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Authors: Cordova, Kismet A., and Cullings, Harry M.

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Assessing the Relative Biological Effectiveness of Neutrons across Organs of Varying Depth among the Atomic Bomb Survivors

Kismet A. Cordova[a,1] and Harry M. Cullings[b]

[a] *Department of Statistics and* [b] *Consultant, Radiation Effects Research Foundation, 5-2 Hijiyama Park, Minami-ku, Hiroshima, Japan 732-0815*

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When assessing radiation-related risk among the atomic bomb survivors, choices in modeling approach can have an important impact on the results, which are then used to inform radiation protection standards throughout the world. The atomic bombings of Hiroshima and Nagasaki produced a mixed-field radiation exposure from two sources: neutrons and gamma rays. Neutrons are more densely ionizing and cause greater biological damage per unit absorbed dose, resulting in greater relative biological effectiveness (RBE) than gamma rays. To account for this, a combined weighted dose is typically calculated as the sum of the gamma-ray dose and 10 times the neutron dose in the Radiation Effects Research Foundation's reports of mortality, solid cancer incidence and other outcomes. In addition, the colon, which is often chosen as the whole-body representative organ in these analyses, is relatively deep in the body and therefore its dose calculation involves heavy body shielding of neutrons and a low neutron/gamma-ray ratio. With added follow-up and recently updated doses, we used a data-driven approach to determine the best-fitting neutron RBE for a range of organs of varying depth. Aggregated person-year tables of solid cancer incidence (1958–2009) from the Life Span Study were created with separate neutron and gamma-ray DS02R1 doses for several organs including breast, brain, thyroid, bone marrow, lung, liver and colon. Typical excess relative risk models estimating the linear effect of radiation dose were fitted using a range of neutron weights (1–250) to calculate combined dose for each organ, and model deviances were compared to assess fit. Furthermore, models using separate terms for gamma-ray and neutron dose were also examined, wherein the ratio of the neutron/gamma-ray linear terms indicated the best estimate of the RBE. The best-fitting RBE value for the traditional weighted colon dose was 80 [95% confidence interval (CI): 20–190], while the RBEs for other organs using weighted doses ranged from 25 to 60, with the best-fitting weights and confidence interval widths both incrementally increasing with greater depth of organ. Models using separate neutron- and gamma-ray-dose terms gave similar results to weighted linear combinations, with a neutron/gamma-ray term ratio of 79.9 (95% CI: 18.8–192.3) for colon. These results indicated that the traditionally modeled RBE of 10 may underestimate the effect of neutrons across the full dose range, although these updated estimates still have fairly wide confidence bounds. Furthermore, the colon is among the deepest of organs and may not be the best choice as a single surrogate organ dose, as it may minimize the role of the neutrons. Future work with more refined organ doses could shed more light on RBE-related information available in the Life Span Study data.

INTRODUCTION

The atomic bombings of Hiroshima and Nagasaki produced a mixed-field radiation exposure from two sources: neutrons and gamma rays. Absorbed neutron doses were much smaller, comprising only 2% or less of total dose, and decreased much more rapidly with distance from the hypocenter than gamma rays. Furthermore, due to the different types of atomic bombs used, the two cities differed with respect to their neutron exposure, with much higher neutron doses in Hiroshima than Nagasaki (*1*). The dosimetry system used by the Radiation Effects Research Foundation (RERF) to calculate doses for the atomic bomb survivors has evolved over time in its precision and capacity to accurately capture both sources of radiation exposure to various organs for each survivor based on self-reported information on survivor age, location, structure and terrain shielding, orientation and body position (*2, 3*). When calculating absorbed doses to specific locations throughout the body, neutron doses are also known to decrease more rapidly than gamma-ray doses at greater depths due to shielding from overlying tissues (i.e., the neutron/gamma-ray ratio decreases with increasing organ depth). Furthermore, the absorbed doses estimated using dosimetry system DS02 for relatively shallow organs such as breast depend more substantially on each individual survivor's reported orientation at the time of the bombing, while the radiation risk estimates reported in RERF studies reflect population-level, rotationally-averaged values.

[1] Address for correspondence: Department of Statistics, Radiation Effects Research Foundation, 5-2 Hijiyama Park, Minami-ku, Hiroshima, Hiroshima 732-0815, Japan; Email: Cordova@rerf.or.jp.

Although the neutron doses received by the atomic bomb survivors were substantially smaller than the gamma-ray doses, it is also known that a single neutron track through a cell nucleus produces more biological damage, and thus neutrons are thought to produce more cancers per unit absorbed dose. Specifically, the ratio of the number of cancers per unit of absorbed dose for neutrons to the number of cancers per unit of absorbed dose for gamma rays represents the relative biological effectiveness (RBE) of neutrons. Appropriately estimating and accounting for the neutron RBE when modeling the joint exposure received by the atomic bomb survivors is important for achieving accurate estimates of the risk of cancer (and other outcomes) from each of these combined sources of radiation exposure.

Because the absorbed neutron doses were so limited in the atomic bomb survivor cohort, and because gamma-ray effects are of predominant interest to many radiation protection bodies, it has often been considered beneficial to simplify the modeling of the radiation dose response in RERF reports by scaling the neutron dose (D_n) to what is thought to be an equivalent gamma-ray dose (D_γ) and adding the two doses together to include as one combined, weighted-dose variable in radiation risk models (i.e., $D_{weighted} = D_\gamma + \sigma * D_n$, where σ represents the neutron weight approximation of the neutron RBE relative to gamma rays). If one assumes a linear-linear dose-response model, then this σ equates to the usual definition of the neutron RBE, such that the scaled absorbed dose of neutrons is equivalent in biological effect to the absorbed dose of gamma rays. With this approach, the question arises as to how much weight should be assigned to the neutrons to scale their biological effect to be roughly equivalent to that of gamma-ray exposure.

Several attempts have been made to estimate the neutron RBE (and thus, ideal neutron weighting factor) using the Life Span Study (LSS) cohort of atomic bomb survivors, with limited success and lacking the ability to draw definitive conclusions. With the release of the revised dosimetry system DS86, attempts were made by RERF scientists to explore whether there existed any newly available insights regarding the neutron RBE within the LSS data. At that time, it was found that very little conclusive information was available, but that RERF data and other sources such as ICRP recommendations indicated a value of approximately 10–20 as the best approximation of the neutron RBE (*4–9*). Since then, a neutron weighting factor of 10 has typically been applied to colon dose, the most commonly chosen whole-body representative organ, in recent RERF reports of the radiation dose response for mortality, solid cancer incidence and a range of other outcomes (*10*, *11*). With the release of dosimetry system DS02, an attempt to gather information about the neutron RBE was again undertaken, but it was concluded that due to the lowered neutron doses, no reliable estimation of the neutron RBE could be ascertained directly from the LSS data (*12*). Since then, LSS dose estimates have been further refined with the recent release of DS02R1, which enhanced the precision of the geographical and shielding inputs to the DS02 dosimetry system (*2*). However, to date these updated doses have not been used to examine information about the neutron RBE.

More recent efforts to assess the neutron RBE using atomic bomb survivor data have also been undertaken by researchers outside of RERF, several of whom have indicated that the best-fitting neutron RBE may be much larger than the often-modeled neutron weight of 10 (*13–17*). While estimates of the neutron RBE have been found upwards of 100, these analyses have usually been limited in power and the resulting estimates are generally accompanied by large confidence intervals. It has been noted that this is partially due to the fact that publicly available aggregated person-year tables from RERF reports are typically not stratified separately by the two types of radiation exposure, making it difficult to model the independent contributions of neutrons and gamma rays to the radiation dose response (*1*, *16*).

Contemporary recommendations of the International Commission on Radiation Protection (ICRP) would suggest that the neutron RBE in Hiroshima and Nagasaki should be approximately 20, based on the neutron energies involved, and that it would change somewhat with distance from the hypocenter due to the change in average neutron energy with hardening of the neutron spectrum (*18*). This would suggest in turn that there could be some effect on curvature for models with a quadratic term in gamma rays.

When assessing radiation-related risk among the atomic bomb survivors, choices in modeling approach can have an important impact on the results, which are then used to inform radiation protection standards throughout the world. Therefore, the purpose of this analysis was to explore information about the RBE of neutrons for a range of organs of varying depths using the most recently available cancer incidence data from the LSS cohort. In relationship to prior work in this area, this analysis benefits from 51 years of extensive follow-up, the most precise currently available DS02R1 dose estimates for seven different organs and enhanced power by utilizing person-year tables that are stratified separately by gamma-ray and neutron doses. Although it has been suggested that the neutron RBE likely varies across the dose range based on a curvilinear dose response for gamma rays (*1*, *19*), to be consistent with most prior modeling in RERF reports we assessed the best-fitting constant RBE assuming a linear dose response for both radiations using two approaches: models which include a single combined, weighted-dose variable as well as models which include separate variables for gamma-ray and neutron doses. While it has historically been difficult to reliably estimate the neutron RBE using the LSS cohort data, the extension of follow-up time as well as recently revised DS02R1 dose estimates, in addition to systematic examination of doses to organs at different depths in the body,

may provide an opportunity to gain some fresh insight from this valuable source population.

MATERIALS AND METHODS

This study utilized highly stratified person-year tables of counts of solid cancers and accrued person-years from LSS subjects with available DS02R1 doses and follow-up from 1958–2009 (n = 105,444), using the same population, design and stratification as described in greater detail in the most recently published study of Grant *et al*. (*11*). For our analysis, the neutron RBE estimation was based only on residents of Hiroshima and Nagasaki who were present at the time of the bombings; therefore not-in-city residents (n = 25,239) were excluded. Survivors with untruncated DS02R1 total shielded kerma doses exceeding 4 Gy (n = 251) were also excluded to avoid any undue influence from a small subset of subjects with extremely high (and perhaps less reliable) doses. After these exclusions were applied, 79,954 LSS subjects remained in the analysis.

Although the structure of the data was mostly consistent with the prior cancer incidence report, the stratification of the person-year tables was slightly modified to appropriately accommodate topics of interest to the current study. Specifically, separate person-year tables were created for each of seven different organ doses (listed in order of increasing depth): breast, brain, thyroid, marrow, lung, liver and colon. Furthermore, each person-year table was stratified separately by gamma-ray- and neutron-dose categories, in contrast to the more common approach of stratification by categories of weighted dose (which applies an assumed value for the neutron RBE). Using the distribution of neutron and gamma-ray doses specific to each organ, stratification cut-offs were created by distributing the subjects evenly across 20 dose categories, with 5% of subjects inhabiting each group. As noted previously, neutrons are more heavily attenuated by body shielding. Therefore, as organ depth increased, the neutron categories slightly decreased to accommodate the shift in the neutron dose distribution, while the gamma-ray dose categories remained largely unchanged across organs.

Statistical Analysis

To characterize the relationship between gamma-ray and neutron DS02R1 doses assigned to atomic bomb survivors, and to understand the role of body shielding by depth of organ, it is useful to examine the transmission factor (TF) applied to each survivor's shielded kerma dose to estimate the absorbed dose for each specific organ, which differs substantially by dose type because neutrons are more heavily attenuated by body tissue than gamma rays. The neutron/gamma-ray TF ratios and each of the gamma-ray and neutron dose distributions were examined by depth of organ and city. Descriptive statistics were used to characterize the variability and correlation of the two exposures across different organs and across the dose range.

All models used a linear excess relative risk (ERR) model for all solid cancer informed by Grant *et al*. (*11*). Specifically, the background rates were parameterized as sex-specific quadratic splines for log age, with adjustment for age at exposure and city (though unlike the referenced source report, not-in-city subjects were not included in this analysis, and thus a not-in-city factor was not modeled in the background). The radiation dose response was assumed to be linear, with effect modification of the ERR modeled with two log-linear terms including log attained age (centered at 70) and age at exposure (centered at 30), as well as a sex-averaged product linear term. Although Grant *et al*. included adjustment for smoking information, it was shown that its inclusion did not greatly effect radiation risk estimates, and therefore smoking was not included as a factor in this analysis.

After establishing the basic radiation risk model, the linear ERR for the radiation effect from the joint exposure to both neutrons and gamma rays was parameterized using two approaches to estimate the best-fitting neutron RBE. First, a typical weighted dose was calculated as:

$$D_{weighted} = D_\gamma + \sigma * D_n,$$

wherein a variety of neutron weights (σ) were applied ranging from 1–250, which were then each used as the single linear dose term of the ERR model. Model deviances were compared to assess fit, wherein $\chi^2_1 > 3.84$ indicated $P < 0.05$, which was used to determine likelihood-consistent values for the best-fitting estimate of the neutron RBE.

In addition to the weighted-dose approach commonly used in LSS analyses, we also explored a separate-dose approach for each organ. ERR models included separate linear terms for the gamma-ray and neutron doses, such that:

$$\rho(D_\gamma, D_n) = \beta_\gamma D_\gamma + \beta_n D_n.$$

The linear portion of the ERR model was then re-parameterized as:

$$\beta_\gamma(D_\gamma + \sigma D_n),$$

in which σ represents the ratio of the neutron term to the gamma-ray term as the best estimate of the neutron RBE, along with its 95% confidence interval. This approach is analogous to the method of assessing curvature as the ratio of the quadratic to linear terms reported by Grant *et al*. (*11*).

We then assessed the impact of the correlation between the gamma-ray and neutron doses as a potential source of bias due to collinearity in the separate-dose model by comparing a range of models with different parameterizations of the radiation exposure. All of these models incorporated the same background terms, as well as effect modification by age at exposure, attained age and sex. We noted changes in the ERR estimates, standard errors, variance inflation factors (VIF) as a measure of collinearity and Akaike information criteria (AIC) as a measure of model fit.

When examining the RBE of neutrons in the atomic bomb survivor cohort, it is notable that the bulk of neutron exposure occurred in Hiroshima. Therefore, city and neutron exposure are somewhat correlated, and any measured differences in the radiation dose response could be conflated with other city-specific effects. To allow for other potential city-related differences in the radiation dose response and to assess the impact on neutron RBE estimation, a sensitivity analysis was conducted which included a city indicator as an effect modifier of the linear ERR in the above-described weighted-dose model, as well as an analysis excluding Nagasaki residents. It should be noted that these sensitivity analyses are likely underpowered because the city effect and neutron exposure are highly correlated, and analysis within one city substantially reduces the sample size, but these secondary analyses were employed to assess consistency of the observed results under different scenarios.

RESULTS

We first examined the transmission factors applied to each survivor's shielded kerma dose to estimate the absorbed dose for each organ. The transmission factors applied to gamma-ray doses decreased very gradually with greater organ depth, such that the median gamma-ray TFs ranged from 0.854 for breast dose to 0.730 for colon dose. Meanwhile, neutron transmission factors dropped much more rapidly with increasing organ depth, such that the median neutron TFs ranged from 0.576 for breast dose to 0.159 for colon dose. Figure 1 shows the ratio of neutron to gamma-ray TFs for each of the seven organs in order of increasing depth.

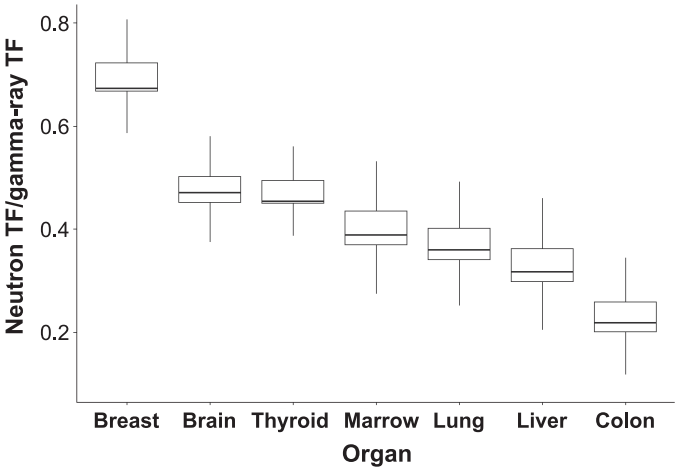

FIG. 1. Distribution of ratios of neutron-to-gamma-ray transmission factors by organ.

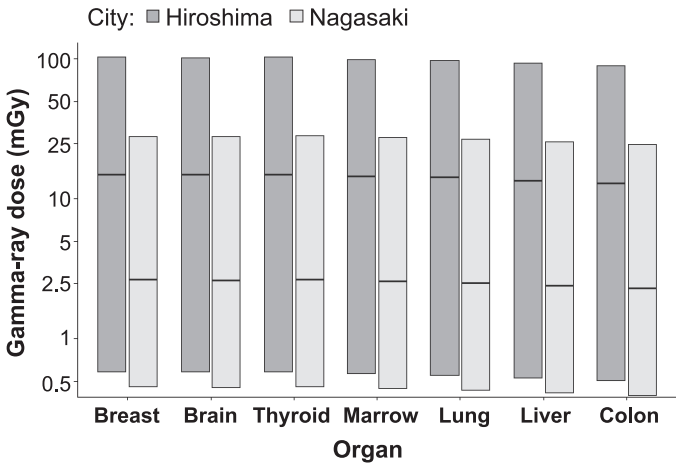

FIG. 3. Distribution of gamma-ray doses by organ and city, displayed as medians (think lines) and interquartile ranges (boxes).

The distributions of DS02R1 neutron and gamma-ray doses by city and organ are shown in Figs. 2 and 3, respectively. Both gamma-ray and neutron doses among survivors were higher on average in Hiroshima than Nagasaki, due to the geographical difference in the location of the hypocenter in relationship to each city's urban center. Furthermore, neutron doses comprise only a tiny fraction of overall absorbed dose, with the vast majority of subjects exposed to less than 1 mGy of neutron dose, and the bulk of the neutron exposure affecting Hiroshima. Once again, it can be seen that absorbed gamma-ray doses remain fairly constant across different organs, while absorbed neutron doses show attenuation by depth of organ.

As would be expected, the correlation between gamma-ray and neutron DS02R1 dose estimates was quite high, with some variation by city, organ and dose. For the full sample, the Pearson correlation of the two dose types ranged from 0.833–0.848 across the seven organs examined. Furthermore, when stratified by city, the correlations increased, ranging from 0.929–0.943 in Hiroshima and from 0.933–0.956 in Nagasaki. While the observed correlations are very high and require careful consideration for problems with collinearity when both are included in a model with separate dose parameters, it is also notable that among the highest-dose subjects, who provide the greatest contribution to the estimation of the neutron RBE, the correlation is less severe. For example, among subjects with at least 5 mGy of neutron dose (n = 1,641), the Pearson correlation between doses was 0.680, with corresponding correlations of 0.798 in Hiroshima (n = 1,584) and 0.426 in Nagasaki (n = 57). To illustrate the increasing variability in neutron doses as a function of increasing gamma-ray dose (especially in Hiroshima, where most of the neutron exposure occurred), a scatterplot of the DS02R1 gamma-ray and neutron doses to the colon by city is shown in Fig. 4. The degree to which the high correlation of the two dose types impacts parameter estimates, in a model including them both as separate terms, is explored in greater detail below.

The best-fitting estimates of the constant neutron RBE and likelihood-consistent values for each organ using a weighted-dose approach are shown in Table 1, while in Fig. 5 the changes in model deviance are shown after a range of

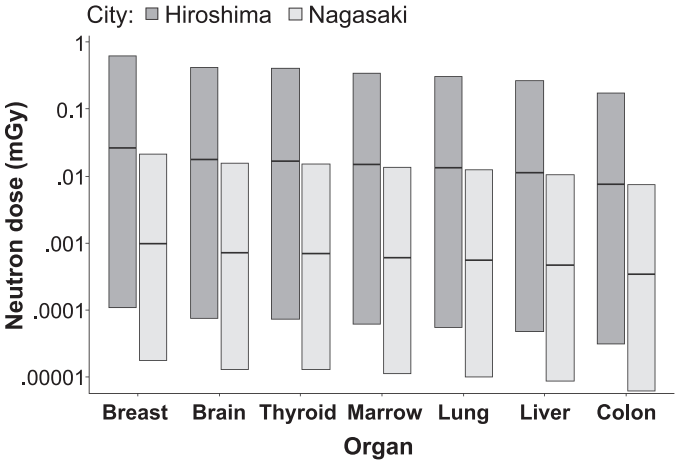

FIG. 2. Distribution of neutron doses by organ and city, displayed as medians (think lines) and interquartile ranges (boxes).

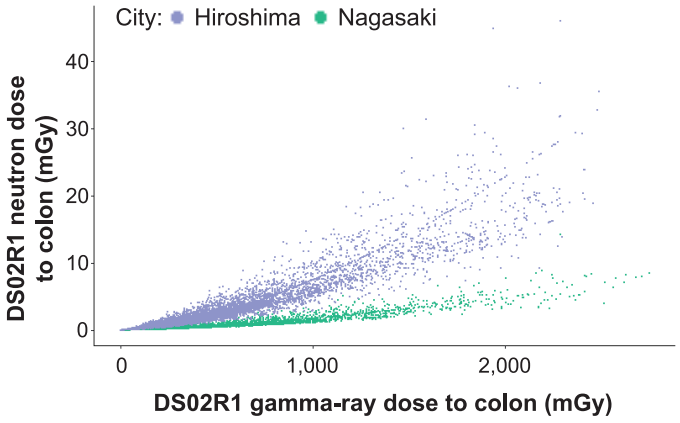

FIG. 4. DS02R1 gamma-ray and neutron colon doses by city.

TABLE 1
Best-Fitting and Likelihood-Consistent Neutron RBE Values by Organ Using Weighted-Dose and Separate-Dose Approaches

Organ	Weighted-dose model RBE estimate (95% CI)	Separate-dose model RBE Estimate (95% CI)
Breast	25 (10–50)	23.8 (6.3–54.2)
Brain	35 (10–80)	34.9 (7.9–82.5)
Thyroid	40 (15–90)	40.3 (10.8–92.8)
Marrow	45 (15–95)	42.9 (11.4–98.7)
Lung	50 (15–115)	51.3 (13.7–119.5)
Liver	60 (20–135)	59.9 (17.7–136.7)
Colon	80 (20–190)	79.9 (18.8–192.3)

neutron weights are applied. For colon dose, the best estimate of the neutron RBE was 80 [95% confidence interval (CI): 20–190]. With increasing organ depth, the best-fitting neutron RBE estimate also increased, as did the width of the confidence interval for each estimate, such that for breast dose, the shallowest organ examined, the best-fitting neutron RBE was 25 (95% CI: 10–50). Nonetheless, all of the best-fitting RBE values were well above the traditionally used neutron RBE of 10, while only the confidence intervals for breast and brain included this value. The results of the modeling approach including separate gamma-ray and neutron dose parameters are also shown in Table 1, and the results of the two approaches were consistent.

To explore the effect of the high correlation of gamma-ray and neutron doses on linear ERR models including separate dose terms, we compared models with various parameterizations of the radiation dose to the colon (Table 2), although the observed patterns were comparable in other organs (results not shown). Compared to a gamma-ray dose-only model, the gamma-ray VIF increased by approximately 11 with the addition of the highly correlated neutron dose term, and the standard error for the gamma-ray dose ERR estimate increased by 34%. Meanwhile, the neutron VIF increased by approximately 5 when the gamma-ray dose term was added to the model, and the neutron term's standard error increased by 29%. Relative to the separate-dose model, VIF terms for weighted, combined radiation doses were expectedly lower. The weighted-dose ERR term with an assumed RBE of 10 had a similar estimate and

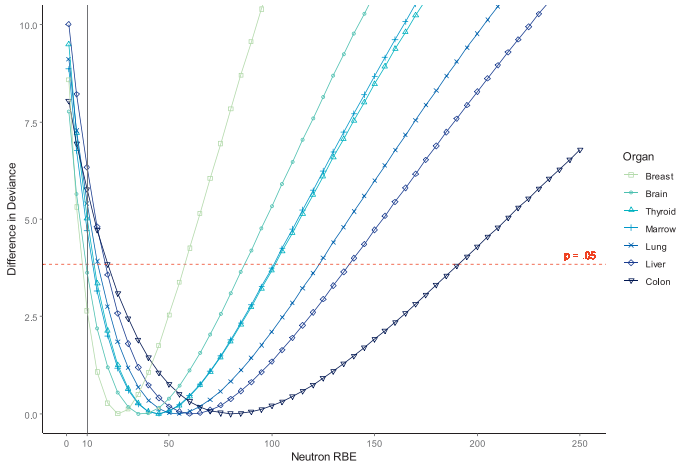

FIG. 5. Difference in model deviance for a range of assumed neutron RBEs by organ.

standard error to the gamma-ray dose-only model, while the weighted-dose term with an assumed RBE of 80 had a similar estimate to the gamma-ray term in the separate-dose model, but with a substantially lower standard error. The weighted-dose model with an assumed RBE of 80 and the separate-dose models also showed the best fit with the lowest AIC values.

We then conducted sensitivity analyses to assess the extent to which the estimation of the best-fitting neutron RBE might be affected by unmeasured confounding due to other possible differences in the observed effects of the atomic bombs aside from the larger neutron exposure seen in Hiroshima (*20*). Table 3 shows the results of the weighted-dose modeling approach when including an indicator term for Nagasaki survivors as an effect modifier of the combined radiation dose linear ERR term with a range of applied neutron weights. The best-fitting RBE estimates increased substantially across all organs, with neutron weights of 90 to 230 showing the best fit for breast and colon, respectively. It is also notable that the confidence intervals for these estimates also increased dramatically, with upper limits exceeding a neutron RBE of 250 for all of the organs examined, while none of the lower bounds were consistent with an RBE as low as 10. Similarly inflated values with widened confidence intervals were also seen

TABLE 2
Model Comparison to Assess the Impact of Various Parameterizations of DS02R1 Colon Dose on Estimates of the Radiation-Associated Linear ERR/Gy for Solid Cancer Incidence, along with Standard Errors (SE), Variance Inflation Factors (VIF) and Akaike Information Criterion (AIC)

	Combined dose			Gamma dose			Neutron dose			
Radiation dose parameter(s)	Estimate	SE	VIF	Estimate	SE	VIF	Estimate	SE	VIF	AIC
Separate gamma-ray and neutron doses				0.38	0.06	24.13	30.68	11.45	10.47	56,089
Gamma-ray dose only				0.52	0.05	13.38				56,095
Neutron dose only							98.99	8.86	5.50	56,131
Weighted dose, RBE = 10	0.50	0.05	12.89							56,093
Weighted dose, RBE = 80	0.38	0.03	10.63							56,087

TABLE 3
Best-Fitting and Likelihood-Consistent Neutron RBE Values in Weighted-Dose Models including City Term as Effect Modifier of the ERR, and Hiroshima-Only Subsample

Organ	Including City Term RBE Estimate (95% CI)	Hiroshima Only RBE Estimate (95% CI)
Breast	90 (20–250+)	85 (15–250+)
Brain	140 (25–250+)	140 (20–250+)
Thyroid	120 (25–250+)	135 (20–250+)
Marrow	175 (35–250+)	175 (30–250+)
Lung	195 (35–250+)	185 (30–250+)
Liver	250+ (50–250+)	250+ (45–250+)
Colon	230 (40–250+)	250+ (45–250+)

when analyzing the best-fitting neutron RBE in the Hiroshima-only subsample.

DISCUSSION

Utilizing two modeling approaches to estimate the best-fitting neutron RBE when assessing radiation risk for incident solid cancer among atomic bomb survivors exposed to a mixture of gamma rays and neutron radiation, both combined and separate-dose methods resulted in relatively consistent neutron RBE estimates for a range of organs of varying depth. The lowest neutron RBE estimates were seen in the shallowest organ, the breast, while neutron RBE estimates and confidence interval widths both increased with greater depth of organ. The highest neutron RBE estimate of 80 was seen when using colon dose, which is most commonly chosen as the whole-body representative organ dose in RERF radiation risk reports. Notably, the neutron RBE of 10, which is commonly used in weighted-dose models, was largely outside the 95% confidence intervals across organs, including the colon. The observed pattern of neutron RBE estimates across organs appears to be a function of the relative neutron/gamma-ray ratio for each organ, i.e., a shallow organ with a higher neutron/gamma-ray ratio results in a lower estimate of the neutron RBE. The general relationship between the excess cases and the neutron dose is common among different organ doses, because the organ doses are so highly correlated with each other.

The observed results are consistent with several prior findings, not only in the LSS cohort (*13–17*), but also in some animal models (*21–24*). However, these results should be interpreted with caution, since the confidence intervals remain quite wide. Furthermore, the magnitude of the neutron RBE seen in the current study is generally higher than that which has been found in an abundance of prior published studies, of animals, plants and cells, which inform current radiobiological knowledge and are outlined in detail in current and previous ICRP recommendations (*18*).

When considering these results, it is important to note that weighted-dose models that apply a higher neutron RBE would result in a lower overall radiation-associated ERR, which could result in harm if the true radiation risk was underestimated. Therefore, a cautiously conservative approach is warranted, which continues to incorporate information from other sources (including the ICRP recommendation of approximately 20 for the LSS neutron exposure) (*18*), because the neutron exposure in this population was so limited, and the estimation of the neutron RBE could be impacted by unobserved confounders. It is also noted that the neutron RBE is thought to be variable across the dose range based on a curvilinear dose response for gamma rays, with a higher neutron RBE corresponding to lower gamma-ray doses. Because the radiation exposure in this cohort is heavily skewed to low doses, this could result in inflated estimates of a constant neutron RBE for the full sample when it may in fact be lower for those with higher doses (where the radiation risk is typically assessed and more clearly detectable).

As this analysis has shown, choice of organ and corresponding neutron dose has a substantial effect on the best-fitting neutron RBE associated with that organ dose, which impacts corresponding radiation risk estimates. Colon dose, the deepest organ assessed with the smallest distribution of neutron doses, showed the highest neutron RBE estimate, which would be expected as a result of neutron dose attenuation from body shielding. Thus, the choice of colon as the whole-body representative organ in many RERF reports with an assumed neutron RBE of 10 may minimize the role of neutron dose when estimating the radiation-associated ERR. The ideal organ choice would be one in which its depth in the body is equal to the average depth at which radiogenic cancers (or whatever outcome of interest is under study) arise. This is based on the concept that the site at which a radiation-induced cancer arises is the site at which the radiation energy creating the causative molecular lesion is imparted to tissue. We cannot calculate this depth without knowing the true neutron RBE in, e.g., radiation-induced human cancers, along with the fraction of those cancers that is radiogenic in each organ, but the best-fitting depth examined empirically in this analysis and prior work (*15*) indicates that the ideal organ is substantially shallower than colon. An organ of medium depth, such as the lung, may be a better choice for modeling overall cancer incidence and mortality to adequately account for the contribution of neutrons to the overall radiation exposure.

We explored multiple approaches to modeling the LSS subjects' mixed radiation exposure in this analysis, including the comparison of the traditionally used weighted-dose model against a separate-dose model including both gamma-ray and neutron terms. There are benefits as well as drawbacks to both approaches. The separate-dose model does not require any ad hoc assumptions about the true value of the neutron RBE, and allows for the greatest flexibility when modeling the dose response for each of these exposures independently. For example, when squaring the weighted-dose term to test for curvature in the dose response, the weighted neutron dose response is forced to be

quadratic along with the gamma-ray dose, when in fact radiation biology indicates that we would only expect curvature to be present in the gamma-ray dose, while the neutron dose response is generally expected to be linear (*1*). On the other hand, the high correlation between the neutron and gamma-ray doses needs to be handled carefully, since problems with collinearity can result in inflated standard errors and thus widened confidence intervals for both radiation-related ERR terms, resulting in a potential underestimation of the true risk. Therefore, the results of a separate-dose model must be interpreted with caution, especially in the context of radiation protection.

This project had many strengths in the context of prior work in this area, including considerable extension of the follow-up period, more accurate assessment of the role of radiation using the most recently refined DS02R1 dose estimates for a range of organs and assessment of the independent contribution of gamma-ray and neutron doses using person-year tables stratified separately by the two dose types. However, the range and distribution of neutron doses in this population is extremely low, resulting in estimates with wide confidence bounds, and a lack of definitive information about the neutron RBE. Therefore, other studies will remain the primary sources of information for this important issue. RERF is currently considering a revised approach to calculating organ doses that may provide more accurate organ doses in the future, which could shed more light on RBE-related information available in the LSS data (*25*). In future work, estimation of the neutron RBE using other outcomes, such as cancer mortality and non-cancer diseases will be explored, as well as the impact of other informative factors, such as shielding category. Furthermore, the recent emergence of sex-specific curvature in the LSS (*11*) prompts investigation of the viability of estimating the neutron RBE as a function of sex, in conjunction with the well-supported notion of a variable RBE that would accompany observed curvature in the gamma-ray dose response.

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