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EVIDENCE SUPPORTING RADIATION HORMESIS IN ATOMIC BOMB SURVIVOR CANCER MORTALITY DATA

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□ A recent update on the atomic bomb survivor cancer mortality data has concluded that excess relative risk (ERR) for solid cancers increases linearly with dose and that zero dose is the best estimate for the threshold, apparently validating the present use of the linear no threshold (LNT) model for estimating the cancer risk from low dose radiation. A major flaw in the standard ERR formalism for estimating cancer risk from radiation (and other carcinogens) is that it ignores the potential for a large systematic bias in the measured baseline cancer mortality rate, which can have a major effect on the ERR values. Cancer rates are highly variable from year to year and between adjacent regions and so the likelihood of such a bias is high. Calculations show that a correction for such a bias can lower the ERRs in the atomic bomb survivor data to negative values for intermediate doses. This is consistent with the phenomenon of radiation hormesis, providing a rational explanation for the decreased risk of cancer observed at intermediate doses for which there is no explanation based on the LNT model. The recent atomic bomb survivor data provides additional evidence for radiation hormesis in humans.

Keywords: Radiation Hormesis, Atomic Bomb Survivors, Cancer Mortality, LNT Model, Systematic bias

A cohort of atomic bomb survivors has been studied systematically during the past several decades to document the health effects of radiation and reports have been published periodically with the updated data, e.g. (Pierce et al., 1996; Pierce and Preston, 2000; Preston et al., 2003). The general conclusion from these reports has been that the data are consistent with a linear, dose dependent increase in excess cancers without a threshold dose. However, on closer examination of the data, and observing reduced cancers for the survivors exposed to low doses, alternative interpretations of the data have been given by some researchers. For example, a trend toward a reduction in leukemias has been reported for the survivors exposed to low doses of radiation (Land, 1980; UNSCEAR, 1994). Reduction in overall cancer mortality has also been reported for the survivors subjected to low doses (Luckey, 1991). A trough in cancer mortality has been noted among the atomic bomb survivors in the low dose region for lung cancer, colon cancer, and leukemia (Kondo, 1993). Since these observed reductions in cancers for low doses do not have a strong statistical power, these observations may be consid-

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ered as being suggestive of the phenomenon of radiation hormesis. It would be interesting to see if the pattern of reduced cancer mortality continues to be observed for the low dose cohorts as the survivors age and new updated cancer mortality reports become available.

A recent publication has provided an update on the cancer mortality data of atomic bomb survivors for the period of 1950-2003 (Ozasa et al., 2012), increasing the period of follow-up by six years compared to the previous comprehensive report (Preston et al., 2003). In their analysis, the cancer mortality data was fitted to an excess relative risk (ERR) model using a function of the form:

$$\text{Cancer Mortality Rate (Observed)} = \text{Baseline Cancer Mortality Rate} \times [1 + \text{ERR}].$$

ERR was studied as a function of radiation dose (d) using a linear no threshold (LNT) model ($\text{ERR} = \beta_1 d$) and a linear plus quadratic model ($\text{ERR} = \beta_1 d + \beta_2 d^2$). The results of their analysis are shown in Figure 1, where ERR is plotted as a function of reconstructed weighted colon dose, which is the sum of γ ray dose plus 10 times the neutron dose. Since there is likely to be a large uncertainty in the retrospectively reconstructed dose scale for the survivors, I will mostly use qualitative terms to refer to dose

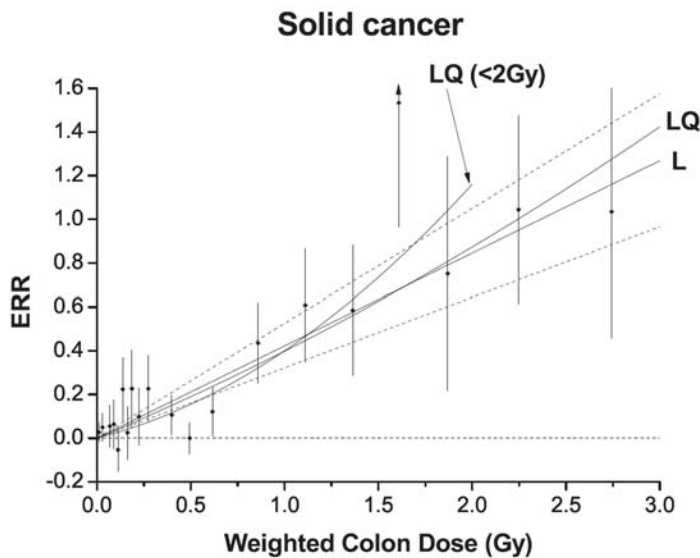


FIGURE 1. From (Ozasa et al., 2012). Excess relative risk (ERR) for all solid cancer in atomic bomb survivors in relation to radiation exposure (reconstructed colon dose). The black circles represent ERR and 95% CI for the dose categories, together with trend estimates based on linear (L) with 95% CI (dotted lines) and linear-quadratic (LQ) models using the full dose range, and LQ model for the data restricted to dose < 2 Gy. Figure reproduced with permission from the Radiation Research Society.

ranges, using the terms low dose for 0-0.3 Gy in the graph, intermediate dose for 0.4-0.6 Gy, and high dose for >0.75 Gy. For high doses, ERR rises approximately linearly with dose. For intermediate doses, ERR is lower than the expected values from a linear extrapolation of high dose data, reaching a minimum value of about zero. When the ERR data in the dose range of 0 to 2 Gy was fitted using the linear plus quadratic model, there was a statistically significant ($P=0.02$) upward curvature related to the lower cancer mortality in the intermediate dose range. The authors stated that there is no current explanation for the lower than expected cancer mortality in this dose range. For low doses, the ERR data is seen to have a large amount of variability as it fluctuates between approximately -0.05 and +0.23, with a mean value of about +0.094.

The conclusion the authors reached after a detailed dose threshold analysis of all the data is that zero dose is the best estimate of dose threshold for the risk of excess solid cancers from the radiation exposure, apparently justifying the current radiation safety paradigm using the LNT model to estimate cancer risk from low dose radiation. Since the atomic bomb survivors are the largest, most thoroughly studied radiated population group in the world and have provided probably the most important justification for the present LNT model based radiation protection policies, it is important that we examine the validity of their conclusions.

Though the ERR analysis used in the above study has been the standard method of analyzing cancer mortality data of population groups exposed to radiation (and other potential carcinogens), the ERR formalism has a major flaw in that it ignores the potential for systematic bias in the measured baseline cancer mortality rate. Since age-adjusted cancer incidence (and mortality) rates have a considerable year-to-year variation, there is a potential for a large systematic bias in determining lifetime cancer risks from long-term studies because of the compounding of the year-to-year variations in the cancer rates (Doss, 2012). In Japan, the percentage change between successive years in age-adjusted cancer mortality rate has spanned the range of -2.7% to +1.5% during the period 1960-2009¹ (see Figure 2), with the magnitude of the 1-year change averaging to ~0.87%, using data from (FPCR, 2010). During the 53 year period of the atomic bomb survivor study, similar year-to-year variations can compound and result in a considerable systematic bias, estimated to be ~7% in the baseline cancer mortality rate for this study. Another source of systematic bias is the large variability in the cancer mortality rates between adjacent population groups, e.g. between nearby prefectures in Japan. For example, in 2009 in the Kyushu region that includes Nagasaki, the percentage standard deviation of age-adjusted cancer mortality rates in the eight pre-

¹Data for change between 1994 and 1995 was not included as the method of identifying cancer deaths was changed between these two years.

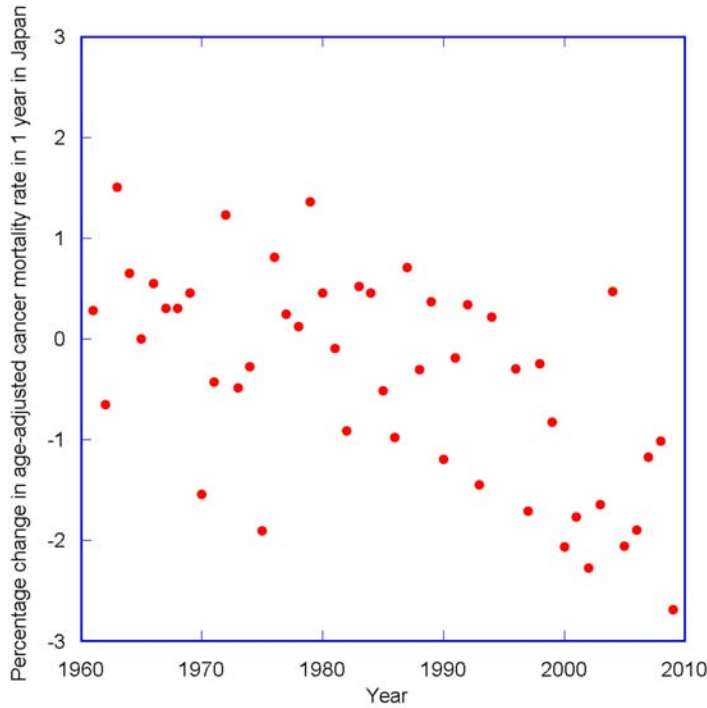


FIGURE 2. Percentage change in age-adjusted cancer mortality rate in 1 year during 1960-2009 using data from (FPCR, 2010). Data for change between 1994 and 1995 was not plotted as the algorithm for identifying cancer deaths was changed between these two years.

fectures was ~11%, and in the Chugoku region that includes Hiroshima, it was ~4% for five prefectures (FPCR, 2010). Using an average of these two standard deviations, and compounding with the systematic bias from temporal variations, we can estimate an overall systematic bias of ~10% in the baseline cancer mortality rate from these two considerations. There are also additional systematic biases from other confounding factors that have not been accounted for in this analysis. Thus, a single measurement of the baseline cancer mortality rate can be subject to a large systematic bias. If the measured baseline cancer mortality rate has a large systematic bias, it can have a major influence on the ERRs, and can shift the ERR values up or down significantly.

For the data plotted in Figure 1, if δ is the percentage systematic bias in the baseline cancer mortality rate, the ERR values of the data points in the figure can be corrected for the systematic bias with the equation (see Appendix A):

$$ERR(\text{corr}) = \frac{(1 + ERR) \times (100 + \delta)}{100} - 1$$

where $ERR(\text{corr})$ is the ERR corrected for the systematic bias.

To visualize the influence of δ on the ERR vs Dose graph, the corrected ERR has been calculated for each data point in Figure 1 and plotted in Figure 3 for δ values ranging from 0 to -30. In these graphs, the ERR values of the data points for low doses have been averaged and plotted at the mean dose of the data points, in order to smooth the large fluctuations in the ERR values seen at low doses in Figure 1. The obvious requirement that $ERR=0$ at zero dose has been added as an additional data point for each of the curves. The error bars have not been shown in the figure for clarity in plotting the multiple curves.

For $\delta=-10$, the negative ERR values cover a small dose range in the intermediate dose region, peaking at ERR of approximately -0.1, corresponding to ~10% reduction in cancer mortality. For larger δ values of -20 and -30, the negative ERR values cover the low and intermediate dose ranges, with the peak negative values of ERR (occurring at intermediate doses) being approximately -0.20 and -0.30 respectively, corresponding to nearly 20% and 30% reduction in cancer mortality respectively. We are not

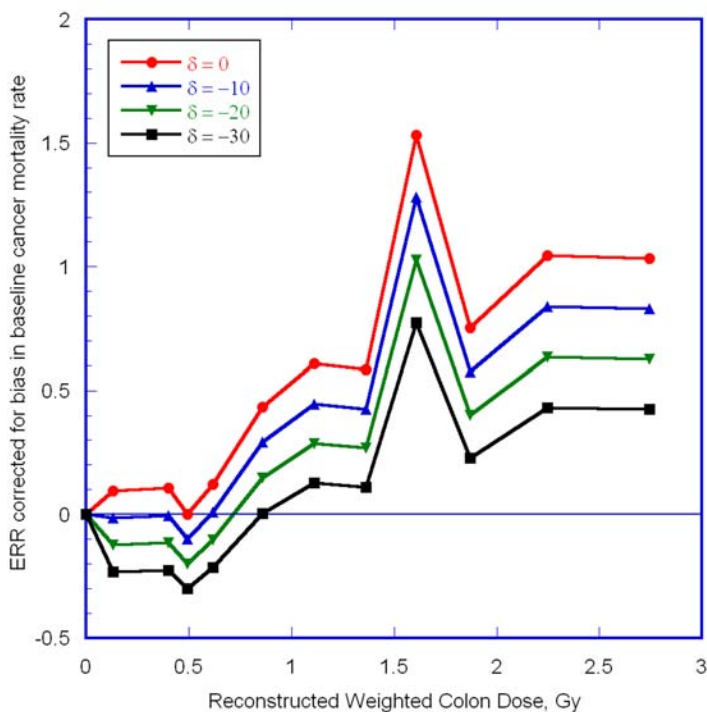


FIGURE 3. Excess relative risk (ERR) for all solid cancer in atomic bomb survivors corrected for bias in baseline cancer mortality rate, plotted as a function of reconstructed colon dose, for different values of δ , the percentage bias in baseline cancer mortality rate. Error bars are not shown for clarity in displaying the multiple curves. ERR values of the data points for reconstructed colon dose < 0.3 Gy have been averaged and plotted at the mean dose (~0.13 Gy) of the data points, in order to smooth the large fluctuations in the ERR values below 0.3 Gy seen in Figure 1. The obvious requirement that $ERR=0$ at zero dose has been added as an additional data point for each of the curves.

able to determine the value of δ from these curves. However, the curve for $\delta=-20$ may be more plausible in comparison to the one for $\delta=-10$ as the ERR changes gradually in the low to intermediate dose range compared to the rapid change for $\delta=-10$. Considering the large range of ERR/Sv reported in multiple compilations and reports e.g. (Cardis et al., 2005; NRC, 2006), and considering that part of the reason for the large spread in these values is the systematic bias in the baseline cancer mortality rates, it may not be unreasonable to assume a -20% bias in the baseline cancer mortality rate. Figure 4 shows the graph of ERR(corr) vs reconstructed colon dose (including the 95% CI error bars), for the case of $\delta=-20$. The graph displays the classic J shaped curve indicative of radiation hormesis, with reduced risk of cancer for low and intermediate doses.

Thus, the consideration of systematic bias in the baseline cancer mortality rate has uncovered the phenomenon of radiation hormesis in the atomic bomb survivor data, and we have a rational explanation for the decreased cancer mortality observed for intermediate doses in the atom-

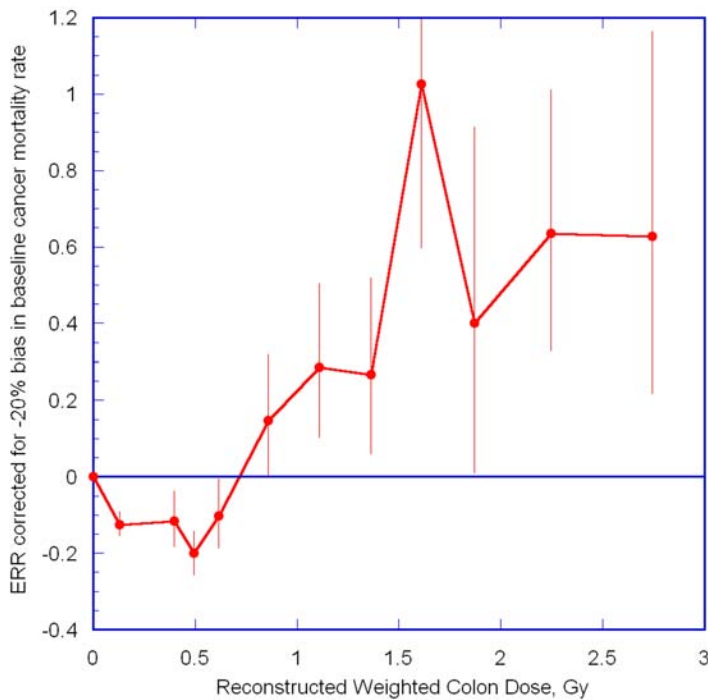


FIGURE 4. Excess relative risk (ERR) for all solid cancer in atomic bomb survivors corrected for bias in baseline cancer mortality rate, plotted as a function of reconstructed colon dose, for δ (percentage bias in baseline cancer mortality rate) = -20. ERR values of the data points for reconstructed colon dose < 0.3 Gy have been averaged and plotted at the mean dose (~0.13 Gy) of the data points, in order to smooth the large fluctuations in the ERR values below 0.3 Gy seen in Figure 1. The obvious requirement that ERR=0 at zero dose has been added as an additional data point. Error bars: 95% CI.

ic bomb survivors. In contrast, using the LNT model, there is no explanation for the observed reduced cancer mortality at intermediate doses. If these conclusions are confirmed, we would be justified in reconsidering the current radiation safety paradigm based on the LNT model, and exploring the possibility of utilizing the phenomenon of radiation hormesis to reduce cancer mortality.

Though hormetic effects of low dose ionizing radiation have been recognized in the scientific literature for several decades, e.g. (Luckey, 1980), the fear of low dose radiation based on the LNT model has dominated our society's response to low dose radiation over the past five decades, preventing any prospective human studies of radiation hormesis. If the hormetic effect observed in the atomic bomb survivors is confirmed in prospective human clinical trials, and applied to the whole population, it may result in a significant reduction in cancer mortality.

In summary, consideration of the effect of systematic bias in the baseline cancer mortality rate has uncovered the phenomenon of radiation hormesis in the atomic bomb survivor data. This provides a rational explanation for the observed reduced cancer incidence in the intermediate dose range among the atomic bomb survivors, whereas the LNT model is incapable of explaining this significant feature of the data. If this conclusion is confirmed on further investigation, it may be advisable to consider rescinding the current radiation safety regulations based on the LNT model and begin investigating the phenomenon of radiation hormesis to determine its validity for wider application.

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APPENDIX A

Derivation of *ERR* corrected for percentage bias in the measured background cancer mortality rate

Let *B* and *R* be the measured cancer mortality rate of the baseline cohort and the radiated cohort respectively. Then, *ERR* is defined by the equation:

$$\frac{R}{B} = 1 + ERR \tag{1}$$

Let *B(corr)* be the correct baseline cancer mortality rate and let δ be the percentage bias in the measured baseline cancer mortality rate. *B* is then given by:

$$B = B(corr) \times \left(1 + \frac{\delta}{100}\right) \tag{2}$$

Hence,

$$B(corr) = \frac{100 \times B}{(100 + \delta)} \tag{3}$$

The *ERR* corrected for the bias in the measured background cancer mortality rate would be defined by the equation:

$$\frac{R}{B(corr)} = 1 + ERR(corr) \tag{4}$$

Substituting Equation (3) in (4),

$$\frac{R \times (100 + \delta)}{100 \times B} = 1 + ERR(corr) \tag{5}$$

Substituting for *R/B* from Equation (1),

$$\frac{(1 + ERR) \times (100 + \delta)}{100} = 1 + ERR(corr) \tag{6}$$

Solving for *ERR(corr)*,

$$ERR(corr) = \frac{(1 + ERR) \times (100 + \delta)}{100} - 1 \tag{7}$$