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COMMENTARY

Mechanistic Models for Radiation Carcinogenesis and the Atomic Bomb Survivor Data

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Recently, Heidenreich *et al.* (*Radiat. Res.*, 158, 607–617, 2002) suggested that the Radiation Effects Research Foundation (RERF) A-bomb survivor cohort study is not large enough to discriminate between various possible carcinogenic mechanisms. At least with the current follow-up, this is true to some extent, but I think the specific issues are rather different than they suggest. In particular, I do not think it is true—as they further indicate—that various models fit the data about equally well while estimating very different patterns of excess risk, which would imply that these patterns cannot be reasonably well characterized. I will point to specific criticisms of their approach to the data and offer some more general comments on mechanistic modeling approaches. Although there are important distinctions, I suggest on a very optimistic note that the two major approaches may be converging, and soon the main differences may not be in the assumptions made but in the aims of the modeling.

INTRODUCTION

In a recent paper (*1*), Heidenreich *et al*. concluded that the Radiation Effects Research Foundation (RERF) A-bomb survivor cohort study is not large enough to discriminate between various possible carcinogenic mechanisms. Although this is true to some extent, I think that the issues are quite different than they indicate. In particular, they come to the more specific conclusion that various mechanistic models ''fit the data about equally well'' but estimate very different age–time patterns of excess cancer risk. The logical consequence of this would be that these patterns of excess risk cannot be reasonably well estimated, whereas in fact it is in many ways demonstrable that they can. This is why RERF results are useful for radiation science and protection. The real issue in my view is that fairly well characterized patterns of observed excess risk can be compatible with different mechanistic models. I will return in the section on the conclusions of their paper to matters of how well characterized the age–time patterns are, and why these patterns happen to be consistent with both of the major modeling approaches.

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AN OPTIMISTIC VIEW ABOUT MODELING

Before indicating evidence for the claims above, I would like to emphasize something on a very positive note. I think the two major viewpoints on stochastic modeling of carcinogenesis—that based on multistage models following ideas of Armitage and Doll, and that based on the two-stage clonal expansion (TSCE) model—are probably converging toward a point where the difficulty at issue will be less important. In ref. (*2*), two of the authors of ref. (*1*) provide initial development moving from the TSCE model to corresponding formulations involving more than two mutations. This is an important step toward what I think many would consider more realistic models. Moreover, in refs. (*3, 4*), Pierce and Væth provide their more current viewpoint on radiation effects in multistage models, which has come a long way from that expressed earlier in ref. (*5*) and addressed in ref. (*1*). We consider our current work less as involving a specific ''model'' than as exploring what highly tractable stochastic analysis of mutations, radiation effect, and cancer can be achieved with some basic idealizations. Although these idealizations differ from those in the TSCE model through allowing only implicitly for cellular selective growth advantage (clonal expansion), we are attentive to the need for trying to incorporate this more explicitly. I consider here only the two major modeling viewpoints, whereas ref. (*1*) refers to several implementations of mechanistic models. In our view the various ''exact'', rather than asymptotic, multistage model results in ref. (*1*) are employed in a manner that is not highly relevant to the main issues.

Thus I can readily envision that soon there will remain relatively minor differences between what have so far been quite different favored stochastic models. There will surely remain, though, major distinctions between the fundamental aims of (1) those seeking models biologically based in a very strong sense, where a substantial number of model parameters play an important role in both the risk estimation and interpretation, and (2) those seeking on the contrary only a fundamental type of stochastic analysis of the cellular accumulation of mutations, where it turns out that parameter values are much less important and serve mainly to provide guidance in descriptive analyses. My presumption is that the difference in viewpoints will come to involve mainly this distinction between fundamental aims, which is healthy, rather than substantially different underlying modeling assumptions.

REGARDING THE CONCLUSIONS OF THEIR PAPER

The primary aspects of ref. (*1*) with which I take exception arise from (a) the authors' attitude toward combining information from the sexes and different cancer types and (b) inordinate (but I think largely inadvertent) emphasis on the quality of fit to baseline, rather than excess, rates. In regard to (a), it is their view that when using biologically based models it is inappropriate to combine data on the sexes and tumors at different sites. It is simply a foregone conclusion that without attempting to combine *in some manner* sex- and site-specific information about patterns of excess cancer rates, it is impossible learn much about these patterns, quite aside from discrimination between mechanistic models. As I will show here, one does not have to simply pool *data* on tumor types and sex to combine *information* about age–time patterns of excess rates. It is indeed important to consider differences by tumor type and sex, while emphasizing the possibility that there may be considerable commonalities—an approach I will exemplify in what follows. The authors of ref. (*1*) do, with reservations, consider the class of major cancer sites used in ref. (*5*), and here I will try to clarify the nature of excess cancer rates for those sites: stomach, lung, liver, colon, rectum, gallbladder, pancreas, bladder and esophagus. These are the major sites that are not sex-specific.

Turning to (b), overall goodness-of-fit measures are dominated by relatively minor lack of fit of idealized models to baseline rates, thus failing to assess the quality of fit to radiogenic excess rates. Parameter estimation is similarly dominated by fitting baseline rates. This is why the authors of ref. (*1*) can have different models supposedly ''fitting the data about equally well'' but estimating very different patterns of excess rates. Although mechanistic modeling is indeed concerned with age–time patterns of both baseline and excess rates, the conclusions in ref. (*1*) pertained mainly to the study of radiation effects. It is precisely because the information on baseline rates is so much greater than that on excess rates that the fit to the former dominates in overall goodness-of-fit measures and parameter estimation. For example, in their comparison for males and the collection of sites mentioned above, the TSCE model leads to an overall χ^2 goodness-of-fit statistic that is better by 40 (a very large value) than the so-called Pierce-Mendelsohn model. But virtually the entire value of 40 is contributed from those exposed at under 0.2 Sv, who have essentially baseline rates. For that example, all of the better fit of the TSCE model pertains to what I consider relatively inconsequential detail of baseline rates rather than important aspects of excess rates.

This is not to imply that we would currently defend the baseline rate aspects of the so-called Pierce-Mendelsohn model, where the idealizations have more effect than is desirable. That we would in this sense no longer strongly defend that model is a key issue in understanding the points made here, and this change in our view has led us in the subsequent work in refs. (*3, 4*) to analysis focusing more on excess rates.

A means of dealing with both difficulties (a) and (b) is now considered. A useful descriptive approach is to take a very flexible statistical model (see endnote A) for baseline rates of each cancer type and sex separately, along with statistical models for *sex- and type-specific* excess rates of form $\theta\ dose\ \exp\{\alpha\ tsx + \beta\ agex + \gamma\ age\}$, where *tsx* denotes time since exposure, *agex* age at exposure, and *age* attained age (see endnote B). In a joint analysis for sexes and cancer types as developed in ref. (*6*) and applied here, consideration can then be given to the extent that the parameters of this excess risk description should vary by cancer type and sex. This analysis does not involve simply ''pooling'' cases for the sexes and types, but simultaneously fitting sex- and type-specific models so that commonality of parameters can be investigated (see endnote C).

The age–time variables are linearly dependent since $agex + tsx = age$, so at most two parameters in the excess rate exponent can be fitted. I will show that this is largely what leads to limitations in identifying mechanistic models. The insight gained from models of the above form was first pointed out by Kellerer and Barclay (*7*). Somewhat better fits are possible through replacing *age* with log(*age*), leading to descriptions currently used by RERF and those arising in refs. (*3–5*), but this is not crucial to considerations here and complicates understanding of the basic ideas.

A key point is that for time since exposure up to 50 years the fitted TSCE excess rate model of ref. (*1*), i.e. the second term in their equation (A40) reproduced here in endnote D, is almost exactly equivalent to the above form when $\beta = \gamma = 0$. That is, over that time span the variation in numerator of that term of (A40), which is exactly loglinear in *tsx*, totally dominates the variation in the denominator. Further, I am confident that the authors considered relaxing the condition $\beta = 0$ as in previous TSCE papers, that is, multiplying the second term of (A40) by $\exp(\beta\ agex)$ to modulate the effect of radiation on induction of the first mutation. Presumably they did not find statistically significant

need for this in their separate sex-specific analyses, but it appears they would have if they had pooled information from the sexes as done below. Thus, for a given sex and cancer type, the excess rate part of the TSCE model can be taken essentially as θ *dose* $\exp\{\alpha\ tsx + \beta\ agex\}$, at the expense—or gain—of separating the model implications for baseline and excess rates. Issues regarding this separation are central and are discussed in the final section. The expense is that when we fit this excess rate model by the means indicated above, the estimates are different from fitting the TSCE model, because we have broken the link between baseline and excess rates in the TSCE model. The gain is that the parameter estimates for the excess rate in fitting the TSCE model are determined largely from time patterns of baseline rates, and they may not fit the observed excess rates very well. Overall goodness-of-fit measures will not detect this, since, as with the parameter estimation, the goodness-of-fit measures are dominated by the fit to baseline rates.

On the other hand, in the Pierce-Mendelsohn-Væth stochastic analysis (*3–5*), the primary excess rate variable is attained *age*, although as noted in ref. (*4*), section 4, there are simple and plausible modifications allowing for a residual effect of *agex*. This suggests a model of the form θ *dose* $\exp\{\beta\ agex + \gamma\ age\}$, where β may be relatively small. Although *age* enters logarithmically in the results of refs. (*3–5*), this distinction has a modest effect over the adult age range. We note that aside from the Pierce-Mendelsohn-Væth results, a model of essentially this form, involving *age* rather than *tsx*, is used at RERF and elsewhere for purely descriptive analyses.

It is through encompassing major aspects of both modeling approaches that sex- and site-specific descriptive models of the form θ *dose* $\exp\{\alpha\ tsx + \beta\ agex + \gamma\ age\}$ become useful for the needs here. The joint-analysis descriptive approach indicated above, by necessity always taking at least one of the parameters $\{\alpha, \beta, \gamma\}$ equal to zero, provides substantial information on the nature of radiation-related excess rates for the selection of cancers considered. I will here employ the publicly available data through 1987 used in ref. (*1*) and restrict it as done there to $agex > 20$ and $age < 80$, although results are similar for the current follow-up and without those age restrictions. The parameter θ depends markedly on cancer type in largely the same ratios as seen in baseline rates, but it does not depend significantly on sex. There is no statistically significant variation with sex of any of parameters $\{\alpha,\beta,\gamma\}$. Although there is undoubtedly some true variation of $\{\alpha,\beta,\gamma\}$ with cancer type, this is not statistically significant (in tests on 9 *df*) for the data considered here. More detailed analysis of possible dependences of $\{\alpha,\beta,\gamma\}$ on sex and cancer type are given in ref. (*8*) for cancer mortality and will be provided for cancer incidence in a forthcoming RERF report. Although it is important to consider such differences, it is even more important to do this in a way that capitalizes on the commonalities. As discussed in ref. (*8*), it is becoming increasingly clear to us that such variations have more to do with secular trends in baseline rates than with generalizable radiation effects. At any rate, the model for excess rates of form θ_{type} *dose* $\exp\{\alpha\ tsx + \beta\ agex + \gamma\ \text{age}\}$, with no dependence of $\{\alpha,\beta,\gamma\}$ on sex or cancer type, provides a useful, if not perfect in detail, description of excess rates for the nine cancer types considered.

When we take $\gamma = 0$, along TSCE lines for excess rates, the estimates are $\hat{\alpha} = 0.085 \pm 0.017$, $\hat{\beta} = 0.097 \pm 0.015$. When we take $\alpha = 0$, along lines of the Pierce-Mendelsohn-Væth approach, and usual descriptive analyses, the estimates are $\hat{\beta} = -0.013 \pm 0.016$, $\hat{\gamma} = 0.085 \pm 0.017$. Bear in mind that since $age = agex + tsx$, these are precisely the same fits to the data, with the only distinction being how this fit is interpreted in terms of parameters. This duality in interpreting the same fit is the key to understanding the main issues, meaning that either of the two basic modeling approaches is highly compatible with the well-determined empirical description of the radiation-related excess cancer rates. It was precisely the point of Kellerer and Barclay in ref. (*7*) that the approximate equality of *tsx* and *agex* coefficients in the $\{\alpha,\beta\}$ representation along with the relation $agex = age - tsx$ implies mathematically that the *agex* effect is quite small in the $\{\beta,\gamma\}$ representation. This does not in itself mean that either interpretation (of the same fit) is the ''correct'' one, and the equality (to within estimation error) of coefficients in the $\{\alpha,\beta\}$ representation could be coincidental. However, the results in refs. (*3–5*), not known at the time of ref. (*7*), may add clarification to this issue by suggesting reasons that attained *age* could be the primary time scale.

On a minor point, the referee noted that in Fig. 2 of ref. (*1*), for those exposed as children, the fit of the so-called Pierce-Mendelsohn model provides notably smaller stomach cancer risks than does the fit of TSCE model. Of the nonsignificant variations of $\{\beta,\gamma\}$ with cancer type, one of the larger is that the exposure age effect β is greater for stomach cancer than other cancers, in the direction of those exposed as children having larger radiation risk. The Pierce-Mendelsohn model takes $\beta = 0$, which likely explains what is seen in that figure. In ref. (*8*) we note that there is a strong decrease with calendar time (or birth cohort) of baseline stomach cancer rates in these data, and the large exposure age effect in the relative risk may be reflecting this trend more than representing a generalizable radiation effect.

My main point is that the overall conclusion reached above is very different from that drawn in ref. (*1*), which was that the two modeling approaches can lead to about equally good fits to the data but *with very different* indications of excess rates. On the contrary, the patterns of excess rates can be estimated reasonably well by combining information from the sexes and cancer types, and to an extent these patterns conform to either modeling approach. The distinction in excess rates between the TSCE model and the stochastic analysis in refs. (*3*, *4*) is mainly whether

it is time since exposure or attained age that is the primary time scale. At least in the TSCE excess rate model, exposure age is also seen here to be important. It is unfortunate that the linear dependence in the three age–time scales seriously inhibits discriminating between the models. However, I should say that it has been over 20 years since statisticians primarily involved with the RERF data have thought that time since exposure has much to do with excess rates for solid cancers. The common view is that ''excess cases are mainly seen when people reach the cancer age'', rather than ''excess cases are mainly seen long after exposure.'' Indeed it is true that excess cases for those exposed at a young age tend to occur longer after exposure than for those exposed at older ages. An interpretation of that is that attained age is more important than time since exposure, but as indicated here, this view cannot be confirmed simply in terms of goodness of fit without further considerations.

MORE GENERAL COMMENTS

Before turning to the final conclusions, I will at the request of the Editors take this opportunity to offer some more general comments on the current state of cancer modeling. Especially to the extent that the authors of ref. (*1*) may take exception to some of what I will say, it may be useful to put the matters on the table for discussion.

I have mentioned earlier that in my view the extension of the TSCE model to allow for more than two mutations will be important. The view is sometimes expressed that if one can fit data reasonably well with the TSCE model (which I think is generally the case), then there is little reason to consider the need for more than two mutations. What concerns me with this rationale is that restricting to two mutations may place too much demand, in explaining data, on the role of clonal expansion. In particular, has been argued in refs. (*9–11*) that in applications of the TSCE model there is evidence that prolonged radiation exposure substantially affects the rate of clonal expansion, in contrast to causing mutations. However, it seems logical that such indications might arise erroneously if the clonal expansion aspect of the model were compensating for the assumption of too few required mutations. In another vein, regarding the assumption that only two mutations are involved, it has been suggested that the first transformation in the TSCE model might be interpreted as the composition of several mutations. But then it would be inappropriate to assume, as is usually done, that the rate of this first transformation is constant in age since if it involved m mutations then the rate should tend to increase as age^{m-1}. Finally, I note that Brugmans *et al.* (*12*) have criticized use of clonal expansion modeling involving very large growth and death rates, but with a modest difference between them to govern the net expansion rate. This typically arises in application of the TSCE model to fit a leveling off (or decline) at old ages of baseline rates, and it is argued in both refs. (*4, 12*) that capturing that phenomenon in models for individual rates may be inappropriate. Generally, I find it easier to accept idealized stochastic analysis regarding accumulation of mutations than extremely idealized models regarding cell growth. The former at least involves individual cells, whereas it seems likely that the latter involves cellular interactions and may be less homogeneous over time.

On the other hand, the stochastic analysis in refs. (*3, 4*) does not explicitly allow for selective growth advantage of partially transformed cells, i.e. clonal expansion, and we tend to agree with the authors of ref. (*1*) that analysis not accommodating this may be misleading. However, the formulation in refs. (*3, 4*) implicitly allows for this to some extent, in that the cellular transformation rates can depend *arbitrarily* on the current mutational status of the cell. There is some approximate stochastic correspondence between clonal expansion and increased mutation rates for a partially transformed cell representing the clone. The matter certainly requires further attention, and since maintaining tractability of our stochastic analysis precludes this, we have turned to simulation. Preliminary indications taken up shortly are that although very substantial cell growth may affect some aspects of analytical results, it has little effect on the most important ones.

It seems rather implausible to me that even for a particular type of cancer, a certain given number k of mutations are required to render a cell malignant. In this regard, it seems likely that there are different pathways to malignancy of a cell. The primary conclusions of the work in refs. (*3, 4*) regarding excess cancer rates do not depend on any such assumption, but only on the notion that the malignancy of a cell is determined in some way by its mutational status.

In particular, without assuming any given number of required mutations, the idealized stochastic analysis indicates that, after termination of prolonged or acute exposure of total dose d, cancer rates for exposed persons should at age a be about $\lambda_0(a + \beta d)$, where $\lambda_0(a)$ is the baseline rate for unexposed persons. That is, the radiation effect is equivalent to what would have otherwise occurred in carcinogenic processes in time βd. It appears in simulations that the validity of this age-shift result for excess rates is little affected by very substantial selective growth advantage. The relative risk then takes the form $\lambda_0(a + \beta d)/ \lambda_0(a)$, but in the absence of assumptions regarding the number of required mutations, the form of the denominator must be determined empirically.

Implications that are affected by substantial cell growth include the following. If one assumes, perhaps unrealistically or for a given pathway to malignancy, that k mutations are required, then the classical stochastic analysis indicates that baseline rates should have a log-log age slope of about $k - 1$. But very substantial selective growth advantage can increase this slope, for example by around 1 or 2. So to the extent that very substantial cell growth prior to malignancy is important, this may suggest that the required number of

mutations is rather smaller than has traditionally been indicated by multistage modeling. The main point, however, is that although cell growth affects conclusions about baseline rates, it seems to have little effect on primary conclusions about excess rates.

The most dubious, but most critical, of the postulates leading to the above result about excess rates is that an increment of radiation exposure increases briefly by a common factor the rate of all relevant mutations. What seems suspicious about this is that radiation may be more effective in causing certain types of mutations than others. However, perhaps this does not matter greatly, since it is shown in refs. (*3, 4*) that the above age-change argument agrees remarkably well with the RERF solid cancer data. In particular, the radiation effect appears effectively equivalent to increasing one's ''cancer age'' by about 20–30 days per 10 mSv, more for females than males due to their effectively slower cancer process.

Finally, in contrast to suggestions in ref. (*1*), also made elsewhere by those authors, we do not believe that—given the idealized postulates—the asymptotic nature of the analysis in refs. (*3, 4*) leads to much error in regard to *age–time patterns* of risk. I note for those not conversant with the matter that the asymptotics pertain to the mutation rates for a given cell becoming small, which they surely are. Specific numerical consideration of these issues is given in the Appendix to ref. (*4*).

SUMMARY AND CONCLUSIONS

I have indicated that although the RERF data may not be adequate (at this time) to distinguish between the idealized assumptions of the TSCE and those used in refs. (*3, 4*), it is not in my view the case that different modeling assumptions necessarily lead to very different patterns of excess rates. The essence of the TSCE model in regard to radiation effects is that excess rates depend on time since exposure, perhaps with a simple multiplicative effect of exposure age when needed to obtain an adequate fit. In fitting the excess rates under the TSCE model, I have here ignored the link (common parameters) between its provision of baseline and excess rates, and the authors of ref. (*1*) could object to this with considerable justification. In both modeling approaches under discussion here, age–time patterns of excess rates are closely related to those of baseline rates. One must be cautious regarding this to avoid having the immensely greater information on baseline rates inordinately affect conclusions about the excess rates of primary interest. I know from personal interactions that at least some of the authors of ref. (*1*) are concerned about this matter. It is technically difficult, even if desired, to deal with it in fitting the TSCE model by placing more weight on the apparent excess rates than naturally arises, and completely separating excess and baseline rates as I have done here is not the perfect solution.

The matter may come to a head in continued follow-up of the RERF cohort. With currently fitted parameters for the pooled nine-sites data, the excess rates under the TSCE model will decrease sharply during the lifetime of survivors—for men, excess rates increase rapidly for the first 60 years after exposure and then drop equally rapidly after that, to less than one-fourth the 60-year level by 80 years after exposure (see endnote D). I doubt that many will take this projection seriously until data supporting it begin to emerge. If indeed excess rates continue to increase for all of lifetime, as many expect and as is predicted by the analysis in refs. (*3, 4*), the TSCE model may not accommodate that very well when it is fitted to the future data, due to the dominant effect of baseline rates in parameter estimation.

There are many considerations in addition to goodness of fit to data in evaluation of different modeling approaches, and I have tried to raise some of these here. But as indicated at the outset, I believe that as those preferring the TSCE approach move to consideration of a few more mutations, and those preferring the alternative approach gain better understanding of the role of selective growth advantage, there may remain little difference in the assumptions made. The real differences could then, as I have noted, involve only quite different fundamental aims of the mechanistic modeling. I think perhaps we would all be much more comfortable with that distinction than with one where the underlying assumptions are very different. An enhanced unity of assumptions, in broad conformance with modern general views of carcinogenesis, would help both camps to persuade others in radiation science and protection of the usefulness of their efforts.

I believe that stochastic, or pseudo-mechanistic as a referee has called it, modeling is indeed quite useful. A primary value is to provide guidance for descriptive analyses, in particular helping to sort out variations in risks with the highly correlated variables age, time since exposure, and exposure age. Our work has been helpful to us in this respect in providing a rationale for why excess relative risks should, as observed, decrease with attained age. We now believe that much of what was once considered an exposure age effect is actually this attained-age risk variation. For prolonged exposures, descriptive analyses are much more challenging, and guidance in this is even more important than for acute exposures.

ENDNOTES

A. The baseline rate models used, for each sex and cancer type, take log rates as piecewise quadratic in log age, with smooth join points at ages 40 and 60, along with birth cohort trends linear in exposure age.

B. On a fairly minor point, as in refs. (*1*) and (*5*), the birth cohort trends for baseline rates were also taken as factors applying to the excess rates, which affects the *agex* parameter estimates in the excess rate model to some extent.

C. To reduce to a manageable number the parameters to be estimated in the joint analysis, the baseline rate models were first fitted for each of the 18 sex and cancer type combinations. The resulting fitted baseline rates were then taken as fixed in the joint analysis of excess rates for the 18 combinations.
D. The TSCE excess rate at given dose is proportional to $(\gamma + 2q)^2 \exp\{(\gamma + 2q)tsx\}/[\gamma + q + q \exp\{(\gamma + 2q)tsx\}]^2$, and courtesy of the authors the parameter estimates for the pooled nine sites are $\hat{\gamma} = 1.479 \times 10^{-1}$, $\hat{q} = 1.638 \times 10^{-5}$ for males and $\hat{\gamma} = 0.906 \times 10^{-1}$, $\hat{q} = 9.387 \times 10^{-5}$ for females.

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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.

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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.

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