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Accounting for Neutron Exposure in the Japanese Atomic Bomb Survivors

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The Japanese atomic bomb survivors that were directly exposed to both γ rays and neutrons have been followed by the Radiation Effects Research Foundation (RERF). The estimation of the γ-ray risks requires some adjustment for the greater biological effect of the neutrons per unit dose. Because the small neutron doses and the predominant γ-ray doses are highly correlated, the neutron relative biological effectiveness (RBE) cannot be reliably estimated from the survivors' data and information from radiobiology must be invoked. As data became available on neutron doses, RERF has used a constant neutron RBE value of 10, even though radiobiological studies indicate that the RBE values appear to have considerably larger values at low doses. The approximation RBE = 10 assumes that if the RBE is variable it takes roughly this value in the range of total dose most relevant for linear risk estimation, namely about 1 Gy. We consider some possible RBE functions to explain the correct use and the impact of a dose-dependent RBE. However, we do not advocate any particular choice or even that a variable RBE be employed. Rather we show that the assumed neutron RBE, within a wide range of choices, is far less important to the outcome of risk assessment of the RERF data than generally believed. Some of these misperceptions have been related to the consideration of variable RBE functions, and without due attention to the fact that in the case of the A-bomb survivors' data, the mixed field of neutrons and γ rays must be considered. Therefore, the RBE value of neutrons is much lower than the RBE in pure neutron fields that are used in radiobiological experiments. Thus, applying the pure neutron field RBE to the mixed-field A-bomb radiation can lead to an overestimation of the actual neutron RBE for moderate total dose levels of 1 Gy by a factor of more than four. While in a pure neutron exposure the RBE depends on the neutron dose, in the mixed field it depends on both components of exposure, and in particular, we show that in the RERF setting the RBE depends mainly on the accompanying γ-ray dose.

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INTRODUCTION

The Life Span Study (LSS) of late effects such as the increased incidence of leukemia and of solid cancers among the atomic bomb survivors in Hiroshima and Nagasaki has long been the major basis for radiation risk assessment. Although this large epidemiological study of the Radiation Effects Research Foundation (RERF) has successfully evolved for more than half a century, it continues to provide new insights and to improve the methods of analysis. However, one critical issue that continues to be discussed is the impact of the neutron dose on risk assessment because even though neutrons contribute only a very small fraction to the absorbed dose in A-bomb radiation, it nevertheless must be taken into account because neutrons are a densely ionizing radiation that create more effect per unit dose than the predominant γ rays.

The primary motivation for considering the neutron effects in the LSS data is to account for them in order to more precisely estimate the γ-ray effects. To assess the dose contribution of neutrons, information on their relative biological effectiveness (RBE) is required for comparison to the high-energy γ rays of the A-bomb radiation. It is well known that the neutron doses in the LSS data are too small and are too highly correlated with the γ-ray doses to allow useful estimation of the RBE from the late effects data.

In published articles by Shimizu *et al.* and other colleagues (*1–4*) the obtained neutron dose estimates have very broad confidence limits. Several of these studies attribute any city differences in late effects to the larger neutron doses in Hiroshima, which is questionable. Little (*3*) for example, used tentative revised Hiroshima neutron estimates that turned out to be much too large. It should also be noted that analyses outside of RERF have been done without access to neutron and γ-ray dose estimates for individual survivors, using instead the mean values in cross-tabulations based on weighted total dose described below.

In view of increasing statistical capabilities and improved dose estimates in recent years, RERF analysts have continued to assess this matter. The most recent work remains unpublished, further demonstrating the difficulty of this approach. These new findings confirm that, as is typical with such highly collinear variables, statistical methods for this purpose are non-robust and unsatisfactory [e.g., see

section 3.8 of ref. (*5*)]. In particular, it was found that the estimation of RBE remains grossly oversensitive to small portions of the data.

Since there are no other data available in humans for leukemia or solid cancers caused by exposure to neutron radiation we must rely on the dose-effect relationships for cell damage obtained in experimental radiation studies. These dose relationships are often linear quadratic for sparsely ionizing radiations, such as γ rays; the initial slope is small, but there is substantial upward curvature, i.e., the added effect of an increment of dose increases as the dose increases. For densely ionizing radiation, such as neutrons, the dose relationships are steep but roughly linear, and the effect per unit dose is high but does not increase with dose. Under these circumstances the efficiency of neutrons relative to γ rays is large at lower doses of γ rays and decreases at higher doses. How to potentially utilize such experimental information for neutron RBE will be outlined later in this article.

It is important to note that RBE is similar to, but must be distinguished from the radiation weighting factor, w_R, which was adopted by the International Commission on Radiological Protection (ICRP) for radiation protection purposes. w_R relates to low doses and/or low dose rates, and is intended as a regulatory factor rather than for risk estimation. In this article, we use the term ''RBE'' to refer to the function that takes on values R to be applied as weight factors for the neutron component in the A-bomb radiation.

The concept of neutron RBE does not merely refer to low doses or low dose rates, nor is it restricted to the comparison of a neutron dose with the equivalent γ-ray dose. Suppose that, for a given biological end point, the effect of a joint dose (D_γ, D_n) is the same as that of a γ-ray dose $D_\gamma + \Delta$ alone. Then the additional γ-ray dose, Δ, is equivalent to the neutron component and the RBE value is defined as $R = \Delta/D_n$. Note that this implies that R will generally depend on both D_γ and D_n. The product RD_n equals the additional γ-ray dose, Δ, equivalent to D_n, and is here termed the ''weighted dose'' due to the neutrons. The sum $D_\gamma + RD_n$ is the total weighted dose and equals the γ-ray dose that is equivalent to $D_\gamma + D_n$.

If the dose-effect relationships are linear both for neutrons and γ rays, the RBE is dose independent. Otherwise, if for example the γ-ray response is upward curved and the neutron response is linear, R decreases with increasing γ-ray dose since decreasing increments of γ-ray dose are then required to produce a given increase in effect. While R decreases with the increase of the neutron dose when a pure neutron exposure is compared to a γ-ray exposure, the RBE of a neutron dose decreases with increase of both the neutron dose and γ-ray dose when a neutron dose is accompanied by a γ-ray dose, as in the A-bomb survivor setting (Fig. A3). The RBE function will thus be different for the two settings: (1) converting a pure neutron dose to an equivalent γ-ray dose; and (2) converting the neutron dose to an equivalent additional increment of γ rays when the exposure is already a combination of neutrons and γ rays (for details about this distinction, see the Appendix section). For clarification, the term ''pure neutron RBE'' refers to a neutron exposure alone, while the term ''mixed-field neutron RBE'' refers to the neutrons in the combined exposures to the A-bomb radiation.

The dependence of the RBE on neutron and γ-ray dose is central to our analysis, because there have been several instances where the pure neutron RBE has been applied to mixed-field A-bomb radiation and the decrease of the RBE due to the simultaneous, much larger γ-ray dose has been disregarded. This has led, for example, Sasaki *et al.* (*7*) to conclude that neutrons are responsible for more than 40% of the solid cancer risks in Hiroshima. This type of error, confusing the pure neutron RBE with the mixed-field neutron RBE, was also made by Rossi and Zaider (*6*).

Even though it was anticipated that the *DS*02 revision would lead to substantially increased neutron doses, [e.g., Straume *et al.* (*9*)], this did not materialize, and the belief in a substantial neutron contribution to the late effects among the A-bomb survivors remained because of the confusion discussed above. In the current analysis the dosimetric data for the LSS cohort are employed to elucidate the choice of the RBE function and to demonstrate that, within broad limits, it has such a small effect on the RBE-weighted doses that it cannot appreciably affect the γ-ray risk estimates obtained from the LSS late effects data.

We present the main results here not in terms of actual risk estimation, which would require a very different type of article, but by considering merely the change of weighted dose caused by different RBE functions. A minimal exception is made for some comments on Figs. 2 and 3, where the specific points are best supported by cancer risk estimates.

OVERVIEW OF THE γ-RAY AND NEUTRON DOSES TO THE A-BOMB SURVIVORS

Scatter Plots of Individual Doses in the Life Span Study (LSS) Cohort

The dosimetry data used in this study are the current dosimetry system DS02 colon dose estimates used for analysis of all solid cancers together, with some suitable downward adjustment for dose estimation errors (*10*). The data are described in an earlier article on the DS02 doses (*11*). The adjustment for dose estimation errors applies equally to the neutrons and the γ rays, and it varies with dose, ranging from none at total doses around 0.05 Gy to about a 10–15% dose reduction in the higher part of the dose range. The LSS cohort comprises 120,321 individuals, of whom 26,580 were not in either city at the time of bombing, and another 7,070 do not have calculated dose estimates due to difficult shielding situations. After omitting 317 survivors with unweighted total (neutron + γ ray) shielded kerma estimates greater than 4 Gy as calculated by dosimetry system DS02, there were 58,324 survivors who

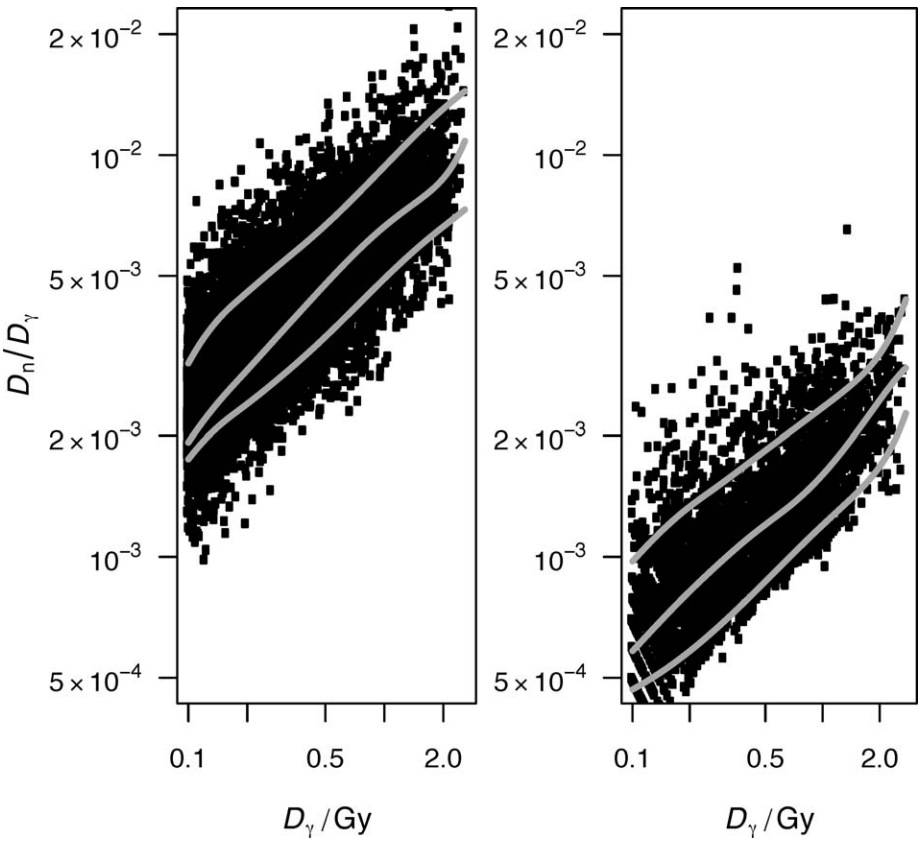

FIG. 1. Neutron/γ-ray ratios, ρ_n vs. γ-ray dose for Hiroshima (left panel) and Nagasaki (right panel). The points represent individual survivors. The three gray curves indicate the median and the 10 and 90% quantile at each γ-ray dose.

were in Hiroshima and 28,030 survivors who were in Nagasaki at the time of the bombing and have dose estimates. Many of these have very small or zero doses and for most purposes here we restrict to those with unweighted total (neutron + γ ray) colon dose estimates above 0.05 Gy: 19,307 survivors in Hiroshima and 4,961 in Nagasaki. For some plots, such as the first one, we further restrict our analysis to those with colon doses greater than 0.1 Gy.

Figure 1 shows scatter diagrams pertaining to these adjusted colon-dose estimates in Hiroshima and in Nagasaki. Logarithmic dose scales are employed on both axes for better readability at low doses, and furthermore the graph is simplified by plotting the neutron/γ-ray dose ratios, ρ_n, on the ordinate, instead of the neutron dose. The three gray curves indicate the median, 10% quantile and 90% quantile at each γ-ray dose, obtained by a suitable nonparametric smoothing procedure.

The fractional contribution of the neutrons to the absorbed dose is roughly 5 times larger in Hiroshima than in Nagasaki. In Nagasaki the neutron doses are too small relative to the γ-ray doses to be of much interest, however even in Hiroshima they are only about 0.2% of the γ-ray dose at a γ-ray dose of 0.1 Gy, 0.7% at 1 Gy and about 1% at 2 Gy. The ratios ρ_n for shallow organs such as thyroid and breast are somewhat larger than those for colon, but not so much that the conclusions of the following analysis would be affected. Neutron doses are proportionally smaller at larger distances and lower γ-ray doses because neutrons are more rapidly attenuated in air than γ rays.

The equation:

$$\rho_n = D_n/D_\gamma = 0.007 D_\gamma^{0.5} \quad (1)$$

with dose expressed in Gy, serves as a rough parametric approximation for the average neutron/γ-ray ratio in Hiroshima. The standard deviation of the neutron dose at a specified γ-ray dose is of the order of 30% of the mean, due to differences in radiation shielding among individual survivors.

ASSESSMENT IN TERMS OF CONSTANT RBE

We begin with the simplest treatment of neutron effectiveness: a constant RBE for neutrons as found with effects such as point mutations where the dose relationships are linear both for sparsely ionizing and densely ionizing radiation. For the purpose of the current analysis, we leave open whether a constant or a variable RBE applies. Information from experimentally observed linear-quadratic dose relationships for photons and linear relationships for neutrons will be considered in the subsequent sections.

Although a constant RBE need not apply to the late effects in the LSS, this is a very conservative approach that has served as a reasonable approximation in the major analyses at RERF. The rationale has been that even if the RBE varies with dose, the value $R = 10$ represents its value in the dose range most influential for linear risk estimation, namely about 1 Gy. An alternative, conservative choice for a constant R at the value 20 will be considered later.

According to Eq. (1) the average weighted dose due to neutrons in Hiroshima is approximately:

$$RD_{\mathrm{n}}=0.007RD_{\gamma}^{1.5}, \tag{2}$$

for dose in Gy. With the customary RERF choice of a constant $R = 10$, the weighted dose from neutrons is 5% of the γ-ray dose when the γ-ray dose is 0.5 Gy, 7% at 1 Gy and 10% at 2 Gy. For $R = 20$ these values are doubled. This gives a perspective on the fraction of effect attributable to neutrons. Since the neutron/γ-ray dose ratio increases with γ-ray dose, the inferred relative contribution of neutrons is greatest at high doses if the value of R is taken as constant.

However, there are reasons to believe that the true RBE is not constant, but decreases with increasing dose, and it is the concept of such a variable RBE that has given rise to most of the issues that we intend to address. The appropriate low-dose RBE to use for the LSS cancer data is uncertain, but could well be close to 100. The rest of this article mainly concerns the significance of such a variable RBE for the many RERF purposes.

ASSESSMENT IN TERMS OF VARIABLE NEUTRON RBE

Parameters Inferred from Radiobiology

In a wide range of experimental radiation studies, and in line with microdosimetric parameters, the dose-effect relationships for cell damage, such as chromosome aberrations, have been linear quadratic with linear terms substantially dependent on the linear energy transfer (LET) of the radiation. We review here potential implications for the RBE of neutrons, although they need not necessarily apply to the cancer risk estimation from the LSS data.

At the energies prevalent in the A-bomb radiation the linear term of the dose response for (high-LET) neutrons dominates sufficiently that the quadratic term can be disregarded. Accordingly the effect, E, of a combined exposure with γ-ray dose D_{γ} and neutron dose D_{n} is taken to be:

$$E(D_{\gamma}, D_{\mathrm{n}}) = \beta(D_{\gamma} + R_{\max}D_{\mathrm{n}} + \theta D_{\gamma}^{2}). \tag{3}$$

The coefficient β is the initial slope of the dose-effect relationship for γ rays. With this factorization, the formula for RBE involves the two parameters $R_{\max}$ and θ. The parameter $R_{\max}$ is the ratio of the initial slopes for neutrons and γ rays. $R_{\max}$ equals as indicated by the notation, the maximal neutron RBE at low doses. The other parameter θ is the ratio of the coefficients of the quadratic and the linear term in the dose relationship for γ rays. Although θ has the dimension Gy^{-1}, it is termed ''curvature'' because a large value implies a strongly curved dose-effect relationship. Its reciprocal is referred to as the crossover dose, since $1/\theta$ is the dose where the quadratic term equals the linear term.

With the RERF data in view, Sasaki *et al.* (*7, 8*) have performed an in-depth study of chromosome aberrations by neutrons and γ rays in human lymphocytes. The parameters they inferred were roughly $R_{\max} = 90$, $\theta = 4\ \mathrm{Gy}^{-1}$. These parameters agree well with data for chromosomal aberrations obtained in earlier studies with neutrons and γ rays (*12–14*). They are also consistent with LET data and microdosimetric parameters for neutron and photon radiation (*15*). Detailed investigations on the yield of chromosome aberrations in dependence on neutron and photon energy (*16–18*) suggest that the above parameters apply to the hard γ rays and the moderately energetic neutrons (<1 MeV) that prevailed in the A-bomb radiation.

In addition to deriving precise results for chromosome aberrations, Sasaki *et al.* (*8*) sought to obtain data from animal cancer experiments in the literature. From eight studies on solid cancers in rodents they inferred widely varying parameters with mean values, $R_{\max} = 87 \pm 35$ and $\theta = (4.5 \pm 2.1)\ \mathrm{Gy}^{-1}$ that were consistent with those for chromosome aberrations. Therefore, they applied essentially the same parameters to their analysis of the chromosome aberration and the solid cancer data in the A-bomb survivors. For comparison, Brenner and Hall (*19*) in their assessment of the neutron contamination in proton therapy beams referred to the analysis in NCRP Report No. 104 (*20*) and the majority of Ullrich's mouse data which, likewise, provided widely varying values of 59, 36, 6, 19 and 33 for $R_{\max}$.

The parameters from the animal studies must be viewed with caution not only because of their inherent differences, but because they are derived under the assumption of linear and linear-quadratic dose relationships although the observed relationships for cancer in rodents bend over at moderate and high doses and tend to be poorly defined at low doses. This also underscores the need to distinguish the dose relationship for primary cellular lesions and that for the ultimate late effects that develop at much later time periods.

Primary Lesions vs. Late Effects

A variable RBE may appear implausible for human cancer, because the excess cancer rate in the LSS is far more linear than that seen in chromosome aberration studies or in animal tumor studies. For all solid cancers together in the RERF data the upward curvature on 0–2 Gy is quite small, and on the full dose range there is distinct leveling off above that dose range [see Fig. 2 from ref. (*10*)]. For leukemia there is somewhat more curvature but nothing like that seen in chromosome aberration experiments.

However, there is no reason to assume that the excess relative risk (ERR) for late effects must be proportional to the number of initial lesions. The observed increase of ERR may have less curvature than the dependence of the initial lesions because of intervening processes, such as the body's mechanisms for dealing with malignant cells. To the extent that such mechanisms act independently of radiation quality, the appropriate RBE for analysis of cancer will still be that for the initial cellular damage. The studies with neutrons and X rays on the incidence of mammary tumors in rats by Shellabarger *et al*. (*21, 22*) are a case in point. These experiments were specifically focused on low neutron doses and they demonstrated that depending on the end points considered, e.g., tumor incidence at specified time after exposure or mean time to the tumor, the dose relationships differed substantially. But even when the dose relationship was roughly linear for X rays and roughly proportional to the square root of the neutron dose, high values of $R_{\max}$ near 100 were consistently obtained, as was the decrease of RBE with increasing dose.

The need to distinguish the dose relationship for initial lesions and for late effects appears to have been overlooked when a highly variable RBE was rejected in view of the nearly linear cancer rates in the LSS. However, we emphasize that even if a dose-dependent RBE is used, the ''risk extrapolation'' from moderate to low γ-ray doses must be based on the observed dose relationships for the end point in question and not, as is often assumed, on a postulated linear-quadratic dependence for initial lesions.

In the subsequent sections we evaluate the impact of the neutrons on the LSS data in terms of some parameter sets that are representative of the range suggested by the experimental results. For this purpose we do not invoke definitive parameter estimates for human cancer. The aim is to demonstrate the impact on the γ-ray risk estimates in terms of a wide range of potential values.

Parameters to be Considered in the Analysis

We provide an equation in the appendix section [Eq. (A3)] for the mixed-field neutron RBE, as appropriate for the LSS data. For comparison we also present an equation in the appendix section [Eq. (A5)] for the pure neutron RBE because it was used by Sasaki for the A-bomb survivors' data, in spite of the mixed-field setting, which resulted in much larger values of R than does Eq. (A3). As it happens, Eq. (A3) is rather complicated, however, the RBE for the relatively small neutron doses in the mixed-field A-bomb exposures can be well approximated by the simpler relationship in Eq. (A4), which means that it depends only on the γ-ray dose as in Eq. (4):

$$R = \frac{R_{\max}}{1 + 2\theta D_\gamma}. \tag{4}$$

The magnitude of the RBE at 1 Gy is particularly relevant to RERF linear risk estimates, i.e., to estimates based on the assumption of linear dose relationships. Statisticians at RERF have long realized (*22*) that nearly the same linear risk estimate is obtained whether one uses a dose dependent or a constant RBE, provided the values are equal at 1 Gy. The linear risk estimate is simply rescaled by the inverse value of the weighted dose at 1 Gy. This result is specific to the particulars of the LSS cohort, where the neutron fraction is vanishingly small at low doses (see Fig. 1), and it applies to linear risk estimation that uses most of the available dose range. For cancer risk estimation with constant RBE, changing R from 10 to 20 reduces the linear risk estimate by about 5%, which is about half of the standard error of the risk estimate. According to the reasoning just given, this reduction factor will also roughly apply for variable RBEs with R values of 20 instead of 10 at a 1 Gy total dose.

The RBE at 1 Gy total dose being the essential reference value, we can use instead of ($R_{\max}$,θ) the more directly descriptive parameters ($R_{\max}$, R_1), where $R_1 = R_{\max}/(1 + 2\theta)$ is, according to Eq. (4), the RBE at 1 Gy for the mixed field with dominant γ-ray contribution. Eq. (4) is then re-expressed as

$$R = R_{\max}/(1 + (R_{\max}/R_1 - 1)D_\gamma) \tag{5}$$

with D_γ in Gy.

There has been a consensus view that the value of a variable RBE suitable for the middle range of doses for A-bomb survivors, namely about 1 Gy, should be around 10 or 20. The chromosome aberration experiments provide in terms of Eqs. (4) or (5) the value $R_1 = 10$. A mixed-field neutron RBE of about $R_1 = 10$ is also the correct result of the Sasaki (*8*) synopsis of the eight experiments involving solid cancer in rodents, although those authors obtained a much larger value by employing the formula for a pure neutron RBE.

The parameter pair $R_{\max} = 90$, $\theta = 4$ Gy^{-1} is equivalent to $R_{\max} = 90$, $R_1 = 10$ and the corresponding RBE is denoted by RBE(90,10). However, for our purposes in the subsequent sections of this article, we will utilize a rather wide range of RBE functions that have been chosen to reflect the possibilities indicated by the results considered above. We will express these choices in terms of the parameter pair $R_{\max}$, R_1 as RBE(100,10), RBE(100,20), RBE(10,10), RBE(20,20). The wide range of $R_{\max}$ is in line with the chromosomal and solid cancer experiments, and the two values of R_1 are employed because this variation affects the risk estimation differently.

THE LIMITED IMPACT OF THE NEUTRONS

To judge the impact of the use of various RBE functions one can compare the total weighted dose, $D_w = D_\gamma + RD_n$, for various assumed RBE functions. In Fig. 2, three

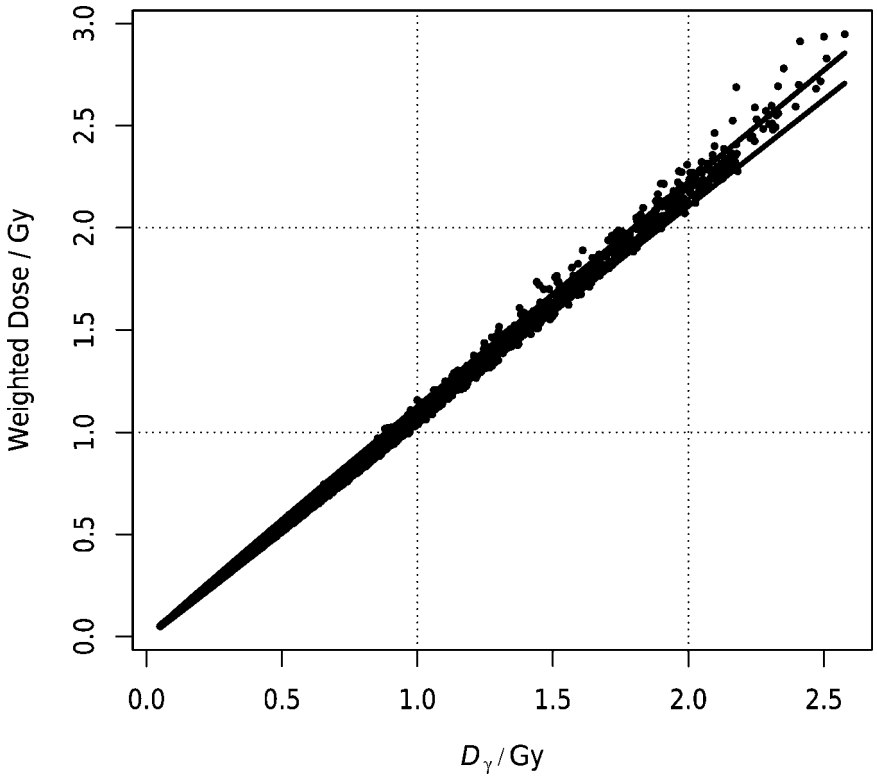

FIG. 2. The total weighted dose, $D_w = D_\gamma + RD_n$, that results for Hiroshima with the mean neutron doses [Eq. (1)] and the RBE according to Eq. (5) with RBE(100,20) (upper solid line) or RBE(100,10) (lower solid line), i.e. with RBEmax = 100 and with RBE at 1 Gy equal to 20 or 10; the corresponding curvature parameters θ are 2 Gy^{-1} and 4.5 Gy^{-1}. The points represent the individual values obtained with constant $R = 10$. The comparison shows that there is small difference between the use of the variable and the constant RBE.

alternative total weighted doses for Hiroshima are plotted versus D_γ. The solid lines give the median total weighted dose, D_w, which results with the choices of RBE(100,10), upper curve and RBE(100,20), lower curve. The narrow cloud of points represents the total weighted doses for the A-bomb survivors obtained with the RBE(10,10) commonly assumed in the analyses of the LSS data. The scatter of the points is entirely due to the variations of the neutron/γ-ray ratio for individual survivors due to shielding.

The risk estimation changes corresponding to the alternative weighted doses in Fig. 2 are well within the statistical uncertainties of risk estimation from these epidemiological data. For the cancer mortality data of LSS Report 12 (*23*) the coefficient of variation of nonparametric ERR estimation (i.e., smoothing of dose-category ERRs) is about 20% for doses over 0.25 Gy, about 60% for doses of around 0.15 Gy, and greater than 80% for doses of 0.05 Gy or less. For the most recently evaluated cancer incidence data (*24*), the corresponding coefficients of variation are about two thirds of those for the cancer mortality.

Figure 3 illustrates the comparison (left and right panels) in terms of ratios rather than differences. The panels show the ratio of the total weighted dose computed with the variable RBE and with constant $R = 10$. The variable RBE corresponds to the parameters of RBE(100,10) (left panel) or RBE(100,20) (right panel). The gray lines represent the medians of the dose ratios.

It was noted above that the magnitude of the RBE adjustment at 1 Gy is particularly relevant to linear cancer risk estimates from the LSS data. Either choice, RBE(100,20) or RBE(20,20) results in about 5% smaller excess relative risk estimates than the choices of RBE(100,10) or RBE(10,10), respectively. This is roughly one half the standard error of the risk estimates. On the other hand, linear risk estimates for choices RBE(100,10) and RBE(10,10) differ by less than 0.5%, and the same applies for choices RBE(100,20) and RBE(20,20). These relationships hold for either Hiroshima or both cities together.

The variation in Fig. 3 raises the question of whether with RBE(100,10) or RBE(100,20) the larger weighted doses under 0.5 Gy might alter perceptions about low-dose cancer risks from γ rays based on the constant $R = 10$, that is, perceptions regarding possible thresholds or low-dose linearity. However, this is not the case, largely because the neutron/γ-ray ratio is so small for small doses [see Eq. (1)]. For either of those variable RBE functions the excess relative risk estimates for low-dose ranges of 0–0.025 Gy, 0–0.05 Gy and 0–0.075 Gy decrease by about 3%, and those for low-dose ranges of 0–0.10 Gy, 0–0.15 Gy and 0–

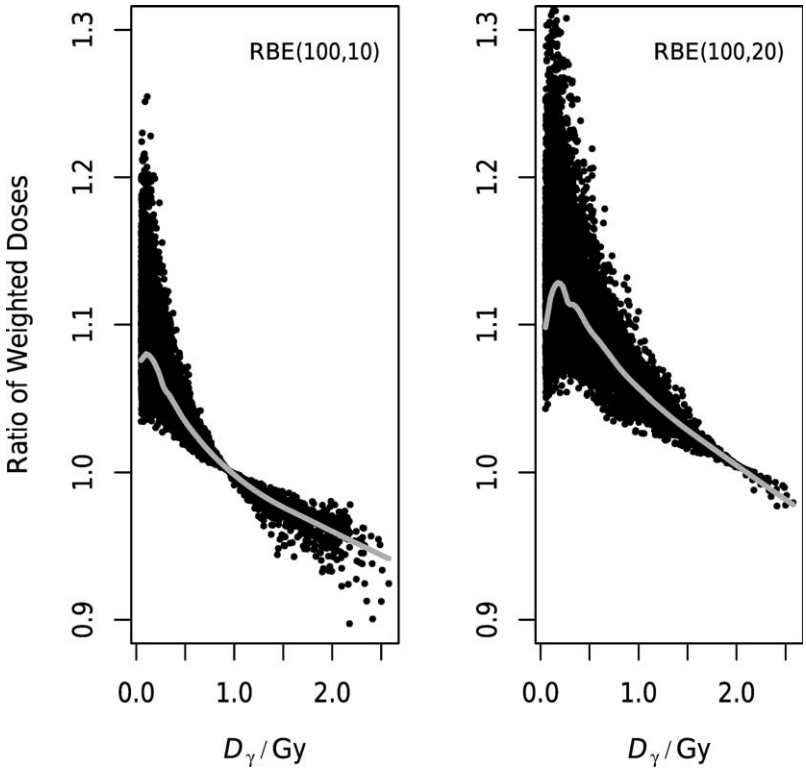

FIG. 3. The ratio of the total weighted doses, D_w, computed with variable RBE to the weighted dose obtained with the constant $R = 10$. The points represent the values obtained with RBE(100,10) (left panel) and RBE(100,20) (right panel), the corresponding curvature parameters θ are 4.5 Gy^{-1} and 2 Gy^{-1}. The gray lines are based on the median neutron doses.

0.20 Gy decrease by about 6%. These risk estimates are computed from the dataset of this article, we used the same methodology as that used for Fig. 5 from the LSS Report 14 (*25*), which has long been standard in RERF reports. These 3 and 6% reductions are very small relative to the risk estimation standard errors in these low-dose ranges, resulting in no change of perceptions regarding low-dose cancer risks from γ rays.

Figure 4 compares the constant $R = 10$ (left panel) to the variable RBE(100,10) (right panel) in terms of the ratio of total weighted dose, D_w, to absorbed dose. This ratio can be termed the ''net RBE'' of the radiation in Hiroshima, and is about 1.07 in the most relevant dose range, confirming again that the neutrons are not a critical issue in the risk estimates derived from the LSS data.

The essential finding we have made here is that it makes little difference whether the simple approach in terms of a constant $R = 10$ or a variable neutron RBE is used. Past suggestions that the neutrons have substantially contributed to the late health effects were based on the large RBE values that are inferred by using the pure neutron RBE instead of the mixed-field RBE. As mentioned, based on a wide array of experimental data, Sasaki *et al*. (*7, 8*) arrived at an RBE function with approximately $R_{max} = 90$ and curvature parameter $\theta = 4.5$ Gy^{-1}, which corresponds approximately to our RBE(100,10). By using the RBE formula for pure neutron exposures [see Eq. (A5)], they arrived at a value of about $R_1 = 40$, rather than the value $R_1 = 10$ that would actually be calculated from parameter values in the mixed-field radiation equations. Thus their conclusions correspond roughly to an RBE function we would denote as RBE(100,40). Because LSS risk estimation hinges substantially on the RBE at 1 Gy, this led to considerably underestimated cancer risk estimates for γ rays and to their claim of a substantial contribution of the neutrons to the late effects in the LSS.

CONCLUSION

The findings presented here indicate that γ-ray risk estimation from the LSS data is affected very little by the choice of the RBE for neutrons. We refer here to the use of a constant RBE versus variable, dose-dependent RBE that has been suggested based on radiobiological experiments. This topic may benefit from the clarification provided here, because many observers have been skeptical of RERF's use of a constant RBE in light of evidence from experiments that the low-dose neutron RBE tends to be larger than at intermediate or high doses. In addition, there has been some misperception about the formulation of a variable RBE that is suitable for LSS data, because the distinction between pure-neutron and mixed-field exposures has been neglected.

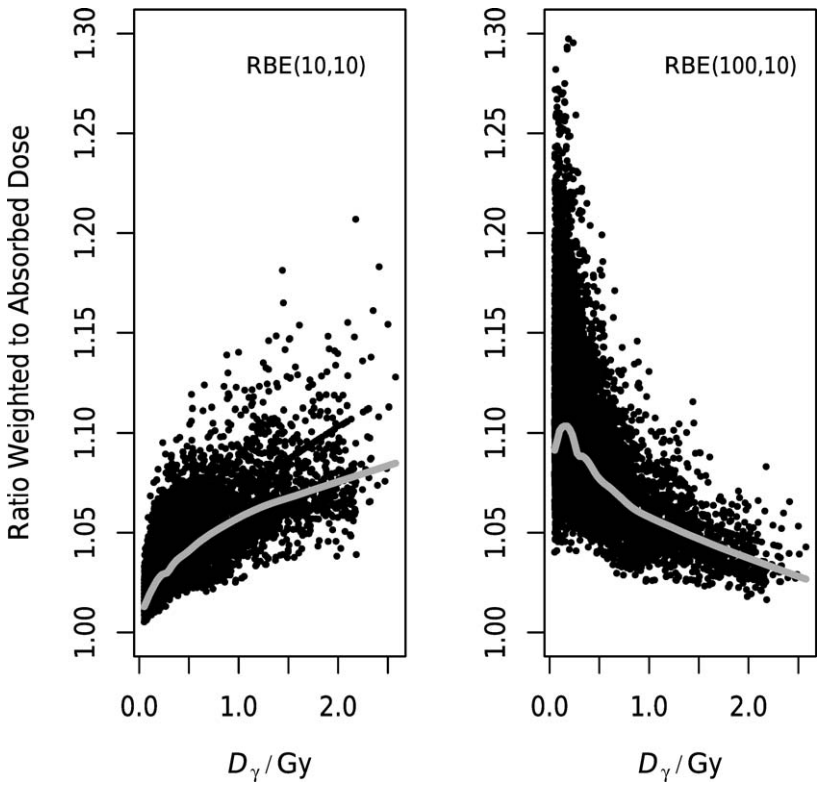

FIG. 4. The ratio of total weighted dose, D_w, to absorbed dose, i.e., the ''net RBE'' of the A-bomb radiation in Hiroshima, as it is obtained in terms of the constant $R = 10$ (left panel) and the dose-dependent RBE(100,10) (right panel).

We hope that the findings in this article will be helpful to RERF.

We believed that our primary investigation should, to the extent possible, be based on the effect of the RBE function on the total weighted doses used in risk estimation, rather than on fitting specific risk models. Thus, Fig. 2 indicates that for linear risk estimation over a wide dose range, results will be nearly equivalent for a constant RBE of 10 versus a variable one with the same value of 10 at 1 Gy, but much larger values at low doses. We express the value at 1 Gy as R_1 and the limiting value at low doses as R_{max}. RBE functions with $R_1 = 20$ versus $R_1 = 10$, somewhat independently of R_{max}, do result in a modest decrease in linear risk estimates of about 5%. This decrease is not totally negligible in comparison to the inherent uncertainty of the risk estimation, since it is about one half of the standard deviation in the risk estimate.

However, it is difficult to be sure that in every respect the risk estimation would be negligibly affected by assuming a large low-dose RBE, such as $R_{max} = 100$. This is the reason that we investigated the distinction in low-dose risk estimates presented in relationship to Fig. 3. Those results support the general conclusions above, but we do not want to overstate the position that for nearly all risk estimation purposes, the choice of RBE function matters little.

Postulating a plausible dose-dependent RBE function remains conjectural, but guidance by the family of LQ models of Eq. (3) is valuable and it provides the RBE function given by Eq. (A3). The fact that this equation is rather complicated may be one reason for the repeated error of using in its place the simpler Eq. (A5) that corresponds to the familiar experimental setting where pure neutron doses are compared to pure γ-ray exposures. Fortunately, a much simpler formula based on Eq. (A4) and Fig. A3 applies to the LSS data, where the neutron component is always relatively small. In those circumstances, the RBE depends only on the γ-ray dose, and as seen in Eq. (5), the R_{max} at small doses and R_1 at 1 Gy.

Our use of LQ models corresponding to $R_{max} = 100$ and $R_1 = 10$ or 20 involves far more curvature than is seen in the LSS cancer data, while it is not uncommon for experimental settings for either chromosome aberrations or cancer induction in animals. The concepts of a highly variable RBE, and approximate linearity in dose of the cancer risk, can be reconciled by the hypothesis that the unobserved initial cellular damage had dose response curvature as seen in radiobiological experiments, while the loss of curvature in the cancer response is due to subsequent repair and suppression processes. If such mechanisms depend on the level of the initial cellular damage, but not on the quality of the radiation, the appropriate RBE function for analysis of the late cancer effects will be that applied for the initial cellular damage. This rationale applies only to the neutron

RBE issue, and the extrapolation of γ-ray risk estimates from moderate to low doses must still be based on the observed dose relationship.

APPENDIX

General RBE Relationship

In this appendix we review in detail the RBE functions related to the linear-quadratic dose-response functions. For current purposes it would be sufficient to disregard, in line with Eq. (3), the quadratic component in the dose response for neutrons. On the other hand, it is useful to have the formula for the general case, because it permits the comparison not only to earlier investigations by Rossi and Zaider (*6, 26*), but also to the extensive analysis by Sasaki *et al*. (*7, 8*) who included in their considerations high-energy neutrons (>>1 MeV) for which the quadratic component cannot be disregarded. The linear-quadratic relationship for a mixed-field exposure is then:

$$E(D_\gamma, D_n) = \beta\left[D_\gamma + R_{max} D_n + \theta(D_\gamma + D_n)^2\right]. \quad \text{(A1)}$$

Setting $E(D_\gamma,D_n)$ equal to $E(D_\gamma + \Delta, 0)$ one obtains the relationship:

$$R(D_\gamma, D_n) = \frac{\Delta}{D_n} = \frac{2c}{1 + 2g + \sqrt{(1+2g)^2 + 4nc}} \quad \text{(A2)}$$

with the abbreviations: $g = \theta D_\gamma$, $n = \theta D_n$; $c = R_{max} + 2g + n$ (if the squared term is included in the neutron dose response); and $c = R_{max}$ (if no squared term is included in the neutron dose response). These abbreviations are used to make the complicated equation more readable.

Special Cases

Below are three important special cases obtained by setting to zero, respectively, the quadratic term for the neutron dose response, the neutron dose and the γ-ray dose.

Mixed-field radiation with linear relationship for the neutrons ($c = R_{max}$):

$$R(D_\gamma, D_n) = \frac{2R_{max}}{1 + 2g + \sqrt{(1+2g)^2 + 4nR_{max}}} \quad \text{(A3)}$$

Limit of small neutron doses ($n = 0$):

$$R(D_\gamma) = \frac{c}{1+2g} = \frac{R_{max}}{1 + 2\theta D_\gamma} \quad \text{(A4)}$$

Equation (A4), is important as a suitable approximation for the LSS data where the neutron dose is small relative to the γ-ray dose and is further justified below.

Pure neutron exposure ($g = 0$):

$$R(D_n) = \frac{2c}{1 + \sqrt{1+4nc}} = \frac{2R_{max}}{1 + \sqrt{1 + 4\theta D_n R_{max}}} \quad \text{(A5)}$$

The above equation [Eq. (A5)] corresponds to the one employed by Sasaki (*8*), it is important to note that the RBE for such pure neutron exposure is often confused with that for the mixed-field exposures of the A-bomb survivors.

With different notation and in different form, Eq. (A3) has been given by Rossi and Zaider (*26*) in an analysis that inferred, on the basis of the revised dosimetry system DS86 (*1*) that the mixed-field weighted dose in Hiroshima did not exceed the γ-ray dose anywhere by more than a factor of 1.25.

In a later assessment the same authors (*6*) mistakenly used the RBE for pure neutron exposure when they referred to tentative activation data by Straume *et al*. (*9*) and to the implied larger neutron doses. They concluded that the neutron contribution to the weighted dose exceeded the γ-ray contribution in Hiroshima at distances less than about 1,200 m from ground zero. Pierce *et al*. (*27*) objected to this conclusion, since it had been incorrectly based on neutron RBE values that were obtained from the relationship for pure neutron exposures, i.e., a relationship that corresponded to Eq. (A5) rather than to Eq. (A3) for the mixed-field radiation.

Sasaki *et al*. (*7, 8*) derived, in careful studies of the RBE of neutrons for chromosomal aberrations, a relationship that corresponded correctly to Eq. (A5). Since they were also concerned with neutrons of high energy, i.e., with intermediate LET, they included the quadratic term for the neutrons. However, they too applied this relationship, which is valid for the comparison of the neutron experiments to the γ-ray experiments, and subsequently to the mixed γ-ray and neutron exposures in Hiroshima. Thus, they disregarded the decrease of the RBE due to the simultaneous γ-ray dose, which led to a substantial overestimate of the neutron contribution.

Figure A1 shows the magnitude of the error that is incurred when the formula for a pure neutron exposure is applied to the mixed-field exposures in Hiroshima. The lower curve gives the RBE values from Eq. (A3) for the parameters $R_{max} = 100$ and $\theta = 4.5$ Gy^{-1}. The upper broad scatter cloud of values shows the much larger values that result, again for $R_{max} = 100$ and $\theta = 4.5$ Gy^{-1}, when Eq. (A5) for a pure neutron exposure is erroneously applied to the neutron doses in Hiroshima. The neutron contribution is then overestimated by a factor between 3 and 7 in the relevant dose range of 0.5–2 Gy.

Figure A2 shows the corresponding diagram for the weighted dose in analogy to Fig. 2 but with the upper point cloud of values resulting from the erroneous use of Eq. (A5). Compared to the lower point cloud, which corresponds to Eq. (A3), it is again shown that the resultant point cloud considerably overestimates the proper mixed-field weighted doses for the parameters $R_{max} = 100$ and $\theta = 4.5$ Gy^{-1}.

Simplified Formula for the Neutron RBE when Neutron Doses are Relatively Small

The exposure situation of the atomic bomb survivors allows the RBE to be approximated very well by a simplified formula that depends only on γ-ray dose, because the survivors' neutron doses are much less than their γ-ray doses. Figure A3 gives for $R_{max} = 100$ and $\theta = 4.5$ Gy^{-1} the resulting contours of constant $R(D_\gamma,D_n)$ versus D_n and D_γ using Eq. (A3).

For small neutron doses the RBE is close to 10 at the 1 Gy γ-ray dose, which is notable because the constant $R = 10$ has been used in the major studies at RERF to account for the effectiveness of the neutrons. Since there is agreement at 1 Gy, and linear fits over a range up to 1.5 or 2 Gy largely depend on the point at 1 Gy, the use of the constant RBE is a tolerable approximation in spite of the fact that the diagram shows RBE values for small neutron doses from 25 down to 5 in the dose range 0.3–2 Gy.

The superimposed scatter diagram corresponds to the data in Fig. 1 and represents the individual dose estimates (D_γ,D_n), for Hiroshima. Notably all points lie on the vertical part of the contours of constant RBE. Their associated RBE values are thus close to the limit, $R(D_\gamma,0)$, for small neutron doses. This confirms the considerably simplified treatment in terms of Eq. (A4) that is applicable to the A-bomb radiation since the neutrons contribute only a minor fraction of the absorbed dose. Equation (A4) agrees with Eqs. (4) and (5).

The gray curves in Fig. A4 correspond to Eq. (5) for the cases RBE(100,10) and RBE(100,20). They correspond to the parameters $R_{max} = 100$ and $\theta = 4.5$ Gy^{-1} and $R_{max} = 100$ and $\theta = 2$ Gy^{-1}. The exact values according to Eq. (A3) for the individual dose estimates (D_γ,D_n), of the survivors in Hiroshima are represented by the bands of points. The

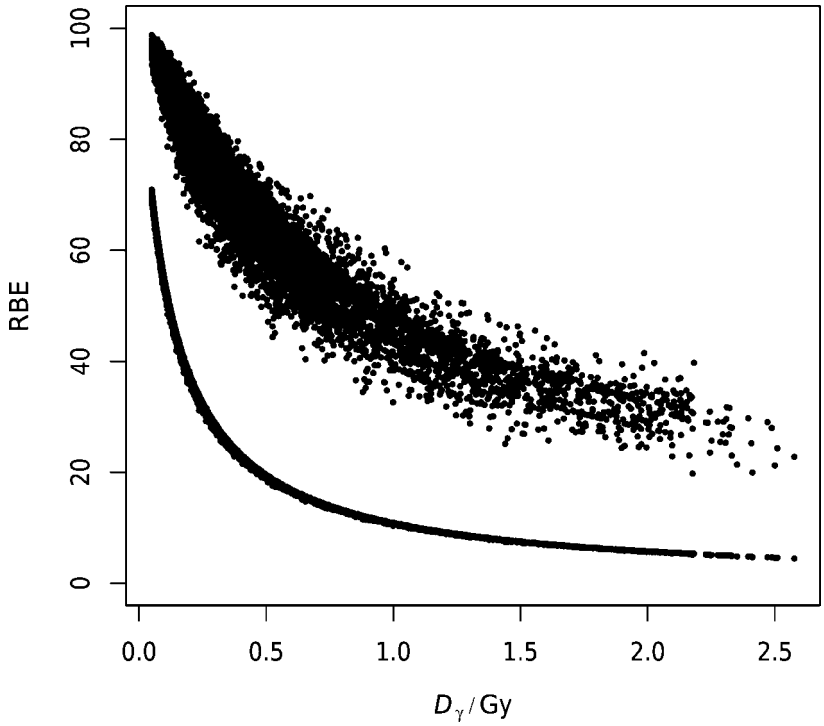

FIG. A1. The RBE of the neutrons in Hiroshima vs. the concomitant γ-ray doses. Both curves represent the parameter pair $R_{max} = 100$ and $\theta = 4.5$ Gy^{-1}. The lower series of points gives the individual RBE values obtained correctly from Eq. (A3). The upper broad cloud of points gives the much larger values inferred in terms of the Eq. (A5) which does not account for the concomitant γ-ray exposures.

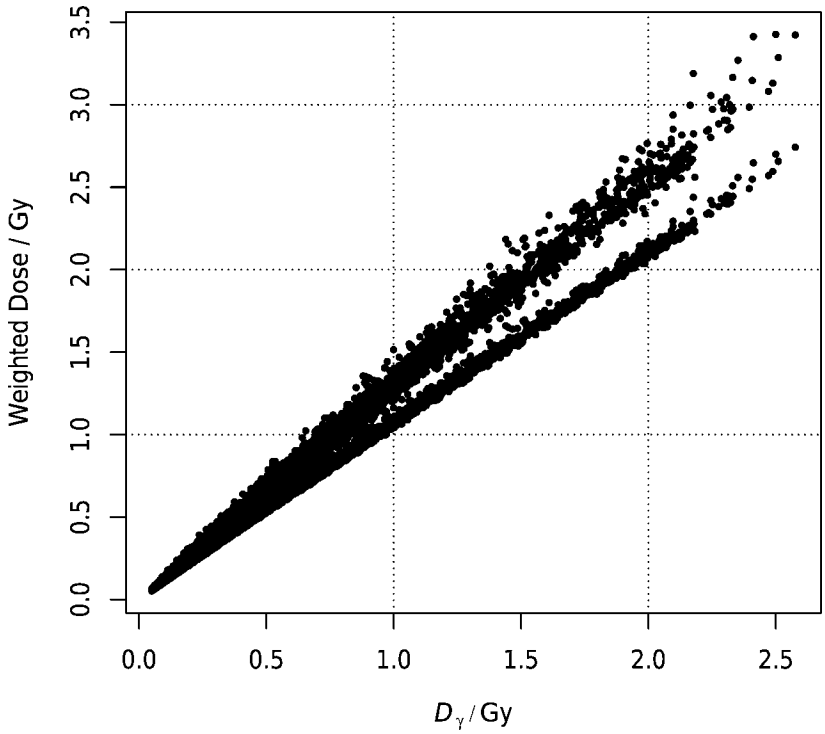

FIG. A2. Diagram of the total weighted dose as in Fig. 2 for the parameters $R_{max} = 100$ and $\theta = 4.5$ Gy^{-1} (lower cloud of points) and, for comparison, the total weighted doses that result with the same parameters from the incorrect use of Eq. (A5) (upper cloud of points).

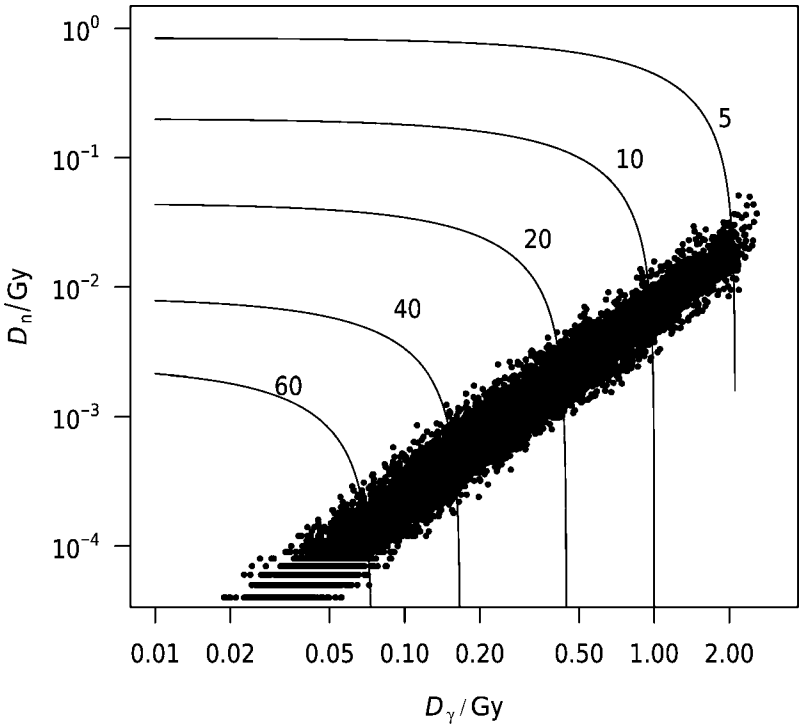

FIG. A3. Lines of constant $R(D_\gamma,D_n)$ for $R_{max} = 100$ and $\theta = 4.5$ Gy^{-1} according to Eq. (A3) and superimposed, the scatter diagram of the individual neutron doses, D_n, for Hiroshima. Of note, all RBE values for the individual neutron doses are close to the limit for small neutron doses, and the same applies *a fortiori* to Nagasaki where the neutron/γ ratios are considerably smaller.

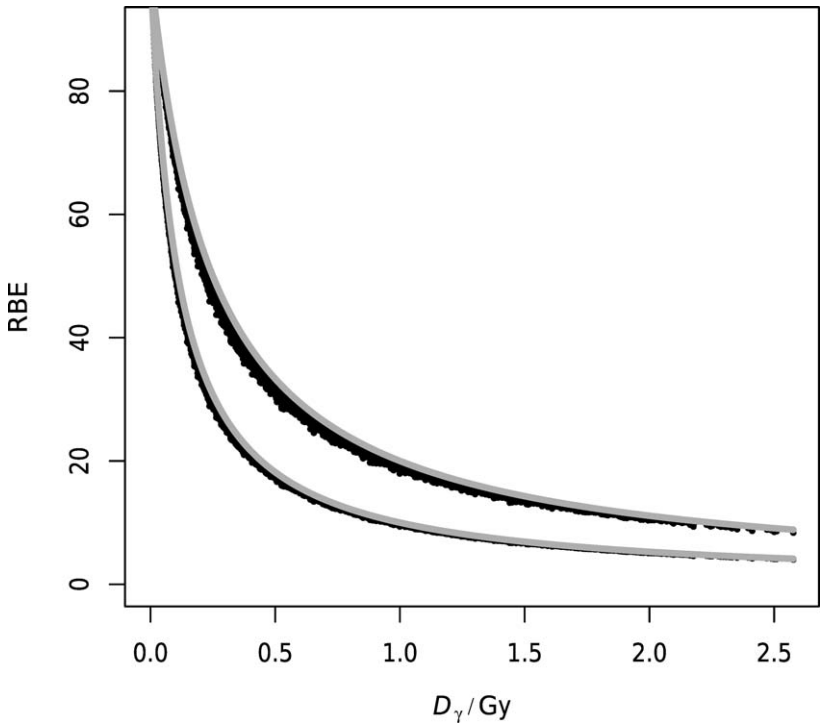

FIG. A4. The gray curves give the RBE of small neutron doses for $R_{max} = 100$ and $\theta = 4.5$ Gy^{-1} (upper curve) or $R_{max} = 100$ and $\theta = 2$ Gy^{-1} (lower curve) versus the accompanying γ-ray dose [Eq. (A4)]. The exact values of the RBE according to Eq. (A3) for the individual dose estimates (D_γ, D_n) of the survivors in Hiroshima are represented by the points and they agree well with Eq. (A4).

relationship for the RBE at small neutron doses is seen to be a good approximation.

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