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The Future of Human Radiation Research

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Exploratory analysis—a visualization of the data from RERF by non-parametric methods

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Assessing the risk of small doses of ionizing radiation is an indirect procedure. Animal experiments, cell studies and the advances of molecular radiation biology have led to general insights, but they cannot provide numerical risk estimates. Such estimates must be linked to epidemiological findings at doses that are sufficiently large to produce observable excess cancer rates. They are thus extrapolated from complex data on the basis of uncertain models. These limitations are unavoidable, but they can lead to controversy and to highly divergent claims.

The uncertainty of risk estimates is not specific to ionizing radiations. In fact, the major radioepidemiological studies and the principal compilations of their results might well serve as models for quantitative risk estimation in other fields. But this is not generally appreciated—instead there has been growing public and scientific controversy about the risk estimates for ionizing radiation. The re-evaluation of the follow-up of the atomic bomb survivors is widely seen as a renouncement of earlier results, not as their improvement and extension. The critical attitudes have been amplified and have become extraordinarily unbalanced after the reactor catastrophe in Chernobyl. In the Soviet Union itself we witness escalating problems—five years after the accident—and a general failure of the population and even of the medical community to arrive at a realistic perception of radiation risks. The social and economic consequences are grave. It is therefore more urgent at present to make risk estimates understandable than to refine them.

Modern numerical and mathematical methods are necessary, but to some degree they are black box approaches. There is therefore a need, even for experts, to visualize the data more clearly and to precede computations and modelling by fairly simple exploratory steps. The subsequent considerations are to indicate the potential of such a stepwise analysis by an application to the cancer mortality data of the atomic bomb survivors.

This paper will not start with the most elementary steps to elucidate the data, but one may note that there are open questions even on this elementary level. The basic task in the study of radiation induced cancer is the determination of cancer rates, *i.e.* of hazard functions. In epidemiological investigations suitable statistical methods are usually applied. But in animal studies it is still not infrequent that crude estimates are used, where competing risk corrected "actuarial estimates" would be required for meaningful results. For "right censored" data (see *e.g.* Peto et al, 1980) such estimates can be obtained readily by a method that was first employed by Daniel Bernoulli (Bernoulli, 1766), although it is now better known as the Kaplan–Meier estimate, or in a different form as the sum-limit estimate (see *e.g.* Kellerer & Chmelevsky, 1982). For "doubly censored" data a somewhat more complex procedure is required, termed isotonic regression (Hoel & Walburg, 1972); the method has rarely been utilized in radiation studies, although it is required in all those cases where tumours are non-lethal and are only discovered incidentally (Barlow et al, 1972). Studies of precancerous lesions, or even of molecular changes preceding the development of cancer, will play an increasing role in future radiobiological studies, and isotonic estimates may then become a more important tool. A generalization of isotonic regression will be employed in the subsequent computations.

Although these matters will not be dealt with here, it is of interest to note certain unsolved problems concerning the derivation of error limits for isotonic regression. Equally interesting is the question of non-parametric tests for the comparison of hazard functions. For right-censored data one can use the log-rank test (Gehan, 1965; Mantel & Ciminera, 1979) or modified rank-order tests, such as the Breslow test (Breslow, 1970; Peto & Peto, 1972; Prentice, 1978). But these tests can be faulty if they are used for the comparison of two samples of substantially different sizes (Kellerer & Chmelevsky, 1983), and there is no generally known method to extend the tests to small samples. For doubly censored data the problem is even more difficult; one can employ makeshift procedures for the comparison of large samples, but there appears to be no suitable non-parametric test for this condition.

Such open questions might invite a more systematic discussion. But the subsequent considerations deal with practical examples. They are intended to demonstrate, in terms of the data from RERF, that elementary analysis can be a useful support for more complex calculations.

Non-parametric analysis applied to the Japanese data

The subsequent analysis deals with the Japanese data, but it will be apparent that the approach would be equally applicable, and perhaps even more suited, to long term exposures. In fact, assumptions will be utilized

that have in the past been applied for the analysis of lung cancer in uranium miners (NCR, 1980).

A recent discussion of model construction and fitting is found in the report BEIR V (NCR, 1990). In the present context it is sufficient to consider the most general relations only. Consider a short time exposure with dose D. The cancer incidence or mortality rate at age a subsequent to the exposure at age e can then, in a fairly general way, be described through several functions that depend on age at exposure, e, on age attained a, on time $t=a-e$, since exposure, and on dose D:

$$r(a,D,e)=r_0(a)\,[1+h(e)g(a-e)c(a)f(D)] \qquad (1)$$

Simpler assumptions are usually adequate to fit the observed data. The relative risk model for solid cancers, as usually applied to the Japanese data has the form

$$r(a,D,e)=r_0(a)\,[1+h(e)f(D)] \qquad (2)$$

where $r_0(a)$ is the age specific spontaneous cancer rate, and where the relation is assumed to apply after a latent period of 5 or 10 years subsequent to the exposure. The analysis of the ankylosing spondylitis patients in the UK (Darby et al, 1987) has suggested the need to include a dependence on time after exposure when eqn. (2) is used. The need to include such a term for the Japanese data might well arise when the follow-up is extended to the higher ages of those who were exposed to the atomic bomb radiation as children or juveniles.

Equation (2) may be termed an age at exposure model. It differs from the age attained model used for the analysis of the lung cancer incidence in uranium miners. In its simplest form, without a dependence on time after exposure, and in its reduction to an acute exposure the relation reads

$$r(a,D)=r_0(a)\,[1+c(a)f(D)] \qquad (3)$$

One may ask whether this simple attained age model, or a more general dependence of the tumour rate on the two variables a and D, can also represent the Japanese data. The problem will here be examined in terms of the total cancer mortality without leukaemia.

The data set released by RERF of cancer mortality in Hiroshima and Nagasaki up to 1985 (RERF, 1989) is utilized for the computations. It contains data for the two sexes, the two cities, for 5 year age classes, for 5 year observation periods and for 10 shielded kerma intervals that are rather crude at the higher doses. The RERF data set reflects the prevalent use of the age at exposure model; it partitions the data into cells of age at exposure and of time since exposure. For the subsequent computations the data are, in a relatively rough procedure, translated into cells of shielded kerma and of age attained.

Naive estimates of the cancer mortality rate

Figure 1 gives, in its lowest panel, a scatter diagram of the person-years at risk for the two cities, for both sexes, and for the entire observation period beginning 5 years after the exposure to the bomb radiation. The

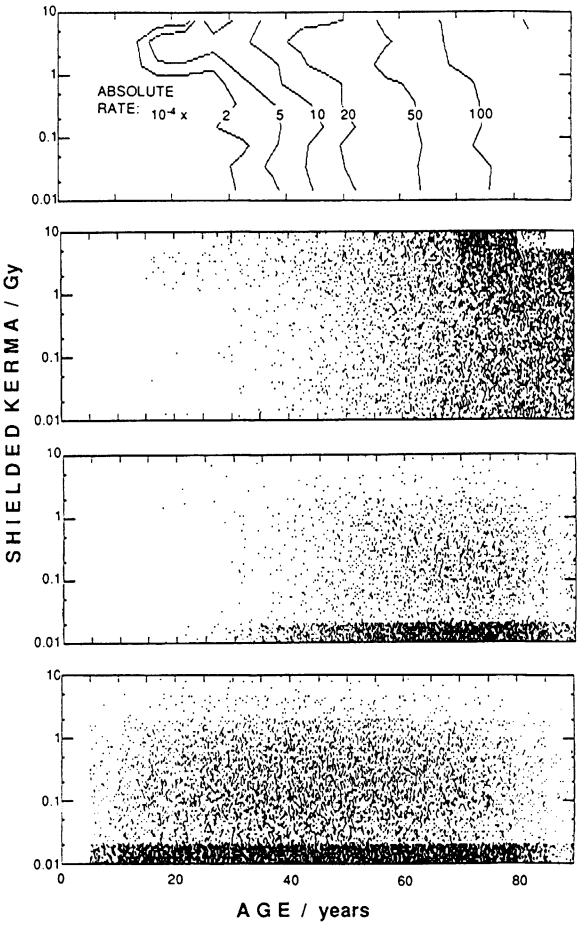

Figure 1. Scatter diagrams of person-years, of cancer deaths (without leukaemias) and of the resulting crude cancer mortality rates among the life-span study sample of the atomic bomb survivors. Each point in the lowest panel corresponds to 100 person-years; each point in the second panel to one cancer death in the period up to 1985. The tick marks on the abscissa and the ordinate indicate the separation into cells of age attained and of shielded kerma that are used in the computations. All kerma values below 20 mGy are assigned to the interval 10–20 mGy. The top panel gives lines of constant rate per year for the scatter diagram of crude rates.

tick marks on the ordinate and on the abscissa in the panels in Fig. 1 indicate the separation into a total of 18×9 cells. Each point stands for 100 person-years at risk: the points are randomly positioned within their cell of attained age and of shielded kerma. For simplicity, all kerma values below 20 mGy are assigned to the kerma interval 10–20 mGy; this accounts for the high point density in the lowest band of the panel. In the subsequent discussion the simple term dose is used instead of shielded kerma, but the correct term is used in the figures.

The intermediate panel of Fig. 1 gives the corresponding plot for all cancer deaths. Each point represents a

cancer death, and, as with the person-year diagram, there is an implicit latency period of 5 years owing to the 5 year delay in the beginning of the follow-up. A longer latency period may be in better agreement with the observations, but the present treatment is aimed at an explanation of the general approach and not at a definitive numerical analysis.

The scatter diagrams are in themselves not highly informative; they merely indicate the magnitude of the LSS sample and the broad range of dose and ages in the observation. It is, however, evident that a series of similar graphs for individual cancer types would be instructive, and that modified diagrams can bring out various essential features of the Japanese data.

The present discussion aims to provide an elementary approach towards the derivation of cancer rates and their dependence on dose and on age attained. The most straightforward procedure uses the naive estimates of the cancer mortality rate that equal the ratio of cancer deaths in each cell to the person-years at risk in the same cell. The result, *i.e.* the ratio of the point densities in the bottom two panels of Fig. 1, is given as the scatter plot in the next panel. Better quantitive information would, of course, be provided by a matrix of numbers, but even in the scatter diagram one recognizes the trend of larger values at higher doses and higher ages. For a more quantitative representation of the data one can compute, by simple linear interpolation within the matrix of estimated values, lines of constant cancer rate in the attained age *vs.* kerma plane. The resulting lines are given in the top panel of Fig. 1.

The lines of equal rates that are obtained by this naive method are evidently affected by statistical uncertainties. But owing to the large size of the total LSS sample they provide a meaningful general picture of the cancer mortality and its increase with age attained and with dose. However, the method is unsuitable for smaller data sets. Even for the subset of data from Nagasaki one obtains curves of very irregular appearance, and the method would be even less applicable to the analysis of the frequency of individual tumour types. Improved methods are therefore required, and they will be considered in the subsequent section.

One can obtain added relevant information directly from the matrices of person-years and cancer deaths. Useful examples are found in the recent reports from RERF (Preston et al, 1987; Shimizu et al, 1988). Figure 2 gives, for comparison with the earlier computations, the cumulative excess cancer deaths as a function of age and dose for Hiroshima and Nagasaki, and for males and females; the observed rates in the kerma band below 20 mGy are used as control cancer mortality rates. Even without detailed consideration one recognizes that the results of the attained age model are largely in line with conclusions from the age at exposure model.

Isotonic estimates of cancer mortality

A variety of smoothing procedures could be employed to improve the naive estimates of cancer mortality rates. The choice of a suitable procedure entails, however, some degree of arbitrariness and any resulting bias may be difficult to judge. A more transparent constraint is therefore desirable. Monotonicity of the rates in age attained and in dose can serve this purpose. It is, of course, not a postulate of general validity. Excess cancer frequencies among the atomic bomb survivors appear to plateau at estimated doses beyond a few gray, and one cannot exclude the possibility that they may actually decrease. Similarly there are cancers with decreasing rates at high ages; lung cancer is one example. Such effects are, however, readily recognized, and their influence can be reduced or eliminated by an appropriate cut-off in age or in dose.

As stated in the introduction, one-dimensional isotonic regression is a suitable and fairly simple algorithm for certain estimations of hazard functions or cancer prevalences. The algorithm can be extended to the two-dimensional case. In this extension it provides monotonous maximum likelihood fits to the ratio of event numbers and person-years at risk.

In contrast to the one-dimensional case, the algorithm is somewhat complicated, but this is irrelevant to the user. We employ for the two-dimensional isotonic regression a version written by Gebhardt (Gebhardt, 1970). It accepts as input the array of cases and of person-years, together with the reference variables. As output it provides the corresponding array with rates that increase monotonically in the reference variables a and D.

Figure 3 gives the results which are the monotonic analogue to the data in Fig. 1. The rough representation in the scatter diagram is, of course, hardly different in appearance from the corresponding point cloud in Fig. 1. The lines of equal rates are different in detail from their analogues in Fig. 1. In the general trend they do not differ; they merely clarify the dependences. Any possible decline at high doses has little influence; computations with a dose cut-off at 2.5 Gy or 5 Gy provide essentially the same results up to these doses.

The diagram of constant rates provides, in a remarkably compact form, the overall cancer mortality rate in Hiroshima and Nagasaki in its dependence on age and dose. The derivation is notable for its directness and the simplicity of the underlying constraint of monotonicity. It has the added advantage that it is insensitive to cell size; it could readily use a data set from RERF that contains less coarse kerma intervals. No examples are given here, but the strength of the method is, of course, that it is equally applicable to the small data sets for individual tumour types.

The isotonic regression can be applied in a variety of modifications. For example, one can multiply the person-year matrix by the observed age specific cancer mortality rates in the unexposed group, *i.e.* in the lowest kerma interval. The ratio of the matrix of cancer deaths to this modified person-year matrix then provides the naive estimates of relative risk. From the resulting lines of constant relative rate it is apparent—and this is in line with all earlier analyses from RERF—that the

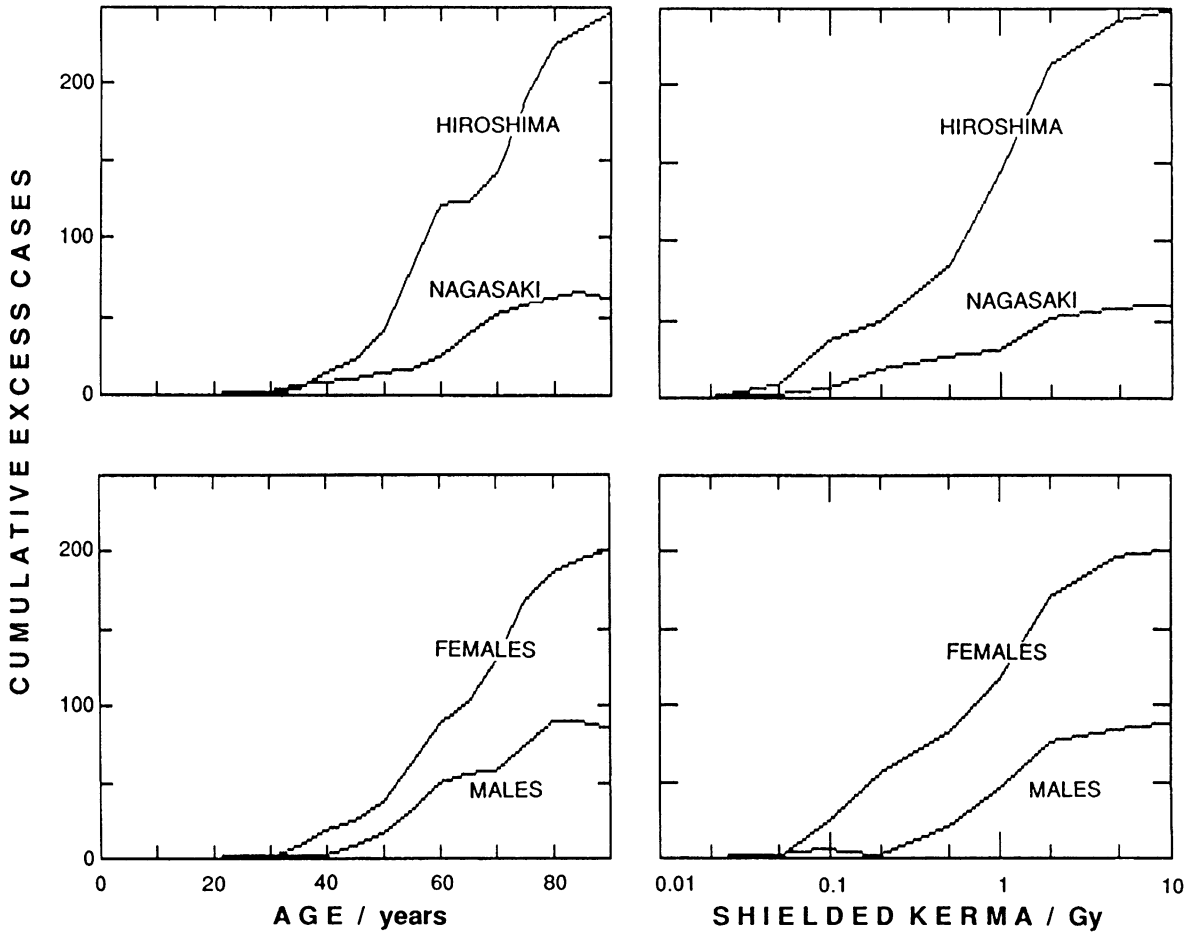

Figure 2. Cumulative distributions of excess cancer deaths computed from the table of crude cancer mortality rates in age attained and shielded kerma. The observed rates at kerma values below 20 mGy are used as controls.

relative risks in specificed dose are largest at lower ages. One can therefore apply isotonic regression—with reversed monotonicity in age—and one obtains results which are given in the top panel of Fig. 3. The result shows that the doubling doses for the cancer rates are 1 Gy or less at ages below 40, and that they are substantially higher, by a factor of 2–4, at ages beyond 55.

There is no known method to obtain standard errors of the isotonic estimates. In the absence of such methods it is useful to compare the results from the separate analysis of different subsets of the data. Figure 4 gives a comparison in terms of isotonic rates for Hiroshima and Nagasaki, and for males and females. The results for the relative rates are shown in Fig. 5; they, too, show consistent overall trends.

Comparisons with analytical models

The elementary analysis and its extension to isotonic regression is useful, but it needs to be seen as an initial step that provides guidance towards the application of more specific models. The age specific spontaneous cancer mortality rate in Hiroshima and Nagasaki, *i.e.* the probability per year at age a to die of cancer, can be adequately represented by a power function in age attained:

$$r_0(a) = 0.0017 t^{4.4} \qquad (t = a/50 \text{ years}) \qquad (4)$$

The scaled age variable t is here used in order to obtain coefficients that are more readily grasped; 0.0017 is thus the probability of dying with cancer between age 50 and 51. A fairly simple model to fit the data in Fig. 3 is of the form

$$r(a,D) = c_0 t^{p_0} + c_1 t^{p_1} D = c_0 t^{p_0}(1 + c t^{-p} D) \qquad (5)$$

with $p > 0$. Linearity in dose D is here invoked for simplicity and in line with the recent results from RERF. The *a priori* assumption of linearity would be avoided in explicit computations.

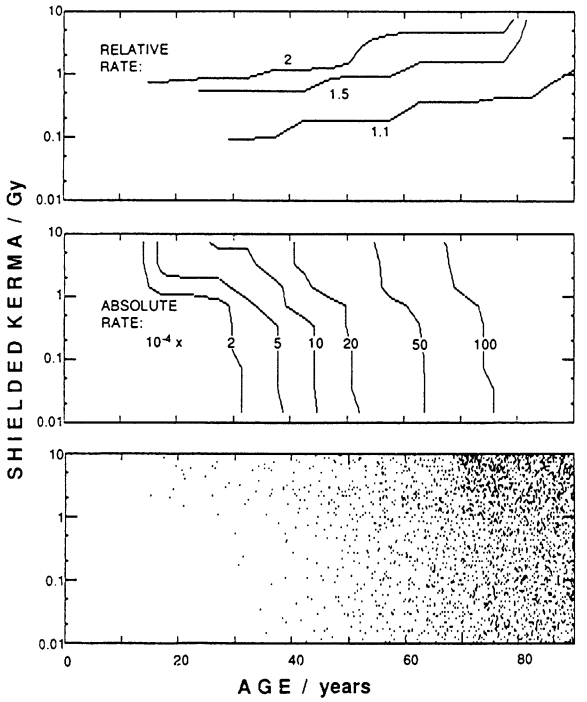

Figure 3. Bottom panel: scatter diagram of the cancer mortality rate in the LSS as a monotonous function of age attained and shielded kerma. Intermediate panel: lines of constant rates per year for the same isotonic function. Top panel: lines of constant relative rates, also obtained by isotonic regression.

The analogous age at exposure model is

$$r(a,D,e)=c_0 t^{p_0}(1+ce^{-pD}) \qquad (6)$$

where e is the age at exposure, and a is the age attained.

Equations (5) and (6) are not applicable at high doses. In the computations one may crudely account for this by a cut-off at a certain dose or by assuming constant rates beyond this dose. In the subsequent computations the cut-off is chosen to be 2.5 Gy. This may appear low, but lethality was high in Hiroshima and Nagasaki at 2.5 Gy, and it is therefore felt that the survivors with estimated doses beyond 2.5 Gy are in fact a group who had on average less dose than deduced from the circumstances of their exposures.

Maximum likelihood fits to the two models are obtained by the computer algorithm AMFIT which is part of the software package EPICURE developed by Preston et al (see *e.g.* Preston et al, 1991) for general use in epidemiological risk computations. AMFIT provides the solutions

Equation (5): $c_0=0.00165$/year $p_0=4.38$, $c=0.55$/Gy, $p=1.37$
Equation (6): $c_0=0.00166$/year $p_0=4.33$ $c=0.48$/Gy $p=0.38$

The deviance is 3130.2 (3395 df) for the attained age model of eqn. (5) and 3134.2 (3395 df) for the age at

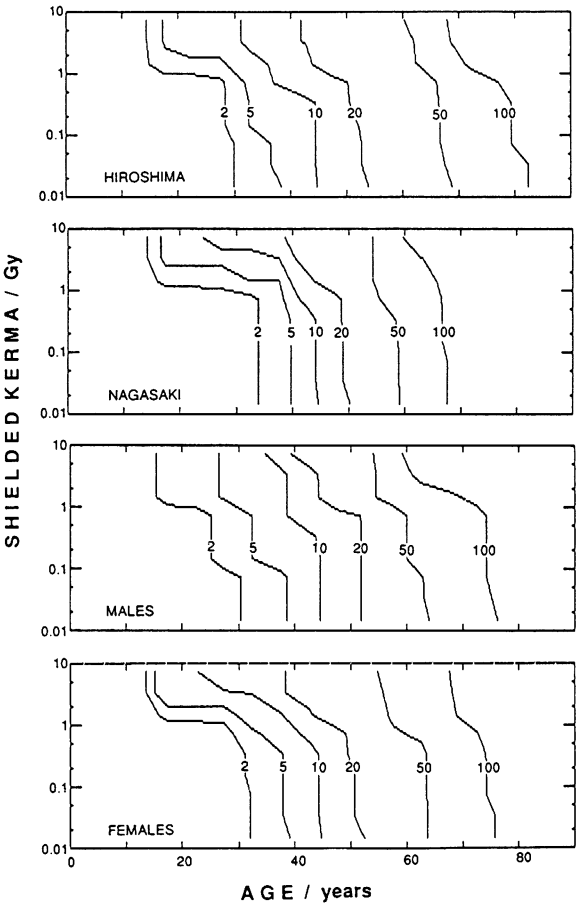

Figure 4. Cancer mortality rates obtained by isotonic regression in the life-study sample, separately for Hiroshima and Nagasaki, and for males and females. The rates are given in 10^{-4}/year.

exposure model of eqn. (6). The somewhat simpler attained age model appears, therefore, to be no less suitable to represent the cancer mortality of the atomic bomb survivors than the age at exposure model. More detailed computations will, however, be necessary to substantiate the comparison.

It is especially uncertain whether the parameter p, *i.e.* the age dependence of the radiation induced excess rate, can be reliably obtained from the overall fit to the data. The deviance is mainly determined by the fit at high ages where most of the cancer deaths occur. The fit to the few cancer deaths at young and intermediate ages has little influence on the deviance. Figure 6 compares the isotonic estimates with the analytical fit in terms of eqn. (5), and there are, indeed, differences at young ages, although they are based on few cancer deaths.

The computations need to be improved, for example by use of a data set that is partitioned into age at

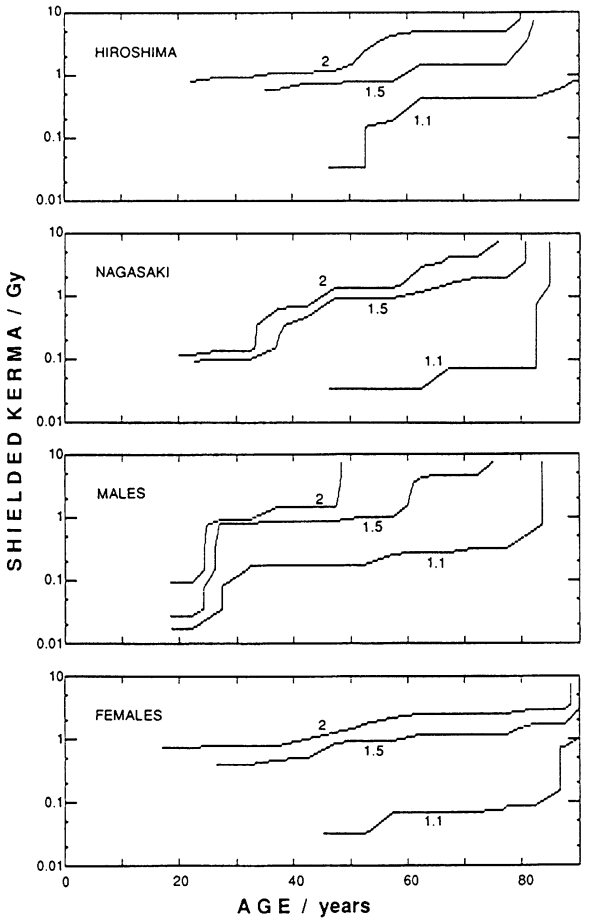

Figure 5. Relative cancer mortality rates obtained by isotonic regression in the life study sample separately for Hiroshima and Nagasaki, and for males and females.

exposure and age attained, rather than age since exposure. But, even in its rough form, the relation

$$r(a,D)=0.0017t^{4.4}(1+0.6t^{-1.4}D) \quad (t=a/50 \text{ years}) \quad (7)$$

is a convenient quantification of the total cancer mortality, without leukaemia, in the atomic bomb survivors. In particular the relation can be used to assess the cumulative risk, which is not substantially influenced by the small frequency of solid tumours at young ages.

The cumulative cancer mortality rate is obtained by integration of eqn. (5) or eqn. (7)

$$R(a,D)=\int_0^a r(x,D)\ dx=k_0t^{p_0+1}+k_1t^{p_1+1}D \quad (8)$$

with $k_0=50$ years (c_0/p_0) and $k_1=50$ years (c_1/p_1). With the parameters obtained from AMFIT:

$$R(a,D)=0.019t^{5.4}+0.017t^4D \quad (t=a/50 \text{ years}) \quad (9)$$

An exposure at age e thus causes a cumulative rate

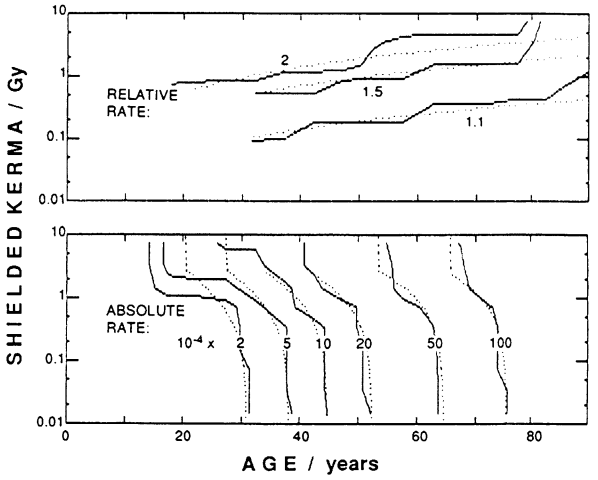

Figure 6. Lines of constant cancer mortality rate per year *vs.* age attained and shielded kerma. The solid lines are those given in Fig. 3. The dotted lines correspond the the solution obtained with AMFIT (see eqn. (7)).

up to age a, *i.e.* a total excess cancer mortality risk that equals

$$R=R(a,D)-R(e+l,D)$$

where l is the latency period. As seen from Fig. 7, the total risk for mortality from solid cancers is, in the attained age model, nearly independent of age at exposure, if the exposure occurs before age 40. It is then roughly equal to $R(a,D)$.

The attained age model is largely equivalent to the more complex age at exposure model with a decline in time of the proportional hazard factors. It is therefore understandable that the integrated risk is somewhat less than values computed from the conventional relative risk model with no decline in time (see eqn. (6)). The values in Fig. 7 are about half as large as recent estimates, *e.g.* in BEIR V (NCR, 1990). Figure 7 indicates that they agree well with the cumulative excess rates

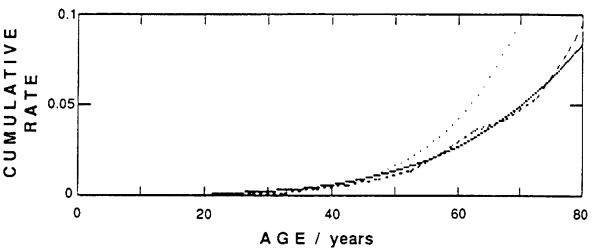

Figure 7. Solid line: cumulative excess cancer mortality rate per Gy, $R(a,D)$, according to eqn. (9). Broken line: crude cumulative rate obtained directly from the tabulation of cancer deaths, person years, and person-year Gy in age attained cells. Dotted line: for comparison, cumulative spontaneous cancer mortality rate inferred from the data below 20 mGy.

which are directly taken from the input grouped into age attained cells.

Conclusion

Sophisticated computations are essential in the evaluation of radioepidemiological data, but they can be supported, and their results can be made more transparent by an exploratory analysis that uses elementary methods. In the present study simple diagrams and computations were employed to examine the possibility that the cancer mortality data of the atomic bomb survivors can be represented by the age attained model that has earlier been applied for the analysis of the lung cancer frequencies among uranium miners. The elementary analysis is seen to provide rather direct and fairly transparent guidance towards more complex modelling of the data.

Analytical models can provide compact descriptions of the dependences of rates and of cumulative rates on dose and on age. However, the overall likelihood is only a summary measure of the fit that is attained; a more explicit comparison of the results with the data is therefore desirable. In the preceding analysis such a comparison has been achieved by the use of isotonic estimates of the cancer mortality rate as a function of dose and age attained. It is felt that non-parametric computations, either with the condition of monotonicity or with modified general constraints, can be a useful addition to analytical fits and to the use of coarse age and dose strata.

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