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Radiation-Related Cancer Risks at Low Doses among Atomic Bomb Survivors

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To clarify the information in the Radiation Effects Research Foundation data regarding cancer risks of low radiation doses, we focus on survivors with doses less than 0.5 Sv. For reasons indicated, we also restrict attention mainly to survivors within 3,000 m of the hypocenter of the bombs. Analysis is of solid cancer incidence from 1958–1994, involving 7,000 cancer cases among 50,000 survivors in that dose and distance range. The results provide useful risk estimates for doses as low as 0.05–0.1 Sv, which are not overestimated by linear risk estimates computed from the wider dose ranges 0–2 Sv or 0–4 Sv. There is a statistically significant risk in the range 0–0.1 Sv, and an upper confidence limit on any possible threshold is computed as 0.06 Sv. It is indicated that modification of the neutron dose estimates currently under consideration would not markedly change the conclusions.

INTRODUCTION

Controversy has intensified regarding cancer risks of low doses of ionizing radiation. Since quantitative risk estimates are derived mainly from the follow-up of A-bomb survivors by the Radiation Effects Research Foundation (RERF), it is important to understand what direct information about low-dose risks is available from that investigation. Although it is often referred to as a high-dose study, e.g. (*1–3*), this characterization is only partly true. It is true that exposures were at very high dose rates, and that linear cancer risk estimates are largely determined from the 0.5–2-Sv range.[2] However, about 75% of the survivors in the significantly exposed part of the population—about 35,000 persons presenting 5,000 cancer cases—had doses in the range of 0.005–0.2 Sv of primary interest for radiation protection policy[3] (*4–10*). The aim here is to clarify the information available from this low-dose range regarding risks of all solid cancers.

Quantitative estimates of radiation-related cancer risks in humans were only roughly assessed prior to the 1970s. A path-breaking 1980 report (*9*) provided estimates for low doses (0.10 Sv), based on the RERF data and using a curvilinear dose–response model suggested by considerations of radiobiology. Contention was recorded regarding the use of a linear or curvilinear model for solid cancer. The extent of curvature for solid cancers was taken as that seen for leukemia, but subsequently the solid cancer risks were found to be increasingly less compatible with that much curvature (*5–8, 10–12*). Radiation protection guidelines (*4*) for solid cancer are now largely based on a linear dose response fitted to the RERF data, but with emphasis on dividing the slope by two for application to low-dose-rate settings and very low acute doses. In recent years, there has been substantial criticism of this ''linear, no-threshold'' approach to radiation protection (*1, 13–15*). As part of an RERF report on cancer mortality from 1950–1990 (*16*), increased attention was given to the low-dose range, but the inherent inaccuracy of death certificate information limits the usefulness of this. Here we consider the RERF cancer incidence data for 1958–1994, which are based on more accurate tumor registry information.

Estimates linear in dose suggest that solid cancer rates are increased about 5% by a dose of 0.10 Sv (see below). Assessing risks at this level greatly strains any epidemiological investigation since, within the scope of a study, cancer rates may vary to at least that degree due to other risk factors correlated with the exposure under investigation. The radiation dose to the atomic bomb survivors decreased with distance from the urban hypocenter, and some lifestyle cancer risk factors correlate with these urban–rural distinctions (*17*). Although this raises concern, we will indicate

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[2] Some perspective on dose: Whole-body or bone marrow doses of 1 Sv would ordinarily require immediate medical attention for hematopoietic acute effects. Annual occupational limits for nuclear workers are 0.02 Sv, with further limitations on cumulative dose, so workers would not routinely acquire 0.10 Sv.

[3] General consideration of radiation risks and protection guidelines is given by the ICRP (*4*). Their recommendations are largely based on reports of scientific committees such as UNSCEAR (*5–8*) and the National Research Council Committee on the Biological Effects of Ionizing Radiation (*9, 10*). The risk estimates in these committee reports are largely based on the RERF data and reports.

TABLE 1
General Summary of the 1958–1994 Cancer Incidence Data

Colon dose, Sv	Subjects	Solid cancers	Estimated excess[a]
beyond >3,000 m	23,493	3,230	0
<0.005 Sv within <3,000 m	10,159	1,301	1
0.005–0.1	30,524	4,119	77
0.1–0.2	4,775	739	60
0.2–0.5	5,862	982	164
0.5–1	3,048	582	177
1–2	1,570	376	165
>2	470	126	80

[a] Fitted values from the model in Eq. (1) below, with linear dose response.

that the particulars of the dose–distance relationship offer some resolution of this. Additionally, RERF has information from several mail surveys on various aspects of lifestyle that are useful, particularly in regard to cigarette smoking. In the most recent analysis (*17*), it has been found that there is no variation in this with dose received or distance from the hypocenter for men, about 70% of whom smoke, while the percentage of smokers increases only from about 12% for women with negligible doses to about 14% for women with doses greater than 0.5 Sv—a difference too small to result in appreciable bias.

The RERF cohort includes most survivors within about 2.5 km of the bombings who lived in Hiroshima or Nagasaki in 1950 and met certain conditions ensuring adequate follow-up. These 54,000 persons are thought to represent roughly half of the survivors within that distance. Interviewing efforts provided assessment of individual location and shielding, which along with calculation of radiation transport in air and shielding effects has led to dose estimates for about 90% of these survivors (*18*). The cohort also includes an essentially unexposed comparison group of about 40,000 sampled from those within 2.5–10 km of the bombings. Cancer incidence is assessed from the Hiroshima and Nagasaki tumor registries (*19*). Table 1 provides a useful general perspective but is inadequate for purposes of risk estimation.

Exposures from the Hiroshima bomb involved non-negligible ratios of neutrons to γ rays: 1% at 1,000 m and 0.2% at 2,000 m. There is presently concern that the neutron doses may have been underestimated, particularly at distances greater than about 1,500 m. Neutrons generally have greater biological effects per unit dose (absorbed energy) than γ rays. The primary aim is to estimate effects of the dominant γ rays, and the standard approach attempts to convert the neutron component of doses to equivalent γ-ray doses. Although the relative biological effectiveness (RBE) of neutrons decreases with increasing dose, it has been adequately taken as constant at 10 (or sometimes 20) in all previous analyses because the neutron:γ-ray ratio is so small at low doses. One of the aims here is to explore the effect on the main results of substantial tentative increases of the neutron doses in the low-dose range, and the use of a constant RBE would be inappropriate for this. Therefore, for the entire paper, we use an RBE taking values around 40 at very low doses and decreasing to about 10 in the higher dose range. The dose in sieverts is then a γ-ray dose equivalent taken as $g + \mathrm{RBE} \times n$. Results using the more conventional approximate RBE constant at 10, as in ref. (*16*), would for all of this paper, except where considering possible revision of neutron dose estimates, be essentially the same as here.

Following the Materials and Methods are two sections in which we aim to clarify what is meant by a ''dose–response'' relationship in view of the fact that the ''response'' to a given dose is not a simple numerical quantity, and to show that there is indeed enough bias associated with urban–rural distinctions to interfere with estimation of low-dose risks. The subsequent section then provides the primary results of the paper, a description of the solid cancer dose response with emphasis on the dose range 0–0.5 Sv. After that, we consider in two sections the extent of curvature, and possible thresholds, statistically consistent with the observed dose response. The penultimate section considers the extent to which conclusions here might be altered by modifications of the presently uncertain Hiroshima neutron dose estimates.

MATERIALS AND METHODS

The analyses here use the 1958–1994 data on solid cancer incidence, primarily in the dose range 0–0.5 Sv but altogether within the dose range 0–2 Sv. Although there are no doubt some variations in the radiation relative risk among types of solid cancers, inferences about low-dose risks for any particular type are very limited. Generally the site-specific linear relative risk estimates seldom differ by more than would be expected from ordinary sampling variation. We note that although the background rates vary greatly, the relative risk estimates obtained here by pooling are precisely the same as would be obtained if the fitting were done by cancer type with the constraint that the radiation relative risk estimates are the same for each cancer type.

The cross-tabulation of cases and person-years used has dose categories with cut points 0, 0.005, 0.02 (0.02) 0.10 (0.025) 0.20, 0.25, 0.3, 0.4, 0.5 (0.25) 2 Sv, along with 5-year intervals of age at exposure, calendar time, and attained age. For the section on Linear vs. Curvilinear Models, a cross-tabulation using both γ-ray and neutron doses is used. Doses used throughout are those estimated for the large intestine, as a representative internal organ. Imprecision in dose estimates results in some downward bias of risk estimates at higher doses, and special statistical methods are used to reduce this effect (*20*). These methods have no effect on inferences specific to the dose range below 0.5 Sv.

All analyses are based on fitting by maximum likelihood versions of Eq. (1) developed in the following section for the relative risk, namely

$$\mathrm{RR} = 1 + \rho(dose)\mu_{sex} \exp(\gamma \times \textit{age at exposure}),$$

with various definitions of ρ(*dose*). Baseline (background) rates for the relative risk are dealt with nonparametrically, essentially stratifying on city, sex, birth cohort, and attained age, as explained in ref. (*16*). The points in the plots describing the RR nonparametrically are obtained by taking ρ(*dose*) as constant within each of the dose categories described above, but otherwise unrestricted; for the lines in those plots, ρ(*dose*) is taken as linear in dose. When considering threshold models, ρ(*dose*) is

taken as zero up to a postulated threshold value, increasing linearly from zero for doses above that value. In the section on Linear vs. Curvilinear Models, $\rho(dose)$ is taken as the form discussed there, namely

$$\rho(g, n) = \beta(g + \theta g^2 + \lambda n),$$

where g and n represent γ-ray and neutron doses, respectively.

The smoothed RR estimate curve in Figs. 1–3 represents a collection of weighted moving averages obtained as follows. First, five-point moving weighted averages of the plotted ERR points were computed. The weights were taken as products of prior weights {0.15, 0.20, 0.30 0.20, 0.15} and the reciprocal variances of the points to be averaged. The standard errors of the weighted averages were computed by treating the weights as fixed. Averages of fewer points were similarly employed at the extremes of the dose range. Then each weighted average RR was plotted as a function of the corresponding weighted average of the category mean doses, along with the standard error limits. The resulting points varied smoothly enough to allow connecting them rather arbitrarily with the continuous curves shown.

For comparison of the cancer rates of survivors beyond 3,000 m with those estimated for zero dose from within 3,000 m, the ratio of background rates for these groups is allowed to vary as $\exp(\delta + \omega \times \textit{calendar time})$. The P value reported is for the likelihood ratio χ^2 test on 2 df that both δ and ω are zero. Of course this particular modeling becomes irrelevant when the distal group is omitted.

When testing for significant response below some dose d_0, it is necessary to use information from doses greater than d_0 regarding the sex and age-at-exposure effects of the RR model. For this we allow different linear slopes for the range 0–d_0 and d_0–2 Sv and test the value zero for the former slope. For this purpose, the two linear fits are not constrained to connect at d_0.

The particular variable RBE function used in all but the section on Linear vs. Curvilinear Models derives from the equation for $\rho(g, n)$ above, taking $\lambda = 40$ and $\theta = 1$ for dose in grays, and defining the RBE from the implicit equation $\rho(g + \text{RBE} \times n, 0) = \rho(g, n)$; for a discussion of this, see ref. (*21*). In doing this, the aim is not to be effectively using a risk model of form given by $\rho(g, n)$, but rather just to obtain a convenient formula for a plausible variable RBE, with values around 40 at low doses and around 10 for higher doses.

In the formula for $\rho(g, n)$, the parameter λ is the limiting RBE as the dose approaches zero, and θ represents the extent of curvature with γ-ray dose. The aim in the section on Linear vs. Curvilinear Models is to determine the extent of this curvature consistent with the data, which involves fitting the model for a wide range of values of θ. The implicit RBE for higher doses as defined above depends on both λ and θ; for example, when $\theta = 0$, the RBE is equal to the limiting RBE λ for all doses. Since the value of λ is quite uncertain, we allow that parameter to vary with θ so that the RBE at higher doses, which is less uncertain, remains constant. In particular, for survivors with $g = 1$ and $n = 0.01$, the implicit variable RBE is for all θ fixed at the same value 13 as employed at that dose in the rest of this paper.

GENERAL NATURE OF SOLID CANCER RISKS

One of the most important things learned from the RERF investigations is that solid cancer radiation risks persist even 50 years after exposure. An adequate description (*16*) is that, given sex and age at exposure, an acute radiation exposure increases normal age-specific solid cancer rates by a dose-dependent factor throughout life. Averaging over sex and age at exposure, the increase is roughly 10% of normal cancer rates for a dose of 0.20 Sv, the mean dose for survivors within 2.5 km of the hypocenter. More formally, in terms of the relative risk RR—the ratio of age-specific cancer rates for exposed and unexposed persons—the characterization can be expressed as

$$\text{RR} = 1 + \rho(dose)\mu_{sex} \exp(\gamma \times \textit{age at exposure}). \quad (1)$$

The effect μ_{sex} largely serves to offset the sex ratio of about two in normal cancer rates, with the absolute increase in cancer rates being about the same for both sexes. The variation with age at exposure amounts to a decrease of about 30% for each 10 years in the excess relative risk (RR − 1).

Although the RR as initially defined refers to age-specific rate ratios and is hence a function of age, the formulation in Eq. (1) is constant in attained age for a given age at exposure. It is difficult to distinguish decreases of RR with age at exposure from decreases with attained age, and an alternative model of form

$$\text{RR} = 1 + \rho(dose)\mu_{sex} (\textit{attained age})^{-\delta}, \quad (2)$$

with $\delta > 0$, also describes the data well. Although the relationship of this characterization to plausible biological mechanisms is intriguing, in particular bearing on how excess risk could persist for decades after exposure (*22*), the former and more conventional model is used here.

These considerations are critical in defining ''radiation dose response'', since the ''response'' to a given dose is not simply a number but a pattern of risks depending on sex, age at exposure, and age. In the above formulations, we can consider the function $\rho(dose)$ as defining the shape of the dose response. As shown by the alternative model in Eq. (2), such a factorization is only an approximation, adequate for many needs but not conducive to extremely precise interpretation. In presenting dose-specific numerical estimates of the RR using Eq. (1), we average with equal weights over sex and take age at exposure as 30 years.

DISTAL vs. PROXIMAL COMPARISON GROUPS

As indicated, there should be concern that rural and urban survivors may have different cancer rates for reasons other than radiation dose. Indeed, there is a statistically significant difference ($P = 0.03$) between the cancer rates for those beyond 3,000 m and the rates estimated for zero dose from those within 3,000 m. The ratio of background rates for distal survivors to those estimated for zero dose from proximal survivors increased from a value slightly less than 1 early in the follow-up to about 1.1 by 1990. In the part of the data most influential for estimating radiation risks, the distal group has about 5% higher cancer rates than estimated for zero dose from the proximal group. A bias of this size has very little effect for analyses over the full dose range, but it does substantially affect assessment of low-dose risks. Since urban–rural differences might be expected and omitting the survivors beyond 3,000 m only modestly reduces the standard error of RR estimates, we mainly omit this group for analyses here. That is, we omit the distal group for primary results but also indicate the effect of this

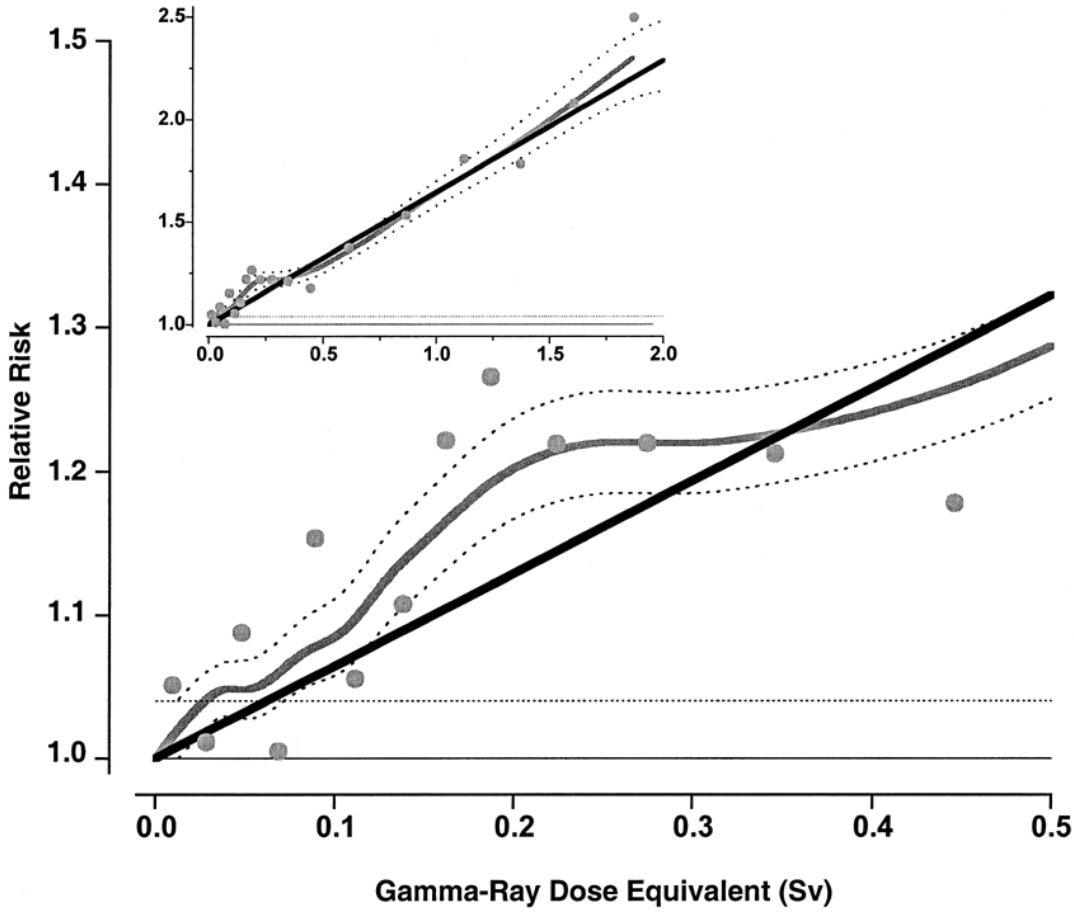

FIG. 1. Estimated low-dose relative risks. Age-specific cancer rates over the 1958–1994 follow-up period relative to those for an unexposed person, averaged over the follow-up and over sex, and for age at exposure 30. The dashed curves represent ±1 standard error for the smoothed curve. The straight line is the linear risk estimate computed from the range 0–2 Sv. Because of an apparent distinction between distal and proximal zero-dose cancer rates, the unity baseline corresponds to zero-dose survivors within 3 km of the bombs. The horizontal dotted line represents the alternative baseline if the distal survivors were not omitted. The inset shows the same information for the fuller dose range.

omission. As seen in Table 1, this reduces the number of negligibly exposed (<0.005 Sv) survivors from about 33,000 to about 10,000.

DESCRIPTION OF SOLID CANCER DOSE RESPONSE

Figure 1 displays the estimated dose response for the dose range 0–0.5 Sv, along with the linear estimate computed from the wider dose range 0–2 Sv. The points are imprecise estimates (standard errors 0.03–0.08) corresponding to narrow dose categories. The choice of dose categories to which the points correspond is rather arbitrary, but this is about as close as usefully obtainable to ''plotting the data''. Some smoothing is necessary for a useful summary of the data, and the curve in Fig. 1 is essentially a weighted moving average of the points shown. If the distal survivors were not omitted, the relative positions of the plotted points would be very nearly the same as shown, but the baseline would correspond to the dotted line. The linear risk estimate would then start at that higher baseline at zero dose, with a 3% decrease in the slope. The smoothed estimate would also begin at the higher baseline but would differ negligibly from that shown beyond the second positive-dose category.

The only suggestion of nonlinearity in dose in Fig. 1 is the elevated pattern in the range 0.15–0.3 Sv. It is difficult to assess the statistical significance of such an anomaly. Formally, the *P* value for evidence of a constant elevation of risk above the linear fit for the range 0.15–0.30 Sv is $P = 0.06$, but substantial inflation of this *P* value should be made to allow for testing an effect suggested purely by the data. Nevertheless, the pattern is striking and has moderate effect on inferences about low-dose risks.

It is at about 0.10 Sv where the effect of omitting distal survivors changes from substantial to minimal in interpretation of the analysis. For example, in Fig. 1 the risk estimate at 0.10 Sv given by the smoothed curve is about 3.7 standard errors above baseline, and it would be about 2 standard errors above baseline if distal survivors were not omitted.

LINEAR vs. CURVILINEAR MODELS

The degree of linearity over the wider dose range is surprising. Experimental work regarding cancer, mutations, and chromosome aberrations—along with corresponding radiobiological theory—generally indicates nonlinear (upward curving) biological responses to low-LET radiation. More particularly, the type of response expected in terms of γ-ray (g) and neutron (n) components is of the form

$$P(g, n) = \beta(g + \theta g^2 + \lambda n). \quad (3)$$

The curvature is determined by θ, which in experimental work is often in the range 0.6–2 for dose in gray (ref. *5*, Annex B, paragraphs 125–127), and the parameter λ is the low-dose neutron RBE. The parameter β represents the risk per unit dose for low doses of γ rays, and when this model is fitted with fixed $\theta > 0$, the estimated β will be smaller than the ordinary linear risk estimate. Effects of possible nonlinearity can be characterized by a linear risk overestimation factor $O(\theta)$, defined as the ratio of the linear risk estimate to the low-dose slope β estimated from these data for a fixed value of θ.

Although the dose response in Fig. 1 appears quite linear, it is useful to consider what degree of curvature is statistically consistent with the data. Analysis of the data for 0–2 Sv, using separate γ-ray and neutron exposures in the above model, yields the estimate $\hat{\theta} = 0.15 \pm 0.23$ and a 95% upper confidence limit of 0.75 for θ, so that even the upper limit is in the lower range of what would be expected. The overestimation factor $O(0.75)$ is 1.9. That is, if the true curvature were at the 95% upper confidence limit for these data, linear risk estimates would overestimate the low-dose risk by about 2. If survivors beyond 3,000 m are not omitted, then using the dose range 0–2 Sv, the estimate is $\hat{\theta} = 0.35 \pm 0.35$; the upper confidence limit for θ is 1.30 with $O(1.3) = 2.4$. Elsewhere in this paper, the restriction to analysis of the data for 0–2 Sv has little consequence, but upper confidence limits θ are more affected by this. When using the dose range 0–3 Sv (and omitting survivors beyond 3,000 m), the estimate is $\hat{\theta} = 0.06 \pm 0.13$, the upper confidence limit for θ is 0.37, and $O(0.37) = 1.5$.

The ICRP recommends (*4*) dividing the RERF solid cancer linear risk estimates by 2 to arrive at γ-ray, and more generally low-LET, risk estimates for low doses and low dose rates. We see that consonance with this strains the statistical limits of the RERF data, in terms of the linear-quadratic model. However, the ICRP aims go beyond consideration of the A-bomb survivor data, attempting to incorporate more general radiobiological evidence and theory into the extrapolation to the desired estimates from the data on acute, high-dose exposures. It is important to consider reasons why the A-bomb survivor results should depart from radiobiological expectations to this extent, even allowing for statistical variation. An often-considered and not implausible explanation is that heterogeneity of survivors, and intervening events during the many years between exposure and the influential latter part of follow-up, might tend to ''linearize'' the effects seen in experiments. However, if this were the explanation, then it should be considered that risk protection should aim for applying to settings with these complications. Another fairly plausible explanation pertains to a plateau in the dose response above 3 Sv, not shown here but elsewhere (*16*). It could well be that this represents some effect, either biological or dosimetric, which is also ''trimming off'' more idealized risks well below 3 Sv. But in this case the resulting linear risk estimate may be nearer to that suitable for low doses than a linear approximation to an uncorrupted, more curved, dose response. This would call for a smaller reduction factor than given by the usual arguments.

THRESHOLD MODELS

There is considerable discussion of the possibility that the linear or curvilinear models considered above are inadequate and that, in particular, there may be a non-negligible threshold below which there is no excess risk (*1, 3, 13–15, 23, 24*). Dose-rate issues may be especially relevant to such considerations, but of course from RERF data we can only address acute exposures. For threshold models of the type usually considered, the estimated threshold is at 0 Sv with an upper 95% confidence limit of 0.06 Sv. Figure 2 combines with Fig. 1 the fitted model when the threshold is taken as this upper confidence limit, with linear response fitted between the threshold value and 2 Sv. Note that the lack of fit to a model with a larger threshold derives more from the apparent risks in the range 0.15–0.3 Sv than from those near the threshold value. A conclusion not affected by this is that there is statistically significant risk ($P = 0.05$, one-sided test) in the dose range below 0.10 Sv.

If survivors beyond 3,000 m are not omitted, the 95% upper confidence limit for a threshold becomes 0.10 Sv, and there is statistically significant risk below 0.18 Sv. There is little difference, particularly in view of the additional follow-up, between these inferences and results based on the data on solid cancer incidence through 1987 publicly available from RERF—used, for example, in refs. (*23, 24*). For those data, the low-dose categories provided are 0–0.01, 0.01–0.10, 0.10–0.20 and 0.20–0.50 Sv, where dose is defined in terms of a constant RBE of 10. There the fit with no threshold is at least as good as that with any positive threshold, which was indicated in ref. (*23*) and was the basis for their statement that the linear model is ''statistically equivalent [to a threshold model]''. The basis for their statement that the data ''agree more with a threshold or nonlinear dose–response model than a purely linear model'' was their observation that for the eight cancer types with statistically significant dose response all had slightly fewer observed cases in the 0.01–0.10 Sv dose category than predicted by a linear fit. Aside from the *ad hoc* nature of this analysis, it represents a fragile result in the sense that most of the relevant case-count ratios were very near

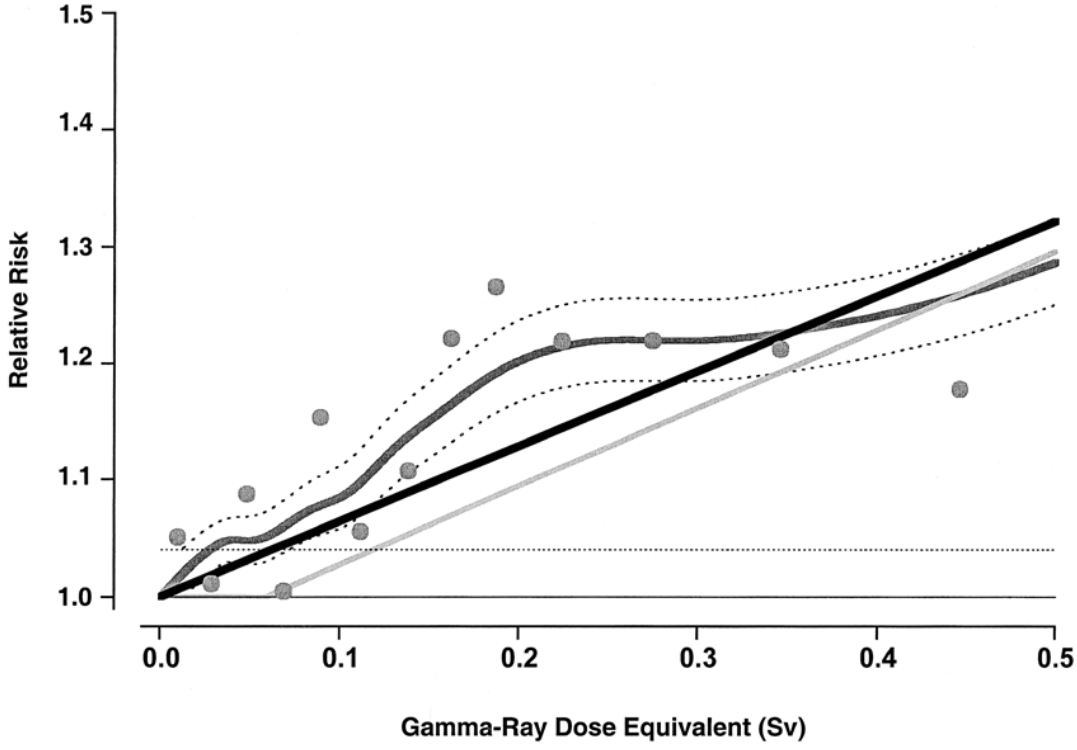

FIG. 2. Upper confidence limit for any threshold. The addition to Fig. 1 of a threshold-type model, with the threshold at 0.06 Sv being the upper 95% confidence limit for such a quantity. Somewhat larger threshold values are contraindicated more by the lack of fit in the range 0.15–0.3 Sv than in the range near the threshold. However, there is statistically significant risk in the interval 0–0.1 Sv without regard to effects of doses above this range.

to unity, and the result does not maintain with the extended follow-up and statistical methods used here. In particular, using Eq. (1) for the RR and nonparametric background modeling, we find that whether or not the distal survivors are omitted, five of those eight types have slightly more observed than linearly predicted cases in this dose range.

Continuing with analysis of the data published previously, for solid cancers together the 95% upper confidence limit for a threshold falls within the dose category 0.10–0.20 Sv. Interpolation within that interval for the 95% limit yields 0.11 when using the details of statistical modeling employed here: Eq. (1) for the RR and nonparametric background modeling. With the slightly different choices made in ref. (*23*), the interpolated values are 0.13 or 0.15 as reported there. Little and Muirhead (*24*) reported an upper 97.5% confidence limit of 0.16. With the previous data there is statistically significant risk on the dose range 0–0.20 ($P = 0.03$, one-sided test), when using the statistical method indicated in the Materials and Methods for that purpose. Little and Muirhead (*24*) reported that this P value is greater than 0.025, without giving the actual value, and their primary statement was that at the 2.5% level of significance one must include as well the next dose category, 0.20–0.50 Sv, to obtain a significant response. This is formally consistent with the result we have calculated above, but as discussed in our response (*25*) to the letter of Little (*26*), the method used there differs from our approach in not using information from the higher dose range regarding sex and age-at-exposure effects.

POSSIBLE REVISION OF NEUTRON DOSE ESTIMATES

There is concern, based on activation measurements in exposed materials, that the current neutron dose estimates for Hiroshima may be substantially too small, the relative error increasing with distance from the hypocenter. Any general increase in neutron dose estimates would decrease risks attributed to γ rays, and in principle a distance-dependent modification would change the shape of the dose response. For physical measurements presented by Straume (*27*), the ratio (r) of measurement-based neutron doses to those from the current dosimetry system has been described by a logarithmic regression on slant distance (s) from the bombs essentially of the form $\log_e(r) = (s - a)/b$, where $a = 800$ and $b = 360$. This gives r values of 1, 9 and 28 at 800, 1,600 and 2,000 m, respectively.

A major issue in the plausibility of tentative modifications of neutron doses is their attenuation with distance, which we will describe in terms of the survivors' mean dose at 2,000 m as a percentage of that at 1,000 m. For current estimates in Hiroshima, this factor is 1.7% for γ rays and 0.2% for neutrons (with explicit mean survivor colon dose ratios of 0.037/2.150 and 6×10^{-5}/0.026, respectively). If neutron dose estimates were modified by the

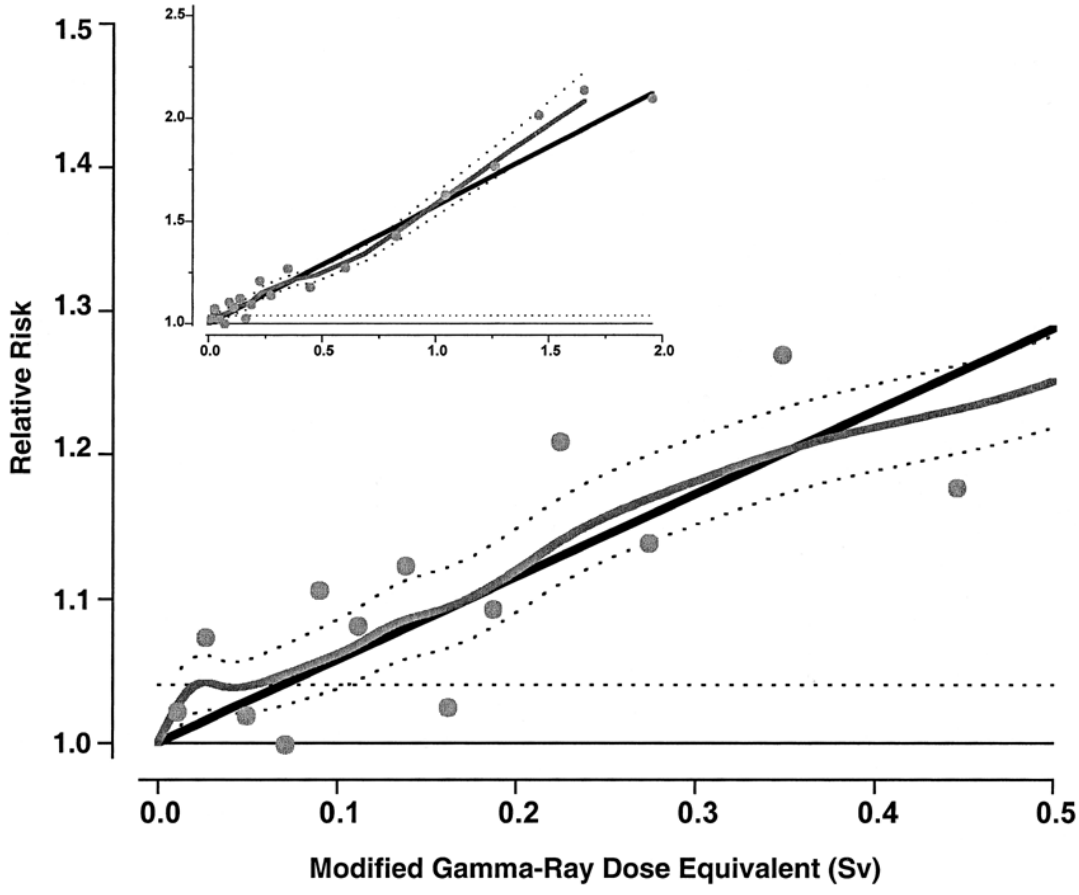

FIG. 3. Response with modified neutron doses. Results of applying the same analyses as in Fig. 1, but using modified neutron doses corresponding to $b = 460$. The linear dose response, fitted on the range 0–2 Sv, is reduced by about 10%.

distance-dependent factor r given above, neutron doses at 2,000 m would be 3.7% of those at 1,000 m. Physicists responsible for calculating source energies and attenuation with distance report that this is physically untenable,[4] suggesting difficulties in taking the activation measurements at face value. For this reason, we consider somewhat less extreme modifications here. The adjustment factor $(r - 1)$ is reduced by half at 2,000 m by changing the denominator b in the above expression for $\log(r)$ from 360 to 460. The resulting relationship of r to distance still conforms moderately well with the activation measurements, which exhibit substantial variation around any log-linear summarization. This change reduces the above-mentioned neutron attenuation ratio 3.7% to 2%. Although this still seems implausibly large, it may be closer to the ultimate resolution, and we will focus here on the consequences of a modification with $b = 460$. With this modification, the RBE-weighted neutron dose at 2,000 m would be roughly equal to the γ-ray dose, whereas for the current dosimetry it is about 5% of the γ-ray dose.

Figure 3 provides results from the same approach used for Fig. 1, replacing the current neutron dose estimates with modified values and maintaining the same RBE function used there. The primary changes are that the linear slope fitted to the range 0–2 Sv is reduced by about 10%, and the data become statistically consistent with somewhat more upward curvature or larger thresholds. Fitting the linear-quadratic model in γ-ray and neutron dose components as before, the estimated curvature parameter is $\hat{\theta} = 0.27 \pm 0.35$ and the upper 95% confidence limit for the parameter θ is 1.5, values about twice those computed before. The linear risk overestimation factor at the upper confidence limit for curvature is $O(1.5) = 2.8$, about 50% higher than before. The 95% upper confidence limit for a threshold value increases from the 0.06 for current dosimetry to about 0.10 Sv. The smallest dose d_0 such that there is statistically significant risk on $0–d_0$, at the 5% level, increases from 0.10 to about 0.125 Sv.

[4] The following information is derived from material presented by D. Kaul and S. Egbert at a 1998 dosimetry workshop held at RERF. Attenuation of neutrons in air is inversely related to their energy. In the current dosimetry the neutrons contributing to survivor absorbed dose are primarily in the range of 0.8–2.3 MeV. The fluence at around 2.3 MeV would have to be increased by an order of magnitude, without a concomitant increase over the remainder of fission-neutron energy range, to explain modified neutron doses with $b = 360$ and still satisfy all measurement constraints. This is considered physically impossible. Changes in the air transport calculations adequate to explain the result are also felt to be untenable. Thus the thermal activation measurements are in considerable question, and their relationship to distance does have hallmarks of difficulties in adjustment for background levels.

This consistency with more upward curvature is a consequence of distance-dependent changes in the γ-ray dose equivalent for Hiroshima, and would occur whether or not there was the anomalous pattern of risks seen in Fig. 1 for the dose range 0.15–0.30 Sv. We note that the removal of this anomaly in Fig. 3 cannot reasonably be interpreted as an indication of inadequacy of the current neutron dose estimates. The peculiar pattern in the dose response derives mainly from the Nagasaki data, and its absence in Fig. 3 is due to compensating modification of the apparent dose response for Hiroshima. So, although removal of the anomaly is literally ''due to'' modification of Hiroshima neutron estimates, it would be implausibly convoluted to consider this effect, for the cities combined, as evidence for inadequacy of the current Hiroshima neutron dose estimates.

Results of the neutron dose modification with $b = 360$ are not radically different from this. The linear slope is reduced about 20% from the current value rather than the 10% discussed above. The apparent dose response remains quite linear, although the data are statistically consistent with somewhat more upward curvature than indicated above. It is likely that the Hiroshima γ-ray dose estimates might be increased by 5–10%, with at most modest dependence of the increase on distance, partly as a result of increased neutron levels since part of their energy is converted to γ rays. The effect of this would be relatively simple, decreasing γ-ray equivalent linear risk estimates by about the same factor as the γ-ray doses are increased, but not markedly changing the apparent shape of the dose response. The full implications of possible revision of the dosimetry are rather unpredictable, but the analysis here may shed some light on the issues.

DISCUSSION

The data shown in Figs. 1 and 2 indicate strongly that risks for low doses are not overestimated by linear estimates based on a wider dose range. There is direct, statistically significant evidence of risk in the dose range of approximately 0–0.10 Sv, but this mode of reasoning and certainly the precise limits of such a range should not dominate interpretation of the data. In the presence of available data, it is neither sound statistical interpretation nor prudent risk evaluation to take the view that the risk should be considered as zero in some low-dose range due to lack of statistical significance when restricting attention to that range. In particular, the absence of any indication of departure from linearity should also be given substantial weight in the assessment.

For inferences about low-dose risks, there is serious concern that survivors might differ in regard to cancer risk factors in a manner correlated with radiation dose. Since evidence of this is seen in the comparison of distal and proximal survivors, we have emphasized analysis omitting the distal group. Of course, the remaining proximal survivors may have substantial heterogeneity of cancer risk factors, but to present serious difficulties this would have to be highly correlated with radiation dose, i.e. with distance from the bombs. However, radiation dose decreases very rapidly with distance, by a factor of about 10 with each 600 m, leaving little scope for cancer risk factors unrelated to the bombings to be highly correlated with dose over the relevant distance range. Differences in cigarette smoking are far too small to cause any appreciable bias in the cancer dose response. The same is likely true regarding survivor access to or attitudes toward health care. Within 3,000 m there are no differences in access to special medical care for A-bomb survivors. Further, survivors' perception of trauma and of their radiation dose was probably less highly correlated with dose than might be supposed. This is both because radiation dose varied so rapidly with distance and because the heat and shock-wave energies, which account for most of the energy released by the bombs, were high over most of the range where radiation doses were non-negligible.

In conclusion, there is substantially more direct information about low-dose cancer risks in the atomic bomb survivor data than is commonly believed, since the vast majority of the cohort members are in the low-dose range. There is no evidence in these data that linear risk estimates from a wider dose range overestimate low-dose risks, and considerable evidence that the linear risk estimates are appropriate.

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