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Quantifying cancer risk from radiation

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Abstract

Complex statistical models fitted to data from studies of atomic bomb survivors are used to estimate the human health effects of ionizing radiation exposures. We describe and illustrate an approach to estimate population risks from ionizing radiation exposure that relaxes many assumptions about radiation-related mortality. The approach draws on developments in methods for causal inference. The results offer a different way to quantify radiation's effects and show that conventional estimates of the population burden of excess cancer at high radiation doses are driven strongly by projecting outside the range of current data. Summary results obtained using the proposed approach are similar in magnitude to those obtained using conventional methods, although estimates of radiation-related excess cancers differ for many age, sex, and dose groups. At low doses relevant to typical exposures, the strength of evidence in data is surprisingly weak. Statements regarding human health effects at low doses rely strongly on the use of modeling assumptions.

Keywords

Radiation; epidemiology; policy

1. INTRODUCTION

An irony of the accident at the Fukushima Daiichi nuclear power plant is that, in response to questions about the long-term health effects of the recent nuclear accident, the Japanese government has found itself referring to findings from the decades-long study of the Japanese survivors of the atomic bombings of Hiroshima and Nagasaki. The 70th anniversary of the bombings was in 2015, and few studies have approached the value to our understanding of radiation's effects on mortality and cancer incidence as the studies of these survivors.

Early analyses of the Japanese atomic bomb survivors involved simple comparisons of observed and expected numbers of deaths in concentric circles defined by distance from ground zero. Dose also varied according to other factors, such as the shielding provided by nearby structures. Over the years, increasingly sophisticated estimates of the doses from these bombings were developed. Most contemporary analyses of atomic bomb survivor data describe variation in disease rates as a mathematical function that depends on the magnitude

of a person's estimated dose, their sex, age when they were exposed, and attained age or time-since-exposure (e.g. (1–5)).

In a setting of environmental radiation exposure, such as Fukushima, policy makers often wish to address questions about the impact of exposure on a whole population. In this situation, age-, sex-, and time period-specific estimates of the effect of radiation dose on cancer rates are summarized to describe the expected excess disease burden in that population over a defined period of time. The standard approach in the radiation literature utilizes the dose-response function as an intermediate step in calculating the population risk. First, the sex-, age-, and time period-specific dose response function is estimated using a parametric model, and then the parameters from this model are used to predict cancer risk at specific exposures to a reference population. When the goal is to estimate excess cancers in the entire population over a protracted time period, however, there is some advantage to be gained by avoiding the first step of estimating the effects of radiation on disease for each sex and for different age and times-since-exposure.

The standard approach is subject to uncertainty regarding a great many aspects of the effects of radiation on cancer. For example, does the effect of dose received early in life persist for the entire lifetime? If so, does it persist at the same level? If not, what is the function by which the effect varies over time, and is that function constant across age and sex groups? Does this complex function vary by cancer type? Does the carcinogenic effect of an additional unit of dose follow an additive model, a multiplicative model, or some other form? Does the population level model follow the expected exposure-response based on mechanistic and animal models? The strength of a parametric approach is that we can derive reasonable answers to these questions using parsimonious models of the radiation-disease association. However, the weakness of this approach is that we *must* answer these questions in order to answer broader questions about population impacts. When the data do not conform exactly to the model, the standard approach can result in smoothing over potentially valuable information in the data.

Here we propose an alternative approach to estimating the population cancer burden due to radiation exposure that does not rely on the parameters of a dose-response model. This method is based on a potential outcomes framework developed by Jerzy Neyman in 1923(6), which is undergoing a revival due to the foundational work of Rubin(7) and Greenland and Robins(8) and the statistical approaches of Robins(9). In a number of settings, this work has demonstrated that the effects of exposure on health outcomes of interest can be derived using an approach that preserves the information in the data regarding the relationships between exposure, time, and disease. For a range of questions about radiation effects on human health, we can derive answers that are firmly rooted in the data at hand. We quantify the effects of the atomic bombings on mortality among Japanese survivors in Hiroshima and Nagasaki.

1.1. Radiation Risk Models

The primary basis for quantitative estimates of radiation effects used to inform radiation protection is the Life Span Study of Japanese atomic bomb survivors.(1, 4, 5) In August 1945, atomic bombs were dropped on Hiroshima and Nagasaki. Approximately 86,000

survivors of those atomic bombings who were still alive at the time of the 1950 Japanese decennial census were enrolled in a cohort study. Radiation doses were estimated based on interview information regarding location at time of bombing and shielding conditions. These individuals have been followed from 1950 by periodic searches of vital statistics records through 2003.

The standard approach to estimating cancer risks from radiation (e.g. the approach of Preston et al.(3)) starts with fitting a model for disease rates of the form

$$rate = e^{\alpha_i} [1 + ERR(d, e, a, c, s)]$$

where α_i is the natural log of the baseline disease rate for group i defined by age at the time of the blast (e), attained age (a), city (c), and sex (s). ERR is the excess relative rate, which describes the stratum specific radiation-related increase in mortality rates. The excess relative rate follows a model of the form

$$ERR(d, e, a, c, s) = \beta d \times \varepsilon(e, a, c, s)$$

where β quantifies the increase in the excess relative rate per unit dose (d), often taken as a linear function, and $\varepsilon(e, a, c, s)$ describes potential variation in the excess relative rate with age at exposure, attained age, city, and sex. These terms imply parametric assumptions about both the dose-response function and its modifiers. For example, the most recent Report on the Biological Effects of Ionizing Radiation (BEIR) from the National Academy of Sciences uses a function similar to

$$\varepsilon(e, a, c, s) = \exp(\gamma e + \delta \ln(a))(1 + \theta s)$$

which assumes that the excess relative rate varies as an exponential function of age at exposure, a power function of age, and a multiplicative function of sex.

Using the model from the BEIR report and a given hypothetical dose, risk is predicted according to the integrated product of the age- and sex- specific cancer rate in a target population and the ERR function (see the Appendix section 6.1.). We refer to this as the standard approach.

1.2. An alternative approach

Fortunately, it is not always necessary to fit complex parametric models of excess relative rates in order to estimate population risk due to exposure, and we can instead make direct estimates using data from the Life Span Study. We can directly estimate population risk without relying on an intermediate step of modeling the dose-response function.

Estimated doses for survivors of the atomic bombings roughly conform to groups defined by concentric circles expanding out from ground zero (Figure 1). Cancer risks can't be crudely

compared between groups defined by estimated dose because people in these groups are imbalanced with respect to characteristics like age and sex that are independently associated with cancer risk.

By using inverse-probability weighting(10) we can account for the imbalance in age and sex between dose categories. The weighted data can be interpreted as the population we would observe if dose groups were balanced with respect to these characteristics. Using only the weighted data, it is straightforward to calculate the proportion of cancer deaths among people in a particular dose category (e.g., 5–100 milliGray [mGy]). The risk in the weighted data can be interpreted as the mortality risk in the population, had they received the average dose in that category.

In addition to correcting for covariate imbalance,(8) inverse-probability weighting can also be used to account for differences in the distribution of modifying factors between a study population (the “source” population) and an external population of interest (the “target” population(11, 12)). The excess cancer risk can be calculated as the difference between the weighted, or standardized, risks in two or more dose groups. In contrast to the parametric approach focused on modeling how the dose-response surface varies across age-, sex-, and exposure groups, a weighted comparison of cancer occurrence between balanced dose groups directly yields the desired marginal estimate of the dose effect in the population. To reduce statistical uncertainty at low doses, we also use a weighted modeling approach (inverse probability weighted estimation of marginal structural rate models) that represents a compromise between our non-parametric approach and the fully parametric standard approach.

Any exposure that increases the risk for one cause of death will necessarily decrease the risk for some other causes. This aspect of risk is often ignored in the standard approach to estimating population risk, as a way to simplify calculations. A further benefit of avoiding the intermediate parametric modeling step is that we can reduce the assumptions necessary regarding which specific causes of death will increase (or decrease) under a population exposure. In this respect, our approach yields a more complete picture of the effect of radiation on human health.

2. METHODS

2.1. Study population and data sources

Our study comprises two populations. The source population is the Life Span Study cohort, a group of approximately 86 thousand survivors of the atomic bomb blasts over Hiroshima and Nagasaki in World War II.(3, 13) The blasts occurred in 1945, and the cohort was enumerated in October, 1950 and has 58 years of follow up through 2003. No information is available for individuals who died between the time of the blasts and 1950. Life Span Study data are publically available(14) in tabulated form by sex, city, 22 colon dose categories, and 5-year categories of age at exposure (14 categories from 0–70, 70+), attained age (20 categories from 0–100, 100+), and calendar year (11 categories from October 1950 to December 2003). Each cell in the tabulated data also contains the person-time-at-risk, number of initially enumerated individuals, the number of deaths from a list of 30 causes,

and the person-time weighted mean organ dose for 10 organs. Our target population is the 1950 population of Japan. We utilized population data stratified by sex and 1-year categories of age and calendar time, which is provided with EPICURE (HiroSoft International Corporation, Seattle, Washington) software.

Information about exposure to ionizing radiation from the atomic bomb blasts is based on extensive interview data describing location and shielding data and physical characteristics of the bombs. We utilize the DS02 estimated weighted dose to the colon as the basis for all analyses. The weighted dose was estimated by summing the gamma and neutron radiation, where neutrons were given a weight of 10 to account for the greater biological effectiveness. (15) The public use dataset uses doses that are modified to reduce the downward bias from random error in estimated doses.(2)

The follow-up for mortality began in October, 1950 and was based on the family registry system (*koseki*) in Japan, which is considered to be nearly complete. Some individuals left the country prior to the end of follow-up on December 31, 2003, and were considered censored, though no information on censoring was given in the public use dataset. Cause of death was classified by trained individuals working for the Atomic Bomb Casualty Commission/Radiation Effects Research Foundation according to the International Classification of Disease (ICD) versions 7–10, with the specific dates of use for each version given by Ozasa et al,(2) p. 243.

2.2. Parameters of interest

Cause specific mortality can be calculated for the Japanese population in 1950 using inverse probability weighting(16) and data from the Life Span Study.

In potential outcomes notation, such assessments are comparisons of $F_{Tg}(t)$, the population distribution of the time of death we would observe if the population is given a radiation dose of g mGy. We also introduce the cause of death J (e.g. death from any solid cancer) and the potential cause $\mathcal{J}$. A population quantity of interest is the cause specific risk $F_{TJ}(t, j) = \Pr(T < t, J = j)$. The risk represents the total proportion of deaths from a specific cause that have occurred in the population up to a given time.

The risk we would expect after exposure to g units of ionizing radiation is $F_{Tg\mathcal{J}}(t, j)$ which, for notational simplicity we denote as $F_{T,J}^g(t, j)$. This quantity can be calculated directly from the data using inverse-probability weights.(16) which can be hand calculated (though this is usually modeled for convenience or when covariates are measured on a continuous scale). Risk can be used to define the excess number of cases per 1000 individuals using

$$1000 \times (F_{T,J}^g(t, j) - F_{T,J}^0(t, j)),$$

where $F_{T,J}^0(t, j)$ is the risk we would expect in the population, had exposure been uniformly zero.

2.3. Inverse probability weights

Inverse probability weighting is a method used to obtain standardized risks(17) that, under some assumptions (discussed by Robins et al.(10)) yield estimates of the average potential outcomes for a population exposed at some constant level. We utilize a two-part weight (W), where the first part is referred to as a generalizability weight (W_1) and the second part is referred to as an inverse-probability-of-exposure weight (W_2).

The generalizability weight, W_1 is based on the principal that the source population can be considered a stratified, random sample from the target population, where the strata are defined by risk factors for disease which might differ between the source and the target population. Such weights calculated the same way as the “selection weights” used to extend the results of clinical trial data(11) or survey subsample data(12) to larger populations within which the source population is nested. That is, the weights are considered to be in the inverse of the probability of “selection” into the Life Span Study (from the Japanese population enumerated in 1950), given as $\Pr(Pop = lss | S = s, E = e)$ for sex s and age (in 1945) e . We define strata by the age in 1945 (rather than the age in 1950), which encodes the assumption that mortality does not depend on dose in the 5 years after exposure.

The generalizability weight can be estimated based on sample proportions, given as $\widehat{Pr}_N(Pop = lss | \cdot) = N(\cdot)_{LSS}/N(\cdot)_{Japan}$ where $N(\cdot)_p$ refers to the stratum specific population size for population p . Thus, the generalizability weight can be seen as a function of (stratum-specific) sample sizes. For convenience, we estimated the weights using a logistic regression model with sex, age in 15 5-year categories, and the 15 sex-by-age category product terms. To apply the weights such that the weighted population resembles the target population, we use the sample odds, given as $\widehat{O}_N(Pop = lss | \cdot) = \widehat{Pr}(Pop = lss | \cdot)/(1 - \widehat{Pr}(Pop = lss | \cdot))$

The final estimated weight component is given as

$$\widehat{W}_1 = \widehat{O}_N(Pop = lss)/\widehat{O}_N(Pop = lss | S = s, E = e).$$

The marginal odds term in the numerator is included to stabilize the weights. The use of stabilized weights improves variance and yields a weighted population the same size as the source population (18).

We derive W_2 using the approach given by Robins.(19) This weight can be estimated by the sex, age, and city (Hiroshima or Nagasaki). specific sample proportion of individuals in each dose category, given as $\widehat{Pr}_N(Dose = g | Pop = lss, S = s, C = c, E = e)$, where C denotes city.

The estimated inverse-probability-of-exposure weight is given as

$$\widehat{W}_2 = \widehat{Pr}_N(Dose = g | Pop = lss)/\widehat{Pr}_N(Dose = g | Pop = lss, S = s, C = c, E = e),$$

The final weight used to derive the population cumulative incidence function is given as

$$\widehat{W} = \widehat{W}_1 \widehat{W}_2.$$

To estimate $\widehat{W}_1$, we used a multinomial logistic regression model in which dose category is treated as the dependent variable. This model is given as

$$\ln(\widehat{O}(\text{Dose} = g \mid \text{Pop} = lss, S = s, C = c, E = e)) = \beta_{0,g} + \gamma_{g,s} + \kappa_{g,c} + \eta_{g,e}$$

where $\beta_{0,g}$ are the log-odds-ratios of being in the exposure group g , relative to being in the referent exposure level at the referent level of all covariates, and $\gamma_{g,s} + \kappa_{g,c}$ and $\eta_{g,e}$ are the sex, city or age-in-1945 specific log-odds-ratios for being in exposure group g , relative to being in the referent level. The category specific probabilities that define the weights are given by transforming the log-odds using the inverse-logit function. We assessed the success of inverse probability weighting at reducing confounding by examining the weight distributions and assessing covariate imbalance across exposure groups before and after weighting (See Appendix)

2.4. Identification and estimation of functions of survival time

We are primarily interested in estimating the number of excess cause-specific mortalities per 1000 individuals, estimated as $\widehat{EC}_{T,J}^g(t, j) = 1000 * (\widehat{F}_{T,J}^g(t, j) - \widehat{F}_{T,J}^0(t, j))$, where we estimate $\widehat{F}_{T,J}^0(t, j)$ using the weighted cause specific risk among the 0–5 mGy exposure group in the Life Span Study. In a closed cohort (i.e. a group of individuals followed from a specific time point until some endpoint of interest, where there is no loss-to-follow-up), the exposure and cause-specific *potential* risk in the population can be estimated using

$$\widehat{F}_{T,J}^g(t, j) = \left(\sum_{i=1}^{n(g)} \widehat{W}_i \right)^{-1} \sum_{i=1}^{n(g)} I(T < t, J = j) \widehat{W}_i,$$

where i indexes the individuals in the source population who had a dose of g mGy (with sample size $n(g)$) and $I(\cdot)$ is a logical indicator function that takes on the value 1 if the value inside the parentheses is true, and zero otherwise. With loss-to-follow-up, the value inside the indicator function would be unknown for some i , implying that this function would not be identified. A great strength of the Life Span Study Cohort is that only 1% of the cohort has been lost-to-follow-up, which minimizes the potential bias, even if there are differences by exposure groups. A Kaplan-Meier estimator of survival with weighting to account for censoring could be used, instead (20).

2.5. Inverse probability weighted estimation of a marginal structural rate model

The risk calculations described above are non-parametric in the sense that we did not impose a model on the risk of mortality (though a model was used to estimate the weights). An alternative approach is to utilize the weights to estimate the parameters of a marginal

structural rate model. A marginal structural model (MSM) is a model for the distribution of potential outcomes in the target population. To estimate the MSM parameters, one need only run a regression in the weighted population, which can be achieved in most standard regression software.

To estimate the risk, we first fit a model to estimate the parameters of a marginal structural excess, relative, cause-specific rate model. Specifically, for solid cancer and non-cancer causes, our MSM is given as

$$\lambda_{T,j}^g(t, j | a) = \exp(\delta_j q(a)) \left(1 + \beta_1 j^g \times \exp(\eta_j r(a)) \right)$$

where $q(a)$ and $r(a)$ are separate functions of attained age, $\lambda_{T,j}^g(t, j | a)$ is the rate of the cause j specific potential outcome at age a under an intervention to set exposure to the value g , assumed to have a Poisson distribution, and $q(a)$ includes a model intercept. In contrast to typical MSMs such as a marginal structural Cox or logistic model, our parameter β_1 estimates the excess relative rate for a one unit increase in exposure for the entire population, while the parameters β_j and η_j estimate the background mortality rate. Here, we follow Ozasa et al (2) and let $q(a)$ represent a quadratic spline for log-age with knots at age 40 and 70, and $r(a)$ represent the log-age. Following previous authors in preferring a linear-quadratic dose model for leukemia mortality, our MSM for leukemia is

$$\lambda_{T,j}^g(t, j | a) = \exp(\delta_j q(a)) \left(1 + (\beta_1 j^g + \beta_2 j^g{}^2) \times \exp(\eta_j r(a)) \right).$$

Using these the leukemia and solid cancer models, as well as a model for other causes of death (with the same functional form as the solid cancer model), the calendar-time specific risk (and hence, the excess deaths) can be easily estimated via simulation from the rate models in the target population over the specified risk period. Defining risk at the start of follow-up as zero, we used the W_1 - weighted, empirical age distribution of the $n=86,611$ LSS participants to simulate the discrete-time risk at each year $t = 1, \dots, 53$ for a number of different exposure values g from these rate models. Using the simulated data for $i = 1, \dots, n$ individuals, the discrete-time risk is estimated by:

$$\hat{F}_{T,j}^g(t, j) = n^{-1} \sum_{i=1}^n \sum_{k=0}^t \hat{\lambda}_{T,j}^g(k, j | a) \exp \left(- \sum_{s=0}^{k-1} \hat{\lambda}_{T,j}^g(s | a) \right)$$

where $\hat{\lambda}_{T,j}^g(t, j | a)$ is the model-based estimate for the cause specific rate, and $\hat{\lambda}_{T,j}^g(s | a)$ is the sum of the estimated age- and cause-specific mortality rates at time s for the potential outcomes. In other words, we estimate risk in strata defined by age and time since the beginning of follow-up, and then average over the age distribution in the target population in order to get the marginal risk at time t . We estimated the risk at the cell-specific mean dose given by the dose categories 0–5 mGy (referent): 0.96 mGy; 5–60: 16 mGy; 60–100: 73

mGy; 100–500 mGy: 259; 500–1000 mGy: 705 mGy; >1000 mGy: 1624 mGy. For an index dose, g , we estimated the excess deaths per 1,000 individuals as

$$\widehat{EC}_{T,J}^g(t, j) = 1000 * \left(\widehat{F}_{T,J}^g(t, j) - \widehat{F}_{T,J}^{0.96}(t, j) \right).$$

For all analyses, we estimated 95% confidence intervals for $\widehat{EC}_{T,J}^g(t, j)$ using the 2.5th and 97.5th percentiles of a non-parametric bootstrap with 5,000 bootstrap samples.

3. RESULTS

3.1. Cancer risk in the Atomic Bomb Survivors and the Japanese population

Using Japanese census data and data from the Life Span Study of atomic bomb survivors, we estimated the effect of specified radiation doses on the population of Japan in 1950 by weighting the Life Span Study data to resemble the Japanese population (Figure 2). Both the Japanese population and the Life Span Study cohort have demographic structures characteristic of post-war populations: however, the Life Span Study cohort (Figure 2A) is younger than the general population of Japan and includes a larger proportion of females (Figure 2B). Inverse probability weighting removed imbalances between dose groups in city, sex, and age at the time of the bombings (Figure A1).

Taking the lowest exposed group of A-bomb survivors (0–5 mGy dose range, weighted mean colon dose = 0.96 mGy) as a reference (approximating the cancer mortality expected in the absence of exposure), we can directly estimate the excess mortality at different doses. Fifty-eight years after exposure, we expect 80 excess deaths per 1000 people who receive the average dose in the 1+ Gray range (95% confidence interval [CI]: 62–99; Table I). We expect approximately 26 excess leukemia deaths in such a population (95%CI: 19–34), most occurring within the first 25 years after exposure.

Fifty-eight years after exposure, we expect 28 excess solid cancer deaths per 1000 people who received the average dose in the 500–1000 mGy+ range (mean= 705 mGy) (95%CI: 15–42) (Figure A2). This figure is slightly below what we would expect if the excess is proportional to dose, but is nonetheless statistically consistent with a linear relationship. The excess deaths from solid cancer increase gradually over time among people who received exposures above 100 mGy while excess leukemia increased promptly in the years after exposure, and mainly among those who received doses over 100 mGy (Figure A3).

Following the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR (4)), we estimated the excess cancers at 1 Gray (i.e., the excess cancers in the 1+ Gray dose group divided by the mean dose). In the absence of exposure, we estimated that there would be 12 deaths from solid cancer and leukemia out of every 100 individuals. Given a population exposed to a dose of 1 Gray, we would expect approximately 5 excess solid cancer deaths and 2 excess leukemia deaths (Figure 3.)

Using our non-parametric approach, we found limited evidence of excess cancer deaths at doses below 100 mGy. The statistical uncertainty in this low dose range is drastically reduced by assuming a parametric model. For example, compared with the expected excess of 0.0 (95% CI: -6.0—6.1) in the 5—60 mGy group from our non-parametric approach, utilizing a set of weighted models, we estimated an excess of 0.8 (95% CI: 0.6—1.0) deaths in this group. Provided the modeling assumptions hold, our results support the hypothesis that ionizing radiation exposure causes cancer even at low doses.

4. DISCUSSION

Epidemiologists are charged with estimating the expected excess burden of disease after nuclear events, such as the release of radioactive materials following the accident at the Fukushima Daiichi power plant (21). We show that such estimates can faithfully reflect the information, as well as the uncertainty, in the data, rather than the projection of the data onto a complex disease model. The use of potential outcomes provides a formal framework for such calculations, and inverse probability weighting provides the statistical machinery. The evolution of disease over time in this weighted population emulates what we would observe in the target population, had they been exposed to ionizing radiation (19). Our primary approach makes no assumptions about the dose-response curve, demonstrating that detailed dose-response analysis is not always necessary for estimating population risk following radiological incidents.

The overarching goal of a risk assessment like ours is to apply knowledge learned in one population to predict hypothetical risks in another. Consequently, such risk assessments are not subject to standard model selection approaches that rely on assessing the agreement between predicted and observed outcomes. While our approach relies on the assumption that the baseline cancer rates (conditional on age and sex) are similar between the LSS population and Japan, our method is much simpler than standard risk assessment approaches and requires fewer assumptions. The accuracy of those assumptions can be assessed by comparing results from our approach to those derived under the complex modeling approach. We compared our estimates of excess deaths due to radiation with those from the committee on the Biological Effects of Ionizing Radiation (BEIR), convened by the National Academy of Sciences(1) (Appendix Tables A1 and A2) At higher doses (the 1000+ Gy and 500–1000 mGy dose groups) our approach estimates an excess risk of solid cancer 58 years after exposure that is lower (79 and 28 excess deaths, respectively) than the estimates using the approach of the National Academy of Sciences (102 and 44 excess deaths). For a population exposed to lower doses (e.g., the 100–500 mGy dose group), our approach yields estimates (15 excess deaths) that are similar to estimates derived using conventional methods (16 excess deaths). Differences by sex between our estimates and those of the NAS BEIR committees, suggest that the sex difference in radiation sensitivity at high doses may be greater than is currently appreciated. Similarly, differences between our estimates and prior estimates for cancer risks among those exposed below age 40, can quantify the sensitivity of the standard approach to some of its parametric assumptions. UNSCEAR estimates that, at 1 Gray exposure, 5 excess solid cancer deaths and 1 excess leukemia death would occur in the Japanese population (Tables 64 and 68 in (4)), similar (or lower, for leukemia) to our estimates shown in Figure 3. Thus, our results for leukemia are intermediate between

estimates of the two committees, while our estimates for solid cancer risk are much closer to those of UNSCEAR.

Unlike the conventional approach, our approach yields formal measures of the statistical certainty of our estimates, which suggests that many of our results and those derived using the conventional approaches are statistically consistent with each other. This observation underscores the substantial uncertainty in radiation risk estimates in certain age and dose groups. While a parametric approach can be used to reduce this uncertainty, the variance reduction comes at the cost of additional assumptions. Parametric modeling assumptions of the conventional approach have often been explored in the LSS data by contrasting model how well the statistical models for cancer mortality predict the observed mortality in the LSS. Such models have shown that model fit can be improved by, for example, allowing the dose-response parameters to differ according to age at exposure or adding a quadratic term to the dose response for leukemia (22, 23). Increasing the complexity of the regression model for an outcome, however, may lead to concern about overfitting of a model to the dataset and thereby reduce generalizability of the findings. In contrast, with a model for IP weights used for confounder control, there is little concern about overfitting and a highly-parameterized model for IP weights to achieve covariate balance will not reduce generalizability of the exposure-outcome estimate derived from the weighted data.

Without the use of models, the evidence for mortality excess due to cancer in the range of doses below 100 mGy is surprisingly unclear in the Life Span Study data (See Appendix). Standard approaches use smoothing of dose response models to stabilize estimates of risk across the observed dose range. We observed that using a weighted modeling approach also resulted in a drastic improvement in the precision of our estimates at low doses, without some of the drawbacks of the standard approach. Primarily, however, we have focused on estimates of population risks that are largely agnostic regarding the shape of the dose-response curve and in particular, the so-called linear-no-threshold hypothesis (24). As Brenner (25) points out, the linear-no-threshold hypothesis may hold over small dose ranges but we should not expect it to hold over the entire dose range in the Life Span Study. As our results in the Appendix show, much of the evidence for exposure effects at low doses is a result of model-based interpolation. Without a model, the results are consistent with a range of hypotheses at low doses. While misspecification of the model for the weights is a possible source of bias in our results, it is unlikely to be the source of discrepancy between our (non-parametric) results and the results of more standard approaches. Rather, it is important to note that the accuracy of current population risk estimates rely heavily on the models used. Further, a simple linear model may not adequately describe multi-stage processes underlying the etiology of cancer in individuals, though a weighting approach could likely be extended to models that explicitly allow for exposure to have effects at multiple disease stages.

Here, we focused on calculation of excess cancers in a population in which the baseline mortality rates were presumed to be similar to those in the Life Span Study. In other populations, the approach would still yield an estimate of the excess mortality from ionizing radiation standardized to an external population, but additional assumptions are required to interpret the results of such an analysis as expected excess rates for that external population. Measuring population characteristics that are responsible for baseline rate differences

between populations may ameliorate this shortcoming, however. Further, even when our weighting approach is not possible, other methods from the potential outcomes literature may be used that reduce reliance on assumptions underlying the standard approach (26). Our example shows one of the many potential applications of this general framework for health impact assessments and population risk estimation.

Notably, our methods address the population impact of large-scale acute exposures that could happen in nuclear incidents or armed conflict. One consequence of using a weight based approach is that we are unable to make inference about the effects of protracted exposure or exposure across multiple time points. Such exposures are common and may occur due to natural sources of radiation (e.g. cosmic radiation during air travel), occupational exposure, or medical exposures. In principal, one could use a similar approach to ours with existing data on protracted exposures to make inferences about population exposures. However, such an approach would be sensitive to the assumption that conditional baseline disease/mortality rates are equivalent between the study sample and the target population. Populations through radiation treatment occupationally may not be suitable for such an approach, because such populations often represent select subgroups of the general population. Research into the generalizability and transportability of causal effects (17) is growing quickly, however, so methods to estimate population effects of protracted exposure using existing data (and the necessary assumptions), may be at hand soon.

Conventional models leverage strong parametric assumptions in order to estimate population risks due to environmental exposures. However, their rigid structures may obscure features of the data that do not agree with the model, and, due to the complexity of models used in radiation research the approach is difficult to communicate to stakeholders. Our results underscore the uncertainty in such calculations and provide suggestive evidence that risks for some groups (males, or certain age groups for example) may have been obscured by the strong model assumptions used in standard calculations. Our weighting approach offers a useful complement to the approaches conventionally used for quantifying health impacts of environmental radiation exposures, potentially improving risk prediction for public health planning in nuclear events.

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5. APPENDIX

5.1. Illustration of standardization using inverse probability weighting

We demonstrate several features of our standardization approaches using a synthetic data example. We use inverse probability weighting to demonstrate the potential to generalize study findings to a specified target population. The simulated data comprise information on a 3 level confounder (Z), a continuous exposure (X), and a binary outcome (Y). We simulated Z from a multinomial distribution with probabilities 0.5, 0.3, and 0.2 of taking on the values 1, 2, or 3. X was simulated by exponentiating a normally distributed variable with a mean given by $-(0.875 + 0.5 * (z - 1.7)^2)$ and a standard deviation of 1.0. Y was simulated as a Bernoulli random variable with a probability given by $1/(1 + \exp(-(0.2 - 0.3 * X + 0.1 * Z + 0.1 * X * Z)))$. Thus the data roughly approximate models of radiation exposure on cancer mortality, which can be represented using a model that is linear in dose. To further emulate the LSS, X was split into a 5-level variable based on the 20th, 50th, 70th, and 90th percentiles, and the categorized variable was given a value equal to the expected mean exposure within each level; we denote the categorical variable by X_C and the scored variable by X_M . The data were used to create a target population of 20,000 individuals, and a study sample was created by sampling, without replacement, from the target population, with the sampling probability equal to $1/(1 + \exp(-(.5 - .5 * (Z - 1.7)^2)))$. We denote selection into the study sample by $S = 1$.

Following our analysis in the main manuscript, we analyzed the simulated data using both a non-parametric estimate of the risk difference and an estimate based on a MSM, we compared risk in the lowest category ($X_C = 0$) with risk in the second highest category ($X_C = 3$). Weights for both approaches were estimated using the sample estimates of

$$W = Pr(X_C = x | Z = z, S = 1)^{-1} Pr(S = 1 | Z = z)^{-1}.$$

The MSM was a logistic model given by $\log(odds(Y^x)) = \beta_0 + \beta_1 X_M$, this approach allows us to compare approaches when the true model for the outcome is on the same linear scale as the MSM. Estimated risk and risk differences, and their associated standard errors were calculated from the MSM using the “margins” and “lincom” commands in STATA (using a robust standard error). We used the Horvitz-Thompson estimator of the risk difference for the non-parametric approach, given by $\frac{1}{N} * \sum_i [y * I(X_C = 3) * W - \sum_i y * I(X_C = 0) * W]$,

where N is the sample size in the target population. We denote estimates of the risk difference as $RD^{3,0}$.

A cross tabulation of Z with X_C and S , as well as the stratum specific estimates of the weight contributions are given in Table A1. For example, the weight given to individuals in the lowest exposure category ($X_C = 0$) with $Z=1$ is given as $W = 1/(0.28 * 0.56)$. If we take the product of the stratum specific sample size and the weight, we get $6.4 * 1555 = 9973$, which is the stratum size in the target population. This holds true for any value of X_C . Thus, this calculation demonstrates that the weighted population of individuals corresponds to what we would expect in the target population, had all of those with $Z=1$ been exposed in the category $X_C = x$. The estimate of $RD^{3,0}$ (standard error) for the example shown in Table A1 was -0.044 (0.016) for the non-parametric approach and -0.041 (0.010) under the MSM. This example demonstrates that both approaches will give roughly similar answer in simple scenarios, but the non-parametric approach will be less statistically efficient.

To further assess the merits of the two approaches, we repeated simulation example 10,000 times and calculated the percent bias for the estimate $RD^{3,0}$ as the average of $(\text{bias}/\text{true } RD^{3,0})$, where true $RD^{3,0}$ was the expected marginal risk difference within each iteration. The truth was evaluated as the risk difference comparing the risk at the expected mean exposure when $X_C = 3$ with the expected mean exposure when $X_C = 0$. We additionally calculated the root-mean-squared error (RMSE) as the square root of the average squared bias across the 10,000 iterations. In this example, the non-parametric approach was less biased (-0.8% bias) than the MSM approach (-5.9% bias), but the non-parametric approach had 1.8 times higher RMSE than the MSM approach. The 95% confidence interval coverage was within 0.1% of the nominal level for both approaches. These results demonstrate that, even when the effect of exposure is linear on the model scale, the MSM approach can be biased because linearity of the Z-specific/stratified effect does not necessarily correspond to linearity of the marginal effect. However, the MSM will generally lead to more precise estimates that may be preferred if the statistical model can be expected to hold approximately.

5.2. Lifetime attributable risk estimation

Contrasts of the expected potential mortality rates and incidence in a population at different levels of exposure are fundamental to understanding the effects of ionizing radiation on population health. In the epidemiologic literature, however, these quantities are not typically quantified. Instead, most analyses focus on the so-called lifetime attributable risk (LAR). Ignoring issues of latency and assuming exposure in infancy, the LAR at age 100 is given as

$$LAR(g, a, s, e) = \int_e^{100} ERR(g, a, s, e) \lambda_{T,C}^{0(a, j | s)} \Pr(T^0 \geq a | s) / \Pr(T^0 \geq e | s) dt,$$

where $ERR(g, a, s, e)$ is the sex-specific excess relative risk at age a for an exposure g , where the exposure occurred at age e (27). $ERR(g, a, s, e)$ is estimated using data from an exposed population of interest (e.g. the cohort of A-bomb survivors), $\lambda_{T,C}^{0(a, j | s)}$ is the sex-

specific cancer mortality rate at age a in the target population, and $\Pr(T^0 = a|s)$ is the sex-specific probability of survival to age a in the target population of interest and $\Pr(T^0 = e|s)$ is the sex-specific probability of survival to age e in the population.

The sex specific LAR quantities can be combined for a given dose by taking a weighted average, where the weight is determined by the number of males and females in the target population. The same averaging procedure can be used to account for different ages at exposure in the population, as well. More formally, the dose specific summary LAR can be calculated as $LAR(g) = N^{-1} \sum_e \sum_s LAR(g, s, e) n(s, e)$, where $n(s, e)$ is the sex and age-at-exposure specific population size at the start of follow-up, and N is the total population size at the start of follow-up.

To allow comparison between classical measures of excess risk and our estimates, we estimated $LAR(g)$ for the population of Japan in 1950. To most closely align the two estimates of population risk, we also estimated this quantity through age 100 or age in 2005, whichever was lower, and we refer to this quantity as the modified $LAR(g)$ or $mLAR(g)$. As in our primary analysis, we allowed for a 5-year lag in exposure effects by allowing no excess deaths between the presumed year of exposure (1945) until 1950, at which point the cohort is defined. We used the $ERR(g, a, s, e)$ given in reference (1), and $\lambda_{TC^0}(a, j|s)$, $\Pr(T^0 = a|s)$ and $\Pr(T^0 = e|s)$ were derived from World Health Organization estimates for the population of Japan in 1990 (<http://apps.who.int/gho/data/node.main>). We calculated the $LAR(g)$, the $mLAR(g)$, and the excess deaths per 1,000 (using our weighting approach) at the mean dose values for the 500–1000 mGy and 1000+ mGy dose groups in the Life Span study (705 mGy and 1624 mGy, respectively). Each analysis was repeated for both solid cancers and leukemia.

As shown in Table A2, the excess solid cancer deaths per 1,000 individuals at 1.6 Gy (79) and at 0.7 Gy (28) was smaller than the $mLAR(g)$ and the $LAR(g)$. Our estimate of the excess deaths and the $LAR(g)$ are not directly comparable because the $LAR(g)$ approximates the expected excess solid cancer risk at age 100. The $mLAR(g)$ better approximates our quantity of interest, which is the excess solid cancer risk for the population 58 years after exposure. Interestingly, when stratifying on sex, our estimate of the excess deaths and the $mLAR(g)$ suggest different magnitudes of the sex difference at high doses. Our estimates suggest that we would observe a much lower excess among males (45) than females (100), while the $mLAR(g)$ suggests that the excess would be more comparable (females=112, males=91.) The estimates also diverge when stratifying on age at exposure. However, based on the confidence interval width in the older age groups, our approach emphasizes that there is a large amount of uncertainty in the Life Span Study data for estimating excess risk for exposure at older ages, where our estimates are consistent with a range of hypotheses regarding radiation effects. When stratifying by age, the $LAR(g)$ and the $mLAR(g)$ are equivalent in the age ranges 50–59 and 60+ years of age because, for individuals over age 40 in 1945, the calculations are identical for the two quantities. Thus, the summary $LAR(g)$ and $mLAR(g)$ estimates are substantially influenced by the quantities in the Life Span Study participants who were under 40 at the time of the blasts. Integrating the $LAR(g)$ quantity to age 100 in this group requires projection into the future. This shows that the $LAR(g)$ is

strongly influenced by extrapolation of the excess cancers outside the range of the data. In contrast, our estimates of the excess deaths are determined only within the range of the data.

We repeated the analysis comparing our estimates of the excess deaths with the $LAR(g)$ and $mLAR(g)$ for leukemia. As in the solid cancer analysis, we based the estimates for this analysis on the parameter values given in reference (1). Our summary estimate of 26 excess leukemias per 1,000 individuals at 1.6 Gy is 20% lower than the estimate of 37 given by the $mLAR(g)$ while the estimates are similar at lower doses. Notably, all sex-stratified estimates show that the burden of excess leukemias following radiation exposure would occur primarily men at higher exposures.

The $LAR(g)$ quantity is problematic because, as Vaeth and Pierce (p 85) note, the lifetime attributable risk for cancer deaths corresponds to “the increase in the proportion of ultimate cancer deaths if all individuals dying from exposure-induced cancer are replaced immediately after death by someone of the same age and sex” (28). As a consequence, the $LAR(g)$ does not correspond to any comparison of a population under two different exposure measures, except under the null. Thus, this quantity should overestimate the true public health burden, which we estimate directly using our weighting approach.

5.3. Further results for weight-based approaches

We assessed the success of inverse probability weighting at reducing confounding by examining the weight distributions and assessing covariate imbalance across exposure groups before and after weighting. The mean weight was 1.00 with a minimum of 0.37 and maximum of 12.6, which suggests that our weights were well behaved and no single group had undue influences on weighted estimates. The mean weight near 1 also suggests that our approach did not suffer from a random violation of the positivity assumption, which states that each level of exposure must be observed in all strata of the covariates (10). We also assessed this assumption by ensuring that no coefficients in our model for the exposure were dropped due to empty strata.

We assessed covariate balance using the absolute covariate imbalance, given as the absolute value of the covariate specific proportion in each exposure group minus the overall proportion in each exposure group. In a perfectly balanced population, such as a large randomized, controlled, clinical trial, these quantities will be zero, and any deviation from zero is indicative of imbalance. As shown in Figure A1, covariate balance for sex, city, and age at exposure improved markedly after applying the weights, suggesting that our weighting approach was successful at reducing confounding by these covariates.

The estimated $\widehat{EC}_{T,j}^g(t, j)$ from the parametric MSM was qualitatively similar to that given by the non-parametrically estimated $\widehat{EC}_{T,j}^g(t, j)$ for solid cancer (compare figures A2 and A4) and leukemia (compare Figures A3 and A5). At high doses, the precision in the estimate derived from the MSM and that from non-parametric approach were similar (Table A4). At lower doses, however, the MSM based estimate of the excess cases had a much higher precision than the non-parametric estimate. Our results demonstrate explicitly that, without the sharing of information across dose ranges implicit in the modeling approach, there is not

strong evidence for an association between low-dose (<100 mGy) ionizing radiation and cancer mortality. Using solid cancer as an example, in the 5–60 mGy dose group (mean dose of 16 mGy), the non-parametric approach yields 0 excess deaths with 95% bootstrap confidence intervals of (–6.0, 6.1), suggesting statistical compatibility with a range of effects. The lack of statistical precision is surprising, given that 70% of Life Span Study participants were in the two lowest dose groups. For the MSM approach, however, the excess deaths (95% confidence intervals) of 0.8 (0.6, 1.0), implying much greater statistical evidence for radiation effects on solid cancer. This difference is solely attributable to the use of model-based interpolation of the results.

Following standard radiation analysis, we also fit a marginal structural excess relative rate model for site-specific cancer mortality. We used the same inverse probability weights from our other approaches to fit a weighted ERR model for each site, which is simply a weighted version of the (age, age at exposure, sex, city) background adjusted ERR model shown in Figure 1 of Ozasa et al.(2) The results, reported in Table A5 do not differ appreciably from those reported by Ozasa et al. Notably, however, under both the modeling assumptions and the causal assumptions implied by the MSERRM, these results can be interpreted as the (age, age at exposure, sex, city) excess relative rate per Gy that would be observed in the Japanese population under a uniform population exposure.

We have demonstrated that the non-parametric approach gives useful measures of the public health impact of radiation. However, this approach results in greater statistical uncertainty, given that we make very few assumptions. We show the explicit impact of adopting a model for the effects of radiation on the cancer mortality rates, and demonstrate that much of the evidence at low doses depends on use of a model. This work supports the careful and thorough exploration of model fit and the use of mechanistic and biomechanical data to inform how low-dose radiation affects human health. Because the results at low doses are driven by model based inference, our results caution against confident assertions regarding low-dose radiation effects using only the data from the Life Span Study. Large studies of individuals exposed to low levels of radiation, such as in certain occupations, may yield more certainty regarding the effects of radiation on human health at very low doses.

Figure A1.

Covariate balance for sex (A), city (B) and age at the time of the blast (C) by dose category in weighted data (open triangle) and unweighted data (open circle). The vertical lines at 0 indicate the point at which the covariates are balanced within an exposure group.

Figure A2.

Excess deaths per 1,000 population comparing the solid cancer mortality in the index dose groups given in the legend with 0–5 mGy group. Curves are smoothed via linear interpolation for presentation purposes. Person-time weighted mean colon doses for each dose category are 0–5 mGy (referent): 0.96 mGy; 5–60: 16 mGy; 60–100: 73 mGy; 100–500

mGy: 259; 500–1000 mGy: 705 mGy; >1000 mGy: 1624 mGy. Shaded areas correspond to 95% confidence regions.

Figure A3.

Excess deaths per 1,000 population comparing the leukemia mortality in the index dose groups given in the legend with 0–5 mGy group. Curves are smoothed via linear interpolation for presentation purposes. Person-time weighted mean colon doses for each dose category are 0–5 mGy (referent): 0.96 mGy; 5–60: 16 mGy; 60–100: 73 mGy; 100–500 mGy: 259; 500–1000 mGy: 705 mGy; >1000 mGy: 1624 mGy. Shaded areas correspond to 95% confidence regions.

Figure A4.
Excess deaths per 1,000 population comparing the solid cancer mortality in test dose groups based on predicted risk from a joint set of weighted models for death from solid cancer, death from leukemia, and other causes of death. Shaded areas correspond to 95% bootstrap confidence regions.

Figure A5.
Excess deaths per 1,000 population comparing the leukemia mortality in test dose groups based on predicted risk from a joint set of weighted models for death from solid cancer, death from leukemia, and other causes of death. Shaded areas correspond to 95% bootstrap confidence regions.

Table A1

Cross-tabulation of a confounder (Z) with exposure categories (X_C) and population. One realization of simulated data for generalizing study results to a target population.

Z	X_C^a [N (%)]					Population ^b	
	0	1	2	3	4	Sample	Target
1	1555 (0.28)	1769 (0.31)	1040 (0.19)	910 (0.16)	343 (0.06)	5617 (0.56)	9973
2	824 (0.22)	1103 (0.30)	729 (0.20)	690 (0.19)	358 (0.10)	3704 (0.62)	6017
3	833 (0.50)	479 (0.29)	205 (0.12)	122 (0.07)	20 (0.01)	1659 (0.41)	4010

^aData given are stratum sample sizes in the study sample and the propensity score (in parentheses), estimated by $Pr(X_C = x|Z = z, S = 1)$

^bData given are the stratum sample sizes and the probability of selection into the study sample (in parentheses), estimated by $Pr(S = 1|Z = z)$

Table A2

Comparison of lifetime excess deaths from solid cancer per 1,000 individuals, Japanese population in 1950

	259 mGy			705 mGy			1624 mGy		
	LAR ^a	mLAR ^b	Excess deaths ^c	LAR ^a	mLAR ^b	Excess deaths ^c	LAR ^a	mLAR ^b	Excess deaths ^c
Overall	35	16	15 (6, 24)	96	44	28 (15, 42)	221	102	79 (62, 99)
Sex									
Females	37	18	14 (5, 22)	101	48	24 (9.8, 39)	232	112	100 (79, 120)
Males	34	15	25 (13, 37)	91	40	34 (14, 55)	210	91	45 (21, 69)
Age at exposure									
Under 40	42	17	24 (16, 33)	114	46	27 (13, 41)	263	107	89 (70, 110)
40–59	14	14	–1 (–18, 15)	39	39	16 (–13, 44)	89	89	40 (4, 75)
60+	11	11	0 (–24, 24)	29	29	90 (35, 150)	68	68	61 (1, 120)

^aLifetime attributable risk, Using the method in the National Academy of Sciences BEIR VII report, applying regression coefficients from the Life Span Study to project excess deaths in a population up to age 100 years for every person.

^bModified lifetime attributable risk, where LAR is calculated to the younger of age 100 or age in 2005

^cCalculated using weighting approach described in the text, 95% confidence intervals reported in parentheses

Table A3

Comparison of lifetime excess deaths from leukemia per 1000 individuals, Japanese population in 1950

	259 mGy			705 mGy			1624 mGy		
	LAR ^a	mLAR ^b	Excess deaths ^c	LAR ^a	mLAR ^b	Excess deaths ^c	LAR ^a	mLAR ^b	Excess deaths ^c
Overall	3	2	1 (–1, 2)	11	9	7 (3, 12)	45	37	26 (19, 34)
Sex									
Females	2	2	1 (0, 3)	9	7	5 (2, 9)	35	30	20 (12, 28)
Males	3	3	0 (–2, 3)	14	11	10 (4, 16)	55	45	33 (22, 44)
Age at exposure									
Under 40	3	2	1 (0, 3)	13	10	10 (6, 14)	51	41	30 (22, 38)
40–59	1	1	0 (–2, 3)	6	6	2 (–3, 7)	25	25	17 (3.6, 30)
60+	1	1	–1 (–2, 1)	6	6	–1 (–2, 1)	22	22	9 (–9, 26)

^aLifetime attributable risk, Using the method in the National Academy of Sciences BEIR VII report, applying regression coefficients from the Life Span Study to project excess deaths in a population up to age 100 years for every person.

^bModified lifetime attributable risk, where LAR is calculated to the younger of age 100 or age in 2005

^cCalculated using weighting approach described in the text, 95% confidence intervals reported in parentheses

Table A4

Excess deaths by 2003 from leukemia and solid cancer per 1000 individuals, Japanese population in 1950

Dose (mGy) ^a			Observed deaths		Excess leukemia deaths (95% confidence intervals)		Excess solid cancer deaths (95% confidence intervals)	
Group	Mean	N ^b	Leukemia	Solid cancer	Non-parametric ^c	MSM ^d	Non-parametric ^c	MSM ^d
0–5	0.96	38509	99	4621	0 (ref)	0 (ref)	0 (ref)	0 (ref)
5–60	16	20966	57	2488	0.3 (–0.8, 1.4)	0.1 (0.0, 0.1)	0 (–6.0, 6.1)	0.8 (0.6, 1.0)
60–100	73	10970	30	1395	–0.3 (–1.4, 1.0)	0.3 (0, 0.7)	0.3 (–7.7, 8.4)	3.8 (3.0, 4.6)
100–500	259	10355	36	1429	0.8 (–0.6, 2.4)	1.5 (0.4, 2.6)	15 (6.5, 24)	13 (11, 16)
500–1000	705	3424	30	519	7.3 (3.5, 12)	6.1 (4.0, 8.5)	28 (15, 42)	35 (28, 43)
1000+	1624	2387	66	477	26 (19, 34)	23 (17, 30)	80 (62, 99)	76 (61, 92)

^aExcess deaths in non-parametric approach evaluated within dose group, excess deaths in MSM evaluated at mean dose for each dose group in the Life Span Study

^bNumber of Life Span Study participants in the given dose group

^cCalculated using weighting approach described in the section *Identification and estimation of functions of survival time*, 95% bootstrap confidence intervals reported in parentheses

^dCalculated using weighting approach described in the section *Inverse probability weighted estimation of a marginal structural rate model*, 95% bootstrap confidence intervals reported in parentheses

Table A5

Estimates from marginal structural excess relative rate models, standardized to the Japanese population in 1950

	ERR ^a	95% confidence intervals ^b
All causes	0.22	(0.19, 0.26)
All solid cancers	0.54	(0.46, 0.63)
Cancers of specific sites		
Esophagus	0.42	(0.05, 0.91)
Stomach	0.38	(0.24, 0.54)
Colon	0.44	(0.16, 0.79)
Rectum	0.13	(–0.17, 0.54)
Liver	0.51	(0.32, 0.73)
Gallbladder	0.87	(0.42, 1.43)
Pancreas	0.25	(–0.02, 0.62)
Other digestive system	1.45	(0.32, 3.36)
Lung	0.80	(0.57, 1.06)
Breast ^c	2.30	(1.46, 3.39)
Uterus ^c	0.13	(–0.17, 0.53)
Ovary ^c	0.84	(0.13, 1.91)
Prostate ^c	0.70	(0.07, 1.6)
Bladder	0.88	(0.18, 1.91)
Kidney	0.74	(0.00, 2.01)
Renal pelvis and ureter	3.43	(1.04, 8.22)

	ERR^a	95% confidence intervals^b
Other solid cancer	0.54	(0.27, 0.87)
Lymphoid and hematopoietic malignancies		
Leukemia	4.63	(3.47, 6.1)
Malignant lymphoma	0.28	(−0.06, 0.75)
Multiple myeloma	0.66	(0.02, 1.78)

^aExcess relative rate

^b95% confidence intervals based on profile, weighted likelihood

^cModels fit among women (breast, uterus, ovary) or men (prostate) only

Figure 1.

Location of survivors on a map of Hiroshima with color denoting estimated radiation doses. (red=1000 mGy; orange=500–1000 mGy; yellow=200–500 mGy; brown=5–100 mGy; pink=5 mGy; gray=unknown). Rings represent 2- and 3-km distances from the hypocenter (+).

Figure 2. Age and sex distributions of (A) the Life Span Study population, a study of survivors of the atomic bomb blasts over Hiroshima and Nagasaki, N=86,611 and (B) the 1950 Japanese population (age distribution in 1945 is shown after subtracting individuals born 1945–1950), N=72 million

Figure 3.

In the 1950 Japanese population, we would expect a background 58-year risk of solid cancer and leukemia mortality of about 12 per 100 (gray figures). Following exposure of the population to 1 Gray, we would expect about 5 excess solid cancer deaths (gray figures with gray stars) and 2 leukemia deaths (gray figures with black stars). Figure based on expected mortality per Gray in the 1+ Gray dose group from the Life Span Study.

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Table 1

Estimated excess cancers by time since exposure. Standardized to the Japanese population of 1950 (Figure 2B).

Years since exposure	Solid Cancer risk (per 1000 people)			Leukemia risk (per 1000 people)		
	Low exposure (0–5 mGy)	High exposure (>1 Gy)	Excess per 1000 (95%CI)	Low exposure (0–5 mGy)	High exposure (>1 Gy)	Excess per 1000 (95%CI)
15	11	15	4 (–0.22, 9.4)	0	12	12 (7.2, 17)
25	26	42	16 (8, 24)	1	16	16 (10, 22)
35	47	76	29 (18, 40)	2	19	17 (14, 23)
45	73	114	41 (28, 55)	2	22	20 (14, 27)
55	107	179	71 (55, 89)	3	26	23 (17, 30)
58	118	197	80 (62, 99)	3	29	26 (19, 34)