

Utilizing the Life Span Study Data in NASA Astronaut Cancer Risk Assessment

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Abstract

During space missions, astronauts are continuously exposed to extraterrestrial radiation that differs in quality and dose rate than terrestrial radiation. As such, astronauts are considered special radiation workers and are subject to a unique set of standards in place of the Occupational Safety and Health Administration (OSHA) standards that cover terrestrial radiation workers. To accurately estimate and communicate the risk of cancer from space radiation to astronauts and mission managers to facilitate decision making, the NASA Space Cancer Risk (NSCR) model was developed and has been used operationally at NASA since 2013. The Life Span Study (LSS) of the atomic bomb survivor cohort serves as a key foundational dataset for NSCR that enables quantification of health risks from space radiation. Here, we provide description of how the LSS data and models are currently used within the NSCR model and discuss future perspectives for utilizing this robust dataset to improve risk estimation.

Summary

This report provides an overview of how NASA uses Life Span Study data to model astronaut cancer risk, describing the application of epidemiological models and future opportunities to enhance risk projections for space radiation exposure.

Introduction

Humans on missions in low Earth orbit (LEO) or beyond LEO (BLEO) to the moon and Mars are exposed to a complex and highly penetrating radiation environment in the form of galactic cosmic rays (GCR). The GCR environment is encountered at a chronic low dose rate and consists of high atomic number and high energy (HZE) nuclei (1%) as well as high energy protons (87%) and helium ions (12%). The HZE component of space radiation has a high relative biological effectiveness (RBE), as traversal of HZE ions through biological matter elicits clustered DNA damage and complex lesions which are difficult to repair, as compared to x-rays or gamma rays. Accumulated radiation-induced damage throughout a mission increases the likelihood for various adverse health outcomes such as cancer, which is considered the paramount long-term human health risk attributable to GCR exposure [1].

Accurately estimating the excess cancer risk from space radiation is needed to establish permissible exposure limits, guide mission planning, and inform crewmembers and other stakeholders. Such health risk projections are also vital for future exploration and potential colonization of celestial bodies, where total mission durations and accumulated exposures far exceed anything experienced by humans in space to date [2]. Moreover, radiation exposures and corresponding health risks are reduced in LEO compared to beyond LEO due to protection from the Earth's magnetosphere. Yet, a lack of directly relevant spaceflight and ground-based data plagues space radiation-induced cancer risk projection accuracy. There has only been a small cohort of humans that have travelled to LEO and an even smaller sub-cohort have flown beyond LEO. Most of these missions were also of limited duration, resulting in very low dose exposures (<0.1 Sv) compared to what is expected for a Mars mission (~1 Sv) [3]. The combination of these two factors

hinders the use of historical spaceflight data to guide risk assessments for long duration missions beyond LEO [4].

Given these limitations, the approach for projecting space radiation induced health risks has relied upon computational modeling and probabilistic risk assessments using epidemiological data associated with terrestrial exposures and extrapolating them to space radiation environments. The Life Span Study (LSS) of the atomic bomb survivor cohort has provided the key dataset allowing such extrapolations, thereby enabling the estimation of space radiation health risks. In this paper, we first briefly describe the LSS cohort. A summary of how LSS data and models are currently used within the NASA space cancer risk model is provided. Finally, paths for future research involving the LSS cohort that could notably impact space radiation risk projections are discussed.

What is the Life Span Study?

The Life Span Study (LSS) of the atomic bomb survivor cohort, ongoing since the 1950's [5, 6, 7], provides the foundational dataset from which space radiation health risks are projected [8, 2]. The cohort includes ~120,000 individuals representing ~93,000 atomic bomb survivors and ~27,000 unirradiated persons who were not in Hiroshima or Nagasaki at the time of the blasts. The exposure level assigned to each of the bomb survivors is quantified in terms of the weighted absorbed colon dose (Gy), and irradiated subjects are assigned to one of several dose categories between 0 Gy and 3 Gy (an additional high dose category exists for > 4 Gy). Further classifications are applied to account for sex, age at exposure, attained age and smoking status (pack years smoked). The resulting data allow site-specific disease incidence and mortality risks to be quantified for each of the categorial stratifications.

Due to its scale, the LSS provides a solid basis for risk estimation for low-linear energy transfer (LET) radiation. Using these data, models for cancer incidence and mortality were developed with the assumption that they would be scalable to other populations, dose rates, and radiation types (high-LET) [8]. To enable practical risk assessment, models must be developed to represent the excess incidence and mortality data inferred from the

LSS cohort in terms of the key covariates—sex, age at exposure, attained age, smoking status, and dose. Consideration must also be given to translating LSS population risks to other populations of interest (e.g. the modern-day US population). A significant amount of effort has been spent in developing such models and associated uncertainties, as summarized by United Nations Science Committee on the Effects to Atomic Radiation (UNSCEAR) [9], Biological Effects of Ionizing Radiation BEIR-VII [10], National Council on Radiation Protection and Measurements (NCRP) [11], and more recently by Stabilini et al. (2023) [12]. Additional translational components are required for space radiation risk projections to account for differences in radiation quality and dose rate. That is, the LSS cohort was exposed to an acute dose of primarily low-LET gamma-rays, while the space environment is characterized by a continuous low dose rate of highly energetic particle species including pions, neutrons, hydrogen, and higher LET ions up to Ni. Continued research into radiation quality and dose-rate effects is needed to clarify the dose-to-risk relationship for space radiation exposures [8, 2]. Here, we provide a detailed description of the methods adopted at NASA to estimate cancer risk in astronauts using the Radiation Effects Research Foundation (RERF)-managed LSS cohort.

How does NASA estimate cancer risk for astronauts?

Excess cancer risk attributable to space radiation exposure is currently assessed and communicated using the risk of exposure induced death (REID) and risk of exposure induced cancer (REIC). In this section, a condensed summary of the REID and REIC calculations implemented within the NASA space cancer risk (NSCR) model is given. The information provided in this section was drawn from Cucinotta et al. (2013) [8] and Simonsen et al. (2021) [2] where further details can be found. Generally, the REID and REIC are calculated by folding a radiation hazard rate for mortality and incidence (respectively) against a survival probability and integrating over all ages after exposure. The hazard rates are obtained from tissue-specific models derived from the LSS dataset accounting for sex, age at exposure, attained age, and exposure level (Sv). Adjustments are made to account for differences in radiation quality and dose rate; the LSS cohort received a nearly instantaneous dose of low-LET gamma radiation with some neutron contamination, while humans in space encounter a continuous low-dose-rate mixed field

irradiation including both low- and high-LET components. A population transfer model is incorporated to account for the differences between the LSS cohort characteristics and the modern-day US population. Smoking history is also included to account for the never-smoker characteristics of the astronaut population. The survival probabilities are obtained from publicly available sources such as the National Vital Statistics Reports, published by the CDC's National Center for Health Statistics.

Baseline NASA Space Cancer Risk Model

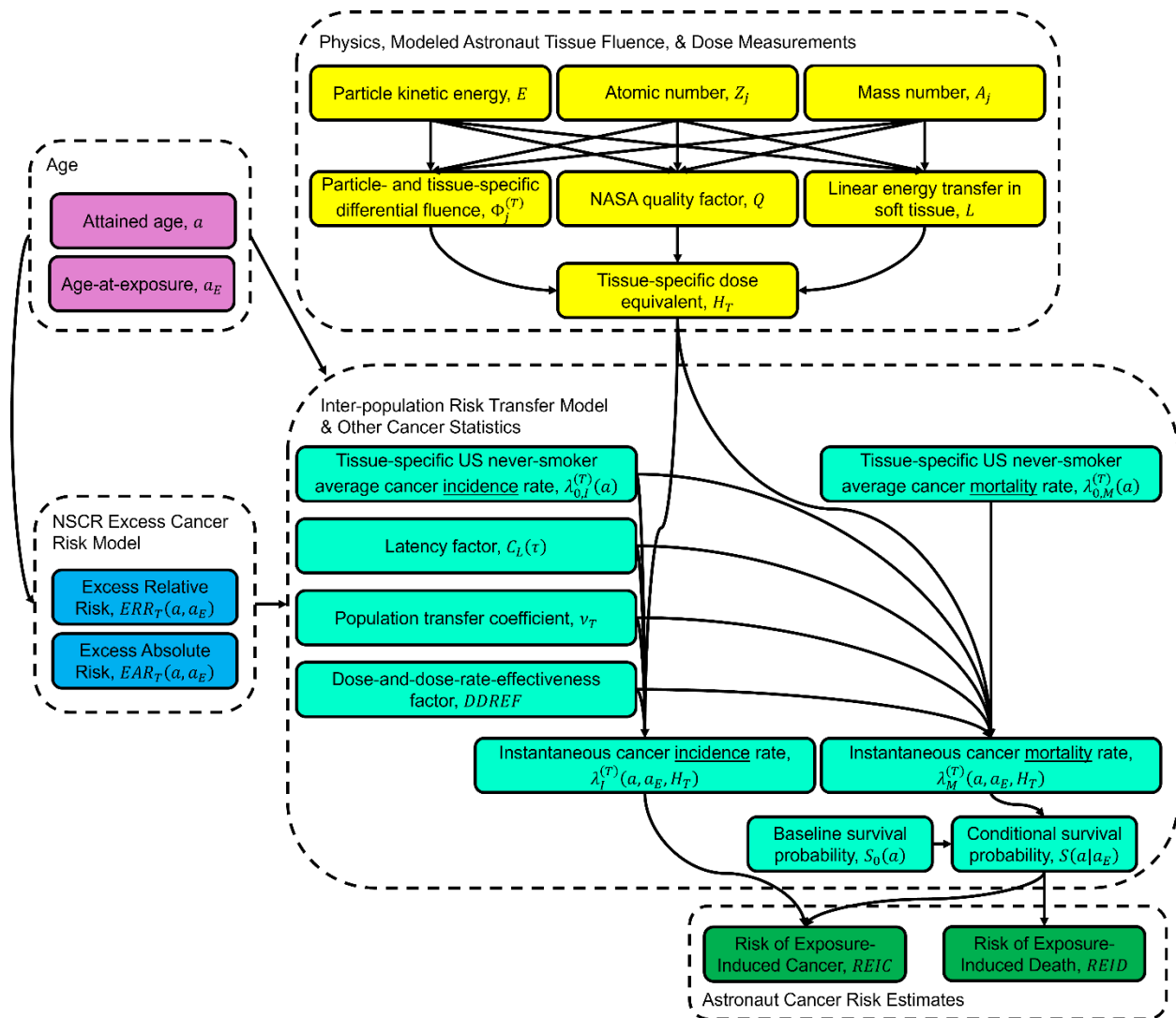


Figure 1. Schematic overview of NSCR model.

The basic workflow of the NSCR model is summarized in Figure 1. The REID and REIC are calculated as

$$REID = \sum_T \int_{a_E}^{\infty} \lambda_M^{(T)}(a, a_E, H_T) S(a|a_E) da, \quad (1)$$

$$REIC = \sum_T \int_{a_E}^{\infty} \lambda_I^{(T)}(a, a_E, H_T) S(a|a_E) da, \quad (2)$$

where T is the radiosensitive tissue, a_E is the age at exposure, a is the attained age, H_T is the tissue-specific dose equivalent (Sv), and S is the conditional probability of survival adjusted by the radiation hazard. The quantities $\lambda_M^{(T)}$ and $\lambda_I^{(T)}$ are the sex- and tissue-specific radiation cancer mortality and incidence rates derived from the LSS dataset and associated dose-response models and transferred to an astronaut-like population, described in more detail later in this section.

The conditional survival probability in equations (1) and (2) is calculated as

$$S(a|a_E) = \frac{S_0(a)}{S_0(a_E)} e^{-\sum_T \int_{a_E}^a \lambda_M^{(T)}(a', a_E, H_T) da'}, \quad (3)$$

where $S_0(a)$ is the survival probability for persons at age a . The survival data are obtained for the average US population from National Vital Statistics Reports, with adjustments applied to account for enhanced survival in the never-smoker sub-population [8].

The tissue dose equivalent is calculated as

$$H_T = \sum_j \int_0^{\infty} \Phi_j^{(T)}(E, A_j, Z_j) Q(E, A_j, Z_j) L(E, A_j, Z_j) dE, \quad (4)$$

where $\Phi_j^{(T)}$ is the mission fluence of type j particles with atomic mass A_j and charge number Z_j , Q is the NASA radiation quality factor [8], and L is the LET in soft tissue (keV/ μ m). The charge and energy dependent quality factor used within NSCR is used to translate between the complex mixed-field space environment and the low-LET (primarily) gamma exposure associated with atomic bombs.

The cancer incidence and mortality rates, $\lambda_I^{(T)}$ and $\lambda_M^{(T)}$, are obtained from excess risk models derived from LSS data and may be written as

$$\lambda_I^{(T)}(a, a_E, H_T) = C_L^{(T)}(\tau) \left[v_T ERR_T(a, a_E) \lambda_{0,I}^{(T)}(a) + (1 - v_T) EAR_T(a, a_E) \right] \frac{H_T}{DDREF}, \quad (5)$$

$$\lambda_M^{(T)}(a, a_E, H_T) = C_L^{(T)}(\tau) \left[v_T ERR_T(a, a_E) \lambda_{0,M}^{(T)}(a) + (1 - v_T) EAR_T(a, a_E) \frac{\lambda_{0,M}^{(T)}(a)}{\lambda_{0,I}^{(T)}(a)} \right] \frac{H_T}{DDREF}. \quad (6)$$

In equations (5) and (6), the term in brackets represents the excess cancer risk per Sv in the average US population or never-smoker sub-population. The dose and dose-rate effectiveness factor (DDREF) accounts for the differences between the acute exposure of the atomic bomb and the low-dose-rate space radiation environment. NSCR considers a nominal DDREF value of 1.5 obtained from Bayesian analyses [8]. The quantity $C_L^{(T)}(\tau)$, with $\tau = a - a_E$, is the latency factor describing the time-lag between age at exposure and first appearance of cancer. The latency factor is zero for $\tau \leq 5$ years (2 years) for solid cancer (leukemia) and unity otherwise.

The excess risk term in brackets involves models derived from the LSS dataset as well as a population transfer methodology as discussed in the introduction of this section. The terms $\lambda_{0,I}^{(T)}$ and $\lambda_{0,M}^{(T)}$ are the cancer incidence and mortality rates in the average US population with adjustments applied if the never-smoker sub-population is considered. ERR_T and EAR_T are the sex- and tissue-specific excess relative risk and excess absolute risk functions dependent on age (a) and age at exposure (a_E). A generalized equation that can be used to represent either ERR_T or EAR_T is

$$ER = \hat{\beta}(s) e^{\hat{\gamma} f(a_E) + \hat{\eta} g(a) + \hat{\delta} h(a - a_E)}. \quad (7)$$

Table 1 provides the functional forms, parameter values, and sources from which the information was obtained for each tissue. The quantity v_T is the population transfer

coefficient used to weight the excess relative risk (ERR) and excess absolute risk (EAR) terms. Values for ν_T used in NSCR are given in Table 2. Figure 2 graphically summarizes how LSS data is incorporated into the broader NSCR model.

Table 1. Tissue-specific parameters and functions used in NSCR to compute ERR_T and EAR_T ; the units for $\hat{\beta}(s)$ are Sv^{-1} for ERR_T model parameters and $(10^4 Sv \text{ person-years})^{-1}$ for EAR model parameters.

Tissue	Source	$\hat{f}(a_E)$	$\hat{g}(a)$	$\hat{h}(a - a_E)$	$\hat{\beta}(\text{male})$	$\hat{\beta}(\text{female})$	$\hat{\gamma}$	$\hat{\eta}$	$\hat{\delta}$
ERR model parameters									
Leukemia	[13]	$\ln\left(\frac{a_E}{25}\right)$	$\ln\left(\frac{a}{50}\right)$		1.599	1.599	0.233	-1.98	
Stomach	[9]		$\ln(a)$		4025	4025		-2.253	
Colon	[9]		$\ln(a)$		1.481×10^6	1.481×10^6		-3.526	
Liver	[9]				0.3951	0.3951			
Bladder	[9]				0.8989	0.8989			
Lung	[9]				0.3182	1.399			
Esophagus	[9]				0.5278	0.5278			
Oral Cavity	[6]		$\ln\left(\frac{a}{70}\right)$		0.39	0.39		-1.65	
Brain	[9]	$\ln(a_E)$			7.431	7.431	- 0.9897		
Thyroid	[10]	$\frac{a_E - 30}{10}$			0.53	1.05	-0.83		
Other	[9]		$\ln(a)$	$\ln(a - a_E)$	143.2	143.2		-2.939	1.645
Prostate	[6]		$\ln\left(\frac{a}{70}\right)$		0.11			-1.65	
Breast	[10]								
Ovary	[6]		$\ln\left(\frac{a}{70}\right)$			0.61		-1.65	
Uterus	[6]		$\ln\left(\frac{a}{70}\right)$			0.10		-1.65	
EAR model parameters									
Leukemia	[13]			$\ln\left(\frac{a - a_E}{25}\right)$	1.187	$1.187e^{-0.594}$			-0.574
Stomach	[9]		$\ln(a)$		3.969×10^{-3}	3.969×10^{-3}		1.828	
Colon	[9]			$\ln(a - a_E)$	2.875×10^{-5}	2.875×10^{-5}			3.204
Liver	[9]		$\ln(a)$		1.037×10^{-6}	1.037×10^{-6}		3.479	
Bladder	[9]		$\ln(a)$		6.135×10^{-11}	6.135×10^{-11}		5.748	

Lung	[9]	$\ln(a)$	1.008×10^{-7}	1.505×10^{-7}	4.211
Esophagus	[9]		0.1453	0.1453	
Oral Cavity	[6]	$\ln\left(\frac{a}{70}\right)$	0.56	0.56	2.38
Brain	[9]		0.4924	0.4924	
Thyroid					
Other	[9]	$\ln(a - a_E)$	2.208×10^{-3}	2.208×10^{-3}	2.161
Prostate	[6]	$\ln\left(\frac{a}{70}\right)$	0.34		2.38
Breast	[10]	$\frac{a_E - 25}{10} \ln\left(\frac{a}{50}\right)$		10	-0.5 $\begin{cases} 3.5, a < 50 \\ 1, a \geq 50 \end{cases}$
Ovary	[6]	$\ln\left(\frac{a}{70}\right)$		0.56	2.38
Uterus	[6]	$\ln\left(\frac{a}{70}\right)$		0.56	2.38

Table 2. Population transfer weights, v_T , used in NSCR.

Tissue	Population transfer weight, v_T
Leukemia	0.5
Stomach	0.7
Colon	0.7
Liver	0.7
Bladder	0.7
Lung	0.5
Esophagus	0.7
Oral Cavity	0.7
Brain	0.7
Thyroid	1.0
Other	0.7
Prostate	0.7
Breast	0
Ovary	0.7
Uterus	0.7

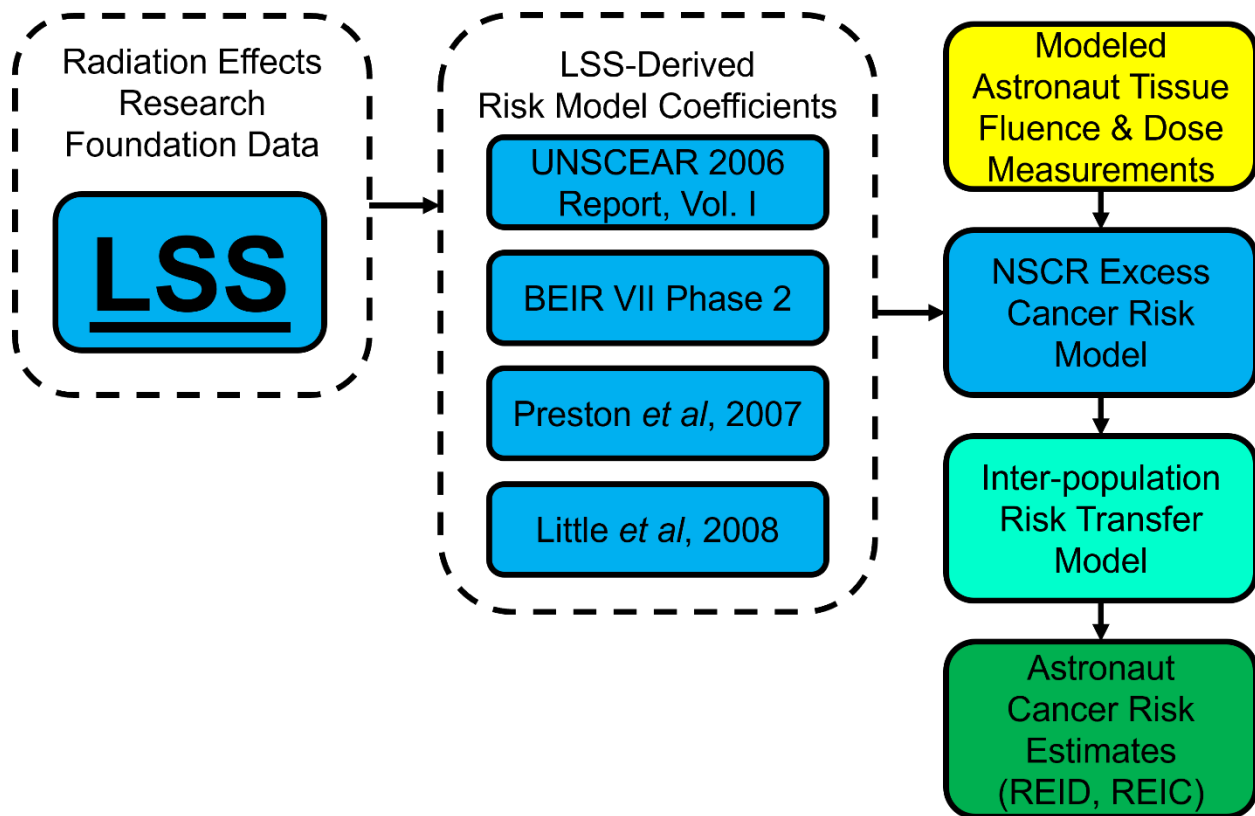


Figure 2. Description of how LSS data supports the NSCR model.

LSS data, obtained/managed by RERF, serves as the backbone for the excess cancer risk models. Scientific organizations and research groups use LSS data to derive situation-specific risk model coefficients. The excess cancer risk models developed by the groups listed here [9, 10, 6, 13] are those that are (at least partially) included in the NSCR's excess cancer risk calculations. The excess risk models are combined with calculated tissue fluences and dosimetry measurements within NSCR along with adjustments for radiation quality, dose-rate, and population transfer. The primary outputs from NSCR are REID and REIC. For more granular detail on the structure of the NSCR model, see Figure 1.

Uncertainties

Uncertainty quantification is a critical aspect of risk communication [14], particularly in the context of long duration spaceflight where multiple hazards and unknowns must be considered simultaneously. It has been well documented that radiation quality and dose-

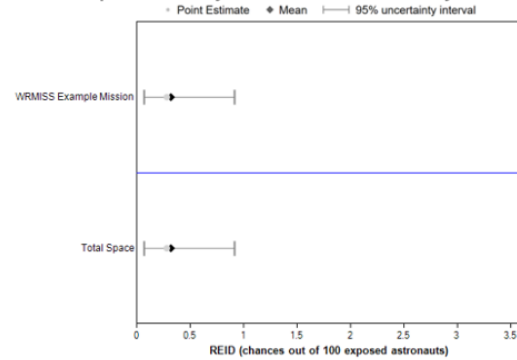
rate effects drive uncertainties in space radiation risk projections [8, 2]; however, uncertainties associated with excess risk models derived from the LSS cohort are also substantial, leading to approximately a 1.5-fold uncertainty in space radiation cancer risk projections (fold uncertainty calculated as the ratio between the 97.5th percentile and mean value for REID) [2].

Monte Carlo procedures are used to propagate uncertainties through equations (1) and (2) to produce probability distributions for REIC and REID. The procedures rely on either objectively or subjectively (subject matter expert opinion) assigned distributions assigned to quantities/parameters appearing in the quality factor, DDREF, latency factor, excess risk, transfer weights, and tissue fluence [8, 2]. The resulting probabilistic REIC and REID distributions allow quantities such as the mean and 95% confidence levels to be determined. The current NASA cancer risk model carries an uncertainty of approximately 2.8-fold for a Mars mission [2].

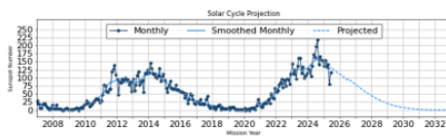
Operational Implementation

The NASA space cancer risk model has been in operational use since 2013 and is currently used to conduct radiation risk assessment analyses for NASA (and Canadian Space Agency) astronauts. Since 2013, the NASA Space Radiation Analysis Group (SRAG) has compiled and produced at least 700 astronaut radiation risk reports, for at least 138 unique astronaut and astronaut candidates, that include an estimate of mean and 97.5th percentile REID values on a per mission basis, alongside other radiation exposure statistics. See Figure 3 for an example of one page of a typical astronaut radiation report constructed using the Risk Analysis Environment (RAE) tool [15]. In addition to producing radiation exposure history reports for astronauts, NSCR, through tools like RAE and the Crewed Interplanetary Mission for Radiation risk Analysis Environment (CIMIRAE), is also used for risk projection and mission planning purposes.

Mission Exposure History and Cancer Risk Summary



Total Radiation Exposure Affecting Flight Eligibility	CPD (mGy)	Effective Dose (mSv)	REID (%) Mean	REID (%) 97.5th Percentile
WRMISS Example Mission (projection) Crew-worn dosimeter	50.00	78.86	0.32	0.92
Mission Total		78.86	0.32	0.92
SPEL (Career Cancer Limit)		600		
Effective Dose remaining until SPEL reached		521.14		



Solar Cycle Projection Figure source credit: Space Weather Prediction Center, NOAA, <https://www.swpc.noaa.gov/products/solar-cycle-progression>, Royal Observatory of Belgium Solar Influences Data Analysis Center, <https://www.sidc.be/SILSO/datafiles>

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Notes:

- The SPEL is 600 mSv mean effective dose.
- The Permissible Mission Duration (PMD) to remain within career limit is calculated by subtracting all mission exposures from the NASA SPEL of 600 mSv mean effective dose.
- The reported PMD values for specific missions and mission dates are updated annually. They rely upon projections of future missions with variables including dynamic and uncertain space radiation environments, vehicle trajectory, and shielding.
- Risk of Exposure Induced Death (REID) from cancer is a statistical quantity. A distribution incorporating the current state of knowledge is created to estimate the REID. The bands in the above chart represent a two-sided 95% uncertainty interval surrounding the mean. The upper bound is the 97.5th percentile.

Figure 3. Example astronaut report page that includes 1) a graph that shows the REID point estimate, mean REID, and 95% confidence interval associated with the mean REID, 2) a graph of the total number of sunspots as a function of time, 3) a graph of 180-day ISS-mission effective dose estimates, 4) a table of mission-specific and total measured absorbed dose, NASA effective dose, mean REID, and 97.5th percentile REID, and 5) the longest possible ISS mission the astronaut could potentially undertake without exceeding the NASA career space permissible exposure limit. Other pages (not shown) include a list of medical imaging exposures, internal nuclear medicine exposures, exposures associated with biomedical research studies, and granular space mission analysis parameters.

How could the results of the Life Span Study be used in the future?

There are several opportunities for additional research based on the LSS cohort that may support space radiation risk projections, some of which are discussed below. The NASA space cancer risk model is based on a specific choice of models for radiation quality, dose rate, and excess risk, as described in the previous section. It has been shown that consideration of equally plausible models for these same components yields widely

varying mean REID values (almost a factor of 2) [2]. NASA utilizes mean REID as the basis for a 600 mSv career effective dose limit [17], suggesting that robust mean risk projections are needed. Multi-model ensemble methodologies continue to be advanced in a variety of scientific fields and offer the potential to provide more robust central estimates of risk despite large uncertainties and sparse data (Figure 4). Stabilini et al. (2023) have applied multi-model ensemble methods to all solid cancer LSS data based on objective statistical weights and rigorous uncertainty quantification [12]. Such methods can be extended to tissue-specific LSS data to align with the NSCR framework and improve central estimates for mean REID. On these lines, scientists at NASA are utilizing NSCR along with other models and exposed population cohorts to create a multi-modal ensemble risk assessment (MERA) model. The MERA model is also expected to assess non-cancer long-term health risks such as cardiovascular disease and central nervous system decrements—in addition to REIC and REID—with the eventual goal of incorporating individual radiation susceptibility parameters and assessing the effectiveness of countermeasures at reducing risk (Figure 4).

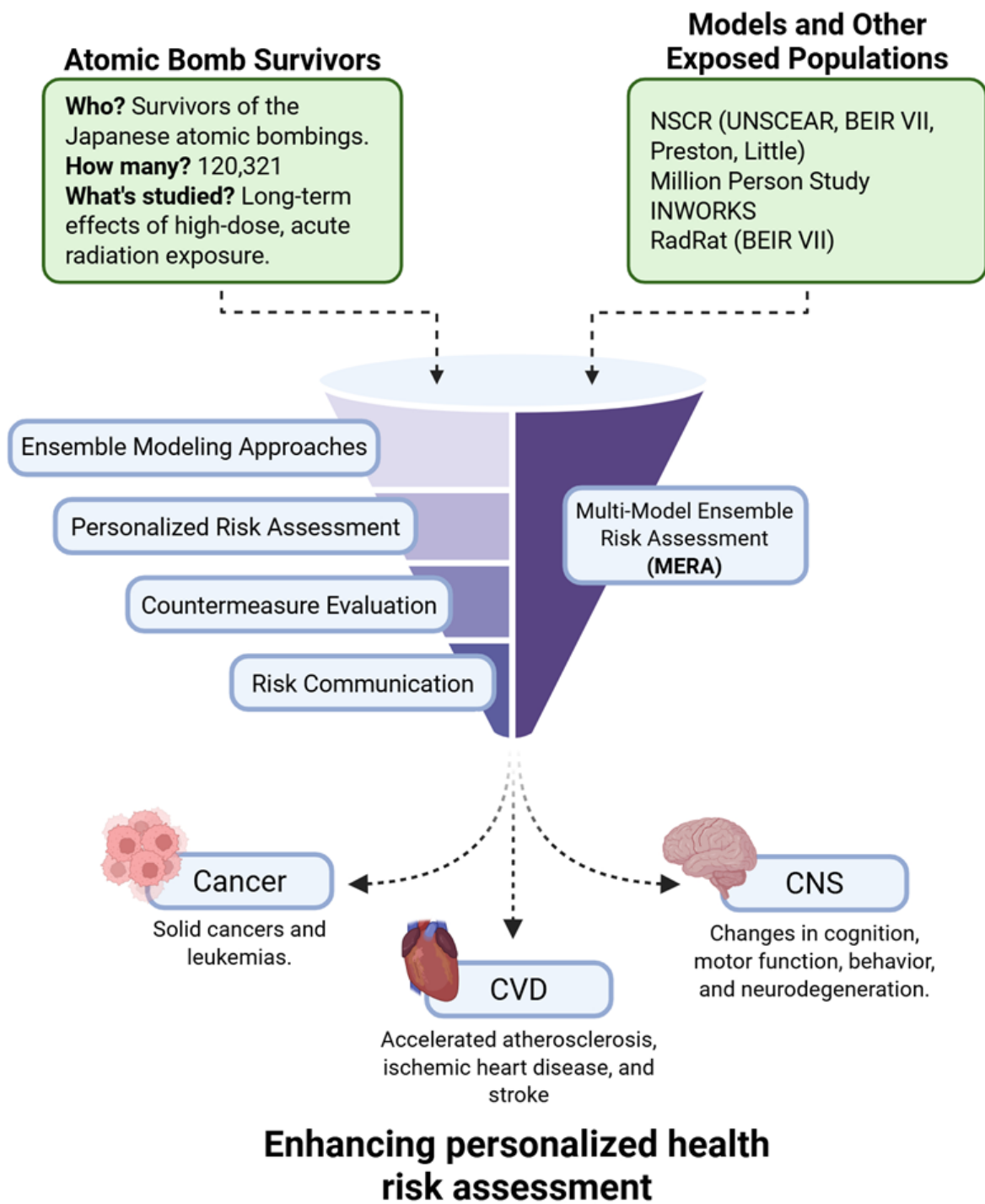


Figure 4. Description of Multi-Model Ensemble Risk Assessment Project

Additionally, archived biospecimens are available from the LSS atomic bomb survivor cohort. Since lung cancer is estimated to account for the single largest fraction of space

radiation-induced lifetime cancer mortality (REID) even when the (reduced) smoking habits of modern space travelers as compared to the LSS cohort are considered, analysis of stored tissue samples from deceased individuals in the cohort may offer direct evidence of combined effects of smoking and radiation exposure on lung cancer risk. Additionally, analysis of archived blood samples may help identify associative biomarkers of radiation-induced accelerated aging diseases such as clonal hematopoiesis of indeterminate potential (CHIP), which was recently shown to confer a notably increased risk of leukemia amongst CHIP carriers exposed to space radiation as compared to average US population [16]. Comparative analyses of the molecular and immune landscapes of exposed vs background tumors may offer mechanistic insights that broadly inform strategies for disease prevention/mitigation and surveillance in astronauts and commercial space crews. Further analyses of the impact of age, sex, and other non-modifiable and modifiable risk factors on cancer incidence, as well as understanding the contribution of genetic and epigenetic factors to individual radiation sensitivity are important areas of research and in the future could be incorporated into risk projections.

Operationally, LSS cancer risk models will continue to serve as a critical input component for generating US-population-applicable cancer mortality and incidence hazard functions for the foreseeable future. As US-based cancer statistics continue to accumulate, background cancer rates used in NSCR/RAE will be updated accordingly. Individualized cancer risk screening recommendations based on space radiation exposure estimates may be considered in the future; early cancer detection is a key component in mitigating mortality rates.

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DECLARATION OF INTERESTS

The authors declare no competing interests.

DATA AVAILABILITY STATEMENT

No new data were generated or analyzed for this report.

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