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Adjustment of lifetime risks of space radiation-induced cancer by the healthy worker effect and cancer misclassification

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Abstract

Background. The healthy worker effect (HWE) is a source of bias in occupational studies of mortality among workers caused by use of comparative disease rates based on public data, which include mortality of unhealthy members of the public who are screened out of the workplace. For the US astronaut corp, the HWE is assumed to be strong due to the rigorous medical selection and surveillance. This investigation focused on the effect of correcting for HWE on projected lifetime risk estimates for radiation-induced cancer mortality and incidence.

Methods. We performed radiation-induced cancer risk assessment using Poisson regression of cancer mortality and incidence rates among Hiroshima and Nagasaki atomic bomb survivors. Regression coefficients were used for generating risk coefficients for the excess absolute, transfer, and excess relative models. Excess lifetime risks (ELR) for radiation exposure and baseline lifetime risks (BLR) were adjusted for the HWE using standardized mortality ratios (SMR) for aviators and nuclear workers who were occupationally exposed to ionizing radiation. We also adjusted lifetime risks by cancer mortality misclassification among atomic bomb survivors.

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Results. For all cancers combined ("Nonleukemia"), the effect of adjusting the all-cause hazard rate by the simulated quantiles of the all-cause SMR resulted in a mean difference (not percent difference) in ELR of 0.65% and mean difference of 4% for mortality BLR, and mean change of 6.2% in BLR for incidence. The effect of adjusting the excess (radiation-induced) cancer rate or baseline cancer hazard rate by simulated quantiles of cancer-specific SMRs resulted in a mean difference of −1.2% in the all-cancer mortality ELR and mean difference of −6.4% in the mortality BLR. Whereas for incidence, the effect of adjusting by cancer-specific SMRs resulted in a mean change of −14.4% for the all-cancer BLR. Only cancer mortality risks were adjusted by simulated quantiles for misclassification, and results indicate a mean change of 1.1% for all-cancer mortality ELR, while the mean change in the all-cancer PC was approximately 4% for males and 6% for females.

Conclusions. The typical life table approach for projecting lifetime risk of radiation-induced cancer mortality and incidence for astronauts and radiation workers can be improved by adjusting for HWE while simulating the uncertainty of input rates, input excess risk coefficients, and bias correction factors during multiple Monte Carlo realizations of the life table.

Keywords: Mathematical simulation, Epidemiology of cancer, Radiation biology

1. Introduction

Historically, US astronauts have been occupationally exposed to space radiation during low earth orbit (LEO) missions associated with the Mercury, Gemini, Apollo, Skylab, Shuttle, and International Space Station programs [1, 2]. The majority of exposure has been to low-energy geomagnetically-trapped protons residing in the South Atlantic Anomaly and to a lesser degree, relativistic high-energy ions, or galactic cosmic rays (GCR) [3, 4]. Greater exposure to GCR occurred during the cis-lunar transits during the Apollo program, when astronauts were not afforded the protection of the Earth's geomagnetic shielding [5]. The potential for exposure to high-energy protons generated during anomalously large solar particle events (flares) is an additional hazard faced by crewmembers who will leave Earth's geomagnetic shielding during interplanetary travel to Mars [6]. Additional information regarding space radiation exposure and research findings has been reported [7, 8, 9, 10].

Surveillance and mitigation of risks from space radiation exposure are key components of NASA's Human Research Program (HRP) which consists of six elements: space radiation, human health counter-measures, exploration medical capability, space human factors and habitability, and behavioral health and performance [11]. These elements provide the HRP's knowledge and capabilities to

conduct research to address human health and performance risks of spaceflight, and they advance the readiness levels of technology and countermeasures to the point where they can be transferred to the customer programs and organizations. NASA has employed lifetime risk projection for radiation-induced cancer risk since the late 1990s [12], and operationally employs lifetime risk projection for comparing each crewmember's projected upper 95th percentile of radiation-induced cancer mortality risk against the 3% career limit prior to all missions [13, 14, 15, 16, 17]. Historical lifetime risk projections are also made for the entire space radiation exposure history archive, which includes previous space radiation exposures, medical radiation exposures, and research-based exposures such as the Apollo and Skylab era low-microCurie quantity flight-based radiopharmaceutical experiments to establish total body water, red cell mass, and plasma volume [18, 19].

When projecting lifetime risk of radiation-induced cancer for astronauts, the healthy worker effect (HWE) presents a unique challenge, since the cancer mortality rates and vital statistics used are derived from the general public – which are upwardly biased [66, 65]. Therefore, lifetime risk projection for healthy workers requires data that are more amenable for a healthy population – which are essentially non-existent. When compared with the general public, a healthy working population will have less chronic disease, longer survival, and may or may not have less cancer and cardiovascular disease, depending on the constellation of competing causes of death experienced by the cohort. Overall, a healthier working population would have a lower all-cause morbidity (mortality) rate, ultimately shifting events to occur later in life. The HWE, also known as the healthy hired effect and healthy survivor effect, is a bias that causes morbidity or mortality to be lower among workers when compared with the general population, because unhealthy individuals are screened from or leave the workplace [20, 21, 22]. The HWE may persist in a workforce if there are factors related to both the end of employment and morbidity (mortality). In manned space activities, astronaut medical selection screening is far more stringent than typical employee or aviator screening because of the physiological demands associated with microgravity and long-duration operations in a harsh working environment. As such, the HWE is likely to be much stronger among astronaut populations.

Several methods have been recommended for controlling for the HWE in occupational cohort studies [23]. The simplest way to minimize bias in modeled risks due to the HWE is to employ an internal control population which is preferentially unexposed, or at least minimally exposed. Partitioning the data for exposed and internal controls into discrete follow-up periods to control for past exposure and employment history is also beneficial. This can be accomplished by adjusting modeled risks with either a continuously- or ordinally-scaled variable representing employment duration. Controlling for current employment status

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using a covariate for active vs. former employment will also control for employees who leave work due to higher exposures and face a greater risk since they are no longer employed. Restricting an analysis to long-term survivors for which the HWE is believed to be minimal will also filter out employees with short work histories who have a greater propensity for mortality. Exposure can also be lagged so that it is only considered for the healthiest participants.

The standardized mortality ratio (SMR) is defined as the ratio of observed to expected deaths for an occupational cohort, where the number of expected deaths is determined by applying age–gender–birth cohort-specific person-years of follow-up to the relevant national mortality rates for the same age, gender, and calendar period. SMRs are the most reliable metric for worker mortality when an internal control group of non-exposed employees is not available. Table 1 lists all-cause and cancer-specific SMRs for occupational mortality studies of pilots, aircrew, and nuclear workers in the nuclear fuel, nuclear power, and nuclear weapons industries – which are relevant occupations representing aviators and workers who are occupationally exposed to ionizing radiation. (Table 2 lists additional SMRs from a published meta-analysis of nuclear workers [46].) As can be noticed, the majority of SMRs are below unity, suggesting that the mortality experience of the workers studied was lower than the mortality experienced by the general public. The presence of elevated SMRs in a cohort study essentially implies a greater mortality rate in the workers, primarily because of a difference in the pattern of proportional mortality ratios within each population, as there is no reason to expect similarity between disease-specific proportional mortality ratios in a healthy working cohort and general population. The occupational hazards associated with this mixture of industries and professions in Table 1 collectively represent a similar hazard to which astronauts are exposed, namely, the risk of occupationally-related radiation-induced cancer mortality.

The least biased approach for minimizing HWE involves use of an internal control population against which the cancer incidence and mortality of exposed workers is compared. The Longitudinal Study of Astronaut Health (LSAH) makes use of such an internal control population, since it enrolls age–gender–BMI-matched controls for each newly selected astronaut. By 1993, the cancer standardized mortality ratio for astronauts was 0.47 (95% confidence interval (CI): 0.1–1.05), which suggests that cancer mortality in the astronaut cohort is approximately half of that in the general population [47]. However, when comparing the astronaut cohort with the LSAH controls, cancer mortality was nearly 3.5 times greater [48], since the SMR was 3.45 (95% CI: 0.66–7.56). The most recent report [24] on cancer SMR in the LSAH for 1980–2009 still indicates much lower risk of cancer among astronauts (SMR = 0.47, 95% CI: 0.19–0.97)

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Table 1. Standardized mortality ratios (SMR) for aviator and nuclear worker studies.

Type of Worker	All causes	All cancers	Buccal cavity	Esophagus	Stomach	Colon	Rectum	Liver	Pancreas	Respiratory	Larynx	Lung	Bone	Melanoma	Non-melanoma	Female breast	Prostate	Bladder	Kidney	CNS	Thyroid	Non-Hodgkin's	Hodgkin's	Multiple myeloma	Leukemia
US Astronauts [24]	0.59	0.37																							
Aircrew [25]	0.56	0.69	0.27	0.5	0.57	0.92	0.83	0.96	0.84	0.83	0.69	0.43		1.57	0.93		1.23	0.74	0.77	1.14	1.06	0.66	0.67	1.14	0.91
Aircrew-female [26]	0.8	0.78			0.83	0.65	0.58	0.63	0.46			0.82		0.36		1.11				0.67		0.82	1.49		0.99
Aircrew-male [26]	1.09	0.9	1.7	1.11	0.46	0.71	0.72	0.61	1.44			0.75		1.93	9.67		1.09		1.59	0.94		2.28			1.32
Aircrew [27]	0.64	0.68	0.54	0.58	0.48	1.07	0.8	0.86	0.85		0.63	0.53		1.78			0.94		0.59	1.2	1.48	0.71	0.86		1.05
Aircrew [28]	0.63	0.61		0.86	0.57	1.23						0.25		1.49			1.52		1.22	1.42		0.62			0.86
Aircrew-female [29]	0.79	0.79			0.73	0.75		0.86				0.57				1.28				0.82		1.66	2.15		0.79
Aircrew-male [29]	1.1	0.71	1.97			0.63	1.04	1.26	1.62			0.77										2.41			0.78
Aircrew [30]	0.32													1.29						0.6					
Aircrew [30]	0.39													0.67						0.27					
Cockpit [31]	0.49	0.64			0.68	0.85	0.5		1.28			0.33		0.98			0.96		0.79	2.13		1.27			0.61
Cabin-female [31]	0.83	0.95			0.91	1.18	1.09		1.17			1.07				1.17				1.18		1.19			0.88
Cabin-male [31]	1.03	0.89	1.41		0.31	0.63	1.02		1.53			0.74					1.42					4.24			1.55
Cockpit-male [32]	0.48	0.56	0.16	0.46	0.57	0.8	0.6	0.7	1.16		0.87	0.29		0.47			1.26	0.52	0.49	1.68	1.6	0.68			0.69
Cockpit-male [33]	0.7	0.6	2.4			0.9	5.9	1.2	0.8			0.1		4				1		1.8					0.9
Nuclear fuels [34]	0.91	0.93	0.86	1	1.02	0.93	1.09	0.83	0.82	0.93	0.86	0.88	0.64	0.88	0.86	0.84	0.9	0.82	0.87	0.91	1.14	0.85	1.09	0.95	0.91
Nuclear fuels [35]	0.55	0.7			0.56	0.53	1.48	0.44	0.99	0.62	0.55						1.08	0.46	0.76	0.84		1.32		1.06	0.96
Nuclear power [36]	0.41	0.65			0.81	0.75			0.62				1.19				0.6		0.79	0.85				0.63	1.07
Nuclear power [37]	0.5	0.65			0.49	0.7			0.93			0.59					0.64			0.74					1.23
Nuclear power [38]	0.59	0.73		0.37	0.63			0.85	0.88		0.57	0.69	0.6	2.41		1.27	0.87	0.63	1.15	1.12		0.7	1.56	1.57	0.7
Nuclear power [39]					0.7	0.96	0.8		0.93			0.72	0.74			0.89	1	0.7		0.6	1.22	1.07	0.71	0.83	1.23
Nuclear power [40]	0.54	0.65		0.37	0.67	0.72	0.72	0.4	1.1		0.38	0.59					0.8	0.33	0.65	1.71					0.26
Nuclear weapons-no lag [41]			0.22	0.81	0.98	1.27	2.1	1.23	1.5		0.91	0.84		2.19		1.36	1.9	0.69	1.71	0.32	7.4	0.53	0.57	0.62	0.42
Nuclear weapons-10 yr lag [41]			0.31	1.03	1.01	0.92	2.09	1.37	1.24		0.92	0.84		1.36		1.51	2.23	0.7	2.39	0	11.05	0.9	0.5	0.97	0.38
Nuclear weapons [42]	0.9		0.97	0.1	0.6	0.91	0.92	0.96	0.92		0.63	0.91	0.39	1.11		1.01	0.87	0.85	1.08	0.62	0.9	0.97	0.56	1.15	0.77
Nuclear power/weapons [43]	0.99	0.98	1.03		1	0.98	0.95	0.99	0.98			0.96	0.98	0.99		1.06	1.04				0.63	0.95	1.04	1.1	
Nuclear weapons (ORNL) [44]			0.82	1.41	1.08	1.11		0.71	0.91		0.92	1.11					1	0.88	1.07	0.96		0.94		0.85	0.91
Nuclear weapons (SR) [44]			0.51	0.75	0.69	0.84		0.63	0.84		0.5	0.67				0.87	0.88	0.76	1.15	0.9		0.98		0.78	1.02
Nuclear weapons (HAN) [44]			0.64	0.78	0.77	0.88		0.85	0.94		0.41	0.82	0.62			1.03	1.09	0.83	0.82	0.98	1.11	0.99		1.02	0.8
Nuclear weapons (IDS) [44]			0.74	0.57	0.59	0.86		0.65	0.91		0.43	0.88				0.85	1.02	0.84	0.68	1.02		0.91		0.78	1.1
Nuclear weapons [44]			0.49	0.69	0.77	0.71		0.63	0.87		0.58	0.67				0.76	1.06	0.84	0.88	0.94	1.14	1.07		0.74	0.9
Chernobyl (nonexposed) [45]	0.83		0.74	0.96	0.59	0.94	0.71	0.82	0.82		0.51	0.85	0	1.17		1	0.82	0.77	1.08	0.67	0.9	1.14	0.84	1.2	0.76
Chernobyl (combined) [45]	1.06		1.48	1.45	0.6	0.85	1.33	1.28	1.12		0.92	1.05	1.1	0.95		1.03	1	1.02	1.08	0.51	0.9	0.58	0	1.06	0.8

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Table 2. Standardized mortality ratios (SMR) adapted from a meta-analysis of cancer mortality among nuclear workers [46].

Authors*	Lung	Larynx	Esophagus	CNS	Kidney	Bladder
Atkinson et al.	0.75	0.75	0.8	0.75	1.05	
Beral et al.	0.75		0.3	0.65		0.7
Beral et al.	0.75	0.9	0.75	0.75	1.4	0.8
Boice et al.	1.1	2.75	1.25	0.8	1.4	0.7
Carpenter et al.	0.8	0.5	1.15	0.8	1.45	0.5
Checkoway et al.	1.3		0.8	1.75	1.2	0.7
Cragle et al.	0.75		0.5	0.4	0.45	1.9
Dupree-Ellis et al.	1.05	1.1	1.4	1.55	1.2	1.2
Dupree et al.	0.95	4.5				
Fraser et al.	0.75	0.8		0.7	0.75	0.8
Loomis et al.	1.2	0.75	0.45	1.4	1.3	0.75
McGeoghegan et al.	0.8	0.75	0.75	0.6	0.55	0.85
McGeoghegan et al.	0.8	0.65	0.45	1.35	0.5	1.1
Pinkerton et al.	1.2		0.2		0.8	
Ritz et al.	1	1.2	1.2	1.3	0.6	1.2
Ritz et al.	1.05	1.2	1.25	1.4	0.65	1.25
Ritz et al.	0.75	2	1.3	1.4	1.3	0.8

* See original publication [46] for citations for each author group listed.

when compared with the general population. When internal control populations are employed, the HWE may, nevertheless, still continue to operate.

This investigation explored methods to adjust for the HWE during projection of lifetime mortality and incidence risk of radiation-induced cancer for radiation workers in general. Risk coefficients were modeled using data from the Life Span Study (LSS) of 120,000 Hiroshima and Nagasaki atomic bomb survivors [49, 50, 51, 52], made available by the Radiation Effects Research Foundation (RERF) [53]. Because the majority of exposures of LSS survivors involved exposure to prompt γ-rays and neutrons, lifetime risks generated in this study are not directly applicable to risks from particulate space radiation exposure because of differences in bioeffects of γ and neutron radiation and space radiation particles [4]. Additional consideration is required for assumptions regarding the radiation dose and dose-rate effectiveness (DDREF) of various sources of ionizing radiation to which workers are exposed. Because of the complex mixture of particulate radiations in space with varying charge and energy, and the magnitude of analyses required for modeling risks from LSS survivors and correctly applying these risks during lifetime risk projection, we chose to limit our investigation to include generation of risk coefficients and adjustment of lifetime risks by the HWE, cancer mortality misclassification, DDREF, and the latency period after exposure. The following sections address Poisson regression to generate risk coefficients, and life table calculations within a framework of Monte Carlo uncertainty analysis for the purpose of projecting lifetime mortality and incidence risks of radiation-induced cancer.

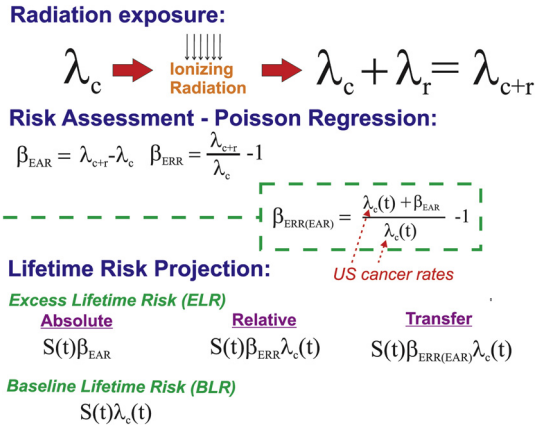

Figure 1. Risk assessment and risk projection framework for the current investigation. An unexposed "zero-dose" population has baseline cancer rate λ_c. Ionizing radiation, a known carcinogen, elevates the baseline cancer rate by inducing an excess risk shown as λ_r. The total risk to the exposed population becomes λ_{c+r} (summation using $c + r$ does not imply additive risk vs. multiplicative risk, but rather, implies risk is greater among the exposed). Poisson regression is used to determine the excess absolute risk β_{EAR}, which is independent of the baseline cancer rate λ_c, as well as excess relative risk, β_{ERR}, which is dependent on the baseline cancer rate. To minimize transfer bias from Japan to the US, the excess absolute risk β_{EAR} (independent of the baseline rate in Japan) is added to the US cancer rate and divided by the US rate to give the relative risk (RR), from which one is subtracted to create a new excess relative risk for the US population, $\beta_{ERR(EAR)}$. Both β_{EAR} and β_{ERR} are specific to age at exposure a and attained age t. Excess lifetime risk (ELR) is determined for the absolute model by multiplying together the life table survivorship function $S(t)$ and β_{EAR}. ELR for the relative and transfer models multiply together $S(t)$, excess relative risk (β_{ERR}, $\beta_{ERR(EAR)}$), and the baseline cancer rate, $\lambda_c(t)$, from US vital statistics, since relative risks depend on the baseline cancer rate. Baseline lifetime risk (BLR) is based on the product of $S(t)$ and $\lambda_c(t)$.

2. Methods

2.1. Risk assessment – Poisson regression

This section describes how risk information needed for projection of lifetime risk of radiation-induced cancer mortality and cancer incidence was derived using Poisson regression of data obtained from the Radiation Effect Research Foundations's (RERF) Lifespan Study (LSS) of 120,000 Hiroshima and Nagasaki atomic bomb survivors [54, 55]. Projection of lifetime risk of radiation-induced cancer for worker populations or medically exposed populations is a common enterprise in the field of radiation protection. Fig. 1 illustrates the framework of risk assessment and risk projection used in this investigation.

Definition of likelihood for Poisson rates. The rate of incidence or mortality, specific to age, gender, and other explanatory variables, is represented by models of two forms:

$$\lambda(d, a, t, \mathbf{z}) = \lambda(a, t, \mathbf{z}) + \epsilon(d, a, t), \tag{1}$$

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or

$$\lambda(d, a, t, \mathbf{z}) = \lambda(a, t, \mathbf{z})[1 + \rho(d, a, t)], \tag{2}$$

or where $\lambda(a, t, \mathbf{z})$ is the background rate at zero dose, d is the dose equivalent in units of Sievert (Sv), a is the age at exposure (years), t is the attained age (years), $\epsilon(d, a, t)$ is the excess absolute risk (EAR/$10^4 n$-Sv) for which n is the person-years of follow-up, and $\rho(d, a, t)$ is the excess relative risk (ERR/Sv). The distinction between these equations is related to how excess risk is expressed, and not so much which representation is true. The models above establish the basis for grouped analysis, since d, a, t are categorical variables derived from models for continuous variables by taking functions as piecewise constant on intervals. For survival data on individuals, the fitted likelihood-based number of cases (deaths) in a group is expressed by the following Poisson regression model

$$c(d, a, t) \sim P[n(d, a, t)\lambda(d, a, t, \mathbf{z})], \tag{3}$$

where $\lambda(d, a, t, \mathbf{z})$ can have either form above.

Fitting generalized models of Poisson rates. Generalized models of Poisson rates were fitted in order to obtain dose-dependent excess absolute risk (EAR) and excess relative risk (ERR) coefficients for lifetime risk projection. Let the gender-specific fitted excess ERR or EAR rate for covariate group j and dose group k be defined as

$$\hat{\lambda}_{jk} = \beta_k x_D \exp\{\beta_a x_{30} + \beta_t x_{70}\}, \tag{4}$$

where j is a combination of age at exposure a and attained age t, β_k is the regression coefficient for dose (Sv) group k, $x_{30} = (a - 30)/10$ is the effect modifier for age at exposure a, β_a is the regression coefficient for age at exposure, $x_{70} = \log(t/70)$ is the effect modifier for attained age t, and β_t is the regression coefficient for attained age.

Poisson regression. Regression coefficients were derived using Poisson regression, for which the gradient update vector at each iteration was determined with the matrix cross-product

$$\boldsymbol{\Delta}\hat{\boldsymbol{\beta}} = (\mathbf{Z}^{\mathrm{T}}\mathbf{W}\mathbf{Z})^{-1}\mathbf{Z}^{\mathrm{T}}\mathbf{W}\mathbf{y}, \tag{5}$$

where the data matrix elements

$$z_{jk} = n_{jk}\frac{\partial g(\mathbf{x}^*_{jk}; \boldsymbol{\beta}^*)}{\partial \boldsymbol{\beta}^*} \tag{6}$$

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are recalculated at each iteration using the generalized fitted rates $g(\mathbf{x}^*_{jk};\boldsymbol{\beta}^*)$, which was equal to $\hat{\lambda}_j + \hat{\lambda}_{jk}$ for EAR models and $\hat{\lambda}_j[1+\hat{\lambda}_{jk}]$ for ERR models. The background rate is given in the form

$$\hat{\lambda}_j = \exp\{\boldsymbol{\beta}^T;\mathbf{x}\}, \tag{7}$$

where $\mathbf{x} = (1, x_{naga}, x_{hiro*nic}, x_{naga*nic}, x_{30}, x^2_{30}, x_{70}, x^2_{70}, \mathrm{I}(t>70)x^2_{70})$ and x_{hiro} and x_{naga} are indicators for city, and x_{nic} is an indicator for ground distance ≥ 3 km. For the leukemia incidence models for males and females $\mathbf{x} = (1, x_{naga}, x_{bc}, x^2_{bc}, x_{30}, x^2_{30}, x_{70}, x^2_{70}, x_{hiro*nic}, x_{naga*nic})$, where $bc = (yob - 1915)/10$ (bc is the birth cohort, and yob is the year of birth). The weights are defined as

$$w_{jk} = (n_{jk}g(\mathbf{x}^*_{jk};\boldsymbol{\beta}^*))^{-1}, \tag{8}$$

and residuals defined as

$$y_{jk} = d_{jk} - n_{jk}g(\mathbf{x}^*_{jk};\boldsymbol{\beta}^*). \tag{9}$$

Iterations started by setting the vector of regression coefficients $\boldsymbol{\beta}$ equal to small near-zero starting values. Successive iterations involved adding the gradient-based update vector to the most recent vector of coefficients in the form

$$\hat{\boldsymbol{\beta}}^{(t+1)} = \hat{\boldsymbol{\beta}}^{(t)} + \boldsymbol{\Delta}\hat{\boldsymbol{\beta}}, \tag{10}$$

until convergence was reached when $\|\boldsymbol{\Delta}\hat{\boldsymbol{\beta}}\| < 10^{-4}$. In most cases, convergence was reached within $T = 50$ iterations.

Poisson regression coefficients and "risk coefficients". The results of a Poisson regression model are the fitted coefficients β_k for radiation dose, β_a for the age at exposure effect modifier, and β_t for the attained age effect modifier for the specific model being fit. There were only two models fitted: excess absolute and excess relative risk, which are defined in (1) and (2). When combining together the coefficients in (4), the result is a function of the excess radiation-induced cancer risk which depends on radiation dose, age at exposure, and attained age. Recall, the generalized cancer rate, $g(\mathbf{x}^*_{jk};\boldsymbol{\beta}^*)$ in the LSS data is fitted, and is equal to $\hat{\lambda}_j + \hat{\lambda}_{jk}$ for EAR models and $\hat{\lambda}_j[1+\hat{\lambda}_{jk}]$ for ERR models. For the EAR model, the "risk coefficient" (not regression coefficient) is represented using the notation $\epsilon(d,a,t) = \hat{\lambda}_{jk}$ and for the ERR model, the notation is $\rho(d,a,t) = \hat{\lambda}_{jk}$. Putting together the previously defined parameters, we have for the EAR model

$$\begin{aligned} g(\mathbf{x}^*_{jk};\boldsymbol{\beta}^*) &= \text{baseline risk} + \text{excess absolute risk} \\ &= \hat{\lambda}_j + \epsilon(d,a,t) \\ &= \hat{\lambda}_j + \hat{\lambda}_{jk} \\ &= \exp\{\boldsymbol{\beta}^T;\mathbf{x}\} + \beta_k x_D \exp\{\beta_a x_{30} + \beta_t x_{70}\}, \end{aligned} \tag{11}$$

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and for the ERR model have

$$\begin{aligned} g(\mathbf{x}^*_{jk};\boldsymbol{\beta}^*) &= \text{baseline risk} \times \text{relative risk} \\ &= \text{baseline risk} \times [1 + \text{excess relative risk}] \\ &= \hat{\lambda}_j[1 + \rho(d,a,t)] \\ &= \hat{\lambda}_j[1 + \hat{\lambda}_{jk}] \\ &= \exp\{\boldsymbol{\beta}^T;\mathbf{x}\}\left[1 + \beta_k x_D \exp\{\beta_a x_{30} + \beta_t x_{70}\}\right]. \end{aligned} \tag{12}$$

The resulting "risk coefficient" for the EAR model is $\epsilon(d,a,t) = \beta_k x_D \exp\{\beta_a x_{30} + \beta_t x_{70}\}$. During lifetime risk projection, the regression coefficients obtained from the fitted EAR model (β_k, β_a, β_t) are multiplied by input values of dose, age at exposure, and attained age to derive a function of EAR whose value changes with attained age. The input value for attained age is based on the specific row being considered of a 1-year complete life table ($t = 1, 2, \ldots, 100$). For the ERR model, the risk coefficient is $\rho(d,a,t) = \beta_k x_D \exp\{\beta_a x_{30} + \beta_t x_{70}\}$, which is determined using regression coefficients obtained from the fitted ERR model (β_k, β_a, β_t), which are multiplied by input values of dose, age at exposure, and attained age to derive a function of ERR whose value changes with attained age. Recall, the EAR and ERR risk coefficients are derived from the LSS data, which is based on Japanese data. Because the EAR model is independent of baseline cancer rates, it can be assumed that EAR coefficients are less biased by baseline cancer rates of the population being studied. However, ERR risk coefficients are a multiple of the baseline cancer rate among the LSS subjects, and therefore are assumed to be more biased when applying them to other populations. For this reason, we introduce (later) a third risk coefficient called the "transfer" coefficient, which is determined by combining the EAR coefficient with cancer rates for the US population to generate a novel type of ERR coefficient for the US population termed "ERR(EAR)."

Goodness-of-fit and regression diagnostics. Record-specific values were generated for the log-likelihood, given as

$$l_{jk} = d_{jk}\log(\hat{d}_{jk}/n_{jk}) - \hat{d}_{jk}, \tag{13}$$

the deviance residual:

$$r_D = d_{jk}\log(d_{jk}/\hat{d}_{jk}) + (\hat{d}_{jk} - d_{jk}), \tag{14}$$

and Pearson residuals:

$$r_P = (d_{jk} - \hat{d}_{jk})^2/\hat{d}_{jk}. \tag{15}$$

Measures of model goodness-of-fit (GOF) were based on the sums $\sum r_D$, $\sum r_P$, which are both χ^2 distributed with $n - p$ degrees-of-freedom (d.f.). Models were assumed to fit if $\sum r_D$ was less than the corresponding d.f., since $\sum r_P$ is more

likely to be biased by sparse information. Overly influential observations were also identified by use of leverage residuals,

$$\mathbf{H} = \mathbf{W}^{1/2}\mathbf{Z}(\mathbf{Z}^{\mathrm{T}}\mathbf{W}\mathbf{Z})^{-1}\mathbf{Z}^{\mathrm{T}}\mathbf{W}^{1/2}, \tag{16}$$

and the change in regression coefficients for removal of any overly influential observation, known as DFBETAS in linear regression, were determined via

$$(\Delta\hat{\boldsymbol{\beta}}^{*})_{-jk} = -(\mathbf{Z}^{\mathrm{T}}\mathbf{W}\mathbf{Z})^{-1}z_{jk}y_{jk}w_{jk}/(1-h_{jk}). \tag{17}$$

Several multicollinearity measures [56] were used to evaluate the degree of between-predictor multicollinearity in each model, which are shown below:

$$q_1 = \sqrt{\frac{(\sum_{j=1}^{p}\lambda_j^2) - p}{p(p-1)}} \qquad q_2 = \left(1 - \frac{\min\{\lambda_j\}}{\max\{\lambda_j\}}\right)^{p+2}, \tag{18}$$

$$q_3 = 1 - \frac{p}{\sum_{j=1}^{p}(1/\lambda_j)} \qquad q_4 = 1 - \sqrt{|\mathbf{R}|}, \tag{19}$$

$$q_5 = \left(\frac{\max\{\lambda_j\}}{p}\right)^{3/2}, \qquad q_6 = \left(1 - \frac{\min\{\lambda_j\}}{p}\right)^{5}, \tag{20}$$

$$q_7 = \sum_{j=1}^{p}\frac{1 - 1/r^{jj}}{p}, \tag{21}$$

where $\lambda_1, \lambda_2, \ldots, \lambda_j, \ldots, \lambda_p$ are eigenvalues of the correlation matrix $\mathbf{R}$, and r^{jj} is the jth diagonal element of the matrix $\mathbf{R}^{-1}$.

Poisson regression input data. Cancer incidence and mortality rate data for LSS atomic bomb survivors were obtained from the RERF [54, 55]. During Poisson regression of ERR and EAR models, deviance and Pearson residuals were calculated, from which GOF was determined. Contour plots of deviance as a function of age at exposure, attained age, and dose for each covariate group (record) were generated and GOF was compared with model degrees of freedom ($n - p$). Leverage residuals were also compared with the criterion $2p/n$, and deletion residuals were compared against $2/\sqrt{n}$. For each model, we also performed logistic regression of leverage-based outliers (yes/no) on background rate covariates for $\hat{\lambda}_j$, in order to address the association between outliers and covariates.

2.2. Risk projection – lifetime risks from life tables

The lifetime mortality risk of multiple exposures to radiation is quantified by applying the risks from each age at exposure to the total force of mortality experienced over a lifetime. In one sense, we are applying radiation risk coefficients obtained from the follow-up of a bona fide exposed cohort to the survival of a theoretically exposed population whose mortality increases

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proportionally with baseline cancer rates (relative projection model) or independently of baseline cancer rates (absolute projection model). The following sections explain succinctly the complexities involved in calculating the lifetime risks of radiation-induced cancer mortality.

2.2.1. Hazard functions for radiation-induced cancer

Assume a complete life table with 1-year age intervals ($t = 1, 2, \ldots, 100$) with a hazard function, $h(t)$, and survivorship function, $S(t)$, at each interval. The hazard function for each age interval under the excess absolute risk (EAR) model is based on the excess absolute risk coefficient (deaths/10^4PY-Sv), $\epsilon(d, a, t)$, at age t for exposure at age a in the absence of baseline cancer rates, given in the form

$$\begin{aligned} h_c(d, a, t) &= \epsilon(d, a, t) \\ &= \beta_k x_D \exp\{\beta_a x_{30} + \beta_t x_{70}\}, \end{aligned} \tag{22}$$

where x_D is a random quantile for radiation dose (Sv), $x_{30} = (a - 30)/10$ for exposure at age a, and $x_{70} = \log(t/70)$ for attained age t.

The "transported" ERR(EAR) excess relative risk hazard function model applies the transported excess relative risk coefficient, $\rho(\epsilon, d, a, t)$, to baseline cancer rates using the relationship

$$h_c(d, a, t) = \rho(\epsilon, d, a, t) h_c(t), \tag{23}$$

where the risk coefficient is determined by applying Japanese LSS excess absolute risk coefficients to the US life table to generate radiation-induced deaths, which are added to baseline cancer deaths among a US population, and divided by baseline cancer deaths to obtain an attained age-specific ERR risk coefficient in the form

$$\begin{aligned} \rho(\epsilon, d, a, t) &= RR - 1 \\ &= \left[\frac{\text{baseline risk} + \text{excess absolute risk}}{\text{baseline risk}}\right] - 1 \\ &= \left[\frac{h_c(t) + \epsilon(d, a, t)}{h_c(t)}\right] - 1 \\ &= \left[\frac{h_c(t) + \beta_k x_D \exp\{\beta_a x_{30} + \beta_t x_{70}\}}{h_c(t)}\right] - 1, \end{aligned} \tag{24}$$

where $h_c(t)$ is the hazard rate for spontaneously occurring cancer at age t generated with cubic splines using 5-year interval number of cancers divided by 10^5, and RR is the relative risk. Any values of ERR(EAR) that were negative after subtracting unity were set to zero.

Finally, the hazard function for radiation-induced cancer at age t from exposure at age a for the excess relative risk (ERR) model is based on the product of the excess relative risk coefficient, $\rho(d, a, t)$, and the baseline cancer rate given as

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$$h_c(d,a,t) = \rho(d,a,t)h_c(t)$$
$$= \beta_k x_D \exp\{\beta_a x_{30} + \beta_t x_{70}\} h_c(t), \quad (25)$$

where $\rho(d,a,t)$ is the excess relative risk at age t for exposure at age a.

2.2.2. Life table

To begin life table calculations, we first set the number at risk at the beginning of the interval starting at the age at exposure a equal to $l(a) = 100{,}000$, assuming a population of 100,000 are exposed. We recall that for a "double-decrement" life table [60] the conditional death probability, $q(t)$, in age interval $(t, t+1)$ due to the combination of death from all causes and deaths due to radiation-induced cancer is

$$q(t) = \frac{2(h(t) + h_c(d,a,t))}{2 + (h(t) + h_c(d,a,t))}, \quad (26)$$

where $h(t)$ is the age-specific central death rate due to all causes in the absence of exposure and $h_c(d,a,t)$ is the age-specific central death rate for cancer due to radiation exposure (see the next section for notation regarding calculation of $q(t)$ from central death rates used in national registries and longitudinal studies with rates based on cases/person-years). The conditional probability that an individual will not die in the interval $(t, t+1)$ is

$$p(t) = 1 - q(t), \quad (27)$$

and the number of expected cases (deaths) from all causes in the absence of exposure and radiation-induced cancer is

$$c(t) = q(t)l(t), \quad (28)$$

where $l(t)$ is the number of individuals alive at the beginning of interval $(t, t+1)$. The number of survivors of interval $(t, t+1)$ at risk at the beginning of the next interval is found recursively as

$$l(t) = l(t-1) - c(t-1), \quad (29)$$

and the number of person-years in each interval $(t, t+1)$ is approximated by

$$L(t) = l(t) - \frac{1}{2}c(t). \quad (30)$$

The survivorship function [61, 62, 63, 64] or cumulative probability of surviving beyond each interval is estimated with the equation

$$S(t) = l(t)/l(a), \quad (31)$$

which is used for estimating the lifetime risks of radiation-induced cancer in an exposed working population.

Expected fraction of *n* years of life. The theoretical rationale for using Equation (26) is described in this section. Central death rates and cancer rates $\lambda(t)$ obtained from RERF [53], CDC Wonder [66], or the National Center for Health Statistics [65] are based on cases per population (person-years). Under this assumption, the rate in interval $(t, t+1)$ is defined as $\lambda(t) = d(t)/L(t)$, where $d(t)$ is the number of deaths and $L(t)$ is the number of person-years that $l(t)$ subjects are expected to live in the interval. Central death rates make no assumption about a uniform death rate within the interval $(t, t+1)$, and therefore the number dying in the first half of an interval is not equal to the number dying in the second half, since it is unknown. In complete (abridged) life tables, however, the instantaneous death rate is assumed to be uniform within each interval, and therefore the conditional probability of death $q(t) = d(t)/l(t)$ is used, where $l(t)$ is the number of subjects alive at exactly time t at the beginning of the interval.

Let ${}_na_t$ be the expected (average) number of years lived by an individual of age t who dies in age interval $(t, t+n)$, and let

$$ {}_nf_t = \frac{1}{n}{}_na_t \tag{32} $$

be the fraction of the last n years lived in this interval. The total number of expected years lived in interval $(t, t+n)$ by l_t subjects of age t over the years t to $t+n$ is ${}_nL_t$, which is comprised of n years for each l_{t+n} survivors and ${}_na_{tn}d_t$ average years for individuals who die in $(t, t+n)$, given as

$$ \begin{aligned} {}_nL_t &= nl_{t+n} + {}_na_{tn}d_t \\ &= n\left[l_t - (1 - {}_nf_t)_nd_t\right]. \end{aligned} \tag{33} $$

Solving for l_t, we get

$$ l_t = \frac{1}{n}\left[{}_nL_t + n(1 - {}_nf_t)_nd_t\right]. \tag{34} $$

Rearranging the central death rate, we have ${}_nd_t = {}_nL_{tn}\lambda_t$, and upon substitution of the number of deaths into the conditional death probability, we obtain

$$ \begin{aligned} {}_nq_t &= \frac{{}_nd_t}{{}_nl_t} \\ &= \frac{{}_nd_t}{\frac{1}{n}\left[{}_nL_t + n(1 - {}_nf_t)_nd_t\right]} \\ &= \frac{{}_n\lambda_t}{\frac{1}{n}\left[1 + n(1 - {}_nf_t)_n\lambda_t\right]}. \end{aligned} \tag{35} $$

By assuming a uniform distribution of the time of death over the interval $(t, t+n)$, we get ${}_na_t = \frac{n}{2}$, or $f = \frac{1}{2}$. When $n = 1$ year, we now have

$$q(t) = \frac{\lambda(t)}{1 + \frac{1}{2}\lambda(t)} = \frac{2\lambda(t)}{2 + \lambda(t)}, \tag{36}$$

which is the necessary transformation when using central death rates (person-year based rates) in a complete (abridged) life table. The next two sections describe the method for obtaining lifetime risks.

Excess lifetime risk (ELR) of radiation-induced cancer. The conditional probability of death due to radiation-induced cancer is estimated using the formula

$$\pi(d, a, t) = h_c(d, a, t)S(t), \tag{37}$$

where $h_c(d, a, t)$ is the hazard function and $S(t)$ is the survivorship function for the exposed population. Over a lifetime, the unconditional probability of radiation-induced cancer mortality (excess lifetime risk, *ELR*) for the annual dose received at age a is given as

$$ELR = \pi(a, d) = \frac{\int_{t=a}^{100} \pi(d, a, t)dt}{DDREF}. \tag{38}$$

The number of radiation-induced cancer deaths (per 10^5 exposed individuals) is $\pi(a, d) \times 10^5$.

Baseline lifetime risk (BLR) of cancer. The lifetime risk of spontaneously occurring (baseline) cancer is determined for comparative purposes, especially when calculating the probability of causation. For baseline risks, a different form of the conditional death probability in interval $(t, t + 1)$ is used:

$$q(t) = \frac{2h(t)}{2 + h(t)}. \tag{39}$$

The conditional probability of death due to spontaneously occurring cancer at age t is estimated using the formula

$$\pi(t, 0) = h_c(t)S(t), \tag{40}$$

where $h_c(t)$ is the hazard function for spontaneous cancer and $S(t)$ is the survivorship function determined when Eq. (39) is used for all life table calculations. The unconditional probability of spontaneously occurring cancer in the comparison nonexposed population over a lifetime (baseline lifetime risk, *BLR*) beginning at age a is

$$BLR = \pi(a, 0) = \int_{t=a}^{100} \pi(t, 0)dt. \tag{41}$$

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The number of baseline cancer deaths in the nonexposed population (per 10^5 individuals) is $\pi(a,0) \times 10^5$.

Probability of causation. Sometimes it is useful to determine the attributable risk caused by one or more radiation exposures. In principle, the attributable risk or probability of causation (PC) is defined as the fraction of radiation-induced cancer deaths out of the total cancer deaths in an exposed population. Using the lifetime risks of radiation-induced cancer explained earlier, the lifetime PC is calculated with the equation

$$PC = \frac{\pi(a,d)/\pi(a,0)}{1 + (\pi(a,d)/\pi(a,0))}. \tag{42}$$

2.2.3. Correction factors

Correction factor for the healthy worker effect. This section describes empirical cumulative distribution fitting (ECDF) of SMRs in order to obtain smooth pdfs, which were employed during simulation. Particle swarm optimization (PSO) was employed for ECDF of SMR values in columns of Tables 1 and 2 [57, 58]. For each set of SMR values in each column of Table 1, SMRs were sorted in ascending order and their percentiles determined, which were assumed to represent ecdf values in the range [0, 1]. ECDF was performed using a variety of probability distributions including beta, normal, log-normal, chi-squared, gamma, F-ratio, Rayleigh, power, logistic, Laplace, and triangle. Let the position (solution) vector for chromosome (particle) l be $\mathbf{r}_l(t) = (r_{1l}, r_{2l}, \ldots, r_{pl})$ and velocity vector for chromosome l be $\mathbf{v}_l(t) = (v_{1l}, v_{2l}, \ldots, v_{pl})$, where p is the number of parameters. The majority of the cdfs fitted had two parameters ($p = 2$): location, a, and scale, b. In addition, let $\mathbf{b}_l = \mathbf{p}_l(t)$ be the best chromosome-specific solution vector ever observed throughout all generations, and let $\mathbf{b}_g = \mathbf{p}_l(t)$ be the best solution vector ever observed throughout all generations. Initialize the position vector elements for all chromosomes with random uniform variates $U(0,1)$, and set the velocity vector elements for all chromosomes to zero. The velocity update for each chromosome is

$$\mathbf{v}_l(t+1) = w\mathbf{v}_l(t) + c_1 U(0,1) \otimes (\mathbf{b}_l - \mathbf{r}_l(t)) + c_2 U(0,1) \otimes (\mathbf{b}_g - \mathbf{r}_l(t)), \tag{43}$$

where w is the *inertia factor*, c_1 is the cognitive parameter and c_2 is the social parameter, $\mathbf{b}_l$ is the best historical fitness for chromosome l, and $\mathbf{b}_g$ is the global best chromosome. The inertia at iteration t is $w(t) = w_{start} - (w_{start} - w_{end})t/T_{max}$. After updating $\mathbf{v}_l(t)$ for each chromosome, the chromosome solution vector update is $\mathbf{r}_l(t+1) = \mathbf{r}_l(t) + \mathbf{v}_l(t+1)$. Parameter values for PSO were set to: #chromosomes = 50, $v_{min} = -0.05$, $v_{max} = 0.05$, $c_1 = 2$, $c_2 = 2$, $w_{min} = 0.4$, and $w_{max} = 0.9$. A total of $T_{max} = 200$ generations were used for fitness calculations.

Table 3. Cumulative distribution functions (CDF) which were fitted to empirical cumulative distributions of SMRs.

Distribution	CDF
Beta	$F(x) = I_x(a, b)$ (Incomplete beta)
Chi-squared	$F(x) = \frac{\Gamma(\frac{\nu}{2}, \frac{\chi^2}{2})}{\Gamma(\frac{\nu}{2})}$ (Incomplete gamma)
F-ratio	$F(x) = 1 - I_x\left(\frac{\omega}{2}, \frac{\nu}{2}\right)$ $x = \omega/(\omega + x\nu)$ (Incomplete beta)
Gamma (Erlang)	$F(x) = 1 - \exp(-x/b)\left[\sum_{i=0}^{c-1} \frac{(x/b)^i}{i!}\right]$
Laplace	$F(x) = \begin{cases} \frac{1}{2}\exp(-(x-a)/b) & \text{if } x < a \\ 1 - \frac{1}{2}\exp(-(x-a)/b) & \text{if } x \geq a \end{cases}$
Logistic	$F(x) = 1 - 1/(1 + \exp((x-a)/b))$
Log-normal	$F(x) = \frac{1}{2}\left[1 + \text{erf}\left(\frac{\log(x)-\mu}{\sigma\sqrt{2}}\right)\right]$
Normal	$F(x) = \frac{1}{2}\left[1 + \text{erf}\left(\frac{x-\mu}{\sigma\sqrt{2}}\right)\right]$
Rayleigh	$F(x) = 1 - \exp(-x^2/(2b^2))$
Student's t	$F(x) = 1 - I_x\left(\frac{\nu}{2}, \frac{1}{2}\right)$ $x = \nu/(\nu + t^2)$ (Incomplete beta)
Triangle	$F(x) = \begin{cases} (x-a)^2/(b-a)(c-a) & \text{if } x \geq a, x \leq c \\ = (b-x)^2/(b-a)(b-c) & \text{if } x \geq c, x \leq b \end{cases}$

ECDF function approximation was based on each chromosome's solution vector (location and scale) and fitness was determined as $1/MSE$ for chromosome l, where MSE is

$$MSE_l = \frac{1}{2}\sum_{i=1}^{n}(\hat{F}_{il} - F_i)^2, \tag{44}$$

where n is the number of SMR values for the cancer considered, $\hat{F}_{il}$ is the predicted cdf value for the ith SMR value based on chromosome l's current location and scale values, and F_i is the observed ecdf value for the corresponding ith SMR value. In other words, F was approximated using the individual SMRs as the x-value in the form $F(x, location, scale)$, where location and scale were the relevant chromosome's solution vector. Fitness was summed over the SMR samples during each generation. The probability distribution with chromosomes presenting the greatest global fitness value was taken as the best-fitting distribution, where location and scale were based on the global best solution, $\mathbf{b}_g$. Descriptions of the various cdfs evaluated are listed in Table 3.

Once the best fitting distribution was determined for each fit, the parameters of the specific distribution were used for simulation of quantiles from the given distribution (see Monte Carlo section).

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Correction factor for misclassification of radiation-induced cancer mortality. Confirmation and detection rates for various cancers were obtained from RERF Pathology report 4, which summarizes statistics acquired from the RERF Autopsy Program [59]. Cause of death among autopsied LSS survivors were compared with underlying cause of death on death certificates identified at the survivors' local *koseki seido* (household registration system). The cancer confirmation rate, θ, is equal to the number of cases with agreement between death certificate and autopsy, divided by the number of death certificates with the given cancer listed as the underlying cause of death. Whereas the detection rate, ϕ, was the number of cases with agreement divided by the number of autopsy cases for the given cancer. Let p represent either rate, $q = 1 - p$, and n the number of cases in agreement. The standard error of each rate was then taken as $\sqrt{pq/n}$. We determined the degree of misclassification as the ratio $\psi = \theta/\phi$, which is greater than one if the cancer was under-reported, and less than one if the cancer was over-reported. The quadrature sum of error of the ratio formed the standard error of the rate, that is, $\sigma_\psi = \sqrt{\sigma_\theta^2 + \sigma_\phi^2}$. We assumed that the correction factors were normally distributed with mean ψ and standard deviation σ_ψ, and these parameters were used for simulation of quantiles for the assumed distributions during Monte Carlo analyses (see next section). Recall, correction factors ψ are only applied to radiation-induced ELR for cancer mortality, since they are representative of mortality statistics for the LSS data.

2.2.4. Monte Carlo uncertainty analysis of lifetime risks

A commonly used approach for using Monte Carlo simulation to determine uncertainty in lifetime risks is to input fixed values of Poisson regression coefficients, fixed values of dose, fixed values of age-specific all-cause death rates, and fixed value of age-specific cancer rates directly into life tables, along with uncertainty distributions for transfer of risk, dosimetry error, etc (see Fig. 2). The current approach used in this investigation simulates the uncertainty in the distributions of all input data, and applies randomly drawn quantiles from each distribution into a life table. In the commonly used approach, the uncertainty distributions are independent of life table input data, which allows investigators to multiply life table results (lifetime risks) by random quantiles from uncertainty distributions in order to obtain uncertainty in lifetime risk. However, under the current approach, the uncertainty data are heavily based on life table inputs and since the survivorship function is recursively derived, the uncertainty simulations need to be performed before each life table is calculated.

Simulating uncertainty in age-specific all-cause death rates. Random quantiles for the number of cases (deaths) $c(t)$ ($t = 1, 2, \ldots, 100$) in each 1-year

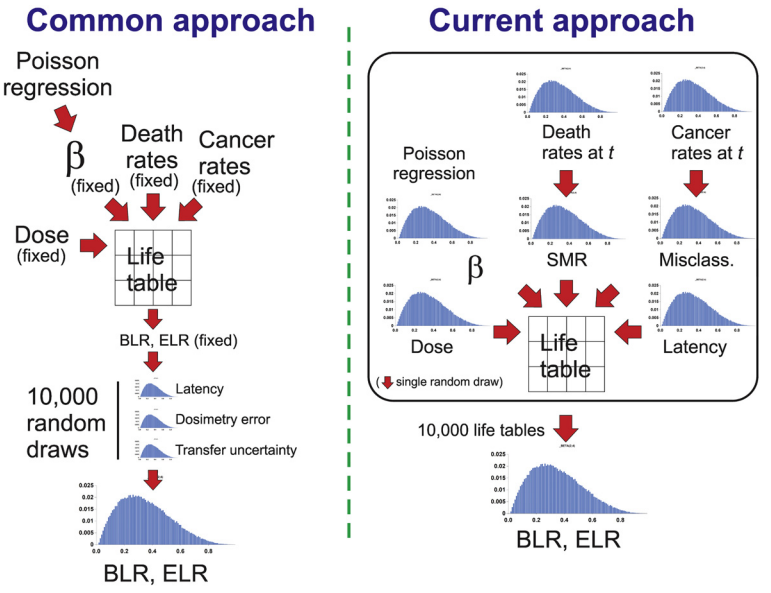

Figure 2. Monte Carlo uncertainty analyses framework for current investigation. The workflow illustrates that in the common approach, the uncertainty in lifetime risks (life table results) are derived from application of uncertainty distributions for latency, dosimetry error, and transfer of risk from Japan to the US directly to lifetime risks form the life table. However, in the current investigation, each life table calculation is based on random quantiles drawn from the distribution of each life table input. BLR and ELR represent baseline lifetime risk and excess lifetime risk.

interval of the US life table [65] were obtained by use of a normal approximation to a binomial proportion, $B(n, p)$, where

$$\begin{aligned}\mu &= np \\ &= L(t)\frac{c(t)}{L(t)} \\ &= c(t)\end{aligned} \tag{45}$$

and

$$\begin{aligned}\sigma &= \sqrt{npq} \\ &= \sqrt{L(t)\frac{c(t)}{L(t)}\left(1-\frac{c(t)}{L(t)}\right)} \\ &= \sqrt{c(t)\left(1-\frac{c(t)}{L(t)}\right)},\end{aligned} \tag{46}$$

and $L(t)$ is the number of person-years for age interval t. As long as $\min(np, nq) > 10$, we simulated the number of deaths $c(t)$ with a normal approximation of the binomial as

$$x_c(t) \sim N(c(t), \sqrt{c(t)(1-c(t)/L(t))}). \tag{47}$$

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If $\min(np, nq) \leq 10$ then the geometric distribution method was used to generate a binomially distributed quantile for death that is $B(n, p)$. In order to generate the simulated life table with deaths $x_c^{(b)}(t)$ in each interval t, however, we must use two life tables. The first life table provides the $\mu = c(t)$ and standard deviation $\sigma = (c(t)(1 - (c(t)/L(t))))^{1/2}$ from the observed data with which we generate the pseudo-random quantiles $x_c^{(b)}(t)$. The second life table recursively keeps track of the simulated number at risk in each $t + 1$th interval by subtracting $x_c^{(b)}(t)$ from $L(t)$. The simulated quantile at each iteration for the hazard rate of all-cause deaths is determined from the simulated life table with the form

$$x_\lambda^{(b)}(t) = \frac{x_c^{(b)}(t)}{L(t)} \tag{48}$$

which is used later during generation of survivorship functions.

Simulating uncertainty in the baseline cancer mortality and incidence rates. We simulated uncertainty in baseline cancer rates obtained from CDC WONDER [66]. Let $c(k)$ be the number of cases in each 5-year age category ($k = 2, 7, \ldots, 97$), and let $L(k) = 100{,}000$ be the total number of person-years at risk in each 5-year age category. To simulate the uncertainty in $c(k)$, we use the normal approximation to a binomial proportion, $B(n, p)$, where

$$\begin{aligned} \mu &= np \\ &= L(k)\frac{c(k)}{L(k)} \\ &= c(k) \end{aligned} \tag{49}$$

and

$$\begin{aligned} \sigma &= \sqrt{npq} \\ &= \sqrt{L(k)\frac{c(k)}{L(k)}\left(1 - \frac{c(k)}{L(k)}\right)} \\ &= \sqrt{c(k)\left(1 - \frac{c(k)}{L(k)}\right)}. \end{aligned} \tag{50}$$

Again, as long as $\min(np, nq) > 10$, we simulated the number of cases $c(k)$ with a normal approximation of the binomial as

$$x_c^{(b)}(k) \sim N(c(k), \sqrt{c(k)(1 - c(k)/L(k))}). \tag{51}$$

If $\min(np, nq) \leq 10$ then the geometric distribution method was used to generate a binomially distributed quantile for cases that is $B(n, p)$. If $p < 0.1$ and $np < 10$, then $P(\lambda)$ is used to approximate $B(n, p)$, using mean $\lambda = np$. Random quantiles for the number of cases in each 5-year age group were then input into cubic splines to interpolate the number of cases for each 1-year age interval from 1 to 100. After

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cubic splines, the simulated 1-year hazard rate at each iteration for baseline cancer is based on

$$x_{\lambda,c}^{(b)}(t) = \frac{x_c(t)}{100{,}000}. \tag{52}$$

Simulating uncertainty in radiation dose, risk coefficients, latency period, and dose and dose rate effectiveness. We also simulated random quantiles for radiation dose for exposure at age a using a normal distribution with mean 1 Sv and standard deviation 0.1 Sv, that is $N(1, 0.1)$. Correlated random quantiles of the regression coefficients β_k, β_a, and β_t were also generated as

$$(\hat{\beta}_k, \hat{\beta}_a, \hat{\beta}_t)^T = \mathbf{V}(\boldsymbol{\beta})^{1/2}\mathbf{z} + \boldsymbol{\beta}, \tag{53}$$

where $\mathbf{V}(\boldsymbol{\beta})^{1/2}$ is the square root matrix of the variance-covariance matrix for regression coefficients from the EAR or ERR Poisson regression model, $\mathbf{z}$ is a random vector of standard normal variates, and $\boldsymbol{\beta}$ are the point estimates of fitted Poisson regression coefficients. The resulting correlated random quantiles for regression coefficients $(\hat{\beta}_k, \hat{\beta}_a, \hat{\beta}_t)^T$ were combined with values for x_D, x_{30}, and x_{70} for each row in the life table to determine the risk coefficient λ_{jk} (Eq. (4)).

The latency period, which is a lagged period when risks are gradually phased in, was simulated as

$$x(t)_{latency}^{(b)} = \frac{1}{1 + \exp(-\frac{\delta t - \mu}{s})}, \tag{54}$$

where δt is the time since exposure at age a, μ is a random variate from the triangle distribution $TRI(5, 7.5, 20)$ for solid cancers and $TRI(2, 2.25, 2.5)$ for leukemia, and S is a shape parameter that enforces risks to be phased in from 0.1 to 0.99 from 4 to 11 years post exposure for solid cancers and from 0.4 to 4.1 years for leukemia [67].

Exposure scenarios. We simulated radiation exposures to 1 Sv for males and females (all races) at ages of 35, 45, or 55 and projected lifetime risks (excess and baseline) using 10,000 life tables with all possible combinations of adjustments by all-cause SMRs (mortality and incidence), cancer-specific SMRs (mortality and incidence), and correction for misclassification (mortality). Most lifetime risk projection studies for radiation-induced cancer report results in units of risk/Sv or %/Sv, so we used a dose of 1 Sv. This was also not a dosimetry investigation or study to project lifetime risks based on radiation doses for historical or planned missions. Outputs for the median and 5th and 95th percentiles of ELR, PC, and BLR are provided for the EAR, ERR(EAR), and ERR models as well as a mixture model ("MIX") where all 30,000 quantiles from EAR, ERR(EAR), and ERR models were combined, sorted in ascending order, and listed in the form of the

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median and 5th and 95th percentiles in tabular notation in the results section. Multiple linear regression analysis was performed for each cancer site for which we regressed ELRs, PCs, or BLRs, on age at exposure (35,45,55), and dummy indicators for applying all-cause SMRs, cancer-specific SMRs, misclassification, and female gender. We multiplied the linear regression coefficient for age at exposure by 10, to reflect the mean change in each dependent variable for a 10-year increase in age at exposure. The regression coefficients are reported in the results along with their z-scores reflecting significance (i.e., $\beta_j / s.e.(\beta_j)$).

Monte Carlo simulation of life table inputs. We employed $B = 10{,}000$ Monte Carlo iterations for uncertainty estimation. At each bth iteration, random quantiles of all-cause death rates and cancer rates were generated for each 1-year age interval in the life table. When random quantiles for all-cause SMRs were applied to adjust for the all-cause HWE, $x^{(b)}_{smrac}$, a single quantile was multiplied by all of the random quantiles for age-specific all-cause death rates, $x^{(b)}_{\lambda}(t)$. When projecting BLR, a single random quantile for each cancer-specific SMR, $x^{(b)}_{smrca}$, was multiplied by each age-specific cancer rate, $x^{(b)}_{\lambda,c}(t)$, during integration to obtain BLR. The entire life table calculation resulted in a subjective realization for baseline lifetime risk, $x^{(b)}_{BLR}$. When projecting ELR, random quantiles for cancer-specific SMRs, $x^{(b)}_{smrca}$, age-specific latency, $x(t)^{(b)}_{latency}$, and correction for cancer misclassification, $x^{(b)}_{\psi}$, were directly multiplied by the radiation-induced cancer hazard function, $h_c(d, a, t)$. Since the EAR model does not use baseline cancer rates, adjustment for cancer-specific SMRs and cancer misclassification must be applied to the radiation-induced hazard function $h_c(d, a, t)$ in order to affect radiation-induced cancer risk. As such, we employed this approach for all excess cancer risk models (EAR, ERR(EAR), and ERR). The entire life table calculation resulted in a subjective realization for lifetime risk from radiation exposure, $x^{(b)}_{rsk}$, which was divided by the random quantile for DDREF, $x^{(b)}_{ddref}$ (distributed $LN(1.5, 1.35)$) in the form

$$x^{(b)}_{ELR} = x^{(b)}_{rsk} / x^{(b)}_{ddref}. \tag{55}$$

The quantile for the PC was obtained using the relationship

$$x^{(b)}_{PC} = \frac{x^{(b)}_{ELR} / x^{(b)}_{BLR}}{1 + \left(x^{(b)}_{ELR} / x^{(b)}_{BLR} \right)}. \tag{56}$$

Median values and 5th and 95th percentiles were obtained for $x^{(b)}_{BLR}$, $x^{(b)}_{ELR}$, and $x^{(b)}_{PC}$. Fig. 3 lists the computational workflow used for $B = 10{,}000$ life table calculations for age at exposure- and gender-organ-specific BLR, ELR, and PC.

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Data: US life table: Gender-specific all-cause death rate, $\lambda(t)$, at age t, person-years at risk $L(t)$, organ-gender-specific cancer rate $\lambda_c(t)$
1. Determine gender- and age-at(time-since)-exposure-specific EAR and ERR Poisson regression coefficients for each cancer. Save regression coefficients $\boldsymbol{\beta}$ and variance-covariance matrix of coefficients, $\mathbf{V}(\boldsymbol{\beta})$
2. **Initialize:** a=age at exposure, $T = 100$, $G = 2$ genders, $L = \#organs$, M=3 models [1-EAR, 2-ERR(EAR), 3-ERR], B=10,000 life tables
for $gender \leftarrow 1$ **to** G **do**
  for $organ \leftarrow 1$ **to** L **do**
    for $model \leftarrow 1$ **to** M **do**
      for $b \leftarrow 1$ **to** B **do**
        Draw random all-cause SMR $\leftarrow x_{smrac}^{(b)}$ from best fitting distribution
        For this *organ*, draw random cancer-specific SMR $\leftarrow x_{smrca}^{(b)}$ from best fitting distribution
        Draw random cancer misclass. factor, $x_{\psi}^{(b)} \sim N(\psi, \sigma_{\psi})$
        for $t \leftarrow a$ **to** T **do**
          $x_{\lambda}^{(b)} \sim N(np, \sqrt{npq})$ $(p = \lambda(t), n = L(t)$; random gender-age-specific all-cause death rate)
          $h(t) = x_{\lambda}^{(b)} x_{smrac}^{(b)}$ (adjusts death rate for HWE)
          $h_c(t) \leftarrow x_{\lambda,c}^{(b)} \sim N(np, \sqrt{npq})$ $(p = \lambda_c(t), n = 10^5$; random gender-age-specific cancer rate)
        endfor
        $l(a) = 100,000$
        for $t \leftarrow a$ **to** T **do**
          $q(t) = \frac{2h(t)}{2+h(t)}$
          $p(t) = 1 - q(t)$
          $c(t) = q(t)l(t)$
          $l(t) = l(t-1) - c(t-1)$
          $S(t) = l(t)/l(a)$
        endfor
        $x_{BLR}^{(b)} = \pi(a,0) = \int_{t=a}^{100} h_c(t) x_{smrca}^{(b)} S(t) dt$
        Draw random dose, $d(a) \leftarrow x_d^{(b)} \sim N(1, 0.1)$
        Draw random value of DDREF, $x_{ddref}^{(b)} \sim LN(1.5, 1.35)$
        Draw random mean of latency period, $x_{\mu}^{(b)} \sim TRI(5, 7.5, 20)$
        for $t \leftarrow a$ **to** T **do**
          $\delta t = t - a$
          $x(t)_{latency}^{(b)} = \left[1/(1 + \exp(-(\delta t - x_{\mu}^{(b)})/s)\right]$
        endfor
        if *model* =1 (EAR) **then**
          Fetch EAR $\boldsymbol{\beta}$ and $\mathbf{V}(\boldsymbol{\beta})$ for this gender-organ
          Generate random set of correlated EAR regression coefficients, $(\hat{\beta}_k, \hat{\beta}_a, \hat{\beta}_t)^T = \mathbf{V}(\boldsymbol{\beta})^{1/2}\mathbf{z} + \boldsymbol{\beta}$
          for $t \leftarrow a$ **to** T **do**
            $\epsilon(d,a,t) \leftarrow \hat{\lambda}_{jk}^{(b)} = \hat{\beta}_k d(a) \exp\{\hat{\beta}_a(a-30)/10 + \hat{\beta}_t \log(t/70)\}$
            $h_c(d,a,t) = \epsilon(d,a,t)$
          endfor
        endif
        if *model* = 2 (ERR(EAR)) **then**
          Fetch EAR $\boldsymbol{\beta}$ and $\mathbf{V}(\boldsymbol{\beta})$ for this gender-organ
          Generate random set of correlated EAR regression coefficients, $(\hat{\beta}_k, \hat{\beta}_a, \hat{\beta}_t)^T = \mathbf{V}(\boldsymbol{\beta})^{1/2}\mathbf{z} + \boldsymbol{\beta}$
          for $t \leftarrow a$ **to** T **do**
            $\epsilon(d,a,t) \leftarrow \hat{\lambda}_{jk}^{(b)} = \hat{\beta}_k d(a) \exp\{\hat{\beta}_a(a-30)/10 + \hat{\beta}_t \log(t/70)\}$
            $\rho(\epsilon,d,a,t) = \left[\frac{h_c(t)+\epsilon(d,a,t)}{h_c(t)}\right] - 1$
            $h_c(d,a,t) = \rho(\epsilon,d,a,t) h_c(t)$
          endfor
        endif
        if *model* =3 (ERR) **then**
          Fetch ERR $\boldsymbol{\beta}$ and $\mathbf{V}(\boldsymbol{\beta})$ for this gender-organ
          Generate random set of correlated ERR regression coefficients, $(\hat{\beta}_k, \hat{\beta}_a, \hat{\beta}_t)^T = \mathbf{V}(\boldsymbol{\beta})^{1/2}\mathbf{z} + \boldsymbol{\beta}$
          for $t \leftarrow a$ **to** T **do**
            $\rho(d,a,t) \leftarrow \hat{\lambda}_{jk}^{(b)} = \hat{\beta}_k d(a) \exp\{\hat{\beta}_a(a-30)/10 + \hat{\beta}_t \log(t/70)\}$
            $h_c(d,a,t) = \rho(d,a,t) h_c(t)$
          endfor
        endif
        if *cancer mortality* **then**
          $h_c(d,a,t)* = x_{\psi}^{(b)}$
        endif
        $l(a) = 100,000$
        for $t \leftarrow a$ **to** T **do**
          $h_c(d,a,t)* = x(t)_{latency}^{(b)} x_{smrca}^{(b)}$
          $q(t) = \frac{2(h(t)+h_c(d,a,t))}{2+(h(t)+h_c(d,a,t))}$
          $p(t) = 1 - q(t)$
          $c(t) = q(t)l(t)$
          $l(t) = l(t-1) - c(t-1)$
          $S(t) = l(t)/l(a)$
        endfor
        $x_{ELR}^{(b,m)} = \pi(a,d) = \frac{\int_{t=a}^{100} h_c(d,a,t) S(t) dt}{x_{ddref}^{(b)}}$
        $x_{PC}^{(b,m)} = \frac{\pi(a,d)/\pi(a,0)}{1+(\pi(a,d)/\pi(a,0))}$
      endfor
      Sort $x_{BLR}^{(b)}, x_{ELR}^{(b,m)}$, and $x_{PC}^{(b,m)}$, determine p5,p50,p95
    endfor
    Generate mixture models:
    Combine all $3B$ values of $ELR^{(b,m)}$ for the 3 models, sort, get p5,p50,p95
    Combine all $3B$ values of $PC^{(b,m)}$ for the 3 models, sort, get p5,p50,p95
  endfor
endfor

Figure 3. Algorithm for Monte Carlo lifetime risks.

3. Results

Results from Poisson regression were not the primary outcome of this investigation, and therefore, the fitted EAR and ERR Poisson regression coefficients for cancer mortality among male and female LSS survivors are listed in Supplementary material Tables S1–S4. The Fitted EAR and ERR regression coefficients for cancer incidence for LSS males and females are listed in Supplementary material Tables S5–S8. The majority of Poisson regression models

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converged within 50 iterations, which was a positive finding given there were more than 10,000 records used for each run. We did compare EAR and EAR regression coefficients with cancer mortality and incidence results published by RERF investigators [54, 55] when a 4-parameter model including a gender effect was run, and the results for coefficients and deviance degrees of freedom were almost identical. However, we ran 3-parameter gender-specific models to derive coefficients for this investigation, because we believed that the smaller gender-specific models would provide better fits. All of the models that were fit using Poisson regression had statistically significant goodness-of-fit results because their deviance was much lower than the model degrees of freedom (see Supplementary material). A voluminous amount of regression diagnostics was performed to identify outliers using standardized residuals, leverages, and DFBETAS, and these are provided in the Supplementary material. The level of work required to fully evaluate the regression diagnostics will be greater than the effort used to present results in this report, and therefore additional interpretation will be needed. Nevertheless, these results are provided for the reader in the Supplementary material tables.

In the following tables and figures, we present results of ECDF of SMRs, and Monte Carlo uncertainty analysis of all-cause and cancer-specific SMRs. Fig. 4 illustrates 10,000 simulated quantiles for cancer-specific SMRs. Regarding ECDF of SMR values, the best fitting distributions for SMRs were log-normal, logistic, and gamma (Table 4). The simulated realizations of all-cause SMRs resulted in an effective multiple for the all-cause mortality rate in the life table, $h(t)$, which reduced the number of deaths thereby prolonging survival – which represents the survival experience of a more healthy population.

Fig. 5 shows histograms for 10,000 quantiles of misclassification correction factors, ψ. Cancer confirmation rates for death certificate agreement with autopsy findings among LSS survivors in the LSS Autopsy Program are listed in Table 5. During the RERF Autopsy Program, autopsies were performed on 4920 (31%) of the 15,929 LSS survivors between January 1961 and December 1975. Results indicate that when compared with autopsy findings, underlying cause of death for most cancers was under-reported. Death certificate-based mortality for all cancers was under-reported by 37.6%, and prostate and bladder cancer was under-reported by 56.9%. Cancers of the liver, gallbladder, and cervix were under-reported via death certificates by approximately 300%. The only cancers that were found to be over-reported on death certificates were oral cavity (10.5%), lung (10%), and leukemia (4.8%). Only cancer mortality risks were adjusted by simulated quantiles for misclassification, and results indicate the all-cancer mortality ELR mean difference was 1.1%, while the mean change in all-cancer PC was approximately 4% for males and 6% for females.

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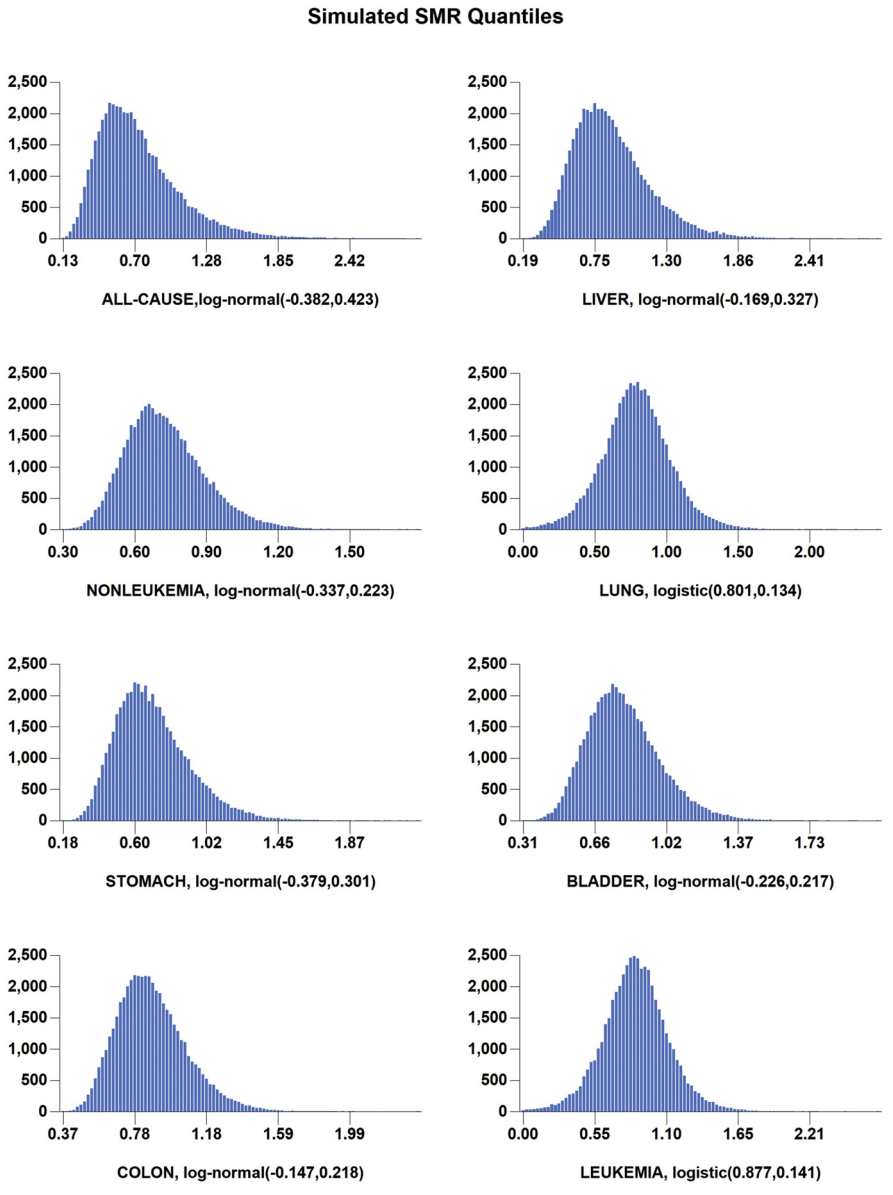

Figure 4. Histograms of 10,000 simulated random quantiles for SMRs based on parameters of best-fitting distributions.

The concept of correcting lifetime risks by the HWE is shown in Fig. 6, which illustrates the survivorship function, $S(t)$, with and without multiplying the underlying all-cause death rate, $h(t)$, by the all-cause SMR. Results shown in Fig. 6 represent the life table survivorship function $S(t)$ and nonleukemia male incidence rate, $h_c(t)$, required for determination of BLR for a US male population of 100,000 exposed to radiation at age 35. Values of $S(t)$ at attained age $t = 100$ without and with correction for HWE (i.e., $h(t) = h(t)SMR$) were $S(100) = 0.016$ and $S(100) = 0.288$, respectively. The integral product $\int S(t)h_c(t)dt$ based on the rate $h_c(t)$ for nonleukemia was 0.526 without HWE correction and 0.816 with correction for

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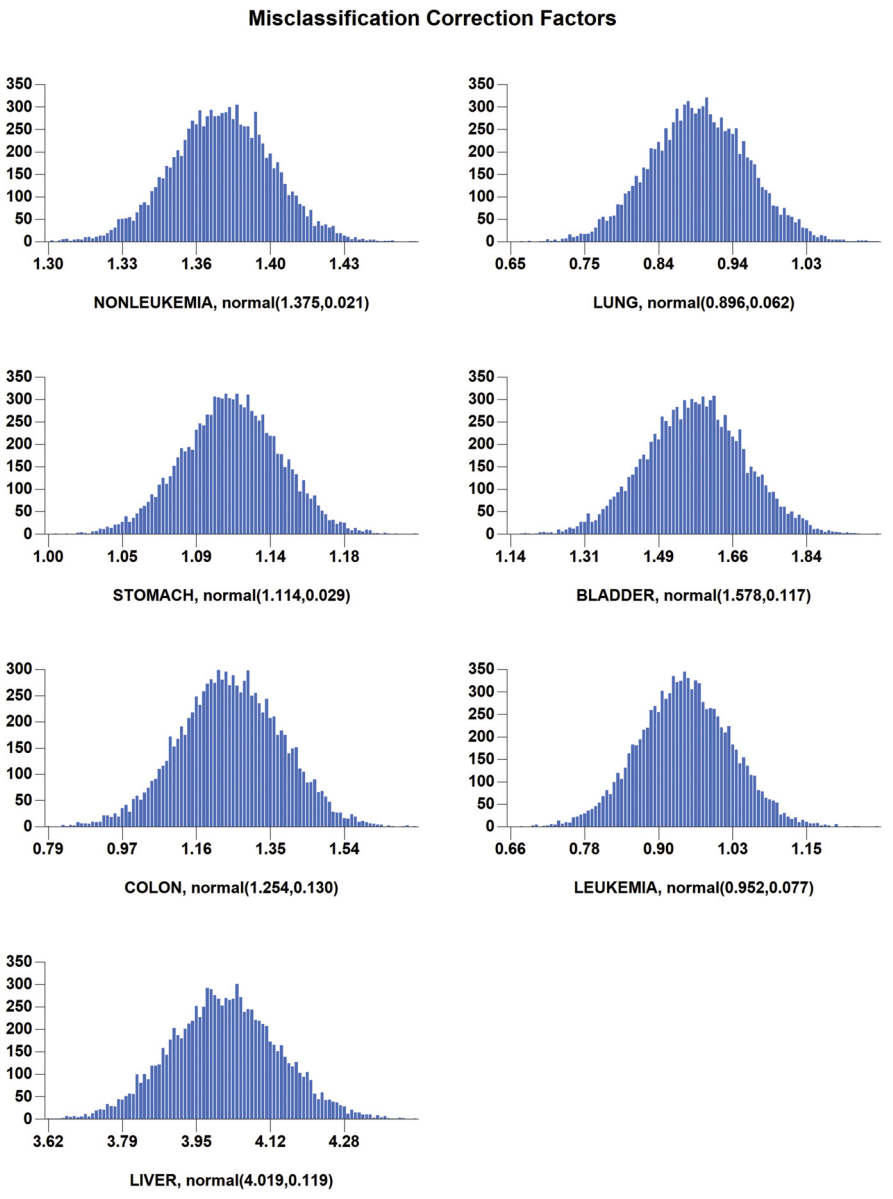

Figure 5. Histograms of 10,000 simulated random quantiles for cancer misclassification factors based on the normal approximation to the binomial distribution.

HWE. Therefore, the mean change in BLR for nonleukemia was 0.29 = 0.816–0.526. This was expected, because a worker cohort whose all-cause SMR is less than one is the result of having fewer deaths when compared with the expected number of deaths based on external rates. Reduction of the all-cause mortality rate by the all-cause SMR increases the $S(t)$, which prolongs survival and shifts deaths toward an older age. Unfortunately, the nonleukemia incidence (mortality) rate is greater at older ages, and therefore the lifetime risk of cancer incidence (mortality) increases with increased survival. Overall, the BLR based on $\int S(t)h_c(t)dt$ is greater when $S(t)$ is adjusted by HWE and the all-cause SMR is less than unity.

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Table 4. Best fitting distributions of SMRs and their location a and scale b parameter values obtained from ECDF.

Cause of death location, a	**Distribution** scale, b
All causes	log-normal
$a = -0.38014$	$b = 0.42032$
Nonleukemia	log-normal
$a = -0.33716$	$b = 0.22020$
Oral cavity	log-normal
$a = -0.30325$	$b = 0.82372$
Digestive	logistic
$a = 0.47840$	$b = 0.11108$
Esophagus	gamma
$b = 2.16876$	$c = 0.30933$
Stomach	log-normal
$a = -0.38190$	$b = 0.30119$
Colon	log-normal
$a = -0.14719$	$b = 0.20620$
Rectum	log-normal
$a = -0.09490$	$b = 0.38529$
Liver	log-normal
$a = -0.17627$	$b = 0.32532$
Pancreas	log-normal
$a = -0.01986$	$b = 0.25942$
Larynx	log-normal
$a = -0.27146$	$b = 0.42053$
Lung	logistic
$a = 0.79975$	$b = 0.13287$
Bone	logistic
$a = 0.71073$	$b = 0.25664$
Prostate	log-normal
$a = 0.00527$	$b = 0.22997$
Bladder	log-normal
$a = -0.22875$	$b = 0.21414$
Kidney	log-normal
$a = -0.05823$	$b = 0.43994$
CNS	logistic
$a = 0.94877$	$b = 0.28094$
Thyroid	log-normal
$a = 0.14510$	$b = 0.34936$
Leukemia	logistic
$a = 0.87669$	$b = 0.14132$

Monte Carlo uncertainty analysis results for lifetime risks and effects of correcting for the HWE, cancer-specific HWE, and cancer misclassification are listed in tables providing all possible combinations of usage of correction factors. The primary outcome from Monte Carlo uncertainty analysis is a distribution of an estimate, based on an underlying model described in the form of an equation. A common approach for reflecting Monte Carlo uncertainty results is to report the lower, middle, and upper percentiles, for example, the 5th, median, and 95th, as indicators of the scale of the outcome. The Monte Carlo uncertainty analysis results provide these percentiles for the various models used. Fig. 7 reflects the uncertainties in ELR of mortality for all cancers except leukemia ("nonleukemia")

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Table 5. Cancer mortality confirmation and detection rates from RERF Pathology Report 4 [59]. Standard errors based on $\sqrt{pq/n}$, where p is the rate, $q = 1 - p$, and n is the number in agreement.

Cancer	Death certificate	Autopsy	Agreement	Confirmation rate, θ	Detection rate, ϕ	Ratio* $\psi = \theta/\phi$
All cancers	1230	1692	929	0.755(0.014)	0.549(0.016)	1.376(0.022)
Oral cavity	19	17	13	0.684(0.129)	0.765(0.118)	0.895(0.175)
Esophagus	50	53	36	0.72(0.075)	0.679(0.078)	1.06(0.108)
Stomach	444	495	374	0.842(0.019)	0.756(0.022)	1.115(0.029)
Colon	43	54	28	0.651(0.09)	0.519(0.094)	1.256(0.13)
Rectum	45	46	32	0.711(0.08)	0.696(0.081)	1.022(0.114)
Liver	42	169	26	0.619(0.095)	0.154(0.071)	4.024(0.119)
Gall bladder	42	169	26	0.619(0.095)	0.154(0.071)	4.024(0.119)
Pancreas	56	81	36	0.643(0.08)	0.444(0.083)	1.446(0.115)
Lung	192	172	117	0.609(0.045)	0.68(0.043)	0.896(0.062)
Breast	40	49	38	0.95(0.035)	0.776(0.068)	1.225(0.076)
Uterus	70	83	57	0.814(0.052)	0.687(0.061)	1.186(0.08)
Cervix	16	64	14	0.875(0.088)	0.219(0.11)	4(0.141)
Prostate	13	24	5	0.385(0.218)	0.208(0.182)	1.846(0.283)
Kidney, Bladder	38	60	30	0.789(0.074)	0.5(0.091)	1.579(0.118)
Lymphoma	40	56	31	0.775(0.075)	0.554(0.089)	1.4(0.117)
Leukemia	42	40	36	0.857(0.058)	0.9(0.05)	0.952(0.077)

* ψ Exceeds unity for under-reported cancers, whereas is less than unity for over-reported cancers.

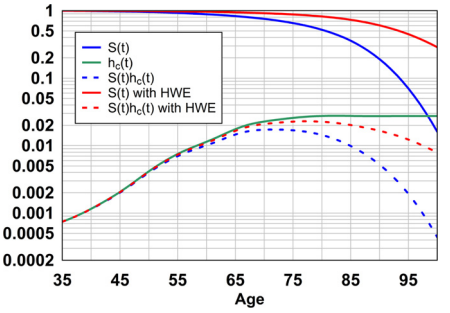

Figure 6. Concept of correcting $S(t)$ for HWE by applying an all-cause SMR of 0.68 (exp(-0.38)) to all-cause death rate, $h(t)$, when estimating survivorship function, $S(t)$, for baseline lifetime risk (BLR) calculation. Values of $S(t)$ at attained age $t = 100$ without and with correction for HWE were $S(100) = 0.016$ and $S(100) = 0.288$, respectively. The integral product $\int S(t)h_c(t)dt$ based on the rate $h_c(t)$ for nonleukemia (all cancers less leukemia) was 0.526 without HWE correction and 0.816 with correction for HWE. Therefore, the mean change in BLR for nonleukemia was 0.29 = 0.816–0.526. (Note: the cancer rate for the 85+ group is applied to all ages above 85).

for males and females exposed to 1 Sv at age 35 for the EAR, ERR(EAR), ERR, and mixture models (latency and DDREF quantiles applied) with and without adjustment by combinations of all-cause SMR values ("AC"), all cancers SMR ("CA"), and all-cancers misclassification ("MC"). Fig. 8 reflects the uncertainties in ELR of male and female nonleukemia incidence for exposure to 1 Sv at age 35 for the EAR, ERR(EAR), ERR, and mixture models (latency and DDREF quantiles applied) with and without adjustment by combinations of all-cause SMR values ("AC") and all-cancers SMR ("CA"). Fig. 9 reflects the uncertainties in ELR of

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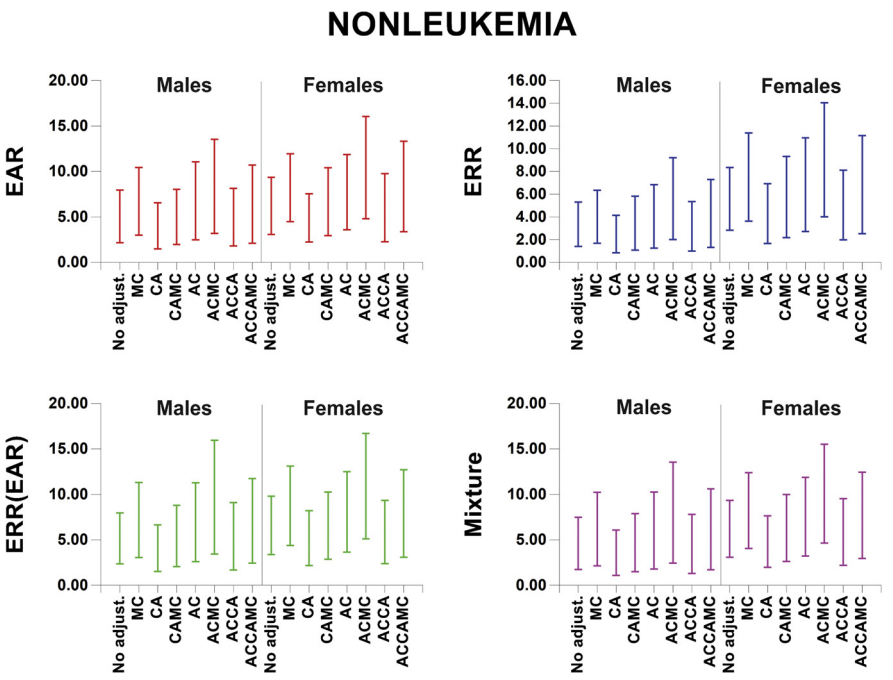

Figure 7. Uncertainties in excess lifetime risk (ELR) of radiation-induced cancer (nonleukemia) mortality for males and females exposed to 1 Sv at age 35 for the EAR, ERR(EAR), ERR, and mixture models (latency and DDREF quantiles applied) with and without adjustment by combinations of all-cause SMR values ("AC"), all-cancer SMRs ("CA"), and misclassification of cancer ("MC"). 10,000 life table calculations performed.

male and female leukemia mortality for exposure to 1 Sv at age 35 for the EAR, ERR(EAR), ERR, and mixture models (latency and DDREF quantiles applied) with and without adjustment by combinations of all-cause SMR ("AC"), leukemia SMR ("CA"), and leukemia misclassification ("MC"). Fig. 10 reflects the uncertainties in ELR of male and female leukemia incidence for exposure to 1 Sv at age 35 for the EAR, ERR(EAR), ERR, and mixture models (latency and DDREF quantiles applied) with and without adjustment by combinations of all-cause SMR values ("AC") and leukemia SMR ("CA"). Table 6 lists ELR, PC, and BLR of cancer mortality risks for nonleukemia projected for US males and females exposed to 1 Sv at age 35 adjusted for all-cause SMR, SMR for all cancers, and misclassification. Table 7 lists ELR, PC, and BLR of cancer incidence risks for nonleukemia incidence projected for US males and females exposed to 1 Sv at age 35 adjusted for all-cause SMR, and SMR for all cancers. Table 8 lists ELR, PC, and BLR of leukemia mortality risks projected for US males and females exposed to 1 Sv at age 35 adjusted for all-cause SMR, SMR for leukemia, and misclassification. Table 9 lists ELR, PC, and BLR of leukemia incidence risks projected for US males and females exposed to 1 Sv at age 35 adjusted for all-cause SMR and SMR for leukemia.

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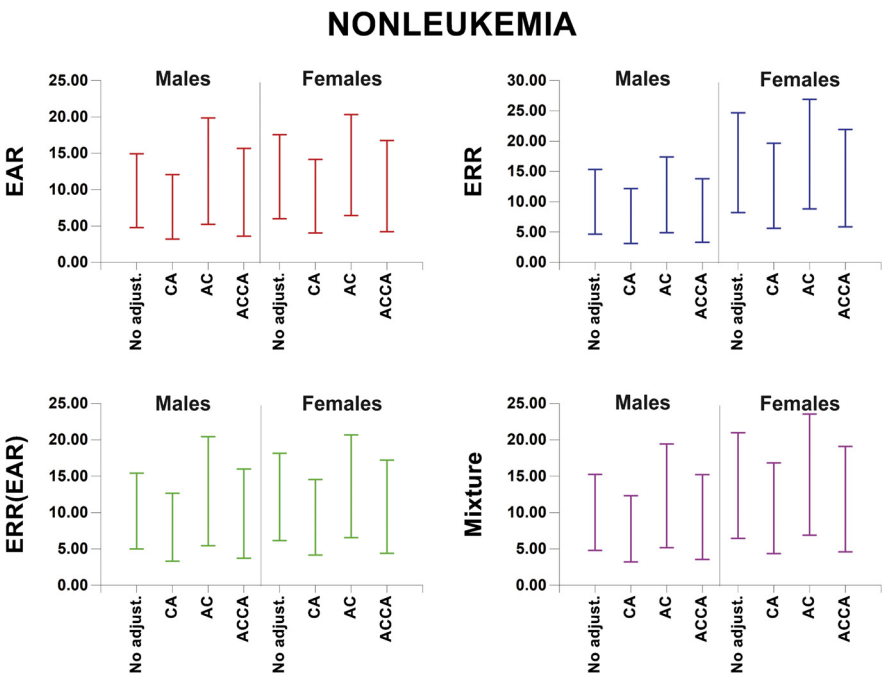

Figure 8. Uncertainties in excess lifetime risk (ELR) of radiation-induced cancer (nonleukemia) incidence for males and females exposed to 1 Sv at age 35 for the EAR, ERR(EAR), ERR, and mixture models (latency and DDREF quantiles applied) with and without adjustment by combinations of all-cause SMR values ("AC"), and all-cancer SMRs ("CA"). 10,000 life table calculations performed.

Lastly, results of multiple linear regression of lifetime risks on binary (yes/no) indicator variables representing the corrections made are provided in the remaining tables. The regression coefficients allowed us to get a handle on the mean difference in lifetime risk due to each adjustment. Table 10 lists regression coefficients (z-score) reflecting the mean change (%) in ELR of cancer mortality for various adjustments. Table 11 lists regression coefficients (z-score) reflecting the mean change (%) in PC of cancer mortality for various adjustments. Table 12 lists regression coefficients (z-score) reflecting the mean change (%) in BLR of cancer mortality for various adjustments. Table 13 lists regression coefficients (z-score) reflecting the mean change (%) in ELR of cancer incidence for various adjustments. Table 14 lists regression coefficients (z-score) reflecting the mean change (%) in PC of cancer incidence for various adjustments. Table 15 lists regression coefficients (z-score) reflecting the mean change (%) in BLR of cancer incidence for various adjustments. For all cancers combined (nonleukemia), the effect of adjusting the all-cause hazard rate by the simulated quantiles of the all-cause SMR resulted in a mean difference (not percent difference) of 0.65% for ELR and 4% for BLR of mortality, and mean difference of 6.2% in BLR for incidence. The effect of adjusting the excess radiation-induced cancer rate or baseline cancer rate by simulated quantiles of cancer-specific SMRs resulted in a mean difference of −1.2% in all-cancer mortality ELR and −6.4% in the all-cancer mortality BLR.

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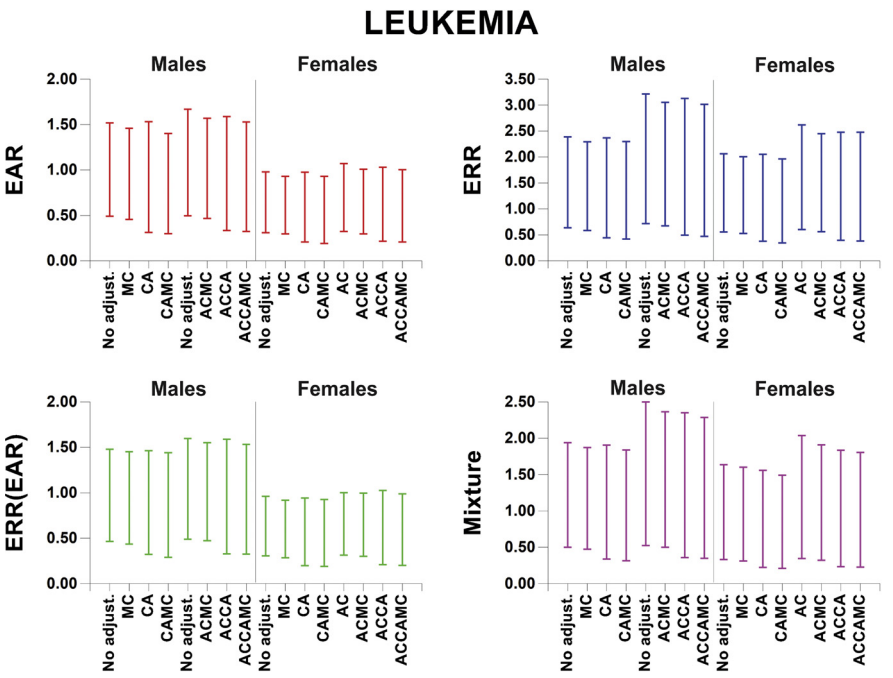

Figure 9. Uncertainties in excess lifetime risk (ELR) of radiation-induced leukemia mortality for males and females exposed to 1 Sv at age 35 for the EAR, ERR(EAR), ERR, and mixture models (latency and DDREF quantiles applied) with and without adjustment by combinations of all-cause SMR values ("AC"), leukemia SMRs ("CA"), and misclassification of cancer ("MC"). 10,000 life table calculations performed.

Whereas for incidence, the effect of adjusting by cancer-specific SMRs resulted in a mean difference of −14.4% in the all-cancer BLR. Correction for cancer mortality misclassification resulted in a mean difference of 4% for the PC of nonleukemia.

4. Discussion

This report presents original results from Poisson regression of LSS data, and presents results of novel applications of Monte Carlo uncertainty analysis for projection of lifetime risks of exposure to ionizing radiation. No fixed values were used as inputs into the life tables that were generated, and instead simulated quantiles from distributions representing the various sources of input information were generated for each gender, organ, and risk model. Within life tables, all 1-year all-cause mortality and cancer mortality and incidence rates were simulated as well.

Many of the Poisson regression models resulted in residuals for which the overly influential observations could have been removed, and the model re-fitted. However, we did not remove outliers because there is typically a very sparse number of events in each cross-tabulation cell in the LSS data. As an example, regarding the LSS cancer mortality data for solid cancers, 88.7% (47,692/53,782) of the person-year cross-tabulation table cells (records) have zero deaths, while for

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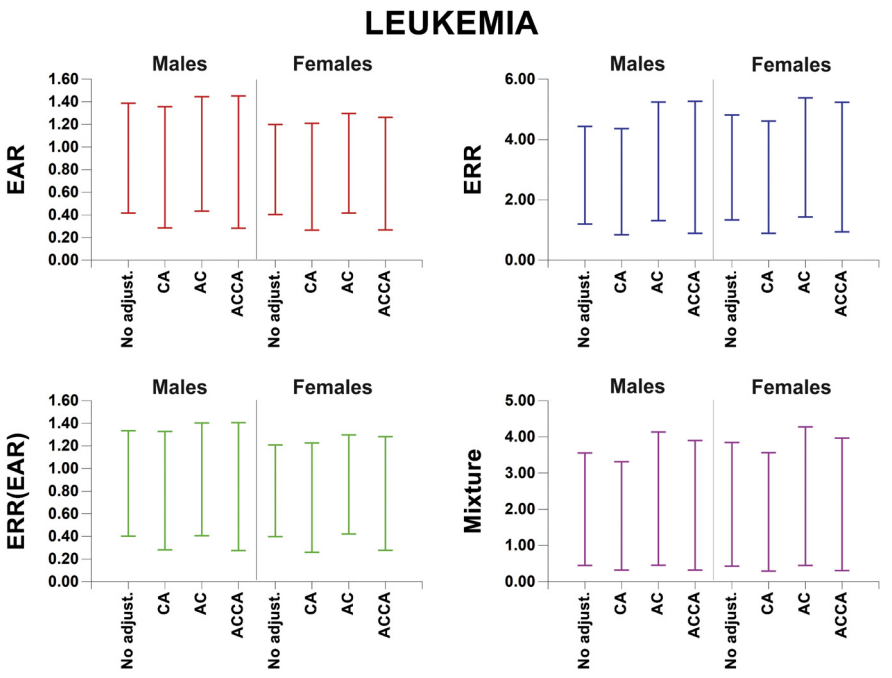

Figure 10. Uncertainties in excess lifetime risk (ELR) of radiation-induced leukemia incidence for males and females exposed to 1 Sv at age 35 for the EAR, ERR(EAR), ERR, and mixture models (latency and DDREF quantiles applied) with and without adjustment by combinations of all-cause SMR values ("AC") and leukemia SMRs ("CA"). 10,000 life table calculations performed.

LSS cancer incidence data (solid cancers), 73.8% (19,790/26,806) of the records have zero cases. Thus, for solid cancers, only 11–24% of the records have non-zero events. This results in very large standardized residuals in records with events and much smaller standardized residuals in records without events (most of the records). Since events are so rare in the LSS data tabulations, removing the largest outliers which mostly occur in records with events, will remove the desperately-needed events – ultimately sacrificing the model. This runs contrary to "textbook"-type Poisson regression methods which have non-zero rates in the majority of records. Overall, the greatest residuals occur in records with events, and since events are rare, removal of these records would be deleterious on the model. The leverage residuals did not load as heavily on records with non-zero events, so leverages are likely more appropriate since they don't present large imbalances in their values. Multicollinearity also did not seem to be an issue using the parameters determined. Additional evaluation of the regression diagnostics is required because of the voluminous output involved.

We believe that overlap of occupational studies may be a potential source of bias among the SMRs reported. None of the reports (SMRs) used were for the same study. Several studies were updates of previous investigations, or novel pooled studies of multiple cohorts, and therefore the published SMR values from those

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Table 6. Excess lifetime risk (ELR), probability of causation (PC), and baseline lifetime risk (BLR) of cancer mortality risks for all cancers except leukemia (nonleukemia) projected for US males and females exposed to 1 Sv at age 35 adjusted for all-cause SMR, SMR for all cancers, and misclassification. Results in each row based on 10,000 Monte Carlo realizations of life tables.

Gender	Adjustment*			Model	ELR(95% CI)	PC(95% CI)	BLR(95% CI)
Males				EAR	4.261(2.256, 7.931)	16.686(9.592, 27.167)	21.279(21.205, 21.351)
				ERR(EAR)	4.475(2.425, 8.289)	17.377(10.234, 28.035)	21.277(21.209, 21.349)
				ERR	2.641(1.291, 5.151)	11.045(5.724, 19.486)	21.278(21.208, 21.348)
				MIX	3.770(1.648, 7.578)	15.055(7.194, 26.260)	21.278(21.207, 21.349)
			MC	EAR	5.770(3.121, 10.520)	21.331(12.785, 33.099)	21.279(21.206, 21.351)
			MC	ERR(EAR)	6.085(3.277, 11.181)	22.242(13.349, 34.447)	21.278(21.207, 21.348)
			MC	ERR	3.606(1.694, 6.851)	14.477(7.377, 24.367)	21.278(21.207, 21.349)
			MC	MIX	5.099(2.227, 10.185)	19.330(9.476, 32.351)	21.278(21.207, 21.349)
		CA		EAR	3.045(1.450, 6.178)	16.717(9.661, 27.094)	15.125(10.421, 21.894)
		CA		ERR(EAR)	3.207(1.570, 6.540)	17.603(10.256, 28.450)	15.094(10.489, 21.764)
		CA		ERR	1.896(0.848, 4.069)	11.164(5.705, 19.542)	15.186(10.442, 21.974)
		CA		MIX	2.690(1.098, 5.916)	15.124(7.231, 26.422)	15.136(10.443, 21.878)
		CA	MC	EAR	4.183(2.056, 8.548)	21.647(12.897, 33.793)	15.119(10.499, 21.841)
		CA	MC	ERR(EAR)	4.445(2.142, 8.843)	22.620(13.271, 35.009)	15.219(10.574, 21.946)
		CA	MC	ERR	2.579(1.139, 5.495)	14.539(7.560, 24.865)	15.206(10.519, 21.911)
		CA	MC	MIX	3.691(1.493, 8.053)	19.573(9.530, 32.875)	15.188(10.525, 21.898)
	AC			EAR	5.215(2.462, 10.695)	16.501(9.485, 26.709)	27.126(16.603, 38.428)
	AC			ERR(EAR)	5.516(2.542, 11.335)	17.248(9.788, 27.978)	27.113(16.590, 38.427)
	AC			ERR	3.107(1.366, 6.572)	10.506(5.239, 18.717)	27.088(16.607, 38.432)
	AC			MIX	4.530(1.794, 10.168)	14.739(6.823, 25.954)	27.113(16.604, 38.432)
	AC		MC	EAR	7.037(3.364, 14.312)	20.897(12.307, 32.735)	27.204(16.879, 38.278)
	AC		MC	ERR(EAR)	7.429(3.556, 15.171)	21.832(12.851, 34.003)	27.215(16.884, 38.282)
	AC		MC	ERR	4.279(1.903, 8.909)	13.893(7.113, 23.836)	27.205(16.897, 38.291)
	AC		MC	MIX	6.156(2.481, 13.552)	18.930(9.074, 31.952)	27.208(16.888, 38.288)
	AC	CA		EAR	3.844(1.662, 8.505)	16.728(9.496, 27.252)	19.359(10.711, 32.184)
	AC	CA		ERR(EAR)	3.990(1.738, 8.887)	17.404(9.911, 28.176)	19.241(10.790, 31.995)
	AC	CA		ERR	2.255(0.928, 5.068)	10.664(5.382, 18.766)	19.254(10.740, 31.804)
	AC	CA		MIX	3.296(1.234, 7.947)	14.901(6.889, 26.211)	19.278(10.745, 32.007)
	AC	CA	MC	EAR	5.193(2.264, 11.234)	21.432(12.556, 33.386)	19.163(10.751, 32.119)
	AC	CA	MC	ERR(EAR)	5.414(2.362, 11.992)	22.264(13.125, 34.716)	19.125(10.779, 31.956)
	AC	CA	MC	ERR	3.069(1.248, 7.064)	14.082(6.969, 24.244)	19.206(10.789, 32.017)
	AC	CA	MC	MIX	4.483(1.664, 10.718)	19.304(9.011, 32.551)	19.159(10.778, 32.028)
Females				EAR	5.514(3.224, 9.532)	23.338(15.104, 34.486)	18.108(18.045, 18.170)
				ERR(EAR)	5.783(3.288, 9.829)	24.210(15.372, 35.168)	18.109(18.047, 18.171)
				ERR	4.745(2.608, 8.422)	20.765(12.576, 31.750)	18.108(18.046, 18.170)
				MIX	5.344(2.949, 9.368)	22.790(14.015, 34.118)	18.108(18.046, 18.170)
			MC	EAR	7.449(4.321, 12.698)	29.157(19.270, 41.218)	18.107(18.046, 18.171)
			MC	ERR(EAR)	7.765(4.462, 13.421)	30.010(19.764, 42.572)	18.109(18.047, 18.170)
			MC	ERR	6.420(3.572, 11.496)	26.171(16.467, 38.827)	18.108(18.047, 18.171)
			MC	MIX	7.199(4.000, 12.667)	28.446(18.093, 41.152)	18.108(18.047, 18.171)
		CA		EAR	4.001(2.036, 7.752)	23.636(15.201, 34.889)	12.847(8.946, 18.794)
		CA		ERR(EAR)	4.208(2.164, 7.990)	24.418(15.668, 35.886)	12.930(8.984, 18.699)
		CA		ERR	3.436(1.716, 6.835)	21.034(12.607, 32.219)	12.952(8.945, 18.731)
		CA		MIX	3.864(1.931, 7.628)	23.056(14.120, 34.571)	12.916(8.961, 18.744)
		CA	MC	EAR	5.411(2.840, 10.185)	29.497(19.513, 41.719)	12.935(8.995, 18.579)
		CA	MC	ERR(EAR)	5.604(2.952, 10.620)	30.332(20.146, 42.878)	12.926(9.043, 18.612)
		CA	MC	ERR	4.625(2.365, 9.135)	26.474(16.713, 38.916)	12.894(8.899, 18.628)
		CA	MC	MIX	5.208(2.651, 10.093)	28.774(18.352, 41.498)	12.919(8.980, 18.612)
	AC			EAR	6.441(3.447, 11.697)	23.088(14.622, 34.014)	21.729(15.374, 27.887)
	AC			ERR(EAR)	6.680(3.593, 12.252)	23.842(15.332, 35.099)	21.737(15.377, 27.889)
	AC			ERR	5.553(2.871, 10.458)	20.511(12.511, 31.727)	21.731(15.376, 27.880)
	AC			MIX	6.199(3.224, 11.513)	22.493(13.857, 33.879)	21.732(15.377, 27.883)
	AC		MC	EAR	8.571(4.669, 15.597)	28.791(18.878, 40.888)	21.686(15.399, 27.704)
	AC		MC	ERR(EAR)	8.988(4.874, 16.260)	29.567(19.479, 42.121)	21.698(15.389, 27.666)

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Table 6. (*Continued*)

Gender	Adjustment*			Model	ELR(95% CI)	PC(95% CI)	BLR(95% CI)
	AC		MC	ERR	7.443(3.873, 13.839)	25.790(16.217, 37.998)	21.690(15.396, 27.706)
	AC		MC	MIX	8.310(4.363, 15.358)	28.053(17.904, 40.737)	21.693(15.396, 27.699)
	AC	CA		EAR	4.615(2.245, 9.265)	23.361(14.841, 34.408)	15.218(9.289, 24.013)
	AC	CA		ERR(EAR)	4.827(2.400, 9.939)	24.226(15.510, 35.441)	15.188(9.240, 24.251)
	AC	CA		ERR	4.001(1.869, 8.162)	20.743(12.564, 32.088)	15.238(9.256, 24.369)
	AC	CA		MIX	4.470(2.127, 9.172)	22.765(13.989, 34.237)	15.216(9.264, 24.204)
	AC	CA	MC	EAR	6.331(3.119, 12.756)	29.357(19.152, 41.821)	15.364(9.520, 24.031)
	AC	CA	MC	ERR(EAR)	6.524(3.226, 12.944)	29.984(19.953, 42.562)	15.276(9.447, 23.727)
	AC	CA	MC	ERR	5.428(2.597, 10.889)	26.161(16.413, 38.947)	15.398(9.455, 24.062)
	AC	CA	MC	MIX	6.080(2.928, 12.308)	28.562(18.178, 41.354)	15.346(9.484, 23.940)

* AC denotes random quantiles of all-cause mortality SMR applied to life table all-cause hazard function, $h(t)$.
CA denotes random quantiles of all-cancers SMR applied to excess risk hazard function, $h_c(d, a, t)$.
MC denotes random quantiles of correction for cancer misclassification applied to excess risk hazard function, $h_c(d, a, t)$.

Table 7. Excess lifetime risk (ELR), probability of causation (PC), and baseline lifetime risk (BLR) of cancer incidence risks for all cancers except leukemia (nonleukemia) projected for US males and females exposed to 1 Sv at age 35 adjusted for all-cause SMR and SMR for all cancers. Results in each row based on 10,000 Monte Carlo realizations of life tables.

Gender	Adjustment*		Model	ELR(95% CI)	PC(95% CI)	BLR(95% CI)
Males			EAR	8.508(4.781, 14.927)	14.441(8.663, 22.850)	50.389(50.287, 50.493)
			ERR(EAR)	8.910(5.002, 15.427)	15.023(9.032, 23.433)	50.390(50.286, 50.496)
			ERR	8.552(4.648, 15.316)	14.507(8.445, 23.313)	50.390(50.286, 50.493)
			MIX	8.646(4.802, 15.232)	14.649(8.701, 23.218)	50.389(50.286, 50.494)
		CA	EAR	6.305(3.195, 12.050)	14.861(8.909, 23.374)	36.096(24.920, 52.018)
		CA	ERR(EAR)	6.510(3.287, 12.561)	15.234(9.232, 24.295)	35.738(24.911, 51.924)
		CA	ERR	6.185(3.086, 12.376)	14.673(8.584, 23.566)	35.926(24.856, 52.113)
		CA	MIX	6.335(3.182, 12.305)	14.930(8.878, 23.743)	35.923(24.898, 52.019)
	AC		EAR	10.322(5.245, 19.895)	14.757(8.815, 23.489)	60.302(43.042, 77.064)
	AC		ERR(EAR)	10.837(5.494, 20.883)	15.427(9.115, 24.294)	60.302(43.011, 77.107)
	AC		ERR	9.564(5.042, 17.601)	13.970(8.021, 22.740)	60.308(43.031, 77.117)
	AC		MIX	10.198(5.239, 19.622)	14.714(8.606, 23.648)	60.303(43.031, 77.093)
	AC	CA	EAR	7.595(3.517, 15.883)	15.069(8.958, 23.893)	42.846(26.403, 67.531)
	AC	CA	ERR(EAR)	7.927(3.678, 16.821)	15.787(9.360, 25.145)	42.755(26.156, 67.452)
	AC	CA	ERR	7.001(3.344, 14.198)	14.117(8.129, 22.922)	42.648(26.139, 67.850)
	AC	CA	MIX	7.509(3.497, 15.712)	15.000(8.713, 24.062)	42.747(26.208, 67.634)
Females			EAR	10.241(6.107, 17.386)	18.790(12.134, 28.212)	44.255(44.160, 44.347)
			ERR(EAR)	10.534(6.195, 17.763)	19.226(12.292, 28.629)	44.254(44.162, 44.347)
			ERR	14.328(8.312, 24.494)	24.454(15.812, 35.637)	44.253(44.162, 44.346)
			MIX	11.506(6.491, 21.036)	20.637(12.788, 32.228)	44.254(44.161, 44.347)
		CA	EAR	7.592(3.948, 14.138)	19.294(12.279, 28.828)	31.529(21.768, 45.814)
		CA	ERR(EAR)	7.666(4.115, 14.483)	19.553(12.488, 29.312)	31.641(21.885, 45.566)
		CA	ERR	10.501(5.565, 19.725)	25.003(16.185, 36.516)	31.518(21.894, 45.401)
		CA	MIX	8.459(4.305, 16.753)	21.059(13.022, 32.873)	31.564(21.825, 45.591)
	AC		EAR	11.622(6.523, 20.214)	19.055(12.038, 28.247)	50.042(39.461, 59.387)
	AC		ERR(EAR)	11.792(6.628, 20.882)	19.235(12.288, 28.794)	50.043(39.475, 59.400)
	AC		ERR	15.315(8.844, 26.672)	23.676(15.274, 34.761)	50.046(39.460, 59.413)
	AC		MIX	12.834(7.009, 23.458)	20.530(12.807, 31.623)	50.043(39.462, 59.403)
	AC	CA	EAR	8.482(4.316, 16.598)	19.236(12.288, 28.765)	35.769(22.977, 54.215)
	AC	CA	ERR(EAR)	8.751(4.427, 16.878)	19.783(12.423, 29.505)	35.629(23.089, 54.043)
	AC	CA	ERR	11.611(6.005, 21.775)	24.525(15.740, 36.028)	35.745(23.197, 54.122)
	AC	CA	MIX	9.520(4.667, 19.130)	21.047(12.985, 32.455)	35.710(23.092, 54.135)

* AC denotes random quantiles of all-cause mortality SMR applied to life table all-cause hazard function, $h(t)$.
CA denotes random quantiles of all-cancer SMR applied to excess risk hazard function, $h_c(d, a, t)$.

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Table 8. Excess lifetime risk (ELR), probability of causation (PC), and baseline lifetime risk (BLR) of leukemia mortality risks projected for US males and females exposed to 1 Sv at age 35 adjusted for all-cause SMR, SMR for leukemia, and misclassification. Results in each row based on 10,000 Monte Carlo realizations of life tables.

Gender	Adjustment*			Model	ELR(95% CI)	PC(95% CI)	BLR(95% CI)
Males				EAR	0.857(0.478, 1.506)	46.465(32.611, 60.397)	0.987(0.972, 1.002)
				ERR(EAR)	0.838(0.467, 1.473)	45.941(32.088, 59.839)	0.987(0.972, 1.002)
				ERR	1.279(0.643, 2.399)	56.455(39.436, 70.847)	0.987(0.972, 1.002)
				MIX	0.956(0.497, 1.948)	49.225(33.485, 66.367)	0.987(0.972, 1.002)
			MC	EAR	0.817(0.451, 1.459)	45.280(31.342, 59.737)	0.987(0.972, 1.002)
			MC	ERR(EAR)	0.803(0.439, 1.426)	44.885(30.768, 59.162)	0.987(0.972, 1.002)
			MC	ERR	1.212(0.610, 2.314)	55.097(38.185, 70.048)	0.987(0.972, 1.002)
			MC	MIX	0.913(0.470, 1.888)	48.035(32.186, 65.688)	0.987(0.972, 1.002)
		CA		EAR	0.731(0.314, 1.506)	46.525(32.895, 60.662)	0.863(0.450, 1.276)
		CA		ERR(EAR)	0.728(0.309, 1.493)	46.177(32.404, 60.379)	0.870(0.464, 1.284)
		CA		ERR	1.080(0.421, 2.334)	56.482(39.504, 70.692)	0.862(0.449, 1.276)
		CA		MIX	0.824(0.333, 1.875)	49.266(33.809, 66.553)	0.865(0.454, 1.279)
		CA	MC	EAR	0.700(0.295, 1.455)	45.161(31.177, 59.700)	0.865(0.458, 1.288)
		CA	MC	ERR(EAR)	0.682(0.293, 1.422)	44.957(30.753, 59.162)	0.862(0.453, 1.274)
		CA	MC	ERR	1.029(0.412, 2.217)	55.209(38.573, 69.830)	0.865(0.458, 1.273)
		CA	MC	MIX	0.781(0.315, 1.799)	47.981(32.316, 65.600)	0.864(0.456, 1.277)
	AC			EAR	0.918(0.504, 1.644)	42.230(27.166, 58.757)	1.296(0.742, 1.915)
	AC			ERR(EAR)	0.892(0.489, 1.613)	41.467(26.313, 58.405)	1.297(0.742, 1.912)
	AC			ERR	1.555(0.702, 3.209)	55.280(38.046, 69.762)	1.297(0.745, 1.912)
	AC			MIX	1.043(0.525, 2.488)	45.961(28.188, 65.804)	1.297(0.743, 1.913)
	AC		MC	EAR	0.857(0.469, 1.564)	40.358(25.546, 57.691)	1.303(0.758, 1.903)
	AC		MC	ERR(EAR)	0.849(0.462, 1.545)	39.991(25.595, 57.305)	1.303(0.759, 1.907)
	AC		MC	ERR	1.474(0.676, 3.069)	53.714(36.652, 68.873)	1.304(0.756, 1.904)
	AC		MC	MIX	0.986(0.494, 2.387)	44.378(26.975, 64.645)	1.303(0.759, 1.906)
	AC	CA		EAR	0.792(0.338, 1.647)	41.841(27.207, 58.421)	1.111(0.498, 2.005)
	AC	CA		ERR(EAR)	0.780(0.329, 1.593)	41.598(26.779, 58.198)	1.116(0.497, 1.989)
	AC	CA		ERR	1.335(0.492, 3.125)	55.094(38.465, 70.235)	1.116(0.499, 1.990)
	AC	CA		MIX	0.911(0.362, 2.370)	45.841(28.492, 65.467)	1.115(0.499, 1.997)
	AC	CA	MC	EAR	0.746(0.320, 1.552)	40.591(25.696, 57.937)	1.101(0.500, 1.997)
	AC	CA	MC	ERR(EAR)	0.733(0.301, 1.517)	40.154(25.370, 57.456)	1.102(0.482, 1.983)
	AC	CA	MC	ERR	1.260(0.457, 2.948)	53.774(36.418, 69.073)	1.106(0.487, 1.979)
	AC	CA	MC	MIX	0.854(0.336, 2.231)	44.426(27.066, 64.582)	1.103(0.492, 1.986)
Females				EAR	0.555(0.311, 0.975)	44.363(30.928, 58.378)	0.695(0.683, 0.707)
				ERR(EAR)	0.545(0.308, 0.964)	43.938(30.715, 58.119)	0.695(0.683, 0.707)
				ERR	1.106(0.553, 2.080)	61.389(44.304, 74.949)	0.695(0.683, 0.707)
				MIX	0.660(0.331, 1.645)	48.695(32.227, 70.318)	0.695(0.683, 0.707)
			MC	EAR	0.525(0.292, 0.941)	42.998(29.595, 57.517)	0.695(0.683, 0.707)
			MC	ERR(EAR)	0.522(0.286, 0.939)	42.853(29.210, 57.522)	0.695(0.683, 0.707)
			MC	ERR	1.057(0.515, 2.011)	60.315(42.563, 74.369)	0.695(0.683, 0.707)
			MC	MIX	0.627(0.308, 1.594)	47.443(30.726, 69.615)	0.695(0.683, 0.707)
		CA		EAR	0.471(0.201, 0.958)	44.260(30.727, 58.360)	0.607(0.323, 0.900)
		CA		ERR(EAR)	0.468(0.203, 0.953)	44.065(30.977, 57.935)	0.609(0.323, 0.888)
		CA		ERR	0.941(0.377, 2.027)	61.320(43.887, 74.920)	0.610(0.321, 0.903)
		CA		MIX	0.568(0.223, 1.559)	48.548(32.299, 70.439)	0.609(0.322, 0.898)
		CA	MC	EAR	0.451(0.189, 0.926)	43.126(29.367, 57.523)	0.610(0.324, 0.901)
		CA	MC	ERR(EAR)	0.443(0.189, 0.921)	42.640(28.954, 57.126)	0.612(0.326, 0.902)
		CA	MC	ERR	0.892(0.352, 1.948)	60.153(42.748, 74.048)	0.606(0.328, 0.898)
		CA	MC	MIX	0.542(0.210, 1.485)	47.346(30.718, 69.491)	0.609(0.326, 0.900)
	AC			EAR	0.584(0.324, 1.058)	40.804(26.853, 56.729)	0.866(0.568, 1.166)
	AC			ERR(EAR)	0.577(0.315, 1.028)	40.512(26.429, 56.076)	0.866(0.569, 1.167)
	AC			ERR	1.290(0.609, 2.597)	60.272(43.109, 74.205)	0.866(0.568, 1.167)
	AC			MIX	0.702(0.344, 2.003)	45.909(28.167, 69.795)	0.866(0.568, 1.167)
	AC		MC	EAR	0.562(0.302, 0.994)	39.798(25.525, 55.502)	0.865(0.569, 1.158)
	AC		MC	ERR(EAR)	0.553(0.298, 0.996)	39.479(25.306, 55.292)	0.864(0.569, 1.157)
	AC		MC	ERR	1.228(0.568, 2.512)	59.210(41.563, 73.884)	0.865(0.570, 1.157)
	AC		MC	MIX	0.673(0.323, 1.947)	44.757(26.999, 68.978)	0.865(0.569, 1.157)

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Table 8. (*Continued*)

Gender	Adjustment*			Model	ELR(95% CI)	PC(95% CI)	BLR(95% CI)
	AC	CA		EAR	0.509(0.214, 1.035)	41.138(27.072, 56.743)	0.737(0.343, 1.242)
	AC	CA		ERR(EAR)	0.498(0.205, 1.023)	40.750(26.468, 56.445)	0.738(0.343, 1.234)
	AC	CA		ERR	1.101(0.410, 2.448)	60.376(42.769, 74.202)	0.738(0.349, 1.237)
	AC	CA		MIX	0.617(0.233, 1.850)	46.025(28.359, 69.608)	0.738(0.345, 1.238)
	AC	CA	MC	EAR	0.477(0.196, 0.995)	39.779(25.262, 55.610)	0.741(0.344, 1.242)
	AC	CA	MC	ERR(EAR)	0.469(0.196, 0.970)	39.178(25.115, 55.487)	0.740(0.353, 1.247)
	AC	CA	MC	ERR	1.057(0.386, 2.381)	59.424(41.634, 73.624)	0.743(0.353, 1.249)
	AC	CA	MC	MIX	0.582(0.219, 1.803)	44.667(26.850, 68.838)	0.742(0.350, 1.246)

* AC denotes random quantiles of all-cause mortality SMR applied to life table all-cause hazard function, $h(t)$.
CA denotes random quantiles of all-cancers SMR applied to excess risk hazard function, $h_c(d, a, t)$.
MC denotes random quantiles of correction for cancer misclassification applied to excess risk hazard function, $h_c(d, a, t)$.

Table 9. Excess lifetime risk (ELR), probability of causation (PC), and baseline lifetime risk (BLR) of leukemia incidence risks projected for US males and females exposed to 1 Sv at age 35 adjusted for all-cause SMR and SMR for leukemia. Results in each row based on 10,000 Monte Carlo realizations of life tables.

Gender	Adjustment*		Model	ELR(95% CI)	PC(95% CI)	BLR(95% CI)
Males			EAR	0.784(0.417, 1.366)	33.925(21.493, 47.241)	1.526(1.509, 1.544)
			ERR(EAR)	0.756(0.401, 1.323)	33.127(20.821, 46.415)	1.526(1.508, 1.544)
			ERR	2.400(1.203, 4.515)	61.128(44.104, 74.786)	1.526(1.508, 1.544)
			MIX	0.961(0.446, 3.569)	38.642(22.626, 70.019)	1.526(1.508, 1.544)
		CA	EAR	0.667(0.280, 1.359)	33.859(21.755, 47.503)	1.346(0.714, 1.988)
		CA	ERR(EAR)	0.649(0.262, 1.324)	33.029(20.802, 46.712)	1.341(0.707, 1.983)
		CA	ERR	2.054(0.820, 4.356)	61.315(44.071, 74.560)	1.346(0.711, 1.972)
		CA	MIX	0.854(0.305, 3.344)	38.653(22.639, 69.986)	1.344(0.710, 1.982)
	AC		EAR	0.821(0.439, 1.445)	30.734(18.327, 45.020)	1.892(1.269, 2.536)
	AC		ERR(EAR)	0.793(0.421, 1.423)	29.915(17.786, 44.682)	1.890(1.265, 2.535)
	AC		ERR	2.727(1.318, 5.266)	59.622(42.208, 73.422)	1.890(1.268, 2.538)
	AC		MIX	1.017(0.466, 4.151)	35.767(19.434, 68.696)	1.890(1.268, 2.536)
	AC	CA	EAR	0.705(0.291, 1.449)	30.621(18.626, 45.186)	1.627(0.775, 2.714)
	AC	CA	ERR(EAR)	0.676(0.274, 1.384)	29.979(17.991, 44.519)	1.614(0.761, 2.733)
	AC	CA	ERR	2.345(0.897, 5.134)	59.503(42.027, 73.713)	1.621(0.781, 2.704)
	AC	CA	MIX	0.905(0.319, 3.882)	35.858(19.752, 68.799)	1.622(0.771, 2.715)
Females			EAR	0.697(0.406, 1.202)	39.429(27.452, 52.897)	1.071(1.057, 1.086)
			ERR(EAR)	0.686(0.387, 1.201)	39.020(26.563, 52.829)	1.072(1.057, 1.086)
			ERR	2.586(1.341, 4.722)	70.719(55.617, 81.508)	1.072(1.057, 1.086)
			MIX	0.870(0.427, 3.795)	44.802(28.471, 77.993)	1.072(1.057, 1.086)
		CA	EAR	0.597(0.254, 1.202)	39.460(27.051, 52.798)	0.940(0.493, 1.392)
		CA	ERR(EAR)	0.595(0.256, 1.185)	39.252(26.652, 52.839)	0.944(0.492, 1.384)
		CA	ERR	2.209(0.901, 4.565)	70.637(55.097, 81.554)	0.942(0.502, 1.391)
		CA	MIX	0.784(0.288, 3.534)	44.798(28.241, 77.860)	0.942(0.495, 1.389)
	AC		EAR	0.736(0.414, 1.281)	37.127(24.746, 51.249)	1.261(0.920, 1.581)
	AC		ERR(EAR)	0.732(0.405, 1.272)	37.099(24.549, 51.014)	1.261(0.921, 1.580)
	AC		ERR	2.847(1.418, 5.393)	69.669(53.963, 80.944)	1.261(0.921, 1.581)
	AC		MIX	0.921(0.440, 4.267)	42.694(25.952, 77.307)	1.261(0.921, 1.581)
	AC	CA	EAR	0.633(0.267, 1.303)	37.281(24.561, 51.623)	1.084(0.533, 1.746)
	AC	CA	ERR(EAR)	0.626(0.267, 1.294)	36.845(24.401, 51.380)	1.095(0.538, 1.767)
	AC	CA	ERR	2.478(0.974, 5.306)	69.713(54.607, 80.796)	1.097(0.542, 1.760)
	AC	CA	MIX	0.829(0.303, 4.021)	42.752(25.938, 77.262)	1.092(0.537, 1.760)

* AC denotes random quantiles of all-cause mortality SMR applied to life table all-cause hazard function, $h(t)$.
CA denotes random quantiles of all-cancers SMR applied to excess risk hazard function, $h_c(d, a, t)$.

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Table 10. Regression coefficients (z-score) reflecting the mean change (%) in excess lifetime risk (ELR) of cancer mortality for various adjustments. ELR regressed on age at exposure and dummy indicator variables for applying all-cause SMR, applying cancer SMRs, applying misclassification corrections, and females.

Cancer	Model	Age at exposure*10	All-cause SMR	Cancer SMR	Misclassification	Female
Nonleukemia	EAR	−1.277(−22.07)	0.759(8.04)	−1.332(−14.11)	1.214(12.85)	1.167(12.36)
	ERR(EAR)	−1.402(−21.88)	0.832(7.95)	−1.366(−13.05)	1.29(12.32)	1.168(11.16)
	ERR	−1.208(−13.81)	0.483(3.39)	−0.937(−6.57)	0.855(5.99)	1.388(9.72)
	MIX	−1.299(−19.85)	0.65(6.08)	−1.204(−11.26)	1.108(10.37)	1.283(12)
Esophagus	EAR	0.06(20.98)	0.019(3.99)	−0.055(−11.78)	0.013(2.7)	–
	ERR(EAR)	0.062(18.22)	0.024(4.27)	−0.059(−10.62)	0.009(1.65)	–
	ERR	0.031(14.22)	0.01(2.88)	−0.045(−12.49)	0.004(0.98)	–
	MIX	0.051(19.36)	0.018(4.1)	−0.055(−12.64)	0.009(2.01)	–
Lung	EAR	−0.241(−10.78)	0.265(7.26)	−0.259(−7.09)	−0.114(−3.12)	0.804(22.01)
	ERR(EAR)	−0.255(−10.92)	0.283(7.4)	−0.271(−7.09)	−0.127(−3.32)	0.868(22.72)
	ERR	−0.073(−1.46)	0.298(3.62)	−0.498(−6.05)	−0.197(−2.4)	2.883(35.04)
	MIX	−0.225(−8.22)	0.304(6.81)	−0.308(−6.9)	−0.136(−3.04)	1.258(28.18)
Stomach	EAR	−0.076(−6.26)	0.116(5.83)	−0.291(−14.69)	0.091(4.61)	0.593(29.92)
	ERR(EAR)	−0.078(−6.6)	0.12(6.21)	−0.311(−16.07)	0.079(4.07)	0.611(31.58)
	ERR	−0.022(−18.69)	0.009(4.68)	−0.022(−11.32)	0.006(2.93)	–
	MIX	−0.088(−10.08)	0.09(6.3)	−0.267(−18.79)	0.065(4.54)	0.286(20.12)
Liver	EAR	−0.59(−7.54)	0.388(3.04)	−0.228(−1.78)	1.689(13.22)	−0.412(−3.22)
	ERR(EAR)	−0.643(−7.99)	0.389(2.96)	−0.252(−1.92)	1.801(13.71)	−0.352(−2.68)
	ERR	−0.091(−7.19)	0.044(2.16)	−0.041(−1.98)	0.281(13.67)	−0.119(−5.78)
	MIX	−0.461(−8.01)	0.208(2.21)	−0.199(−2.12)	1.16(12.35)	−0.352(−3.75)
Colon	EAR	−0.099(−24.22)	0.037(5.48)	−0.031(−4.69)	0.043(6.38)	0.053(7.92)
	ERR(EAR)	−0.108(−22.65)	0.037(4.71)	−0.036(−4.69)	0.045(5.82)	0.048(6.18)
	ERR	−0.105(−23.29)	0.029(4)	−0.036(−4.93)	0.042(5.7)	0.109(14.79)
	MIX	−0.103(−27.02)	0.034(5.52)	−0.034(−5.48)	0.044(6.99)	0.067(10.75)
Kidney	ERR	−0.01(−8.67)	0.002(1.28)	−0.001(−0.75)	0.004(2.24)	–
Bladder	EAR	−0.035(−2.13)	0.14(5.24)	−0.106(−3.98)	0.209(7.82)	−0.227(−8.48)
	ERR(EAR)	−0.042(−2.32)	0.153(5.17)	−0.115(−3.88)	0.234(7.92)	−0.23(−7.8)
	ERR	−0.085(−4.86)	0.144(5.05)	−0.125(−4.4)	0.256(9)	−0.35(−12.3)
	MIX	−0.049(−2.85)	0.146(5.25)	−0.115(−4.12)	0.228(8.21)	−0.257(−9.26)
Leukemia	EAR	−0.075(−15.96)	0.047(6.11)	−0.073(−9.54)	−0.025(−3.32)	−0.182(−23.82)
	ERR(EAR)	−0.071(−15.86)	0.045(6.16)	−0.072(−9.74)	−0.021(−2.89)	−0.171(−23.18)
	ERR	0.026(1.5)	0.227(8.01)	−0.181(−6.41)	−0.055(−1.94)	0.009(0.31)
	MIX	−0.07(−12.27)	0.065(7.02)	−0.083(−8.98)	−0.029(−3.14)	−0.183(−19.68)

studies were different – helping us to establish the full range of uncertainty. While the Cardis et al. study [43] was a 15-country study, we don't discount the value of SMRs reported by other studies, for which data were collected under separate circumstances and had different random and systematic errors under play, which increases the value of these data in the context of replication. In addition, the meta-analysis results in Table 2 can overlap with other studies, however, few of the SMR values for the meta-analysis are the same as those reported by single studies.

Separate model fits using ECDF were employed for the all-cause SMRs and each cancer-specific SMR. With regard to the identification of SMRs, we wanted to sample as many SMRs as possible from the literature to develop the full spectrum of realizations. In doing so, the parametric models used to fit (ECDF) SMRs resulted in smooth approximations of the uncertainty in SMR. When compared with all-cause SMRs, cancer-specific SMRs are more sensitive to the constellation

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Table 11. Regression coefficients (z-score) reflecting the mean change (%) in probability of causation (PC) for cancer mortality for various adjustments. PC regressed on age at exposure and dummy indicator variables for applying all-cause SMR, applying cancer SMRs, applying misclassification corrections, and females.

Cancer	Model	Age at exposure*10	All-cause SMR	Cancer SMR	Misclassification	Female
Nonleukemia	EAR	−4.54(−53.39)	−0.005(−0.04)	0.167(1.2)	4.264(30.67)	7.233(52.04)
	ERR(EAR)	−4.77(−47.13)	0.023(0.14)	0.231(1.4)	4.386(26.54)	7.277(44.02)
	ERR	−4.81(−17.06)	−0.163(−0.35)	0.06(0.13)	3.41(7.41)	7.658(16.63)
	MIX	−4.75(−36.33)	−0.085(−0.4)	0.146(0.68)	3.979(18.64)	7.476(35.01)
Esophagus	EAR	10.29(25.3)	−0.642(−0.97)	0.139(0.21)	1.263(1.9)	
	ERR(EAR)	10.42(27.89)	−0.707(−1.16)	−0.158(−0.26)	1.149(1.88)	
	ERR	7.18(14.75)	−1.432(−1.8)	−0.075(−0.09)	0.732(0.92)	
	MIX	9.6(24.66)	−0.84(−1.32)	0.095(0.15)	1.135(1.79)	
Lung	EAR	−3.02(−14.06)	1.263(3.6)	0.112(0.32)	−1.401(−4)	14.366(41)
	ERR(EAR)	−3.15(−14.37)	1.349(3.77)	0.15(0.42)	−1.588(−4.44)	15.1(42.2)
	ERR	−1.2(−3.31)	−0.011(−0.02)	0.051(0.09)	−1.593(−2.69)	34.086(57.65)
	MIX	−2.74(−12.06)	1.203(3.24)	0.059(0.16)	−1.555(−4.19)	19.324(52.03)
Stomach	EAR	−1.94(−10.38)	−1.103(−3.62)	0.226(0.74)	2.078(6.82)	26.16(85.85)
	ERR(EAR)	−2.2(−9.47)	−0.795(−2.09)	−0.525(−1.38)	1.801(4.74)	26.442(69.64)
	ERR	−5.24(−57.32)	−0.153(−1.03)	−0.138(−0.92)	1.511(10.13)	
	MIX	−2.72(−20.22)	−1.077(−4.9)	−0.095(−0.43)	2.112(9.61)	20.783(94.57)
Liver	EAR	−9.15(−11.29)	2.399(1.81)	−0.109(−0.08)	28.137(21.26)	8.529(6.44)
	ERR(EAR)	−8.94(−10.97)	2.257(1.7)	0.335(0.25)	27.895(20.96)	9.235(6.94)
	ERR	−8.27(−10.77)	1.132(0.9)	0.334(0.27)	25.415(20.27)	5.414(4.32)
	MIX	−11.84(−13.47)	2.418(1.68)	−0.091(−0.06)	30.361(21.15)	7.028(4.9)
Colon	EAR	−4.92(−31.56)	−0.253(−0.99)	0.055(0.22)	1.965(7.71)	3.476(13.64)
	ERR(EAR)	−5.23(−29.83)	−0.35(−1.22)	−0.151(−0.53)	2.148(7.5)	3.315(11.57)
	ERR	−5.08(−30.3)	−0.785(−2.86)	−0.074(−0.27)	1.995(7.28)	6.141(22.42)
	MIX	−5.04(−36.32)	−0.443(−1.96)	−0.081(−0.36)	2.06(9.1)	4.204(18.56)
Kidney	ERR	−1.6(−9.23)	0.124(0.44)	0.122(0.43)	0.697(2.46)	
Bladder	EAR	−2.36(−9.23)	1.502(0.44)	−0.045(0.43)	10.758(2.46)	
	ERR(EAR)	−2.43(−3.59)	1.854(1.4)	0.027(−0.04)	10.987(10.01)	9.591(8.4)
	ERR	−4.21(−3.5)	0.538(1.64)	0.07(0.02)	11.025(9.69)	5.293(8.46)
	MIX	−2.81(−7.69)	1.37(0.6)	−0.037(0.08)	10.872(12.32)	8.293(5.92)
Leukemia	EAR	−3.49(−4.44)	−3.026(1.32)	0.181(−0.04)	−1.341(10.51)	0.414(8.02)
	ERR(EAR)	−3.46(−21.6)	−2.816(−11.46)	0.273(0.69)	−1.17(−5.08)	0.559(1.57)
	ERR	0.44(−22.02)	−0.844(−10.98)	−0.031(1.07)	−1.265(−4.56)	9.669(2.18)
	MIX	−2.86(1.22)	−2.427(−1.44)	0.09(−0.05)	−1.25(−2.16)	1.719(16.47)

of risk factors to which workers were exposed, and may or may not be elevated as a result of culture, risk-taking, and/or exposure to other cancer-related agents in the workplace. It is our belief that cancer-specific SMRs are merely a snapshot of the observed to expected ratio for the given cancer, and are less relevant to the HWE – which is hinged to the all-cause SMR.

Other important factors affecting the SMR include the age distribution of workers, length of follow-up, time since hire, and time since the end of employment. Unfortunately, the SMR is a statistic that is only based on observed and expected counts, so it is impossible to adjust SMRs by other covariates – since SMR analysis is not regression modeling which can control for other factors. Taking the above factors into consideration during selection and identification of SMRs used in our risk projection methods would result in partitioning and parameterization of SMRs. This would reduce the number of SMR values available

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Table 12. Regression coefficients (z-score) reflecting the mean change (%) in baseline lifetime risk (BLR) of cancer mortality for various adjustments. BLR regressed on age at exposure and dummy indicator variables for applying all-cause SMR, applying cancer SMRs, applying misclassification corrections, and females.

Cancer	Model	Age at exposure*10	All-cause SMR	Cancer SMR	Misclassification	Female
Nonleukemia	EAR	−0.085(−0.62)	3.964(17.74)	−6.405(−28.67)	0.039(0.17)	−4.027(−18.02)
	ERR(EAR)	−0.098(−0.7)	3.963(17.37)	−6.437(−28.21)	0.082(0.36)	−4.008(−17.56)
	ERR	−0.037(−0.27)	3.992(17.86)	−6.42(−28.72)	0.038(0.17)	−4.06(−18.16)
	MIX	−0.073(−0.54)	3.975(17.78)	−6.418(−28.71)	0.054(0.24)	−4.031(−18.03)
Esophagus	EAR	−0.012(−4.89)	0.033(8.09)	−0.048(−11.85)	0.004(1.05)	
	ERR(EAR)	−0.011(−5.21)	0.036(10.22)	−0.051(−14.4)	0(−0.12)	
	ERR	−0.011(−5.12)	0.036(9.83)	−0.05(−13.69)	−0.001(−0.18)	
	MIX	−0.012(−5.21)	0.035(9.6)	−0.049(−13.72)	0.001(0.3)	
Lung	EAR	0.027(0.67)	0.997(14.88)	−1.346(−20.08)	0.002(0.03)	−1.886(−28.15)
	ERR(EAR)	0.037(0.9)	0.998(14.93)	−1.345(−20.12)	0.012(0.19)	−1.877(−28.09)
	ERR	0.019(0.46)	0.984(14.17)	−1.362(−19.63)	0.008(0.12)	−1.851(−26.67)
	MIX	0.027(0.67)	0.992(14.75)	−1.352(−20.1)	0.01(0.15)	−1.872(−27.83)
Stomach	EAR	−0.005(−1.25)	0.08(11.71)	−0.14(−20.56)	0.001(0.15)	−0.159(−23.31)
	ERR(EAR)	−0.005(−1.39)	0.081(12.6)	−0.138(−21.65)	0.003(0.4)	−0.162(−25.3)
	ERR	−0.006(−2.76)	0.057(16.89)	−0.111(−32.99)	0(0.1)	
	MIX	−0.005(−1.34)	0.08(12.24)	−0.14(−21.3)	0.002(0.23)	−0.161(−24.53)
Liver	EAR	−0.005(−1.09)	0.089(11.03)	−0.095(−11.81)	0.001(0.14)	−0.455(−56.26)
	ERR(EAR)	−0.007(−1.35)	0.086(10.35)	−0.096(−11.58)	0.002(0.2)	−0.451(−54.14)
	ERR	−0.006(−1.14)	0.085(10.61)	−0.095(−11.86)	0(0.05)	−0.453(−56.49)
	MIX	−0.006(−1.22)	0.087(10.71)	−0.096(−11.8)	0.001(0.14)	−0.453(−55.85)
Colon	EAR	−0.004(−0.64)	0.381(38.02)	−0.251(−25.08)	0.007(0.74)	−0.135(−13.44)
	ERR(EAR)	−0.005(−0.88)	0.382(41.29)	−0.247(−26.75)	0.005(0.51)	−0.138(−14.97)
	ERR	−0.004(−0.72)	0.383(39.63)	−0.249(−25.8)	0.003(0.35)	−0.133(−13.77)
	MIX	−0.004(−0.75)	0.382(40.48)	−0.249(−26.35)	0.005(0.57)	−0.135(−13.77)
Kidney	ERR	−0.001(−0.29)	0.134(28.68)	−0.144(−30.93)	0(0.04)	
Bladder	EAR	−0.012(−0.91)	0.194(8.9)	−0.154(−7.06)	0.001(0.06)	
	ERR(EAR)	−0.012(−0.89)	0.195(8.92)	−0.154(−7.05)	0.002(0.09)	−0.578(−26.63)
	ERR	−0.012(−0.88)	0.193(8.82)	−0.154(−7.04)	0.002(0.11)	−0.579(−26.44)
	MIX	−0.012(−0.9)	0.194(8.91)	−0.154(−7.07)	0.002(0.09)	−0.579(−26.52)
Leukemia	EAR	0.002(0.26)	0.217(18.16)	−0.135(−11.31)	0.006(0.46)	−0.352(−26.6)
	ERR(EAR)	0.002(0.25)	0.217(18.29)	−0.135(−11.36)	0.003(0.28)	−0.348(−29.45)
	ERR	0(0)	0.21(17.56)	−0.135(−11.3)	0.003(0.27)	−0.347(−29.3)
	MIX	0.002(0.21)	0.215(18.16)	−0.135(−11.44)	0.004(0.37)	−0.349(−29.01)

for ECDF within each combination of factor levels. The strength of the Monte Carlo approach employed is hinged to the idea that the full range of observable SMRs are taken into account. As long as we are realizing all possible values of SMRs (for which there is indeed a bulk of the data near a central estimate), we are capturing the majority of data which exists.

It is also likely that the HWE among astronauts was underestimated. SMRs resulting from radiation exposed aviators and nuclear workers will be affected by radiation-induced cancer risks, and may not be amenable for use when establishing baseline risks. While the all-cause SMR among astronauts has historically been lower than most aviator and nuclear worker study all-cause SMRs, it was reported [24] that in the LSAH, the use of an internal matched control population resulted in a cancer mortality SMR = 3.45 (95% CI, 0.66–7.56). This may explain a 3-fold difference in the baseline rate of cancer, which is not discernible with SMRs.

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Table 13. Regression coefficients (z-score) reflecting the mean change (%) in excess lifetime risk (ELR) of cancer incidence for various adjustments. ELR regressed on age at exposure and dummy indicator variables for applying all-cause SMR, applying cancer SMRs, and females.

Cancer	Model	Age at exposure*10	All-cause SMR	Cancer SMR	Female
Nonleukemia	EAR	−2.477(−20.52)	1.001(5.08)	−1.979(−10.04)	1.135(5.76)
	ERR(EAR)	−2.554(−23.68)	1.018(5.78)	−2.029(−11.52)	1.143(6.49)
	ERR	−2.581(−13.5)	0.727(2.33)	−2.456(−7.87)	3.742(11.98)
	MIX	−2.523(−20.94)	0.969(4.93)	−2.087(−10.61)	1.892(9.62)
Esophagus	ERR	−0.029(−3.35)	0.011(0.78)	−0.029(−2.1)	−0.145(−10.39)
Lung	EAR	−0.049(−1.63)	0.283(5.73)	−0.409(−8.29)	0.978(19.82)
	ERR(EAR)	−0.08(−2.28)	0.317(5.55)	−0.414(−7.25)	1.055(18.48)
	ERR	0.135(1.52)	0.362(2.5)	−0.978(−6.76)	4.251(29.37)
	MIX	−0.047(−1.21)	0.398(6.2)	−0.475(−7.4)	1.507(23.48)
Stomach	EAR	−0.33(−12.82)	0.287(6.83)	−0.597(−14.22)	−0.265(−6.32)
	ERR(EAR)	−0.35(−12.84)	0.263(5.91)	−0.613(−13.77)	−0.293(−6.57)
	ERR	−0.026(−15.03)	0.012(4.13)	−0.032(−11.16)	0.035(12.21)
	MIX	−0.309(−13.8)	0.161(4.41)	−0.489(−13.36)	−0.158(−4.32)
Liver	EAR	−0.211(−5.17)	0.099(1.48)	−0.07(−1.05)	−0.721(−10.83)
	ERR(EAR)	−0.219(−5.42)	0.091(1.37)	−0.081(−1.22)	−0.767(−11.62)
	ERR	−0.009(−0.64)	0.012(0.5)	−0.024(−1.02)	−0.11(−4.64)
	MIX	−0.144(−4.76)	0.047(0.95)	−0.056(−1.14)	−0.514(−10.44)
Colon	EAR	−1.085(−9.48)	0.472(2.53)	−0.189(−1.01)	
	ERR(EAR)	−1.149(−9.74)	0.489(2.54)	−0.213(−1.11)	
	ERR	−0.207(−7.03)	0.146(3.03)	−0.192(−3.98)	−0.759(−15.76)
	MIX	−0.471(−5.15)	0.207(1.38)	−0.185(−1.24)	−0.814(−5.45)
Rectum	ERR	−0.121(−11.24)	0.058(3.29)	−0.1(−5.69)	
Bladder	EAR	−0.125(−4.18)	0.164(3.37)	−0.138(−2.83)	0.325(6.68)
	ERR(EAR)	−0.133(−3.83)	0.171(3.02)	−0.146(−2.59)	0.372(6.58)
	ERR	−0.876(−5.89)	1.054(4.34)	−1.449(−5.96)	7.576(31.17)
	MIX	−0.17(−3.95)	0.29(4.11)	−0.19(−2.69)	0.389(5.52)
Leukemia	EAR	−0.025(−5.78)	0.051(7.24)	−0.088(−12.56)	−0.013(−1.85)
	ERR(EAR)	−0.019(−4.74)	0.047(6.98)	−0.08(−11.94)	−0.007(−1.08)
	ERR	0.423(13.6)	0.388(7.64)	−0.383(−7.55)	0.337(6.64)
	MIX	−0.014(−3.11)	0.068(9.1)	−0.077(−10.33)	−0.016(−2.1)

A major observation from this study is that if a worker population exhibits a low value for all-cause SMR, it simply means that the number of deaths is lower than the external population, and hence the workers will, on average, live longer. Living longer implies that being healthy results in longer survival. Longer survival implies a greater risk of cancer since cancer rates increase with age. This creates a dilemma within the LSAH regarding radiation risk assessment, since the greater cancer mortality caused by living longer may confound or mask any signal related to radiation-induced cancer mortality. As such, it would be propitious to perform dose-response modeling within the LSAH in order to compare modeled cancer mortality rates between different dose groups. To our knowledge, the LSAH has not published cancer mortality results based on modeling low vs. high space radiation exposure groups. The accident-specific SMR for astronauts has also been significantly greater than unity, but the overall all-cause SMR is typically low.

This manuscript is neither about the LSAH nor use of an internal control population for assessing HWE. Rather, our approach is one that implemented

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Table 14. Regression coefficients (z-score) reflecting the mean change (%) in probability of causation (PC) of cancer incidence for various adjustments. PC regressed on age at exposure and dummy indicator variables for applying all-cause SMR, applying cancer SMRs, and females.

Cancer	Model	Age at exposure*10	All-cause SMR	Cancer SMR	Female
Nonleukemia	EAR	−4.078(−61.69)	0.31(2.87)	0.189(1.75)	4.163(38.56)
	ERR(EAR)	−4.211(−52.35)	0.257(1.96)	0.329(2.51)	4.192(31.91)
	ERR	−3.944(−25.7)	−0.436(−1.74)	0.208(0.83)	8.688(34.66)
	MIX	−4.073(−54.47)	0.11(0.9)	0.26(2.13)	5.506(45.1)
Esophagus	ERR	−2.764(−4.28)	−0.031(−0.03)	0.142(0.13)	−16.02(−15.19)
Lung	EAR	−0.363(−2.04)	0.761(2.62)	−0.053(−0.18)	13.139(45.27)
	ERR(EAR)	−0.586(−2.82)	0.806(2.37)	−0.056(−0.16)	13.566(39.96)
	ERR	1.007(6.95)	−0.44(−1.86)	0.071(0.3)	31.915(134.94)
	MIX	−0.28(−1.65)	0.904(3.27)	0.009(0.03)	16.869(60.96)
Stomach	EAR	−3.848(−17.3)	0.257(0.71)	0.405(1.11)	8.565(23.59)
	ERR(EAR)	−3.897(−15.69)	−0.044(−0.11)	0.195(0.48)	8.036(19.82)
	ERR	−2.887(−17.43)	−0.218(−0.81)	0.043(0.16)	9.862(36.46)
	MIX	−5.944(−19.53)	0.013(0.03)	0.324(0.65)	10.182(20.49)
Liver	EAR	−11.583(−13.31)	2.454(1.73)	0.418(0.29)	−32.555(−22.91)
	ERR(EAR)	−12.182(−12.49)	1.459(0.92)	−0.609(−0.38)	−32.995(−20.71)
	ERR	2.866(1.61)	−0.058(−0.02)	0.15(0.05)	2.319(0.8)
	MIX	−8.216(−12.15)	1.067(0.97)	0.018(0.02)	−27.144(−24.58)
Colon	EAR	−15.569(−22.63)	2.777(2.47)	0.094(0.08)	
	ERR(EAR)	−15.95(−23.99)	2.548(2.35)	0.19(0.17)	
	ERR	−3.42(−12.65)	−0.523(−1.18)	0.072(0.16)	−12.068(−27.34)
	MIX	−7.481(−6.32)	0.363(0.19)	0.164(0.08)	−11.587(−6)
Rectum	ERR	−7.564(−25.88)	1.986(4.16)	−0.197(−0.41)	
Bladder	EAR	−0.633(−2.38)	0.751(1.73)	0.009(0.02)	3.154(7.27)
	ERR(EAR)	−0.641(−2.09)	0.776(1.55)	0.076(0.15)	3.511(6.99)
	ERR	−2.603(−3.19)	0.865(0.65)	0.49(0.37)	28.606(21.45)
	MIX	−0.748(−2.03)	1.21(2.01)	0.02(0.03)	3.616(6)
Leukemia	EAR	−0.42(−2.93)	−1.894(−8.08)	0.084(0.36)	7.707(32.88)
	ERR(EAR)	−0.341(−2.69)	−1.698(−8.22)	0.125(0.61)	7.874(38.12)
	ERR	3.765(19.05)	−0.834(−2.59)	0.288(0.89)	11.04(34.21)
	MIX	0(0)	−1.742(−9.71)	0.123(0.69)	8.233(45.87)

numerous realizations of SMRs for aviators and radiation workers to assess the effect of adjusting lifetime risks through the use of SMRs. We also make no assumption that the present measures of astronaut HWE will remain in effect during the decades to follow, when lifetime risks for long-term (90–120 day missions) exposures on International Space Station will be realized, or when lifetime risk is realized for Mars missions. The additional uncertainties surrounding radioepidemiologic investigation of human space workers exposed to high-energy ions (GCRs) is unknown, and therefore risks can be greater than assumed. Hence, the higher SMRs among astronauts in the LSAH may not be inadmissible. Readers need to recognize that under the Central Limit Theorem, an SMR value determined from a single worker study is merely a point estimate derived from a distribution centered at SMR = 1. If each of the SMR studies used in this investigation were replicated, then the resulting distribution of SMRs would be different from those presented. Our investigation attempted to address the effects of study replication by using the majority of published SMR values for aviator and nuclear worker studies,

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Table 15. Regression coefficients (z-score) reflecting the mean change (%) in baseline risk (BLR) of cancer incidence for various adjustments. BLR regressed on age at exposure and dummy indicator variables for applying all-cause SMR, applying cancer SMRs, and females.

Cancer	Model	Age at exposure*10	All-cause SMR	Cancer SMR	Female
Nonleukemia	EAR	−1.322(−3.14)	6.089(8.84)	−14.318(−20.8)	−8.539(−12.4)
	ERR(EAR)	−1.327(−3.16)	6.198(9.03)	−14.492(−21.1)	−8.522(−12.41)
	ERR	−1.368(−3.47)	6.396(9.93)	−14.317(−22.23)	−8.453(−13.12)
	MIX	−1.328(−3.22)	6.223(9.25)	−14.383(−21.38)	−8.523(−12.67)
Esophagus	ERR	−0.003(−0.14)	0.064(1.85)	−0.132(−3.81)	−0.784(−22.66)
Lung	EAR	−0.003(−0.04)	1.121(9.74)	−1.768(−15.36)	−2.175(−18.9)
	ERR(EAR)	−0.025(−0.35)	1.119(9.63)	−1.757(−15.11)	−2.135(−18.36)
	ERR	−0.002(−0.02)	1.146(9.91)	−1.767(−15.29)	−2.128(−18.41)
	MIX	−0.009(−0.13)	1.129(9.87)	−1.764(−15.41)	−2.147(−18.76)
Stomach	EAR	−0.014(−1.03)	0.124(5.76)	−0.267(−12.43)	−0.39(−18.14)
	ERR(EAR)	−0.013(−1)	0.124(5.65)	−0.265(−12.08)	−0.387(−17.69)
	ERR	−0.016(−1.27)	0.122(5.79)	−0.263(−12.47)	−0.391(−18.53)
	MIX	−0.014(−1.09)	0.124(5.8)	−0.264(−12.4)	−0.39(−18.28)
Liver	EAR	−0.016(−1.48)	0.089(4.93)	−0.12(−6.64)	−0.651(−36.16)
	ERR(EAR)	−0.016(−1.41)	0.082(4.49)	−0.12(−6.58)	−0.652(−35.76)
	ERR	−0.018(−1.72)	0.083(4.9)	−0.116(−6.85)	−0.656(−38.74)
	MIX	−0.017(−1.53)	0.085(4.78)	−0.119(−6.69)	−0.653(−36.87)
Colon	EAR	−0.052(−2.64)	0.681(21.06)	−0.519(−16.06)	
	ERR(EAR)	−0.034(−1.54)	0.701(19.53)	−0.52(−14.5)	
	ERR	−0.061(−1.25)	0.6(7.56)	−0.843(−10.63)	−0.408(−5.14)
	MIX	−0.058(−1.19)	0.603(7.5)	−0.839(−10.44)	−0.413(−5.14)
Rectum	ERR	−0.052(−5.72)	0.112(7.51)	−0.325(−21.71)	
Bladder	EAR	−0.481(−3.3)	1.375(5.77)	−2.826(−11.86)	−1.886(−7.91)
	ERR(EAR)	−0.484(−3.34)	1.374(5.8)	−2.791(−11.78)	−1.941(−8.19)
	ERR	−0.479(−3.35)	1.363(5.83)	−2.814(−12.04)	−1.941(−8.31)
	MIX	−0.48(−3.31)	1.367(5.78)	−2.807(−11.87)	−1.922(−8.12)
Leukemia	EAR	−0.032(−2.54)	0.238(11.45)	−0.185(−8.92)	−0.504(−24.24)
	ERR(EAR)	−0.029(−2.38)	0.236(11.69)	−0.185(−9.17)	−0.504(−24.96)
	ERR	−0.029(−2.41)	0.246(12.42)	−0.181(−9.13)	−0.514(−25.92)
	MIX	−0.031(−2.48)	0.24(11.94)	−0.183(−9.12)	−0.507(−25.25)

fitting the SMRs with ECDF to develop smooth functions, and combining random quantiles from each source of information for input into 10,000 life table calculations, using different random variates for each table. Because of random sampling of source information, it is highly unlikely that we used the same risk coefficients, same radiation dose, same SMR, same misclassification correction factor, same cancer rates and all-cause mortality rates in the life tables that were generated.

The results of excess and baseline lifetime risks are encapsulated in the form of an uncertainty distribution about some median value that represents the location, and 95% CIs representing the scale (or s.d.). There is no one single scalar value that can be used to determine if the effect of HWE is underestimated or overestimated since the result is a distribution. Since lifetime risks of radiation-induced cancer are commonly presented in units of risk/Sv, we did not focus on historical or future dosimetry issues related to flight (mission) planning in order to project risks for

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various flight scenarios. By not doing so, our results can be directly compared with other results based on the standard units of risk/Sv.

Regarding ELRs, it is noteworthy to point out that the Risk of Exposure-Induced Death (REID) introduced by Thomas et al. [68] as

$$REID_c(e, D) = \int_e^{100} [\mu_c(a|e, D) - \mu_c(a)] S(a|e, D) da \tag{57}$$

is equivalent to $\pi(a, d)$ because the hazard function $\mu_c(a|e, D) - \mu_c(a)$ subtracts out the hazard function for spontaneously occurring cancer. Thus, the hazard functions in Eqs. 6 and 7 of Thomas et al. would be stated in this report as

$$\mu_c(a, e, t, s, y, D) = \beta(a, e, t, s) g(D), \tag{58}$$

for the additive projection model and

$$\mu_c(a, e, t, s, y, D) = \mu(a, y) \beta(a, e, t, s) g(D), \tag{59}$$

for the multiplicative model. Our previous work [69] suggests that results of the Elandt-Johnson and Johnson [60] method of estimating lifetime risks have been found to be similar to those estimated by Bunger et al. [70] and Gail [71]. The only difference between the Elandt-Johnson and Johnson method and Bunger method is that the former is based on the integral product of a hazard function, $h_c(d, a, t)$, and $S(t)$ and the latter is based on the integral product of the conditional probability, $q(t)$, and $S(t)$. Kahn and Sempos [72] suggest that the use of hazard rates will not underestimate risks based on probabilities because the denominator of a rate is comprised of fewer individuals (person-years) since it is based on the midpoint of the interval – probabilities, on the other hand, are based on denominator data at the beginning of the interval where the average person-years of follow-up is greater. Thus, the use of hazard rates in lifetime risk projection will result in estimates that are essentially slightly greater than risks based on probabilities.

Overall, the uncertainties surrounding lifetime risks of radiation exposure have always been complex, since workers are commonly exposed to mixtures of radiation from varying sources such as x- and γ-ray, fission products, etc., with varying energies and varying dose and dose-rate. To date, the National Institutes of Health IREP report and computer algorithm provide the most comprehensive lifetime risk projections for varying type and energies of ionizing radiation [67, 73]. To appropriately address ELRs for particulate space radiation, one needs to consider either a track-based or fluence-based approach and couple the radiation environment models to the system for projecting ELRs [4]. The overall focus of this investigation was mainly devoted to simulation of SMRs and corrections for misclassification, cancer and vital statistics, actuarial life table approaches, and how best to simulate uncertainty for all inputs used in lifetime risk projection.

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Declarations

Author contribution statement

Leif Peterson: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data; Wrote the paper.

Tatiana Kovyrshina: Performed the experiments; Analyzed and interpreted the data; Contributed reagents, materials, analysis tools or data.

Competing interest statement

The authors declare no conflict of interest.

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Additional information

The following supplementary material is associated with this article: Supplementary Material.

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