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The Shape of the Cancer Mortality Dose-Response Curve for Atomic Bomb Survivors

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In this way, the Foundation will be able to more expeditiously report recent findings on the late biological effects of exposure of man to ionizing radiation resulting from the atomic bombings of Hiroshima and Nagasaki.

1989年から，放射線影響研究所の業績報告書は，従来の日英両文を併記した方式では発行しない．主要な報告書については，今後も日英両文で印刷するが，それぞれ別に発行する．内容が高度に専門的であり，一般の関心が少ないと思われる報告書については英文のみとし，日本文の要約を添付する．

これにより，広島・長崎の原爆電離放射線被曝の人体に及ぼす晩発性生物学的影響に関する最近の知見を今までよりも速やかにお知らせできることと思う．

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原爆被爆者における癌死亡率の線量反応曲線の形状§

The Shape of the Cancer Mortality Dose-Response Curve for Atomic Bomb Survivors

Donald A. Pierce, Michael Vaeth

統　計　部

要　約

原爆被爆者のデータにおける癌死亡率についての線量反応曲線の形状を，線形-二次関数モデルに基づいて解析した．結果を白血病以外のすべての癌，白血病，及び両者の曲線の弯曲が同じであると仮定してその両者を合わせたものについて示した．これらのデータ以外に，凹形の線量反応曲線を示唆する十分な情報があるため，ここでは，最良の適合を示す線量反応曲線を推定することよりも，むしろ線形-二次関数モデルに基づいてデータと一致する最大の弯曲を推測することに重点を置く．この種の推論は，線量推定値の不確実性により相当影響されるものであり，それによる偏りに十分に対応できる方法を適用した．ここで弯曲の程度を表すために使用した基本的な方法は，適切な低線量リスク推定値を得るために，線形リスク推定値をある因数で割ることである．幾つかの有力な委員会は，以前に，そのような因数の範囲を2～10，あるいは1.5～3とすることを勧告した．本研究の結果では，およそ2以上の値は，線形-二次関数モデルに基づく限りデータと少なくともある程度の不適合を呈することを示唆している．しかしながら，低線量リスクに関しては，これらのデータに確実な情報がほとんどないことを強調したい．ここでの推論は，線形-二次関数モデルを仮定したことによって得られる低線量と高線量リスクの結合に大きく依存している．

§ 本論文にはこの要約以外に訳文はない

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The Shape of the Cancer Mortality Dose-Response Curve for Atomic Bomb Survivors[§]

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Summary

The shape of the cancer mortality dose-response in the atomic bomb survivor data is analyzed in the context of linear-quadratic (LQ) models. Results are given for all cancers except leukemia as a group, for leukemia, and for combined inferences assuming common curvature. Since there is substantial information aside from these data suggesting a dose-response concave from above, the emphasis here is not on estimating the best-fitting dose-response curve, but rather on assessing the maximal extent of curvature under LQ models which is consistent with the data. Such inferences are substantially affected by imprecision in the dose estimates, and methods are applied which make explicit allowances for biases due to this. The primary means used here to express the extent of curvature is the factor by which linear risk estimates should be divided to arrive at appropriate low-dose risk estimates. In the past, influential committees have recommended ranges of 2–10 and of 1.5–3 for such a factor. Results here suggest that values greater than about 2 are at least moderately inconsistent with these data, within the context of LQ models. It is emphasized, however, that there is little direct information in these data regarding low-dose risks; the inferences here depend strongly on the link between low-dose and high-dose risks provided by the assumption of an LQ model.

Introduction

Given here is some analysis of the shape of the cancer mortality dose-response curve for the A-bomb survivors, as followed up in the RERF Life Span Study (LSS). Emphasis is on all cancers except leukemia as a group. Substantial attention is given to allowing for effects of imprecision in the individual exposure estimates. The recently revised dosimetry[1,2] is used, but inferences regarding the shape of the dose-response curve are not much affected by the revision, except as noted below. As the neutron component of exposures is very small in the revised dosimetry, the main results to be presented will not distinguish between the shape of the dose-response of low-LET and high-LET irradiation.

[§] **The complete text of this report will not be available in Japanese.**

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The motivation for this investigation is that one of the major uncertainties in assessing radiogenic cancer risks involves extrapolation to low doses from epidemiological investigations, in which the primary information pertains to much higher doses. Indeed, there can be little direct information in epidemiological data about low-dose risks, and the most useful approach is based on combining inferences from such data with other sources of information pertaining to the anticipated shape of the dose-response curve. A prominent model for the excess risk arising from experimental and theoretical radiobiological considerations,[3-5] especially for low-LET irradiation, is the "linear-quadratic" (LQ) form: β dose + γ dose^2, with nonnegative γ, giving rise to dose-response curves concave from above. The main analysis reported here is entirely within the context of such LQ models. It is emphasized that the link between epidemiological data and low-dose risks provided by this model is rather weak; see, for example NCRP 64[4] (Section 11.4). Nevertheless, the degree of emphasis on this model in the radiobiological literature, and its use in previous analysis of these data[2,6,7] suggest that the analysis reported here should be of interest.

In regard to changes related to the new dosimetry, some leveling off of the dose-response now occurs above roughly 4 Gy kerma, which was not seen in the previous dosimetry. However, this apparent change in shape is almost entirely due to the fact that the revised kerma estimates are substantially lower than before. (Kerma is the tissue kerma in air at the location of the survivor, adjusted for shielding by the local environment but not for the shielding of organs in the body.) Of the survivors now in the 4-6 Gy kerma range, 90% previously had estimates above 6 Gy kerma, which were truncated to 6 Gy in all analyses. Without this truncation, the shape of the previous dose-response for all survivors would have been very similar to that with the new dosimetry, although in a higher exposure range. The motivation for truncation at 6 Gy was primarily that survival seemed very unlikely at true exposures above this level, and hence such estimates were of questionable value. To what extent the apparent leveling off may be due to imprecision of dose estimates, or due to a plateau in the true dose-response, is a difficult question to answer. Particular attention is given here to considering these issues in the fitting of LQ models.

The other major change in the dosimetry is that the neutron contribution in Hiroshima, which was previously thought to be substantial, is now very small. Previous analyses have considered linear-quadratic linear (LQ-L) models, allowing for nonlinear LQ gamma-ray effects but not linear neutron effects. Some limited results given here indicate that inferences regarding gamma-ray effects are essentially the same now, whether or not allowance is made for such (possibly) different shapes. Previous use of the LQ-L model does affect, however, the comparison of current and previous conclusions, and this will be discussed.

If the validity of the LQ model over a wide dose range is taken seriously, then there is certainly some information in the A-bomb survivor data regarding the plausible extent of curvature in the dose-response, essentially measured by θ =

γ/β. The focus here is not on estimation from these data of a specific value for this ratio, but rather in assessing the range of θ-values which is consistent with the data, with the aim of facilitating the combination of information from these data with that from other sources in radiobiology, which suggests a dose-response concave from above. This perspective reflects the view taken in NCRP 64[4]:

> "It is often stated, however, that a set of human data is 'consistent with' proportionality [linearity]. The 'consistent with', however, then often becomes equated to the linear, no threshold curve being, in fact, the 'best' or only acceptable fit to the data. This emphasis on proportionality is inherent in the purely statistical question often asked, e.g., 'Is a straight line consistent with the data?' or 'Can the fit be improved by functions other than linear?', as opposed to the more radiobiological question, 'Will the limits of error on the data equally well or adequately fit the nonlinear curves that might be expected from animal data, i.e., a linear quadratic or similar function?'."

The major problem in investigation of the shape of the dose-response, aside from questions about the validity of the LQ model, results from the lack of precision in individual exposure estimates. The presence of such uncertainties results in a distortion of the apparent shape of the dose-response curve, in the direction of underestimation of θ (as well as β), see Jablon,[8] Gilbert,[9] and Pierce et al.[10] It is critical to this investigation to make allowance for this, and two methods are used. The statistical methodology developed by Pierce et al[10] is applied to reduce, from parameter estimates in dose-response analyses, the systematic effects of random errors in the exposure estimates. Further, partly because of uncertainties about the adequacy of this approach, some analyses are made restricting the dose range used to exclude the higher range, where the consequences of exposure estimation errors are most serious. Such restrictions are relevant, aside from the issue of random errors in the dosimetry, in regard to the validity of the LQ model over a wide dose range. That is, there may be a plateau in the true dose-response in the high dose range. For inferences regarding low-dose risks, it is obviously appropriate to focus to the maximum extent possible on the lower part of the exposure range.

The primary concern of this report is all cancers except leukemia as a group. There are weaknesses in using such a broad grouping; but serious problems are involved in further disaggregation, and it is felt that results from this broad grouping of primarily epithelial cancers are useful. Inferences of the type drawn here will be very much weaker even for the major sites, e.g., stomach, lung, and breast. It might be useful to follow up on the approach developed here for such sites, but it is unlikely that there will be statistically significantly different shapes, because of the weakness of the site-specific inferences. In such cases, inferences averaging over sites will be at least as useful as those about differences, and that is the aim of our analysis. Leukemia and nonleukemia must always be analyzed separately because the nature of the excess risks is very different. Results are also given on the shape of the leukemia dose-response,

and on combining this with the nonleukemia results. At the time of the BEIR III report,[3] it was felt that inferences based directly on the shape of the nonleukemia dose-response curve were too limited to be useful, and the apparent curvature of the leukemia dose-response curve was used for nonleukemia risk estimation. With the extended follow-up, and perhaps to some extent with the new dosimetry, this situation now appears to be quite different.

The extent of curvature in an LQ model with given parameter values is of primary interest. This is often measured by the reciprocal of the parameter θ defined above, called the *crossover dose* (CD), this being the dose level at which the linear and quadratic components make equal contributions to the risk. Radiobiologists consider the CD as a useful measure of nonlinearity in transferring results from the laboratory to carcinogenesis in man. The BEIR III Committee[3] estimated θ as 0.86 from the LSS leukemia data, and used this value for nonleukemia as well. The committee felt[11] that the corresponding CD of roughly 1 Sv was reasonable, in view of other information. A recent UNSCEAR report[5] (Annex B, Section 153) has suggested use of CD values in the range 0.5 to 2 Sv, considering evidence from chromosomal aberrations, mutations, and some malignancies.

Our results include emphasis on another closely related measure of nonlinearity particularly appropriate for interpretation of epidemiological data; viz., the extent to which linear extrapolation would overestimate low-dose risks in comparison to using an LQ model with a given CD. The measure of this used here is essentially the same as that called the dose rate effectiveness factor (DREF) in NCRP 64,[4] but will be referred to here as the *linear extrapolation overestimation factor* (LEOF). This measure, defined more precisely below, depends not only on θ but on the range of the data used to fit the linear dose-response which is to be adjusted. It is felt that a very useful way to estimate low-dose risks is to rely primarily on linear risk estimates for descriptions of data, and to ultimately divide these by an LEOF for estimation of low-dose risks. This approach has the virtue of providing some separation between the description of epidemiological data and the extrapolation to low doses which should involve considerations other than such data.

In the BEIR III analysis[3] of all cancers except leukemia in the LSS, the result of using the θ of 0.86 was an LEOF of about 2.2 (taken from the projection of lifetime risks, pp 203-7). The UNSCEAR 1986 report[5] cited above suggests that LEOFs in the range of 1.5 to 3 are reasonable in extrapolation from data with dose ranges similar to the A-bomb survivor data. Gilbert[12] used an LEOF of 3.33, chosen as the midpoint, on a reciprocal scale, of the LEOF range of 2 to 10 suggested by NCRP.[4]

The results here, although not totally clear-cut due to the complications discussed above, suggest that within the context of LQ models these choices of LEOF may be rather large to be consistent with the LSS data. However,

it is not the intention here to draw general conclusions about what LEOF values should be used, since these should involve much broader radiobiological considerations. The most plausible motivation for discounting the inferences drawn here would seem to be that the precise form of the LQ model should not be taken so seriously. Much of the scientific information suggesting values for the LEOF (DREF) does not depend on the LQ model, but comes more directly from experiments involving fractionation of doses. It is emphasized that there is very limited information in the LSS data which bears on the appropriateness of the LQ model for extrapolation to low doses. Whether these data fit well to such a model is not a determining factor in this issue, since there is simply little direct information in these data regarding low-dose risks.

Materials and Methods

The data used here

The data used here are LSS cancer mortality for all cancers except leukemia and leukemia during 1950–85,[7] with DS86 dosimetry employed as of December 1987. Discussion of the dosimetry and the DS86 cohort, which excludes some individuals for whom dose estimates were previously available, is given by Preston and Pierce.[2] Estimated organ doses are used here, using that to the large intestine as representative for nonleukemia and that to the bone marrow for leukemia. The BEIR III report[3] used estimated organ doses, but RERF reports published prior to use of the new dosimetry generally did not. It should be understood that, when analyzing a class of cancers like nonleukemia, the analysis cannot be based on the organ dose specific to the cancer site causing the death (e.g., lung dose for lung cancer deaths, stomach dose for stomach cancer deaths). This would leave unresolved the problem of which organ dose to assign to individuals still alive or those who died from causes other than cancer. Although the neutron component is now considered to be quite small, it is advisable to use some kind of low-LET dose equivalent rather than simply summing the gamma-ray and neutron contributions. This is done here by using an assumed constant relative biological effectiveness (RBE) of neutrons of 10. Even though the RBE may truly depend on dose level (among other things) and may be greater than 10 for low doses, the aim here is to choose a reasonable RBE for the range of 1–3 Gy which is most influential in fitting these data. The sensitivity of the results to the assumption of a constant RBE will be addressed briefly.

As in all previous analyses, kerma estimates for survivors which are above 6 Gy have been set at 6 Gy. Corresponding proportional adjustments are made to gamma-ray and neutron components, and to organ doses. When analyses using a more restricted dose range are made, individuals with kerma estimates above 4 Gy are omitted, rather than selecting on organ dose. This corresponds roughly to omitting those with organ dose equivalents above 3 Sv, an important point in interpreting the results given here. These individuals are omitted, rather than setting their exposures at 4 Gy, because a large part of the motivation for the restriction is related to the possible inadequacy of the LQ model, as opposed to inadequacy of the exposure estimates.

Statistical methods

The data are analyzed in cross-classified form, using cancer deaths and person-years at risk in approximately 8,000 cells (with nonzero time at risk) defined by 12 intervals of organ dose-equivalent with the following cutoff points in sieverts: 0.005, 0.1, 0.25, 0.75, 1.25, ... , 4.25; and further by sex, city, and 5-year intervals of calendar time, attained age, and age-at-exposure. Cohort experience beyond 80 years of age is omitted, on grounds that death certificate information on cause of death may be particularly unreliable.

A fundamental issue in discussing the shape of the "dose-response curves" is that the carcinogenic response is not a single numerical quantity, but is a complex pattern of risks depending on age-at-risk, time, sex, age-at-exposure, and possibly other factors. Thus, although it is often not explicitly mentioned, some kind of model representing these effects must underlie description of a single dose-response curve. In regard to sex and age-at-exposure, it is best to stratify on these in the analysis, and then combine inferences over strata into some overall summary of dose-response. In regard to age-at-risk and time, one approach commonly used is to "collapse" over these, and consider the response simply as deaths per person-year-gray. Developments in recent years[13–15] suggest that the following approach is preferable and provides a very useful summary of the data.

Consideration is first given to models for cancers other than leukemia. Write

c = city s = sex a = age (at risk)
p = period (calendar) e = age-at-exposure d = dose

and write λ_{csap} for the age-specific background risk for given values of city, sex, and period. Note that the common practice of using the term "risk" to denote the (cancer) mortality rate is adopted here. The model for background plus excess risk is taken as

$$\lambda_{csap}[1 + \beta_e \delta_s (d + \theta d^2)] \quad , \tag{1}$$

but with the modification, not made explicit in notation, that the excess risk is taken as zero for the first 10 years following exposure. The dependence of β_e on age-at-exposure is modeled in terms of free parameters for intervals of 1–19, 20–34, and 35+ years. For fixed dose, sex, and age-at-exposure, this model specifies a temporally constant excess relative risk. Although there is uncertainty about the appropriateness of projecting risks beyond the current follow-up with such a model, this type of model fits the data extremely well over the extent of the follow-up period.[13] The model (1) is a relative risk model, but it should be realized that the inference about the shape of the dose-response given here is not restricted to this class of models. The model can be reexpressed as an absolute risk model; the parameter θ will still represent the ratio of the coefficients of the quadratic and linear terms.

The model (1) is fitted by maximum likelihood to the data in the grouped format described above. The parameters λ_{csap} are taken as stratum parameters, varying freely with the factors of the cross-classification indicated by the subscripts (but not with dose). This type of analysis is a grouped-data version of the Cox regression analysis for survival data,[14,15] but with an additive rather than multiplicative (or loglinear) form of the relative risk function. Primary attention is on the parameter θ, describing the extent of nonlinearity in the dose-response. Although the maximum likelihood estimates of θ for the two types of cancer are important, the estimates for the case of nonleukemia are near zero (the linear model) and interest focuses on an upper confidence limit for θ.

The primary interest here is in the dose-response for all cancers except leukemia, but analyses are included for leukemia and also for nonleukemia and leukemia combined. The model used for leukemia is discussed below. The inferences based on nonleukemia and leukemia combined correspond formally to the assumption of a common value of θ for these, which may well be an approximation at best. It is noted that this can be interpreted as combining the separate inferences about the respective θ-values, assuming these are estimating approximately the same quantity, weighting according to the information available for each inference. Thus, one result of the combined analysis is to clarify the relative amounts of information available from the two sources.

It is much more difficult to model the temporal patterns of excess risk for leukemia. There was an apparent peak in the risk by around 1950, and the subsequent pattern of decrease (in both relative and absolute excess risk) differs by age-at-exposure.[16] The approach taken here is that mentioned above as the basis of many previous analyses for both types of cancer, for example, as in BEIR III,[3] modeling simply the average excess risk over the entire follow-up. The cross-tabulation above is in essence collapsed over period and age (at risk), fitting the model

$$\lambda_{cse}[1 + \beta_e \delta_s (d + \theta d^2)] \quad . \tag{2}$$

The important difference between this model and (1) is that no attempt is made to model the temporal pattern of excess risk. Although (2) is expressed in terms of relative risk, it could be written equally well in terms of absolute excess risk; the shape of the dose-response would not be changed by this. Analyses for leukemia using models which explicitly represents temporal patterns of risk have been made by Pierce et al[16] and Preston and Pierce.[2] These models are rather complicated, and it was felt that analysis regarding the shape of the dose-response using them would be less clear and reliable than those from the approach taken here.

For either model (1) or (2), it is important to calculate confidence limits more precisely than by simply using the standard error of the estimates of θ. A much more reliable method is that based on analysis of the likelihood function; see, for example, Breslow and Day,[17] Section 6.4. As used here, the implementation of

this method consists of fitting the model for a range of assumed θ-values, and for each given θ-value computing a measure of goodness-of-fit called the deviance, which is based on the likelihood of obtaining the observed data if the assumed value of θ were true. A confidence interval for θ then consists of those θ-values for which the goodness-of-fit is no poorer than some specified value, depending on the desired level of confidence. This is explained in more detail in the Appendix.

The main feature of models (1) and (2) may be expressed as "excess (relative) risk" = β ($d + \theta d^2$). The parameter β is the "low dose slope"; i.e., it can be interpreted as the risk per unit dose for low doses. In general terms, when θ is fixed at assumed values and the remaining parameters are fitted to a set of data, the estimate of β decreases with increasing θ since the curves become increasingly more concave from above. The LEOF is a measure of this, defined as the ratio of the estimate of β for θ=0 to the estimate of β corresponding to an assumed θ-value. The LEOF thus depends upon both θ and certain aspects of the data under analysis, and it has the following useful interpretation. The linear fit and that for the assumed positive θ will intersect at some dose level d_0, and the LEOF can be seen to be given by $1 + \theta d_0$. The value of d_0 will depend somewhat on θ but usually not substantially for interesting ranges of values.

For the data analysis here, there are six βs for any given fit to either data set, corresponding to sex and age-at-exposure groups. For purposes of computing the LEOF as defined above, the βs are taken as the simple average of these six. The computed LEOFs for a given θ-value are virtually the same for nonleukemia and leukemia, and for adjusted doses and those unadjusted to allow for dose-estimation errors, but they do depend on whether the analysis is for 0–4 or 0–6 Gy kerma. The values of d_0 referred to above are approximately 1.5 and 2.2, respectively, for these two analyses.

Allowing for imprecision in exposure estimates

Two approaches are taken to making some allowance for the imprecision of exposure estimates. One is to restrict the range of exposures used by only including survivors with DS86 estimates no greater than 4 Gy kerma. The motivation for this is that i) the magnitude and effect of errors is thought to be much greater at high estimates, and ii) the underlying interest here is on the shape of the dose-response in the lower range. Note, however, that even if the true exposures were used, inferences about the parameter θ would be progressively weaker as the dose-range is restricted. Thus, the comparison here between ranges of exposures used does not reflect the effect of imprecision of dose estimates, and must be interpreted carefully.

The other approach, suggested originally by Jablon[8] and Gilbert[9] and discussed in detail in a separate report,[10] is as follows. The aspect of dose estimates relevant for the present dose-response analyses is the estimate of the mean true dose among those in the cohort having (approximately) any given estimated dose, written here as Avg(true | est). It is emphasized by Pierce et al,[10] that even if

Avg(est | true) is approximately the true dose, Avg(true | est) is, except for low doses, substantially less than the estimated dose because the number of survivors decreases very rapidly with increasing dose, and hence there are far more positive than negative errors leading to a given estimated dose. If assumptions are made about the nature and magnitude of random errors in exposure estimates, it is possible to calculate "adjusted dose estimates" Avg(true | est). Much of the systematic effect of dose estimation errors on parameter estimates in dose-response analyses will be eliminated by replacing the dosimetry estimates by these adjusted estimates. These adjustments depend somewhat on city because of different distributions of true exposures.[8]

In regard to the nature and magnitude of errors in estimation, Jablon[8] suggested that the standard deviation of the error might be about 30% of the true exposure, or perhaps somewhat larger, and that errors may be fairly symmetric on a logarithmic scale. These results were based on assessments of the magnitude of the uncertainty in the input parameters (location of survivor, type of shielding, etc.) for the dosimetry. Although Jablon's study relates to the previous dosimetry system, the main arguments are also valid for the new dosimetry system, since the same input parameters are still being used. Consideration of several error models is made in Pierce et al,[10] and the one primarily used here is the model tentatively recommended in that paper, viz., that the dose estimates have a lognormal distribution with standard deviation of errors about 35% of the true value. More precisely it is assumed that the conditional distribution of the log of estimated dose given a value of true dose is normal with mean equal to the log of the given value of true dose, and a standard deviation of 0.35.

Calculations in Pierce et al,[10] show that, for this error model, Avg(true | est) in terms of kerma estimates are as indicated in the following table. Formulas for these adjustments are given in the Appendix.

DS86 kerma estimate	1	2	3	4	5	6
Avg(true | est)						
Hiroshima	0.95	1.79	2.56	3.28	3.98	4.64
Nagasaki	0.98	1.86	2.68	3.46	4.20	4.92

If the true dose-response is linear then dose-response analysis using adjusted dose estimates of this nature will remove the bias in the estimate of the slope, provided that the error model used to compute the adjustments is correct. Note that the adjustments are nonlinear, so the estimated shape of the dose-response is changed when they are used. In fitting LQ models, it is also necessary to replace the estimated squared doses by Avg(true^2 | est), in order to obtain unbiased estimates of parameters in a true LQ model. It is shown by Pierce et al[10] that, for the error models considered, the ratio Avg(true^2 | est)/[Avg(true | est)]^2 is essentially constant in estimated dose. For the above error model, the

approximation Avg(true^2 | est) = 1.12 [Avg(true | est)]^2 is very adequate over the above dose range, and this is used for fitting the LQ models here. It is important to note that the value of the constant 1.12 is irrelevant in estimation of the LEOF; it serves only to rescale the estimate of θ.

Adjusted organ dose equivalents, as opposed to kerma, are required here. As described by Pierce et al,[10] these should be computed as follows. For each cell of the cross-tabulation described above, the mean kerma is used to calculate the percent reduction in kerma, as indicated in the above table, but actually using the formulas given in the Appendix, and this reduction factor is applied to the mean organ dose equivalent for the cell.

These adjustments for errors in exposure estimates are rather tentative, primarily because of the uncertainty regarding the actual nature and magnitude of the errors. Nevertheless, the results provide useful guidance to the understanding of how much the errors in dose estimation may be affecting the estimation of the shape of the dose-response curve. For nonleukemia cancer, results from additional analyses addressing the sensitivity of the θ-inference to changes in the percent standard error of the lognormal error model are briefly presented.

Results

Figures 1 and 2 indicate the shapes of the cancer mortality dose-response curves for nonleukemia and leukemia. The graphs were made by computing risks specific to the 12 dose categories given above. The dose-specific relative risks for nonleukemia and leukemia were computed by fitting models similar to (1) and (2), but with free parameters for dose categories rather than modeling the risk as LQ in dose. The smoothing was done by replacing each estimated dose-specific rate by the weighted average of it and the two adjacent values, using weights {1/4, 1/2, 1/4}, except for the endpoints which were taken as a simple average of the final two values. These moving averages were only used for making the plots in Figures 1 and 2, not for the main statistical analysis. The plotted points represent averages over the six age ATB and sex categories used in the models. Approximate standard errors are computed for the smoothed points; these should not be interpreted very precisely since a number of approximations are involved. Although it is always important to display the basic data from which inferences are to be made, care should be taken not to overinterpret the apparent shapes of the dose-response curves seen in such figures, as the standard errors of even the smoothed points are very large. Interpretations of these graphs should be supported by further statistical calculations, with a carefully considered purpose.

In regard to the apparent leveling off at high doses, it is emphasized that what is seen in Figures 1 and 2 is not statistically significant. ($P > 0.10$ using an LQ alternative to a linear model.) On the other hand, particularly for nonleukemia, the slope of a linear fit is appreciably affected by omitting the high-dose range,

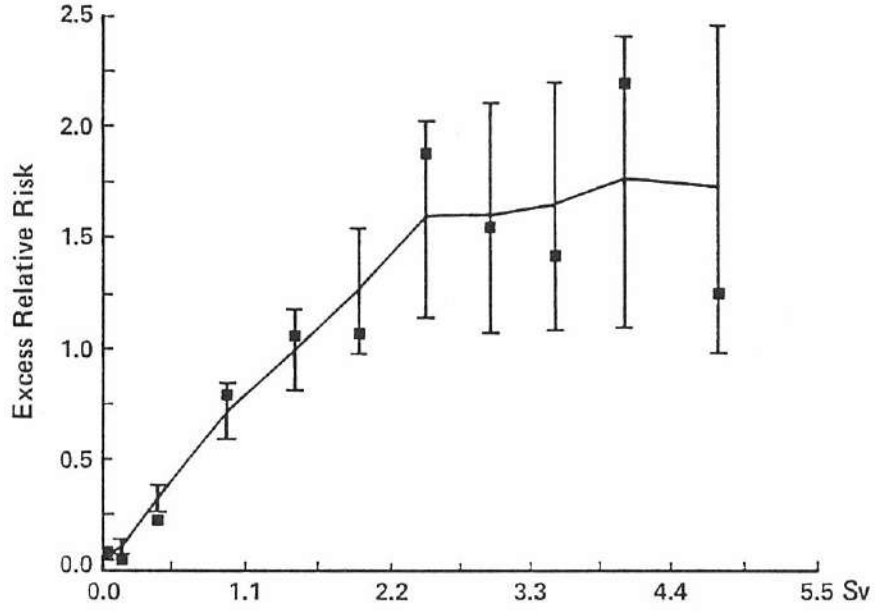

Figure 1. *Dose-response for all cancers except leukemia in terms of intestinal dose equivalent, RBE = 10. Points are estimated response in intervals of 0.5 Sv, and the line is a smoothing of these by moving averages. Error bars refer to the smoothed points. Risks are averages with equal weights over the six age-at-exposure and sex groups used in the paper. The error bars are computed by treating these dose-modification effects as fixed, so that they will be appropriate for inferences about the shape of the dose-response, rather than the actual level.*

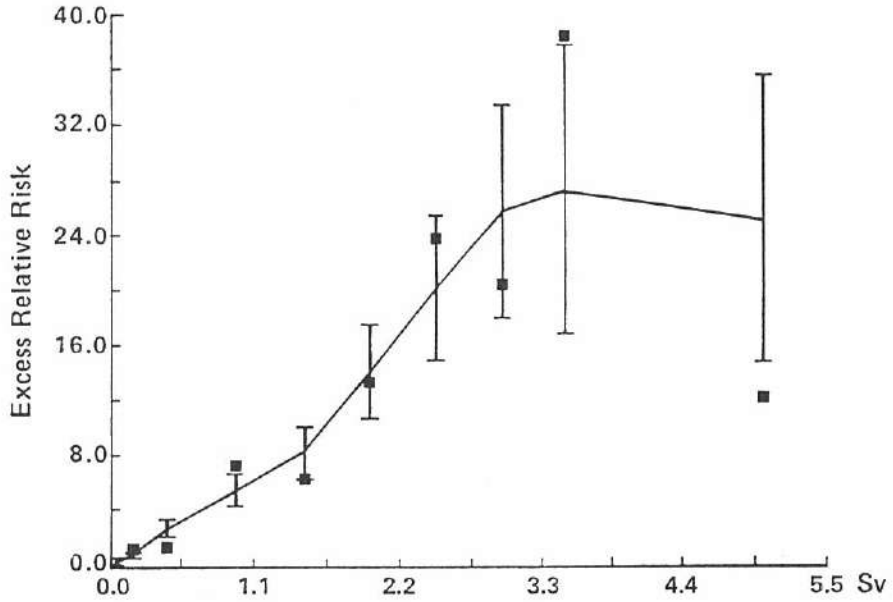

Figure 2. *Dose-response for leukemia in terms of marrow dose equivalent, RBE = 10. Remaining explanation is the same as for Figure 1.*

and the precision of this estimate is decreased very little. The apparent leveling off, if it is not simply sampling variation, may be due to a combination of effects of errors in exposure estimates and a possible plateau in the true dose-response. Although the dose adjustments used here are likely to remove the former effect reasonably well, it may be best, in computing linear risk estimates, to guard against the latter effect by also restricting the range of exposures used.

Although the precision of inferences about linear risk estimates is not greatly reduced by restricting the dose range, that of inferences about the LQ shape is reduced very greatly. Thus, one must strive for a very careful balancing between an apparently strong inference using a wide dose range, but which is questionable because of the effect of imprecision in exposure estimates and possible inadequacies of the LQ model, and a much weaker but less questionable inference based on restricting the dose range. There is no easy escape from this dilemma, and a range of possible conclusions is indicated here.

The incorporation of "cell-killing" terms[4,5] into an LQ model, although perhaps useful for some purposes, does not offer much for inference about low-dose risks. The modeling of this is very uncertain, and estimation of parameters may be very greatly affected by imprecision in dose estimates. If cell-killing is indeed a substantial part of the cause of leveling off at high doses, then the data in that range is simply very uninformative regarding low-dose risks. The end result of using LQ models with cell-killing terms seems to offer little more than a "discounting" of the high-dose data in the LQ fit, along with an effect which is hard to assess in the lower dose range, and it seems better to do this more directly and understandably by restricting the dose range used.

The primary results are summarized in Figures 3 and 4, indicating ranges of θ-values which are consistent with the LSS cancer mortality data. Results are given for four different approaches to the analysis; the combinations of i) using the dose ranges corresponding to 0–6 and 0–4 Gy kerma, and ii) using doses with and without adjustment for the effects of random errors in exposure estimates.

Only nonnegative values of θ are indicated in Figures 3 and 4, and the primary focus is on the question of what are the largest values of θ which are consistent with the data. The far right end of the bars and of the extended lines represent upper confidence limits for θ at one-sided confidence levels of 80% and 90%, respectively. For a few instances, lower confidence limits are similarly displayed, when they are greater than zero. Corresponding to values of θ are indicated the CD, which is simply $1/\theta$, and the LEOF. The relation between LEOF and θ differs between the analyses on 0–6 and 0–4 Gy, but very little by cancer type or whether adjusted doses are used. Therefore, only a single LEOF scale is shown on each figure. Tables of the change in deviances (chi-square statistics with one degree of freedom) and P-values from which these confidence limits are obtained are given in the Appendix.

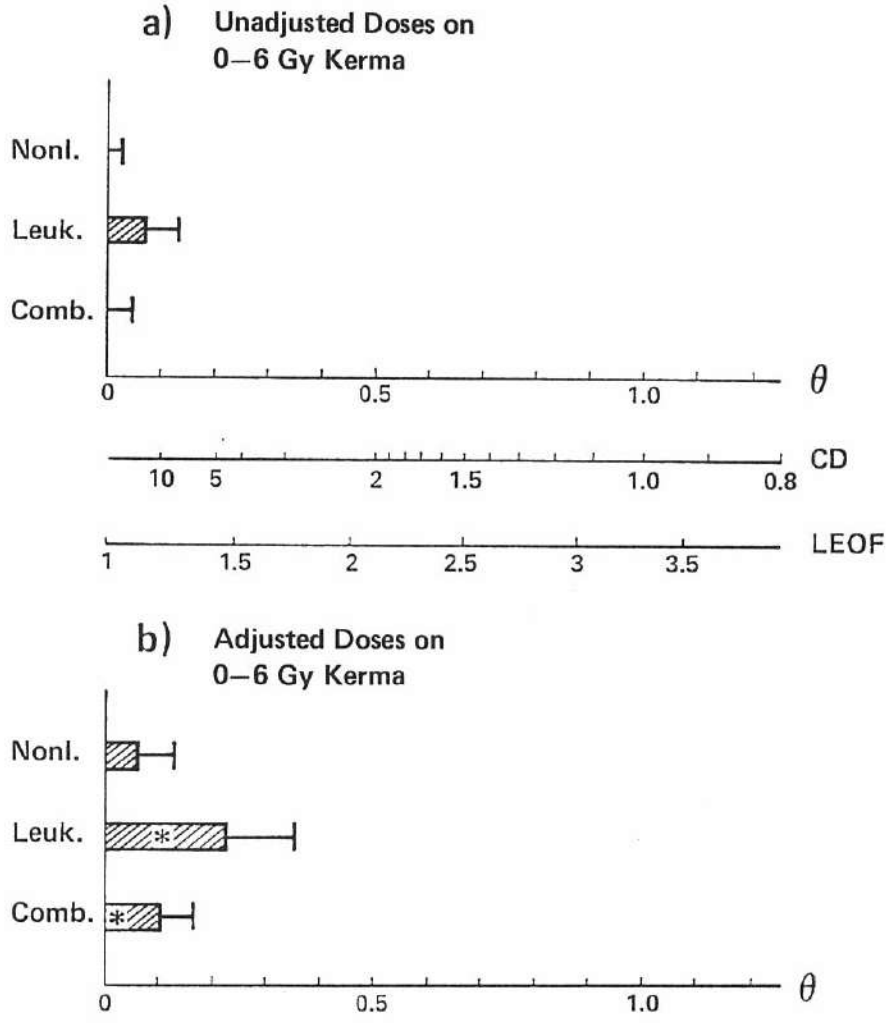

Figure 3. *Confidence limits for nonlinearity on the entire dose range, using organ doses with and without adjustment to allow for random errors in exposure estimates. Survivors at above 6 Gy have kerma estimates set to 6 Gy as usual, with corresponding truncation of organ doses. The upper end of the shaded bar is the 80% upper confidence limit; the upper end of the extended line is the 90% upper confidence limit; the maximum likelihood estimate, when positive, is denoted by an asterisk. Scales are shown for interpreting inferences in terms of: i) θ, the ratio of γ to β in the LQ model: $\alpha + \beta$ dose + γ dose^2; ii) CD = $1/\theta$, the crossover dose; or iii) LEOF, the factor by which the linear slope for the LSS data should be divided to give the low-dose slope β in the LQ model, for a given θ-value.*

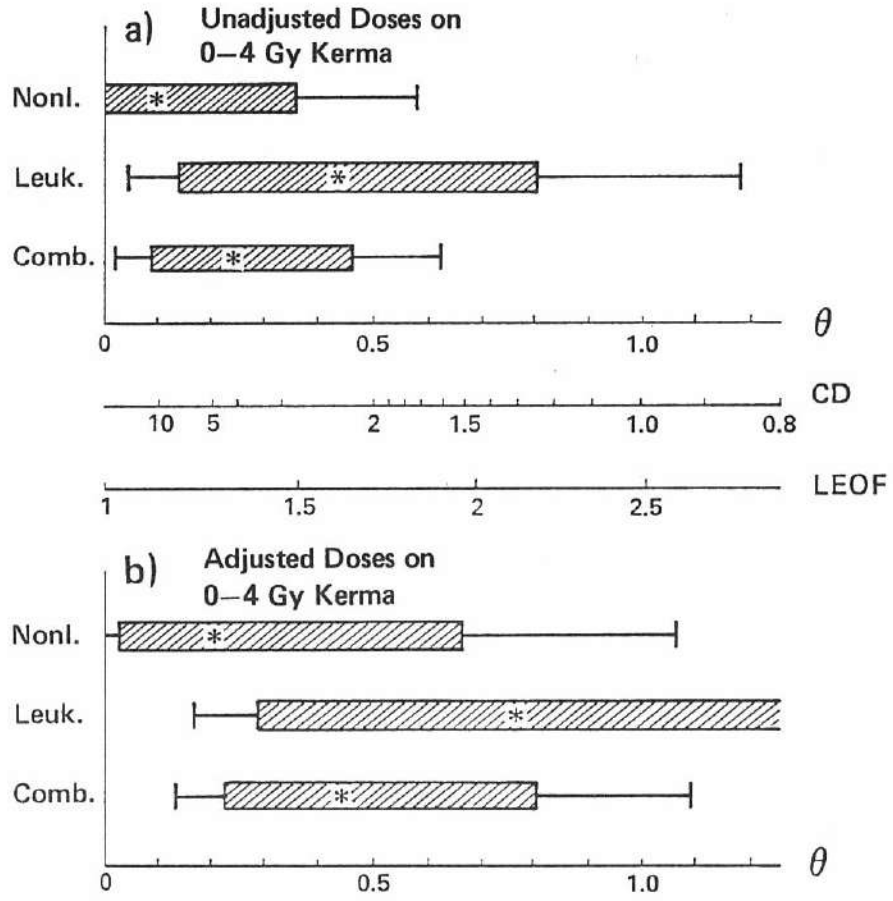

Figure 4. *The same type of inferences as in Figure 3, except that analysis is restricted to survivors in the range 0–4 Gy kerma. The lower end of the shaded bar is the 80% lower confidence limit; the lower end of the extended line is the 90% lower confidence limit. The relation between θ and LEOF is slightly different than in Figure 3.*

Interpretation of the primary results will, at no loss, be phrased largely in terms of the LEOF. Further, discussion will focus to some extent, for simplicity, on the combined inference from nonleukemia and leukemia. These inferences are not substantially different from those based only on the nonleukemia data, so the question of whether the combined inferences are most appropriate is not an overriding concern.

For perspective, recall that the LEOF for both nonleukemia and leukemia used by BEIR III[3] was 2.2, obtained as a point estimate from the leukemia data. The results here suggest that it is no longer appropriate to base conclusions about the shape of the nonleukemia dose-response solely on the leukemia data. The LEOF used by Gilbert[12] was 3.33, taken as the midpoint of a range suggested by NCRP 64[4] on the basis of a very broad consideration of mutagenesis and carcinogenesis in experimental work, as well as the evidence in human data.

The inferences in Figure 3a, taking the unadjusted doses on 0–6 Gy kerma at face value, are of limited interest except as a point of reference. There are undoubtedly substantial random errors in the exposure estimates, and they will certainly result in underestimation of θ. The "best-fitting" θ-values are negative, due to the leveling off at high doses, which is reflected in very small upper confidence limits. Analyses using the previous dosimetry have led to very different conclusions than this, primarily because the leveling off seen here was at exposures above 6 Gy kerma, and doses were truncated at that level.

The inferences in Figure 3b, using adjusted doses on 0–6 Gy, can be taken substantially more seriously. At least, much of the systematic effect of exposure estimation errors has been removed here, using a model allowing for them to be quite substantial. The upper confidence limits for the LEOF are quite inconsistent with commonly used values. It is seen in Appendix Table A2 that if the true θ-value were 0.5, corresponding to an LEOF of about 2, there would be less than a 0.1% chance of obtaining data indicating a θ as small as do these data.

It seems important, though, to consider the possibilities that either the LQ model is not valid over such a wide dose ranges as this, or that the errors in the data are not adequately dealt with by the adjustment method. In regard to the first point, if Figures 1 and 2 are redrawn using the adjusted dose scale, there is still some apparent leveling off and the θ estimate for nonleukemia remains negative. Recall, however, that even without the dose adjustments θ was not statistically significantly less than zero. Thus the apparent plateau, on the scale of adjusted dose, could very likely be simply random variation. On the other hand, there may truly be a plateau, and then it would be inappropriate to use an LQ model over the wider dose range, for the primary rationale underlying it is to model curvature concave from above.

The inferences in Figure 4 are much more conservative. Bear in mind that this would be so even if there were no exposure estimation errors. This analysis also decreases the possible effect of such errors, though, and so it has a dual motivation. The inferences in Figure 4a have the weakness, in addition to that inherent in restricting the range, that exposure estimation errors surely must have some effect, even though it might be fairly small over this dose range. On the other hand, it is quite possible that conclusions shown in Figure 4b are based on a model for estimation errors which is too pessimistic; the model used for them allows for quite large random errors. In drawing conclusions, the reader should not take lightly the restriction to 0–4 Gy kerma, since this inevitably restricts very severely the strength of conclusions from these data.

Discussion

Sensitivity to some modeling assumptions

The dose adjustment used to derive the results presented in Figures 3b and 4b was based on an assumed lognormal error model with a 35% standard error. The inference about θ here depends to some extent on the magnitude of this

percent standard error. To assess the order of magnitude of this dependence, two additional sets of analyses were made for nonleukemia cancers using dose adjustments derived in a similar way, but based on an assumed standard error of 30% and 40%. The use of a 30% error model resulted in a 30% decrease of the upper confidence limits for an analysis on the full dose range (Figure 3b) and a 14% decrease when the analysis was restricted to survivors with kerma no greater than 4 Gy (Figure 4b). Using a 40% error model increased the upper confidence limits by approximately 35% for the analysis on the full dose range and by 20% on the restricted dose range.

It is of some interest to know whether an LQ-L analysis would lead to substantially different conclusions than the analysis here using an LQ model with a constant RBE dose equivalent. The LQ-L model would be of the form

$$\lambda_{csap}[1 + \beta_e \delta_s (d_g + \theta d_g^2 + \rho d_n)] \quad , \tag{3}$$

where d_g is the gamma-ray dose and d_n is the neutron dose. To draw an inference about all three parameters in models of this form requires cross-tabulation by both gamma-ray and neutron doses, and the extent of this cross-tabulation requires a different approach to analysis. This approach is explained in Pierce et al,[18] and the application of it will be made in a subsequent report. Results of this type of analysis, using the nonleukemia data, indicate that, due to very low neutron doses, confidence intervals for ρ, even for fixed θ, are extremely wide. This can be adequately demonstrated for the linear-linear (L-L) case (θ = 0), where the 80% confidence interval for the RBE ρ from the nonleukemia data is from about 2 to 250. Thus, it is necessary to make some kind of assumptions about ρ in order to draw useful inferences about θ in this LQ-L model. If ρ is fixed, then the RBE at a given dose level will vary with θ, which is probably undesirable from a modeling viewpoint. Consider models where ρ is a function of θ, defined such that the RBE (which varies with dose) is 10 at d_g = 1.5, independently of θ. In this case the upper 80% and 90% confidence limits are about 10%–15% higher than those given in this report. The primary reason why they are higher is discussed in the next section. Thus with the new dosimetry, the LQ-L inferences about θ and those given here are not substantially different. This result is not surprising, since the neutron doses are quite small, ranging for dose to the large intestine from 0.0% to 3.9% of the gamma-ray dose in the dose range of 0–6 Gy.

Comparisons to previous results

The most thorough analysis along these lines in the past was that given by BEIR III.[3] Changes to be expected are those related to 10 years of additional follow-up and the revision in dosimetry. The former may have a substantial effect, particularly for nonleukemia, but no explicit analysis of that is made here. The changes related to dosimetry are due to: i) a general change in the level of dose estimates, which depends markedly on whether one is considering kerma or organ dose, and then for which organ, and ii) a large decrease in the neutron component for Hiroshima. Effects of both of these will be discussed briefly.

The LQ inferences based on the exposure range 0–6 Gy kerma are very strongly affected by the apparent leveling off in the high-dose range, even though this is not statistically significant. This phenomenon corresponds to similar behavior in the 6–10 Gy range before, but exposures in this range were not used in analyses. The interpretation of this is perhaps unclear, but it should be understood that the comparison of the results on 0–6 Gy for both dosimetries is dominated by this issue.

More useful is the comparison of the results on 0–4 Gy here and those on 0–6 Gy previously, since this involves roughly the same survivors. Since adjusted dose estimates have not been used for this purpose in the past, one may want to compare the results based on unadjusted doses. It should be noted that θ has the dimension of 1/dose, and thus estimates of it would be increased even by a simple rescaling of doses. This is not an important issue for intestinal dose equivalents for RBE=10, since the general level of these has not changed much with the new dosimetry. It is more important for marrow doses, where the new dose equivalents are generally about 75% of the old. For estimates in terms of kerma, or equivalently for organs with little shielding, such as the breast, this would be an important factor. Due to compensating factors such changes in scale would have no effect on inferences about the LEOF.

Perhaps the most noteworthy comparisons are with the conclusions of the BEIR III report.[3] The LQ inferences from the nonleukemia data alone, even on 0–4 Gy kerma, are much stronger now than were considered possible at the time of BEIR III. The difference in this regard is not in the maximum likelihood estimate of θ which was essentially zero before, as now, but in the upper confidence limits for θ. These are not considered explicitly in the BEIR III report, but the implication was that upper confidence limits would be much larger than the upper limits of 0.03 to 0.59 calculated here. This change may be due in part to issues involving the major change in the Hiroshima neutron component, which is discussed in more detail below for the case of leukemia.

The other striking difference involves the leukemia data, where the maximum likelihood estimate for θ is now much smaller than the 0.86 given in BEIR III, in spite of the increase of about 33% which might have been expected from general reduction in dose levels. The 0.86 value is close to the upper 80% confidence limit in the present analysis of 0–4 Gy. This contrast is the result of the large changes in the neutron component in the new dosimetry. Current analyses using the old dosimetry show that the larger θ-value in BEIR III resulted from use of an LQ-L model, rather than the LQ model used here. The primary reason for this is that the apparent dose-response was quite concave from above in Nagasaki (with almost no neutron component) and quite linear in Hiroshima (with a substantial neutron component). In the old dosimetry, the Nagasaki data play the primary role for the LQ part of the inference under an LQ-L model, since the more linear response in Hiroshima is ascribed to the neutron component. With the new dosimetry, the conclusions from the LQ and LQ-L are very similar, since the

neutron component in Hiroshima is now small. It should be understood that the θ estimate using the LQ-L model and the old dosimetry was very imprecise (coefficient of variation roughly 100%). Generally, intercity comparisons of the shape (and the slope) of the dose-response are very tenuous, differences being well within the range that would be expected from ordinary random variation. Conclusions based on these should be avoided, especially now that there is no clearly ascribable reason for differences.

General conclusions

The analysis here concerns only the LSS data, whereas there is clearly a great deal of other information to be taken into account. The authors are not familiar enough with the general literature to be able to comment broadly, but they are particularly impressed with animal carcinogenesis experiments in which cancer rates, at the same total dose, are quite different for exposures at high and low rates; see, for example, NCRP 64.[4] Although there are acknowledged difficulties[4] in interpreting such experiments, conclusions from them may have inherently much greater strength than those drawn here. This is because they make no reliance on the LQ model, whereas this model is the entire basis for the present conclusions.

Nevertheless, the LQ model is taken fairly seriously in the radiobiological literature, and it is important to investigate the conclusions by applying it to the LSS data. If it is taken as a reasonably appropriate model over the dose ranges considered here, then the upper confidence limits are important even though they correspond only to a single data set. If inferences about the LEOF made in this way are not to be taken seriously, then it would have to be largely on grounds that the LQ model is not appropriate for extrapolation from epidemiological data. It is emphasized that the quality of fit of the LSS data to an LQ model is not relevant to the validity of this model for extrapolation to low-dose risks, since there is very little direct information regarding low-dose risks in these data.

Having emphasized these considerations, it can be said that within the context of the LQ model, the LEOF ranges suggested in the radiobiological literature seem too high to be consistent with the LSS data. If the LQ model is taken seriously for survivors in the entire range 0–6 Gy kerma , then it seems very unlikely that other information suggesting larger values of θ could be strong enough to justify an LEOF as great as 2.

If it is felt that only the analysis of 0-4 Gy kerma (corresponding roughly to a 0–3 Sv organ dose) can be used for these purposes, and the view is taken that other sources of information suggest a larger θ-value than do these data, then the LEOF range of 1.5–3, suggested by UNSCEAR,[5] may not be unreasonable. It should be understood that the point estimate of LEOF in this context (combined data) is about 1.7. Values in the upper part of the 1.5–3 range are upper confidence limits for the LSS data, whose plausibility depends mainly on evidence from other sources. The upper part of the range of 2–10, suggested by NCRP 64,[4]

would only seem reasonable if the LQ model were largely rejected as a means of interpreting epidemiological data of this nature.

There is an important distinction between a range for LEOF which should result in inclusion of the *true* risk at low doses, and one which corresponds to a range of *prudent* estimates for the purposes of radiation protection decisions. The balance between emphasis on epidemiological and experimental data should be made with explicit attention to this distinction. In particular, it would seem that use of LEOF values greater than about 2 should only be based on particularly clear information from experimental settings.

It should be noted that the larger plausible values for LEOF from the analysis on 0–4 Gy is to some (fairly small) extent offset by the fact that the linear model slope for that case is larger when the range is restricted. That is, if one wishes to use upper limits of LEOF from this analysis, then they should be applied to linear estimates resulting from analysis on 0–4 Gy. For nonleukemia this restriction to 4 Gy increases linear risk estimates by about 14% for unadjusted doses and by about 12% for adjusted doses.

Although in the authors' statistical judgment it is correct to be very guarded in drawing conclusions which rely very heavily on the LQ model, and we have emphasized the point that other information may suggest larger LEOF values than indicated here, it is important to note that there is also evidence supporting the use of linear extrapolation for at least some types of cancer. For example, information including epidemiological data involving repeated small exposures has led to some acceptance[19] of a linear model for breast cancer.

Appendix

Adjusted dose estimates, Avg(true | est), are computed by calculating a reduction factor given by the following formula, and applying this factor to organ dose estimates. The reduction factors should be computed in terms of kerma:

$$\text{Hiroshima: } 0.04732 + 0.07623\,x + 0.01336\,x^2 \text{ and}$$
$$\text{Nagasaki: } 0.01900 + 0.06545\,x + 0.01374\,x^2 \quad ,$$

where x is the natural logarithm of kerma in gray. Kerma estimates greater than 6 Gy should be reduced to 6 Gy before making this calculation of the reduction factor. No reduction should be made for exposures under 0.5 Gy. For adjustment of squared doses in the LQ analysis, the approximation $\text{Avg}(\text{true}^2 \mid \text{est}) = 1.12\,[\text{Avg}(\text{true} \mid \text{est})]^2$ is excellent over this range.

Table A1 gives "deviances," i.e., likelihood ratio chi-squared values, with one degree of freedom (df) for comparison of the goodness-of-fit provided by hypothesized values of θ, relative to the maximum likelihood fit. Even if the true value of θ is considered to be nonnegative, this constraint should not be imposed on the maximum likelihood estimation of θ for purposes of using the deviances to compute upper confidence limits for θ. A one-sided P-value corresponding to testing any given θ-value as an hypothesized value, against the alternative that the true value is in the direction of the maximum likelihood estimator, is

computed as one-half the chance that a chi-squared variate on 1 df is greater than the corresponding deviance value. Values of θ, for which this P-value is at least some specified value, constitute a confidence interval. Any θ-value greater (respectively smaller) than the maximum likelihood estimate can then be interpreted as an upper (respectively lower) confidence limit for θ, at confidence level given by one minus this P-value. Table A2 gives P-values for selected values of θ, those greater than 0.40 being replaced by dashes, in order to clearly separate lower from upper confidence limits. The figures of the text were made from these.

Table A1. Maximum likelihood estimates (MLE) of θ and the change in deviances (chi-square statistics with one degree of freedom) for hypothesized θ-values for nonleukemia (NL), leukemia (L), and combined (C).

	Adjusted Doses			Unadjusted Doses		
θ	NL	L	C	NL	L	C
(a) Exposure Range 0-6 Gy						
MLE:	−0.05	0.07	0.01	−0.09	−0.02	−0.06
0.00	0.25	0.34	0.00	1.37	0.07	0.99
0.10	1.43	0.02	0.86	3.88	1.31	4.74
0.20	2.86	0.50	2.77	6.31	3.04	8.90
0.30	4.25	1.26	4.92	8.44	4.80	12.79
0.40	5.52	2.12	7.05	10.25	6.44	16.24
0.50	6.64	2.98	9.03	11.80	7.94	19.29
0.60	7.64	3.80	10.85	13.11	9.27	21.93
0.70	8.51	4.57	12.49	14.25	10.48	24.28
0.80	9.29	5.28	13.98	15.23	11.55	26.33
0.90	9.98	5.94	15.33	16.08	12.51	28.14
1.00	10.60	6.54	16.55	16.84	13.38	29.77
1.10	11.15	7.10	17.66	17.50	14.16	31.21
1.20	11.65	7.61	18.67	18.09	14.87	32.51
1.30	12.10	8.09	19.60	18.63	15.51	33.69
1.40	12.51	8.53	20.45	19.11	16.10	34.76
(b) Exposure Range 0-4 Gy						
MLE:	0.24	0.63	0.46	0.10	0.39	0.24
0.00	0.92	4.56	5.08	0.25	2.69	2.48
0.10	0.25	2.49	2.34	0.00	1.11	0.65
0.20	0.02	1.32	0.94	0.15	0.36	0.05
0.30	0.03	0.64	0.27	0.48	0.06	0.08
0.40	0.16	0.27	0.03	0.88	0.00	0.42
0.50	0.35	0.07	0.02	1.30	0.08	0.92
0.60	0.58	0.00	0.18	1.72	0.25	1.51
0.70	0.81	0.00	0.41	2.12	0.46	2.12
0.80	1.05	0.06	0.71	2.49	0.69	2.72
0.90	1.28	0.15	1.03	2.85	0.94	3.33
1.00	1.50	0.25	1.35	3.18	1.19	3.91
1.10	1.71	0.38	1.69	3.49	1.44	4.47
1.20	1.91	0.51	2.02	3.77	1.68	4.99
1.30	2.10	0.64	2.34	4.04	1.91	5.49
1.40	2.28	0.77	2.65	4.28	2.14	5.96

Table A2. P-values for hypothesized θ-values for nonleukemia (NL), leukemia (L), and combined (C).

	Adjusted Doses			Unadjusted Doses		
θ	NL	L	C	NL	L	C
(a) Exposure Range 0-6 Gy						
0.00	0.309	0.280	0.500	0.121	0.396	0.160
0.10	0.116	-	0.177	0.024	0.126	0.015
0.20	0.405	0.240	0.048	0.006	0.041	0.001
0.30	0.020	0.131	0.013	0.002	0.014	0.000
0.40	0.009	0.073	0.004	0.001	0.006	0.000
0.50	0.005	0.042	0.001	0.000	0.002	0.000
0.60	0.003	0.026	0.000	0.000	0.001	0.000
0.70	0.002	0.016	0.000	0.000	0.001	0.000
0.80	0.001	0.011	0.000	0.000	0.000	0.000
0.90	0.001	0.007	0.000	0.000	0.000	0.000
1.00	0.001	0.005	0.000	0.000	0.000	0.000
1.10	0.000	0.004	0.000	0.000	0.000	0.000
1.20	0.000	0.003	0.000	0.000	0.000	0.000
1.30	0.000	0.002	0.000	0.000	0.000	0.000
1.40	0.000	0.002	0.000	0.000	0.000	0.000
(b) Exposure Range 0-4 Gy						
0.00	0.169	0.016	0.012	0.309	0.050	0.058
0.10	0.309	0.057	0.063	-	0.146	0.210
0.20	-	0.125	0.166	0.349	0.274	-
0.30	-	0.212	0.302	0.244	-	0.389
0.40	0.345	0.302	-	0.174	-	0.258
0.50	0.277	0.396	-	0.127	0.389	0.169
0.60	0.223	-	0.336	0.095	0.309	0.110
0.70	0.184	-	0.261	0.073	0.249	0.073
0.80	0.153	-	0.200	0.057	0.203	0.050
0.90	0.129	0.349	0.155	0.046	0.166	0.034
1.00	0.110	0.309	0.123	0.037	0.138	0.024
1.10	0.095	0.269	0.097	0.031	0.115	0.017
1.20	0.083	0.238	0.078	0.026	0.097	0.013
1.30	0.074	0.212	0.063	0.022	0.083	0.010
1.40	0.066	0.190	0.052	0.019	0.072	0.007

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