Age-Time Patterns of Radiogenic Cancer Risk: Their Nature and Likely Explanations

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Abstract

It is important both for radiation protection and scientific reasons to understand the age-time patterns of radiation cancer risk. This is surprisingly difficult even for acute exposures and much more so for prolonged exposures. I will provide current information on this for solid cancers among A-bomb survivors, pointing out some of the difficulties in description and interpretation. I will then take up some stochastic considerations regarding accumulation of mutations, which may help in dealing with these difficulties. These considerations are highly idealized, and their consequences should mainly be used only for guidance rather than as a primary basis for descriptive analyses. They are particularly suitable for this because of providing insights rather independent of parameter values in the stochastic models involved.

1. Introduction

In considering radiation dose response for cancer, it should be remembered that the radiation risk for a given dose at a specified age is not a number, but a function describing excess cancer rates at all subsequent ages. Sorting out the effects of age at exposure, time since exposure, and advancing age is difficult even for single acute exposures, and much more so for prolonged or multiple exposures (National Research Council 1990, 1999, Pierce et al 1996). Understanding them is not only crucial to description, but can provide insight into mechanisms of both radiation carcinogenesis and carcinogenesis in general. There are some idealized stochastic considerations regarding accumulation of mutations that may provide guidance in this.

Section 2 provides a description of age-time patterns of excess cancer risk among A-bomb survivors, raising some difficulties of interpretation. In Section 3 are presented some of
the stochastic considerations referred to above, which seem helpful in dealing with these
difficulties. I will conclude with more general discussion of the issues raised.

2. Description of Cancer Risks

Results here are for cancer incidence among A-bomb survivors (Thompson et al 1994) during
1958-95, omitting uterine and thyroid cancer. Uterine cancer results for A-bomb survivors are
very different from most solid cancers, in that substantial radiation risk is seen only those
exposed under about 10–15 years of age. Thyroid cancer radiation risks have age-time pat-
terns very different from other solid cancers. Such restrictions can be useful when the pri-
mary aim is improved understanding of age-time patterns. Although any pooling of cancer
types presents problems, the alternative to this leads to even more serious difficulties.

The analysis here involves 10,914 cancer cases, with 6,486 of these to those with posi-
tive radiation dose, of which about 700 are estimated to be radiation related. Figure 1 pro-
vides a description of the excess relative risk \( (ERR = \text{Relative Risk} - 1) \) over follow-up,
according to age at exposure and averaged over sex.

Grasping the reasons for a description of this form, and the main points of the paper, re-
quires some historical perspective. From about 1985 to 1995 the primary descriptions were in
terms of presumed approximately age-constant \( ERR \)'s decreasing substantially with age at
exposure (Preston et al 1987, Thompson et al 1994). In the type of plot here, this would be a
series of horizontal lines at levels decreasing with increasing age at exposure. By about 1995

![Figure 1. Sex-averaged ERR/100 mSv among A-bomb survivors for most solid cancers combined, shown for 4 ages at exposure. Choices are involved in arriving at such descriptions and other forms, with somewhat larger age-at-exposure effect and less general decline with attained age, are possible.](image-url)
it became moderately clear that for those exposed as children the \textit{ERR} decreases over the follow-up, rather as in figure 1 (Pierce \textit{et al} 1996). However, descriptions remained mainly in terms of age-constant \textit{ERR} depending on age at exposure, with a caveat for those exposed as children. Purely in terms of goodness-of-fit testing, such a description is even today only marginally worse than the one shown here. However, there would then be a statistically significant effect of age at exposure, whereas in figure 1 that effect is not significant (P = 0.13), having been replaced by a general decline in \textit{ERR} with attained age. It is indeed difficult in any cohort study to distinguish between these two types of effects. It was long considered by most that age-at-exposure effects are biologically more plausible than a decrease in \textit{ERR} with attained age, but attitudes towards this are changing.

There is another major uncertainty in interpreting so-called age-at-exposure effects. There are substantial birth cohort trends, differing by cancer type, in age-specific background cancer rates — note that in this study birth cohort and age at exposure are equivalent. In the usual formulations, previously and here, the age-at-exposure effect in the \textit{ERR} represents the departure from multiplicative effects of radiation and whatever causes the birth cohort trends in background rates. It is likely, however, that some of these factors act additively with radiation. In statistical models accommodating that — usually, but not necessarily, for the excess absolute rates (\textit{EAR}) — the so-called age-at-exposure effects are quite different from the usual ones for the \textit{ERR}. This difference is exemplified below.

So we see that interpretation of age-time patterns of risk is challenging even for acute exposures. Before turning to considerations that may help with this, I should dispel any thoughts that the patterns seen in figure 1 mean the radiation risk actually diminishes with age or time since exposure. Figure 2 describes the excess absolute cancer rates (\textit{EAR}) for the class of cancers considered; even in more detailed analysis there is no indication of declines in the \textit{EAR}. Note that the apparent age-at-exposure effect is greater for the \textit{EAR} than the \textit{ERR}, which could be interpreted as reflecting the birth cohort trends in background cancer rates — those young at exposure having substantially larger age-specific background cancer rates during the follow-up. The distinction does not pertain to relative versus absolute risks, but to the matter discussed above. I note that the sex difference in the \textit{EAR} is only marginally significant, whereas for the \textit{ERR} it is very large. It could be said that the sex difference in radiation effect is small, and that most of what appears in the \textit{ERR} is due to the large sex ratio in background cancer rates.
3. Stochastic considerations for accumulation of mutations

The following is a substantial generalization of the Armitage-Doll multi-stage model (Armitage and Doll 1954). A fuller account can be found in an unpublished paper by the author and Michael Væth, on the RERF website [www.rerf.jp](http://www.rerf.jp) under Statistics Department, Resources.

Suppose that malignancy of a cell is determined in some way by mutations it has acquired. It is not presumed here that any particular number of mutations is required. For the moment, I will neglect any proliferative advantage for cells having acquired only some of the mutations required for malignancy. First consider the process without the radiation exposure under consideration. A cell has at any time a transition rate for the acquisition of its next mutation. This transition rate is not that of any particular mutation, but the sum of rates of mutations that might next occur in the cell. Consider as an idealization that the transition rate at any age depends arbitrarily on the current mutational status of the cell, but not otherwise on age. This allows not only for the possible next mutations to depend on those that have already occurred in the cell, but more importantly for the likely possibility that some mutations substantially alter the effective rate of subsequent ones, \textit{e.g.} by affecting repair processes. The assumption that the transition rate, given the mutational status of the cell, does not depend on age is a strong one, and I will show later that altered results can be obtained by relaxing this in a specified manner.
As for the effect of radiation exposure, suppose as an idealization that an increment of exposure at age $a$, at dose rate $d(a)$, momentarily increases the transition rate currently in effect by a factor $[1 + \beta d(a)]$. Modifications allowing this factor to be nonlinear in $d(a)$ are straightforward. A limiting process deals with acute exposure. The critical idealization is that the transition rate at which the next mutation occurs, depending arbitrarily on the current mutational status of the cell, is increased by a dose-dependent factor not depending on mutational status. This is a strong assumption, not likely to be exactly true, and the aim is only to examine the consequences of it and compare them to what is seen in studies. It presents no problem in the following if some of the required mutations act recessively (must occur at both alleles to be effective) and some dominantly.

Denote the age-specific cancer (malignancy) rate for an organ or person without radiation exposure by $r_0(a)$. This is basically the malignancy rate for a cell multiplied by the relevant number of cells. Consider the age transformation given by $a^* = a + \beta D(a)$, where $a$ denotes age and $D(a)$ cumulative radiation dose by age $a$. Then under the above assumptions exposed and unexposed organs or persons have the same age-specific cancer rates on the age scale $a^*$. This is because: (i) the differential element $da / da^*$ annihilates the factor $[1 + \beta d(a)]$ in transition rates, and (ii) background rates do not depend on age, given the mutational status of the cell. Transforming back to the age scale, we then have that the cancer rate function for an exposed organ or person is $r_0(a + \beta D(a)) \{1 + \beta d(a)\}$. Note that the final factor is unity subsequent to termination of exposure. Further, subsequent to an acute or prolonged exposure the result holds in the form $r_0(a + \beta D)$, where $D$ is the total dose. That is, under the assumptions made, the effect of radiation exposure is equivalent to an increase, proportional to dose, in subsequent “cancer age”. Figure 3 shows for the data considered above, and for three dose categories, the sex and age-specific cancer rates on such a transformed age scale. Figure 4 shows for men the cancer rates on this scale for three age-at-exposure groups, compared to rates on the ordinary age scale for the unexposed, which differ by birth cohort. There is no indication in either sense of any radiation effect other than the “cancer age” increase.
Figure 3. Age-specific cancer rates for 3 dose categories with cut points 0.005 and 0.75 Sv, on the transformed age scale $a + \beta D$, which accurately accounts for the effect of exposure. There are 3 upper curves for men with $\beta = 0.45 \text{ yrs} /100\text{ mSv}$, and the 3 lower ones for women with $\beta = 0.90 \text{ yrs} /100\text{ mSv}$.

Figure 4. Age-specific male cancer rates for 3 age-at-exposure groups with cutpoints 20 and 40 years. Comparison of rates for entire cohort on the transformed age scale of figure 3, and those for the unexposed on the original age scale. Thus there are two curves for each age at exposure category. The age-at-exposure effect seen is due to birth cohort trends in background rates, and the age transformation accounts for any effect of age at exposure for the full cohort.
Now consider the implications for the relative risk, considering a single sex or more roughly, the relative risk averaged over sex. The above result means that the relative risk (RR) of exposed to unexposed is given by

$$RR(a) = \frac{r_0(a + \beta D(a))}{r_0(a)} \{1 + \beta d(a)\},$$  \hspace{1cm} (1)$$

or subsequent to termination of either acute or prolonged exposures by

$$RR(a) = \frac{r_0(a + \beta D)}{r_0(a)} ,$$  \hspace{1cm} (2)$$

where $D$ is total dose. Note that age at exposure has no effect in this. It is well known that an often-useful approximation to background rates takes form $r_0(a) \propto a^p$, leading to the approximation of (2) as

$$RR(a) = \frac{(a + \beta D)^p}{a^p} = (1 + \beta D / a)^p = 1 + p \beta D / a + \cdots .$$  \hspace{1cm} (3)$$

Although formally the $RR$ is here a polynomial in dose, for $p$ in the usual range of 4–6 and for doses and ages where the $RR$ is no greater than about 3, the linear approximation to the $ERR$ indicated is quite adequate. Thus to a useful approximation the $ERR$ decreases as $1/\text{age}$, with results very insensitive to the value of $p$, noting that it is the product $p \beta$ that would be estimated from data. However, the $1/\text{age}$ form of decrease is sensitive to departures from the approximation $r_0(a) \propto a^p$, and in particular a moderate decrease in the log-log slope at old ages, as often seen, can result in a decrease of the $ERR$ more rapid than as $1/\text{age}$. Extension of the Armitage-Doll multistage theory yields that under the above assumptions, along with the further one that $k$ mutations are required for malignancy, the background cancer rate is approximately of form $r_0(a) \propto a^{k-1}$. We prefer, however, to minimize reliance that further assumption.

Figure 5 compares empirical description of figure 1 with the sex-averaged $ERR$ corresponding to fitting both the polynomial and its linear approximation in (3), where for the former the estimate of $p$ is 3.7. The curve corresponding to figure 1 (for age-at-exposure 30) agrees less closely with the model results than the empirical description, also shown, where only those of age at exposure greater than 20 are used in the analysis. In particular, although the idealized stochastic analysis predicts an $ERR$ declining as $1/\text{age}$, the descriptive curves in
figure 1 decline more rapidly, roughly as $1/\text{age}^2$. This is an important departure from the theoretical predictions, discussed further below.

![Figure 5](image_url)  
**Figure 5.** Theoretical and empirical predictions of ERR. The solid and dashed curves (lower 2 lines at young ages) are fits of the full polynomial and the dose-linear approximation from equation (3). Highest curve at young ages is from figure 1, taking age-at-exposure 30. Light-shaded line is a similar empirical description when restricting to ages-at-exposure at least 20.

### 4. Discussion

Before discussing results above, I note for lung cancer risks of radon-exposed miners the above considerations provide age-time patterns for prolonged exposures that agree reasonably well with the empirical descriptions provided by the BEIR VI Committee (National Academy of Science 1999). This uses equation (1) along with the approximation $r_\text{a}(a) \propto a^p$. We have also found that the results fit remarkably well to data on lung cancer risks following cessation of cigarette smoking at various ages. Both of these results can be found in the unpublished paper by the author and Michael Væth referred to above.

Results in Section 3 can be modified to relax the age homogeneity assumption regarding mutations without radiation exposure. If transition rates in effect at age $a$ are modulated by a given function $s(a)$, which might be called the sensitivity to mutation, all the results hold true if the age transformation is replaced by $a^{\ast} = \int_0^a s(t)[1 + \beta d(t)]dt$. This introduces an age-at-exposure effect in the $\text{ERR}$. 
The approach taken cannot tractably be modified to allow explicitly for proliferative advantage of cells having some, but not all, of the mutations required for malignancy. However, we believe that the results allow implicitly, to an approximation, for modest such effects since transition rates can depend arbitrarily on the mutational status of the cell. There are other modeling approaches (Moolgavkar 1990, Kai et al 1997, Luebeck et al 1999) allowing explicitly, in an idealized sense, for this but at some price in relation to the approach here. These models are more restrictive in the mutational aspect and but nevertheless seem less predictive, without specification of parameter values, of general age-time patterns of risk.

It was noted that a moderate decrease at old ages in the log-log slope of background cancer rates, often seen, can result in the dose-linear term in equation (3) to decrease faster than $1/\text{age}$. However, that pattern in background rates is likely due in large part to individual heterogeneity in susceptibility to cancer, and selection at older ages. It would be misguided to strive for mechanistic models accommodating this. I believe that the likely reason for the age decrease in figure 1 being more like $1/\text{age}^2$ is the difficulty in separating age-at-exposure effects and variations with age. As seen in figure 5, if analysis is restricted to ages-at-exposure over 20 the decrease with age is less rapid.

The type of results indicated in figure 5 are indeed providing useful guidance to RERF statisticians and epidemiologists. It was first observed by Kellerer and Barclay (1992), on purely empirical grounds, that a decrease of the $\text{ERR}$ with attained age might largely substitute for what had been considered an age-at-exposure effect. This observation had less impact than it should have, probably because many considered the age-at-exposure effect more biologically plausible. Results in the direction of this paper, starting with Pierce and Mendelsohn (1999), have resulted in reconsideration of this. See also in this regard Pierce et al (1996), where absence of need for age-at-exposure effects in the $\text{EAR}$ was considered. We are coming to realize that interpretation of age-at-exposure effects is much more difficult than had been thought, for reasons raised in the penultimate paragraph of Section 2 and seen in the contrast of figures 1 and 2. For a cohort study with substantial secular trends in background rates, a generalizable age-at-exposure effect simply cannot be defined without consideration of whether the causes of the secular trends act multiplicatively or additively with radiation effects. The generalizability also depends on the presence of such secular trends in the target population.
In another vein, it seems possible that considerations exemplified in figures 3 may be useful specifically for radiation protection issues regarding risks at very low doses. Suppose that radiation protection remains largely based on the presumption that radiation risks at low doses are small but not zero. Then I believe that progress might be made through clearer understanding and communication of the meaning of very small cancer risks. It seems useful to consider, or perhaps emphasize if widely believed, that radiation exposure does not in itself cause cancers, but contributes to their cause. Certainly, all that we can directly assess is how it increases age-specific cancer rates. A reasonable view is that it achieves this by eliminating the waiting times for otherwise-caused contributions to the carcinogenic process. I believe there are opposing views, and that it would be useful to carefully argue out the matter. The results pertaining to figure 3 suggest, using low-dose linear extrapolation for nominal values, that an acute radiation exposure may be essentially equivalent to a 2 or 3 days/mSv expected increase in “cancer age”. On the other hand, the so-called “lifetime risk” values used in radiation protection are summaries (weighted sums) of the age-specific increases in cancer rates. The sense in which these values refer to additional cancers is a more subtle matter than seems widely realized. Whether the increase in cancer age characterization may have practical advantages over lifetime risk values, for risk communication, is not clear but may warrant consideration. At any rate, it is certainly true that to the extent the cancer age argument is actually valid, it does provide a far more comprehensive summary of age-specific increases in cancer rates than does the lifetime risk.

Carcinogenesis is undoubtedly very complicated, and the best use of highly idealized considerations as in Section 3 and other mechanistic modeling is probably only for possible guidance in descriptive analysis and interpretation. That is, such theoretical results may usefully be taken as suggestions to be explored in data analysis, and suggestions of interpretation to be balanced against other biological considerations.

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References

Armitage P and Doll R 1954 The age distribution of cancer and a multi-stage theory of carcinogenesis British Journal of Cancer **VIII** 1–12

Kai M, Luebeck E G and Moolgavkar S H 1997 Analysis of the incidence of solid cancer among atomic bomb survivors using a two-stage model of carcinogenesis Radiation Research **148** 348-358


Luebeck E G, Heidenreich W F, Hazleton W D, Paretzke H G, and Moolgavkar S 1999 Biologically based analysis of the data for the Colorado uranium miners cohort: age, dose, and dose-rate effects Radiation Research **152** 339-351

Moolgavkar S H and Luebeck E G 1990 Two-event model for carcinogenesis: Biological, mathematical, and statistical considerations Risk Analysis **10** 323-341


Pierce D A and Mendelsohn M L 1999 A model for radiation-related cancer suggested by the atomic bomb survivor data Radiation Research **152** 642-654
