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Age–time patterns of radiogenic cancer risk: their nature and likely explanations

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Abstract

It is important for both 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 shall provide current information on this for solid cancers among atomic-bomb survivors, pointing out some of the difficulties in description and interpretation. I shall then take up some stochastic considerations regarding accumulation of mutations, which may help in dealing with these difficulties. These considerations are highly idealised, 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 they provide insights fairly 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 idealised 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 atomic-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 shall conclude with more general discussion of the issues raised.

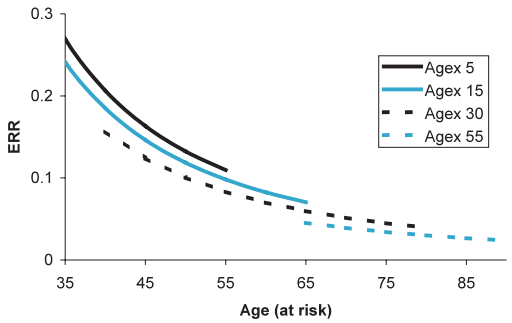

Figure 1. Sex-averaged ERR/100 mSv among atomic-bomb survivors for most solid cancers combined, shown for four ages at exposure. Choices are involved in arriving at such descriptions and other forms, with somewhat larger age-at-exposure effect and less general decline with attained age, are possible.

2. Description of cancer risks

Results here are for cancer incidence among atomic-bomb survivors (Thompson *et al* 1994) during 1958–95, omitting uterine and thyroid cancer. Uterine cancer results for atomic-bomb survivors are very different from most solid cancers, in that substantial radiation risk is seen only in those exposed under about 10–15 years of age. Thyroid cancer radiation risks also have age–time patterns very different from those of most solid cancers (Thompson *et al* 1994). Such restrictions can be useful when the primary aim is improved understanding of age–time patterns. Other cancer types with strong hormonal influence have somewhat distinctive patterns, but to a lesser extent that will not interfere with aims here. 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 6486 of these to those with positive radiation dose (>0.005 Sv), of which about 700 are estimated to be radiation related. Figure 1 provides a description of the excess relative risk (ERR = 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, requires some historical perspective. From about 1985–95 the primary descriptions were in terms of presumed approximately age-constant ERRs 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. During the 1990s it became moderately clear that for those exposed as children the ERR decreases over the follow-up, rather as in figure 1 (Little *et al* 1991, Pierce *et al* 1996). However, descriptions remained mainly in terms of age-constant 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 ERR with attained age. It is indeed difficult in any cohort study to distinguish between these two types of effect. It was long considered by most that age-at-exposure effects are biologically more plausible than a decrease in 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

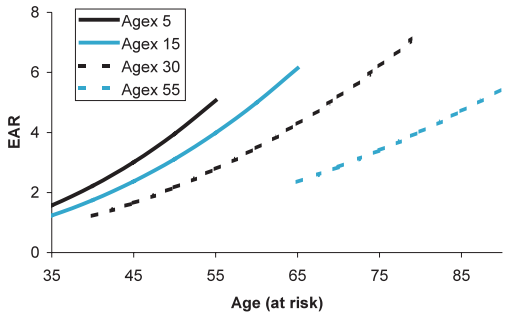

Figure 2. Sex-averaged EAR/10 000 PY 100 mSv among atomic-bomb survivors for most solid cancers combined, shown for four ages at exposure. In contrast to the ERR, the sex difference is not statistically significant. It could be said that the age-at-exposure effects seen reflect birth cohort variation in background cancer rates.

formulations, previously and here, the age-at-exposure effect in the 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 this—usually, but not necessarily, for the excess absolute rates (EARs)—the so-called age-at-exposure effects are quite different from the usual ones for the ERR. This difference is exemplified below.

We see therefore 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 (EARs) for the class of cancers considered; even in more detailed analysis there is no indication of declines in the EAR. Note that the apparent age-at-exposure effect is greater for the EAR than the 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 EAR is only marginally significant, whereas for the 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 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 multistage model (Armitage and Doll 1954). A fuller account can be found in an unpublished paper by the present author and Michael Væth, on the RERF website (www.rerf.jp) under Statistics Department, Resources (to appear in Biostatistics).

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 shall 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 idealisation 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, 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 shall 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 idealisation 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, and for brief exposures would have no effect on the age–time pattern considerations here. A limiting process deals with acute exposure. The critical idealisation 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 its consequences and compare them with what is seen in studies. It presents no problem in the following if some of the required mutations act recessively (must occur at both locus-specific 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 $\mathrm{d}a/\mathrm{d}a^*$ 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 with rates on the ordinary age scale for the unexposed, which differ by birth cohort. Although each of these plots would show substantial dose effect on the original age scale, in neither of those shown is there indication of any radiation effect other than the 'cancer age' increase.

Now consider the implications for the relative risk (RR), considering a single sex or, more roughly, the relative risk averaged over sex. The above result means that the RR of exposed to unexposed is given by

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

or subsequent to termination of either acute or prolonged exposures by

$$\mathrm{RR}(a) = \frac{r_0(a + \beta D)}{r_0(a)}, \tag{2}$$

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

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

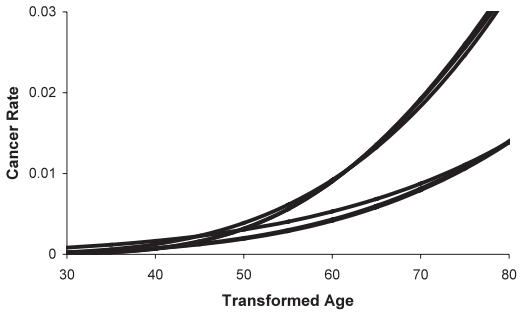

Figure 3. Age-specific cancer rates for three dose categories with cut points 0.005 and 0.75 Sv, on the transformed age scale $a + \beta D$, which accurately accounts for the effect of exposure. There are three upper curves for men with $\beta = 0.45$ years/100 mSv, and the three lower ones for women with $\beta = 0.90$ years/100 mSv.

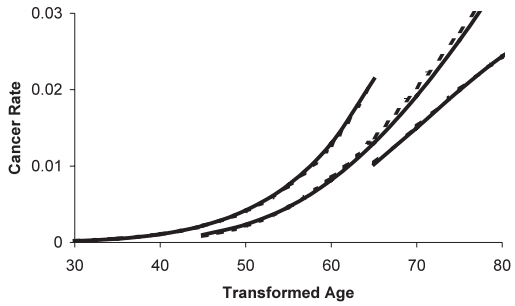

Figure 4. Age-specific male cancer rates for three age-at-exposure groups with cut points 20 and 40 years. Comparison of rates for entire cohort on the transformed age scale of figure 3, and those for the unexposed on the original age scale. Thus there are two curves for each age-at-exposure category. 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.

Although formally the RR is here a polynomial in dose, for p in the usual range of four to six and for doses and ages where the RR is no greater than about three 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 the form $r_0(a) \propto a^{k-1}$. We prefer, however, to minimise reliance on this further assumption.

Figure 5 compares the 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 an age at exposure of 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 idealised 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.

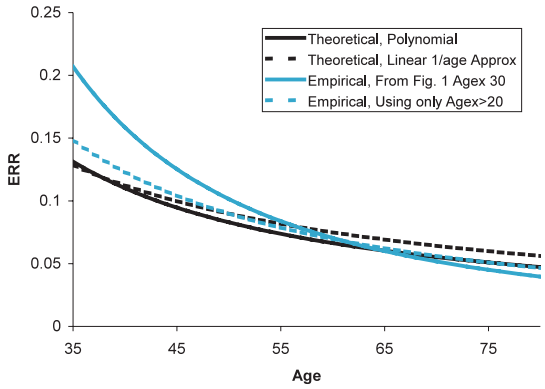

Figure 5. Theoretical and empirical predictions of ERR. The solid and dashed curves (lower two curves at young ages) are fits of the full polynomial and the dose-linear approximation from equation (3). The highest curve at young ages is from figure 1, taking an age at exposure of 30. The light-shaded curve is a similar empirical description when restricting to ages at exposure of at least 20.

4. Discussion

Before discussing results above, I note that 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 Research Council 1999). This uses equation (1) along with the approximation $r_0(a) \propto a^p$. 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 $a^* = \int_0^a s(t)[1 + \beta\, d(t)]\, \mathrm{d}t$. This introduces an age-at-exposure effect in the 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 effects of this nature since transition rates can depend arbitrarily on the mutational status of the cell. There are other modelling approaches (Moolgavkar and Luebeck 1990, Kai *et al* 1997, Luebeck *et al* 1999) allowing explicitly, in an idealised 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) decreasing faster than $1/\text{age}$. However, that pattern in background rates is probably 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 types of result 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 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 EAR was considered. We are coming to realise 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 figure 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 emphasise 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 per 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 realised. Whether the increase in cancer age characterisation 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 idealised considerations as in section 3 and other mechanistic modelling 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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