter is identifiable in the TSCE model from incidence data alone. To estimate them, additional information is needed. For lung cells, the growth rate is measured to be about 1 per month (*10, 11*), while the estimated effective clonal expansion rate for lung cancer is estimated to be about 0.15 per year when the TSCE model is applied to incidence data. Therefore, cell division rates that are two orders of magnitude higher than the effective rate of clonal expansion are suggested from directly measured rates. Similarly measured cell division rates in the colon are about two orders of magnitude higher than the effective rate of clonal expansion estimated in our models. The high growth and death rates could be rescaled without changing the fit of the model. The leveling of the risk function at sufficiently high age in the TSCE model also appears when the death rate parameter is put to zero (*12*).

g. Cancer age: Some of us like this description as a crude guideline. Such a concept may also help to incorporate more easily effects of radiation on non-cancer end points, and thus allow more realistic views of the radiation effects. However, it must be kept in mind that the data,

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for example, lung cancer among ex-smokers, indicate that after exposure stops the incidence function among exposed individuals may revert close to background level. Exact stochastic solutions of fairly general multistage models, including the TSCE model, predict the ultimate reversion of cancer incidence to background levels some years after exposure stops.

CONCLUSIONS

We are confident that this interesting discussion process will help the much-needed development of mechanistic cancer models, as opposed to just re-expressing known views. Thus it will bring the field closer to what is needed for low-dose risk estimates. We are also confident that longer follow-up in the extremely important RERF data set will continue to be a rich source of information for this type of modeling. Finally, we all should not aim too much to unify assumptions made between modelers (we might ''harmonize'' and agree on assumptions which are finally proven wrong!). Instead we should try even harder to identify the true rate-limiting processes in radiation carcinogenesis and to describe them mathematically. Fair scientific argumentation on the correct interpretation of observations resulting from complex processes with many unknowns is a welcome positive sign of leading-edge research and of a healthy publication culture.

Received: October 29, 2003

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Reply to Heidenreich *et al.*

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I agree with these writers in their conclusion that it is useful to have both some ''harmony'' and some ''discord''—that is, some agreement on fundamental model structures but also some scientific controversy. Particularly since there seems no serious shortage of discord, my emphasis on harmony was mainly in the hope that the idealized stochastic modeling might come to be more influential than at present. It is, for example, unfortunate that task groups such as NAS BEIR committees tend to rule out any attention to this, feeling that the work is too speculative. This view is surely due in part to the apparent lack of agreement regarding the most fundamental modeling issues. I really do not see that the modern general view of carcinogenesis is so unsettled as to warrant this, and indeed the lack of agreement may to an extent be more apparent than real.

Although descriptive analyses rule in the end, what makes them challenging is that their use involves matters of cause and effect. Substantial guidance in descriptive analyses can result from the theoretical consideration of mechanisms. For example, based partly on the results in ref. (*4*) of my commentary, I believe that for prolonged exposures to radon we started out in BEIR IV with descriptions placing far too much emphasis on time since exposure. As it should be, I have supporting reasons for this view. For A-bomb survivors, we believe that cancer risks have little to do with time since exposure, and we should be skeptical of whether things are totally different for prolonged exposures to radon.

In the spirit of harmony, I will say that the four-stage model of ref. (*8*) in their letter, which provided the best fit in their analyses, seems fundamentally sensible to me, provided that the main results are not highly sensitive to the number of stages (number of required mutations). Valid analyses under such models using our very different approaches should be complementary, even though as we have all noted our aims may be rather different. My remaining comments here are more in the recommended spirit of discord.

I remain skeptical of their claims in item (e). My point referred to there concerned purported evidence that the radiation effect on clonal expansion might be commensurate with its role in inducing mutations. Although those authors may have considered the effect on such evidence of including more stages in their model, I cannot see that this is provided in their cited ref. (*8*), where I find no mention of radiation or other mutagenic exposure. As for possible unpublished work on this, I note that in their type of parameter-value-driven results, increasingly many parametric restrictions are usually required with more stages. So if their evidence regarding an important role of radiation in clonal expansion maintains with more stages, I would want to consider how this depends not just on the number of stages but on detailed aspects of the modeling.

My larger concern is with the view expressed in item (d) that the ''conventional notion'' is that radiation acts through causing mutations at an ''early stage''. What indeed seems to me too conventional is the terminology ''radiation-induced'' cancer rather than ''radiation-related'' cancer. I think, and I find most biologists to agree upon reflection, that the latter terminology is far more suitable. I think this matters, for the terminology used represents and influences thinking, particularly in regard to whether radiation ''initiates'' cancers. An issue here is what one means by ''early stage'' and ''initiation''. If these terms refer to most of the process of accumulation of mutations, with subsequent ''stages'' being where there is rather uncontrolled cell growth, then I have no problem with the ''conventional notion'' as stated. But aside from all this vague terminology, it just seems logically implausible to me that if several mutations are required to render a cell malignant, radiation could only cause

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the first of these. Certainly, that hypothesis is not *required* to explain what is seen in data; see ref. (*4*) of my commentary. As I have noted both above and in my commentary, I do not think that many of those familiar with the A-bomb survivor data believe that time since exposure plays the prominent role that it would under a hypothesis that in a strong sense radiation only ''initiates'' cancers. To the extent that the ''conventional notion'' may correspond to such a hypothesis, a concerted and systematic effort to investigate its plausibility would in my view be extremely important.

Finally, in regard to their item (g), I note that in the paper just referred to, we found that the same stochastic model leading to the ''cancer-age'' interpretation of radiation effects also provides a remarkably good prediction of how lung cancer rates behave after cessation of smoking. Thus there is no conflict between the ''cancer-age'' interpretation of mutagenic exposures and what is seen after cessation of smoking. The smoking-induced mutations (effectively equivalent to an increase in ''cancer age'') will remain after cessation of smoking, but with subsequently increasing age these mutations (or the corresponding ''cancer-age'' increase) will become a progressively smaller proportion of the total number of mutations (or of the corresponding subsequent ''cancer age''), and the relative risk will therefore decrease. It is noteworthy that there is nothing special about smoking required to explain what is seen after its cessation—the relative risk after cessation of any mutagenic exposure, acute or prolonged, will decrease with subsequent ageing. This not only follows from basic stochastic analysis of mutations and cancer, when allowing for multiple mutations, but is seen in the data on A-bomb survivors and miners exposed to radon. That the effect may seem more pronounced for smoking is, in my view, only because the smoking risk is so much larger than the radiation risks.

Received: November 17, 2003