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Updates to Astronaut Radiation Limits: Radiation Risks for Never-Smokers

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New epidemiology assessments of the life span study (LSS) of the atomic bomb survivors in Japan and of other exposed cohorts have been made by the U.S. National Academy of Sciences, the United Nations Committee on the Effects of Atomic Radiation, and the Radiation Research Effects Foundation in Japan. The National Aeronautics and Space Administration (NASA) uses a 3% risk of exposure-induced death (REID) as a basis for setting age- and gender-specific dose limits for astronauts. NASA's dose limits originate from the report of the National Council on Radiation Protection and Measurements (NCRP) in the year 2000 based on analysis of older epidemiology data. We compared the results of the recent analysis of the LSS to the earlier risk projections from the NCRP. Using tissue-specific, incidence-based risk transfer from the LSS data to a U.S. population to project REID values leads to higher risk and reduced dose limits for older astronauts (>40 years) compared to earlier models that were based on mortality risk transfer. Because astronauts and many other individuals should be considered as healthy workers, including never-smokers free of lifetime use of tobacco, we considered possible variations in risks and dose limits that would occur due to the reference population used for estimates. After adjusting cancer rates to remove smoking effects, radiation risks for lung and total cancer were estimated using a mixture model, with equal weights for additive and multiplicative transfer, to be 20% and 30% lower for males and females, respectively, for never-smokers compared to the average U.S. population. We recommend age- and gender-specific dose limits based on incidence-based risk transfer for never-smokers that could be used by NASA. Our analysis illustrates that gaining knowledge to improve transfer models, which entail knowledge of cancer initiation and promotion effects, could significantly reduce uncertainties in risk projections. © 2011 by Radiation Research Society

INTRODUCTION

In recent years, updates to the assessment of cancer incidence and mortality in the life span study (LSS) of the A-bomb survivors and other radiation-exposed cohorts have been made. Studies include the U.S. National Academy of Sciences Biological Effects of Ionizing Radiation's BEIR VII report (*1*), the United Nations Committee on the Effects of Atomic Radiation's UNSCEAR 2006 report (*2*), and the analysis of tissue-specific cancer incidence data from the LSS by the Radiation Research Effects Research Foundation (RERF) in Hiroshima, Japan (*3*). A new evaluation of organ doses of the LSS cohort, resulting in the Dosimetry System 2002 (DS02) (*4*), preceded these reports, and data for longer follow-ups are available compared to previous analyses. The new dosimetry analysis has been used to make tissue-specific incidence transfer from the LSS to predict fatal cancer risks for an average U.S. population as described in the BEIR VII report (*1*). This approach leads to important differences compared to models based on mortality risk transfer. Several other differences in methodology and error assessments occur in these reports (*1–3*), and a new analysis of the dose and dose-rate reduction effectiveness factor (DDREF) is described in the BEIR VII report (*1*).

Astronaut radiation exposures include galactic cosmic rays (GCR), comprising high-energy protons and high-charge and energy (HZE) nuclei, and medium-energy protons that make up trapped radiation in the Earth's magnetic field and solar particle events (SPE). Based on recommendations from the National Council on Radiation Protection and Measurements (NCRP) (*5, 6*), NASA limits lifetime risks of astronauts to a 3% risk of exposure-induced death (REID). Conversion of exposure to risk uses model calculations derived from human epidemiology data for low-linear energy transfer (LET) radiation, organ doses and LET-dependent particle fluence spectra, and radiation quality factors. The absence of epidemiology data from astronauts and the limited scientific understanding of HZE-particle nuclei and secondary high-LET radiation in space, such as neutrons, lead to large uncertainties in estimating cancer and other risks from space radiation. NASA applies radiation limits with an additional requirement to protect against the upper 95% confidence level of risk projections using an uncertainty assessment of factors that enter into risk calculations (*7–13*). The large

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uncertainties in projecting the risks from space radiation and the potential for unacceptable risks from long-term GCR exposures are major scientific challenges to achieving long-term stays on the International Space Station (ISS) and the goal of Mars exploration.

The purpose of the present report is to compare the results of newer studies (*1–3*) with the earlier NCRP analysis (*6*) used at NASA and to recommend point estimates of risk per unit dose and dose limits to be used for the ISS missions and planning of future exploration missions to Mars. Further analysis of uncertainties and radiation quality functions for cancer risk projections for space radiation will be reported elsewhere. Astronauts and many other radiation workers or medical patients exposed for diagnostic reasons share common healthy attributes such as good nutritional and exercise habits and abstinence from smoking. More than 90% of astronauts are never-smokers (defined here as lifetime use less than 100 cigarettes) and the remainder are former smokers. Use of the average U.S. population as a default reference to estimate risks was not considered in the past, as in the NCRP projection models used at NASA (*5, 6*), may not be appropriate for astronauts. The reference population enters risk calculation in two ways: First, risk models consider competing causes of death from non-radiation risks, with longer life span possibly increasing lifetime radiation risk. Second, multiplicative or additive risk transfer models for applying data from exposed populations to the reference populations are used in models (*1, 2, 6*), with the multiplicative risk projection proportional to the cancer risks in the population under study. For the astronauts, a military aviation population could be an appropriate choice for reference population data; however, data of sufficient accuracy have not been reported. Instead, we studied how cancer and all causes of death rates for all states and the District of Columbia and other demographic factors affected risk calculations. These data sets show a wide variation in average life span and age-specific cancer rates; however, we found that they result in only a small variation of REID probabilities. In contrast, recent analysis of lung cancer risks for never-smokers in the U.S. (*14*) and for radiation exposures of never-smokers in the LSS (*15*) led to a significantly lower lung and total cancer risk estimates. We describe calculations of risks and dose limits comparing the reports cited above (*1–3*) to the NCRP model (*6*) and recommend that astronaut risk models be based on never-smokers as a reference population.

METHODS

The instantaneous cancer rate (mortality or incidence) can be a function of dose D or dose rate D_r, gender, age at exposure a_E, attained age a, or latency L, which is the time after exposure $L = a - a_E$. These dependences may vary for each cancer type that could be increased by radiation exposure. Hazard rates for cancer incidence λ_I and cancer mortality λ_M can be modeled with similar approaches. The REID is calculated by folding the instantaneous radiation cancer mortality rate with the probability of surviving to time t, which is given by the survival function $S_0(t)$ for the background population times the probability for radiation cancer death at previous time and then integrating over the remainder of a lifetime:

$$REID(a_E,D) = \int_{a_E} dt \lambda_M(a,a_E,D) S_0(t) e^{-\int_{a_E}^{t} dz \lambda_M(z,a_E,D)}, \quad (1)$$

where z is the dummy integration variable. Similarly, the risk of exposure-induced cancer (REIC) uses a radiation cancer incidence rate folded with the probability to survive to time t and integrating over the remainder of a lifetime:

$$REIC(a_E,D) = \int_{a_E} dt \lambda_I(a,a_E,D) S_0(t) e^{-\int_{a_E}^{t} dz \lambda_M(z,a_E,D)}. \quad (2)$$

After adjustment for low doses and dose rates though the DDREF, the tissue-specific cancer incidence rate for an organ dose equivalent, H_T , can be written as a weighted average of the multiplicative and additive transfer models, often called a mixture model:

$$\lambda_{IT}(a_E,a,H_T) = [v_T ERR_T(a_E,a)\lambda_{0IT}(a) + (1-v_T) EAR_T(a_E,a)] \frac{H_T}{DDREF}, \quad (3)$$

where v_T is the tissue-specific transfer model weight, λ_{0IT} is the tissue-specific cancer incidence rate in the reference population, the total cancer incidence rate is $\lambda_I(a,a_E) = \sum_T \lambda_{IT}(a,a_E)$, and ERR_T and EAR_T are the tissue-specific excess relative risk and excess additive risk per sievert, respectively. [Note that the BEIR VII report used a geometric average of the multiplicative and additive transfer models instead of Eq. (3)].

Two approaches for estimating the mortality rate can be considered. In the first approach, overall rates for leukemia and all solid cancers can be fitted directly to the LSS mortality data as has been done in the past (*1, 6, 17*). A second model is used in the BEIR VII report (*1*), where the tissue-specific cancer mortality rate is written using ERR and EAR functions fitted to incidence data as

$$\lambda_{MT}(a_E,a,H_T) = \left[v_T ERR_T(a_E,a)\lambda_{0MT}(a) + (1-v_T)\frac{\lambda_{0MT}(a)}{\lambda_{0IT}(a)} EAR_T(a_E,a) \right] \frac{H_T}{DDREF}. \quad (4)$$

λ_{0MT} is the tissue-specific cancer mortality rate in the reference population. In Eq. (4), the ERRs for incidence and mortality are assumed to be the same, and the EAR for mortality risk is assumed as the EAR for incidence adjusted by the ratio of mortality to incidence in the population for which risks are being estimated.

The recent reports from BEIR VII (*1*), UNSCEAR (*2*) and Preston *et al.* (*3*) used different methods to fit functional forms for ERR and EAR to the LSS data. Preston *et al.* (*3*) used Poisson regression models with appropriate adjustments to test several dose–response models with a linear dose–response model providing the best fits of REIC for most solid cancers. Suppressing the subscript for tissue type, the results for ERR from Preston *et al.* (*3*) are represented by the function

$$ERR(a,a_E,D) = \beta_s f(D) \left(\frac{a}{70}\right)^p e^{-c(a_E-30)}, \quad (5)$$

with a similar form for the EAR function. In Eq. (5), β_s is a gender-dependent constant and $f(D)$ represents a dose–response function. Several dose–response functions were considered; however, a linear

function was found to provide the best fit, i.e. $f(D) = D$. These functions have no dependence on latency. The BEIR VII report (*1*) used models similar to Eq. (5); however, they fit lifetime attributable risk (LAR) instead of REIC and assumed no variation of rates with exposure age at ages over 30 years (i.e., $c = 0$ in these equations for $a_E > 30$ years). LAR ignores the radiation effects on the survival probability in Eq. (1) or (2). For breast and thyroid cancers, BEIR VII considered a meta-analysis of several exposed cohorts, replacing results from the LSS with additive transfer models used for breast cancer (*17*) and multiplicative transfer models used for thyroid cancer (*18*).

The UNSCEAR 2006 report (*2, 19*) used Poisson maximum-likelihood methods and Bayesian analysis to represent dosimetry errors to fit generalized ERR and EAR models to the LSS for cancer incidence for REIC. The ERR function fitted to the LSS data was (*2*)

$$ERR(a,a_E,L,D) = (\alpha D + \beta D^2)e^{\gamma D} \exp[\kappa_1 1_S + \kappa_2 \ln(a - a_E) + \kappa_3 \ln(a) + \kappa_4 \ln(a_E)], \quad (6)$$

with a similar form for the EAR function. A linear dose–response model provided the best fits to the tissue-specific cancer incidence data. The addition of the latency dependence, $L = a - a_E$, was significant for several tissues, including EAR models for colon, breast and non-melanoma skin cancer and ERR and EAR functions for the category of all other solid cancer incidence. For overall solid cancer mortality, UNSCEAR found that a linear-quadratic dose–response model fit the recent LSS data best (*2, 19*).

Reference Population and Cancer Risks for Never-Smokers

As shown by Eqs. (1)–(3), age- and gender-specific survival probabilities and cancer incidence and mortality rates representing the population under study enter into risk calculations. We used the 2005 SEER data (*20*) to represent the average U.S. population and also collected data for all states and the District of Columbia (*21*).

Lung cancer rates for never-smokers were recently compiled by Thun *et al.* (*14*) from an analysis of never-smokers in 13 cohorts and 22 cancer registries. Furthermore, Furukawa *et al.* (*15*) considered several interaction models between smoking and radiation in the A-bomb survivor cancer incidence data. A generalized multiplicative model for the combined effects of radiation and smoking was similar in form to Eq. (5), although with distinct coefficients.

For never-smoker risk estimates, we considered the likely longer life span for never-smokers due to their reduced lung cancer mortality. Age-specific rates for all causes of death for never-smokers were not available, and instead we considered the survival probability for the average U.S. population with or without adjusting the age-specific rate for all causes of death for the differences in lung cancer mortality rates between never-smokers of Western European descent (*14*) and the average U.S. population. We also considered other radiogenic cancers that are linked to tobacco use, including cancers of the stomach, esophagus, oral cavity and bladder. Age-specific rates for never-smokers for these cancers were not available. Instead adjustments to rates for an average U.S. population were made using gender-specific relative risks for never-smokers (*22*), which are given in Table 1. These rates are applied to the portion of the radiation rates corresponding to multiplicative risk transfer.

TABLE 1
Estimates of Relative Risks (RR) for Never-Smokers Compared to Average U.S. Population for Several Cancers Related to Both Smoking and Radiation Exposure

	Relative risk to never-smokers			RR for never-smokers to U.S. average
	Current smokers	Former smokers	Never-smokers	
Males				
Esophagus	6.76	4.46	1	0.27
Stomach	1.96	1.47	1	0.71
Bladder	3.27	2.09	1	0.50
Oral cavity	10.89	3.40	1	0.23
Lung[a]	23.26	8.70	1	0.11
Females				
Esophagus	7.75	2.79	1	0.35
Stomach	1.36	1.32	1	0.85
Bladder	2.22	1.89	1	0.65
Oral cavity	5.08	2.29	1	0.46
Lung[a]	12.69	4.53	1	0.23

[a] Lung data shown only for comparison, with calculations in rest of report using age-specific rates described in the text. For males, current smokers, former smokers and never-smokers are estimated at 24, 40 and 36% of the population above age 50 years. For females we use 18, 35 and 47% for these percentages.

RESULTS

We made comparisons of REID and REIC estimates, where each organ dose equivalent is set to an identical value. The comparisons used the published rates from the BEIR VII, UNSCEAR and RERF reports, with all other factors kept the same. This designation should not be confused with other assumptions that may enter into the application of these models. The results in NCRP Report No. 132 (*6*) were based on the older DS86 system and the LSS report 12 (*23*) fits to the LSS mortality data. However, we use the mortality rates from LSS report 13 (*16*), which were also based on the earlier DS86 dosimetry but which considered 7 years of additional follow-up (*23*). Figure 1 shows calculations for a test dose equivalent of 0.1 Sv of the age- and gender-specific REID, using the 2005 average U.S. population in a mixture model with $v_T = 0.5$ (equal weighting for multiplicative and additive transfer). These calculations are based on mortality risk transfer. In Fig. 1 we used the UNSCEAR linear-quadratic fit to the LSS data with only the linear term considered. The results for the BEIR VII and LSS Report 13 model assume a DDREF of 2. The LSS Report 13 preceded the publication of the DS02 assessment; however, the age-at-exposure dependence of the mortality risk is very similar to the linear term of the UNSCEAR model, although the magnitude is lower. These two models would be brought into agreement if a DDREF of about 1.7 was used for the LSS Report 13 model instead of a DDREF of 2, or vice versa if a modest DDREF of about 1.2 was applied to the UNSCEAR linear dose–response term in their LQ model fit. In contrast, the age-at-exposure dependence of the BEIR VII model (*1*) decreased modestly with increasing a_E, crossing the other models for ages between 40 and 50 years, with higher risks at older ages and reduced risk at younger ages compared to the NCRP model (*6*). Predictions for leukemia risk do not include a DDREF and are based on the linear terms of LQ model

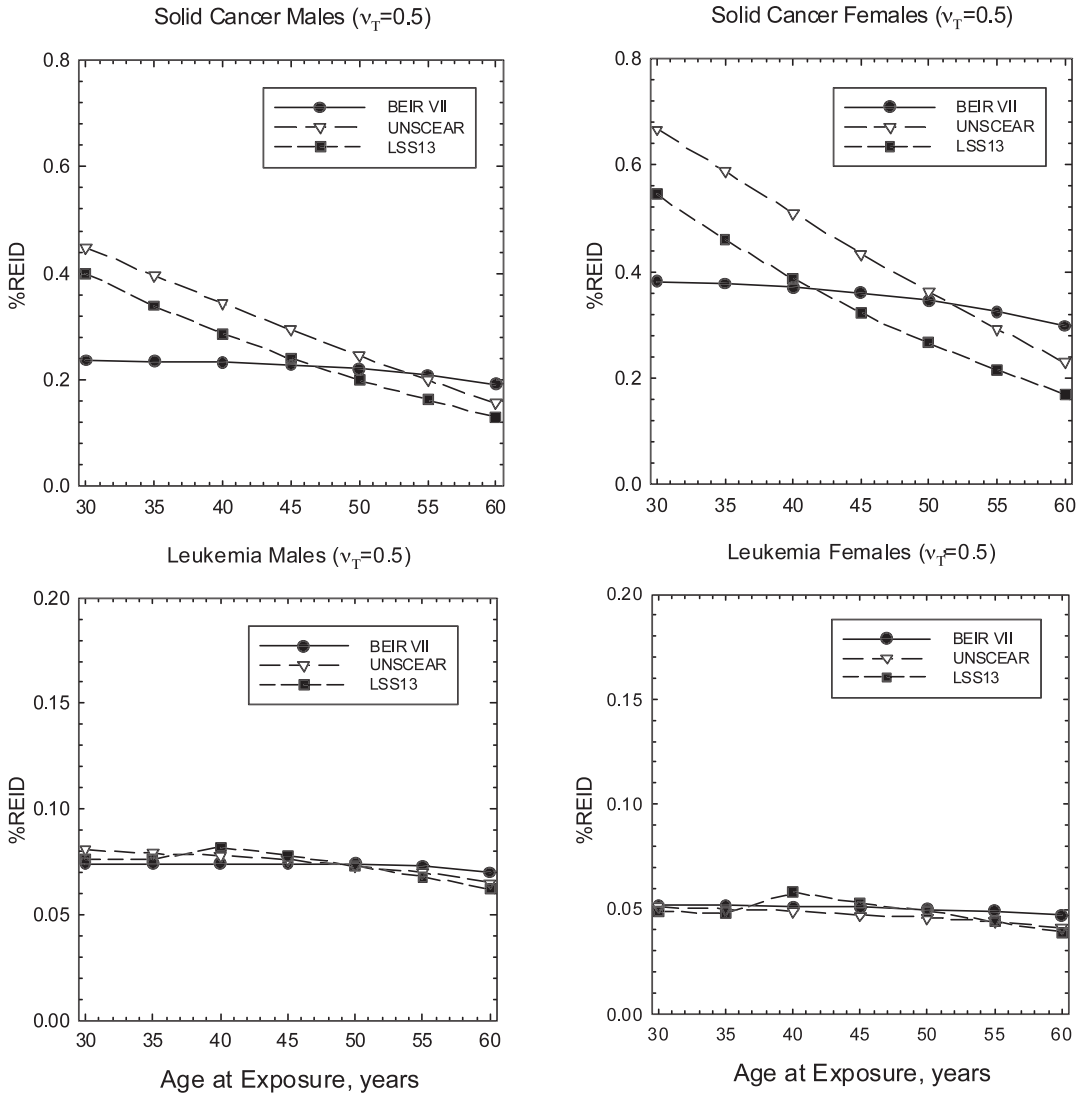

FIG. 1. Comparisons of models for the risk of exposure-induced death (REID) as a function of age at exposure for a test dose of 0.1 Sv. The top panels show results using mortality rates from BEIR VII (*1*) and LSS report 13 models (*16*), with a dose and dose-rate reduction effectiveness factor (DDREF) of 2 for solid cancer estimates and the UNSCEAR linear dose–response model (*2*) with a DDREF of 1. The lower panels show comparison of REID probabilities for leukemia risks using the BEIR VII, UNSCEAR and LSS report 12 (*23*) rates. The transfer weight v_T is equally weighted between the multiplicative and additive models.

fits to the LSS data. Very good agreement for leukemia estimates exists between the different models.

We next considered incidence based risk transfer models for projecting REID and REIC for the 2005 average U.S. population. A DDREF of 2 for solid cancer risk estimates is used for each model. Figure 2 shows comparisons using the cancer incidence rates from the UNSCEAR (*2*), BEIR VII (*1*) and RERF (*3*) models while keeping all other factors in the calculation the same. The age-at-exposure dependence is distinct in the incidence-based models shown in Fig. 2 compared to the UNSCEAR or LSS Report 13 fits to cancer mortality data as shown in Fig. 1. There are differences in magnitude between the incidence-based models and the BEIR VII model shows a more shallow decrease in risk with increasing age of exposure. These results suggest that the reduction in risk due to the competing risks at older ages and diminishing remainder of lifetime is of similar importance as the actual variation of incidence rates with age at exposure. A portion of the differences between the results shown is the BEIR VII use of rates based on meta-analysis for breast and thyroid cancer risk, especially for the REIC comparisons for females.

Influence of Reference Population on Risk Estimates

The influence of the U.S. average rates for all causes of death and cancer incidence or mortality as an appropriate population on which to base risk assessments for healthy

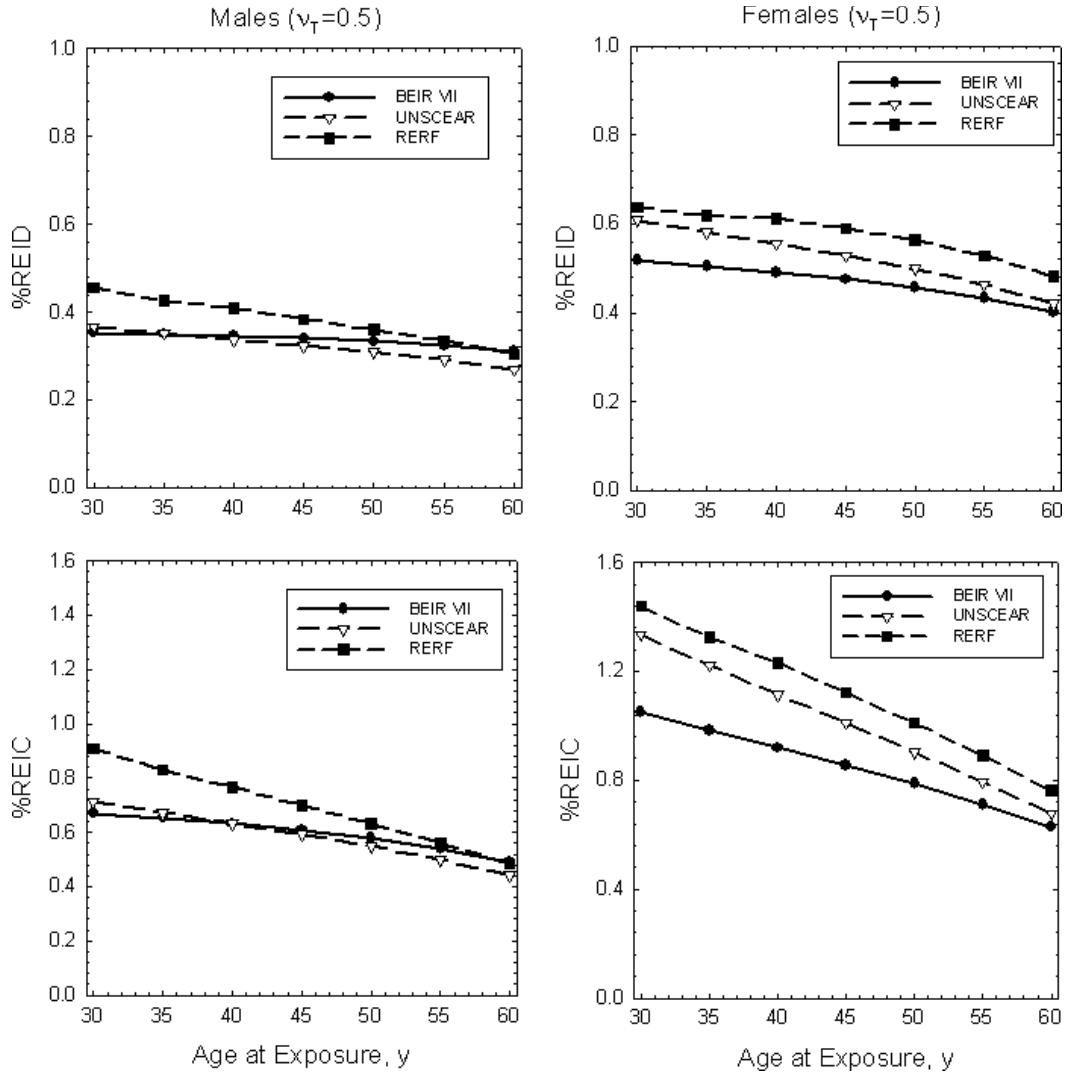

FIG. 2. Comparisons of the BEIR VII (*1*), UNSCEAR (*2*) and RERF (*3*) models using incidence-based risk transfer for the risk of exposure-induced death (REID) (upper panels) and the risk of exposure-induced cancer (REIC) (lower panels) as a function of age at exposure for a test dose of 0.1 Sv. Calculations use a dose and dose-rate reduction effectiveness factor (DDREF) of 2 for solid cancer risk estimates. The transfer weight v_T is equally weighted between the multiplicative and additive models.

workers such as astronauts was investigated. Calculations using the average U.S. rates from 1999–2005 for all causes of death and cancer mortality showed a small trend toward increasing radiation risk as longevity increased. To estimate possible variation in risk estimates due to differences in average life span and background cancer rates, we used data for all causes of death and cancer mortality for each of the 50 states and Washington, DC (*21*). Table 2 shows the average, standard deviation, and minimum and maximum values for these data along with REID projections using the NCRP 132 and BEIR VII models using mixture models for transfer rates (Table 3) (see also Supplementary Data; http:/dx.doi.org/10.1667/RR2540.1.S1). A very small variation of REID estimates was observed in these comparisons. Figure 3 shows the correlation between median life span and age-adjusted cancer rates with REID projections using the BEIR VII model. The general trend is for small increases with REID for longer life span and small decreases with decreasing cancer rates over the ranges inherent in the U.S. data. These differences are intimately tied to the assumptions of additive or multiplicative risk transfer, with larger changes found if multiplicative risk transfer is assumed.

Risk Estimates for Never-Smokers

A larger variation in REID and REIC probabilities was observed when lung cancer risk calculations were adjusted for rates in never-smokers. Figure 4 shows comparisons between the data of Thun *et al.* (*14*) with the SEER 2005 average U.S. population data for lung cancer incidence and mortality rates. We used these rates to estimate lung cancer risks using the BEIR VII, UNSCEAR and RERF models for EAR and ERR as

TABLE 2
Variation of REID per Sv as a Function of Age at Exposure for Females for All States and the District of Columbia

State	Median life span	Cancer rate	BEIR VII			NCRP 132		
			35	45	55	35	45	55
Females								
Average	82.4	133.8	5.4	5.2	4.7	4.7	3.5	2.3
Standard deviation	1.1	17.1	0.2	0.2	0.2	0.2	0.1	0.1
Minimum	80.1	89.6	4.8	4.6	4.2	4.3	3.2	2.1
Maximum	85.6	165.6	5.7	5.5	5.1	5.0	3.8	2.5
Males								
Average	77.7	150.6	3.9	3.8	3.6	3.9	2.9	2.0
Standard deviation	1.8	30.9	0.2	0.1	0.1	0.1	0.1	0.1
Minimum	73.2	96.0	3.5	3.4	3.3	3.6	2.7	1.8
Maximum	80.3	219.0	4.2	4.1	3.8	4.1	3.1	2.1

Notes. Shown are estimates in BEIR VII (*1*) (using DDREF = 1.5) and NCRP 132 (*6*) (using DDREF = 2) models. REID is the risk of exposure-induced death. DDREF is the dose and dose-rate reduction effectiveness factor.

shown in Tables 3 and 4 for estimates of REIC and REID, respectively. A more than 8-fold decrease is estimated in the multiplicative transfer model when never-smoker rates are used compared to the U.S. population average. The difference in radiation risk estimates with a correction for longer life span of never-smokers as described above increased risk estimates by less than 5%, and we used this adjustment for the results described for never-smokers. The use of the model of Furukawa *et al.* (*15*) led to a minor reduction for females compared to the usage of U.S. never-smoker baseline rate estimates alone and was about the same for males. Furukawa *et al.* (*15*) used lung dose estimates for the LSS cohort, while the reports noted above used colon doses to represent all solid cancer risks including lung. A mixture model with $v_T = 0.5$ reduces the lung cancer risk for never-smokers by 2-fold compared to the average U.S. population. Because lung cancer is the largest contributor to overall radiation cancer risks, these lower estimates for never-smokers have large impacts on overall risk estimates as well, as described below.

TABLE 3
Risk of Exposure-Induced Cancer (REIC) for Lung Cancer per Sv in Several Models[a] with Dose and Dose-Rate Reduction Effectiveness Factor (DDREF) of 2

Model type	Age at exposure (years) / Model rates	% REIC, Females			% REIC, Males		
		35	45	55	35	45	55
		Average U.S. population, 2005					
Additive	BEIR VII	1.34	1.33	1.31	0.77	0.76	0.74
	UNSCEAR	1.60	1.57	1.42	0.86	0.83	0.78
	RERF	1.67	1.66	1.59	0.87	0.87	0.83
Multiplicative	BEIR VII	3.92	3.61	2.97	1.23	1.15	0.96
	UNSCEAR	4.65	4.49	3.98	1.45	1.41	1.27
	RERF	5.15	5.56	5.28	1.51	1.65	1.60
Mixture	BEIR VII	2.70	2.54	2.19	0.99	0.96	0.85
	UNSCEAR	3.14	3.03	2.73	1.15	1.12	1.02
	RERF	3.43	3.63	3.46	1.19	1.26	1.21
		Never-smokers					
Multiplicative	BEIR VII	0.54	0.50	0.44	0.16	0.17	0.16
	UNSCEAR	0.69	0.67	0.62	0.17	0.17	0.16
	RERF	0.70	0.76	0.77	0.15	0.17	0.18
Mixture	BEIR VII	1.01	0.99	0.93	0.45	0.44	0.42
	UNSCEAR	1.15	1.12	1.04	0.51	0.50	0.47
	RERF	1.18	1.21	1.18	0.51	0.52	0.50
Generalized multiplicative	RERF, generalized multiplicative for never-smokers	0.50	0.58	0.62	0.16	0.19	0.22

[a] Calculations are made with the model rates from the BEIR VII report (*1*), UNSCEAR report (*2*) or Radiation Effects Research Foundation (RERF) report (*3*).

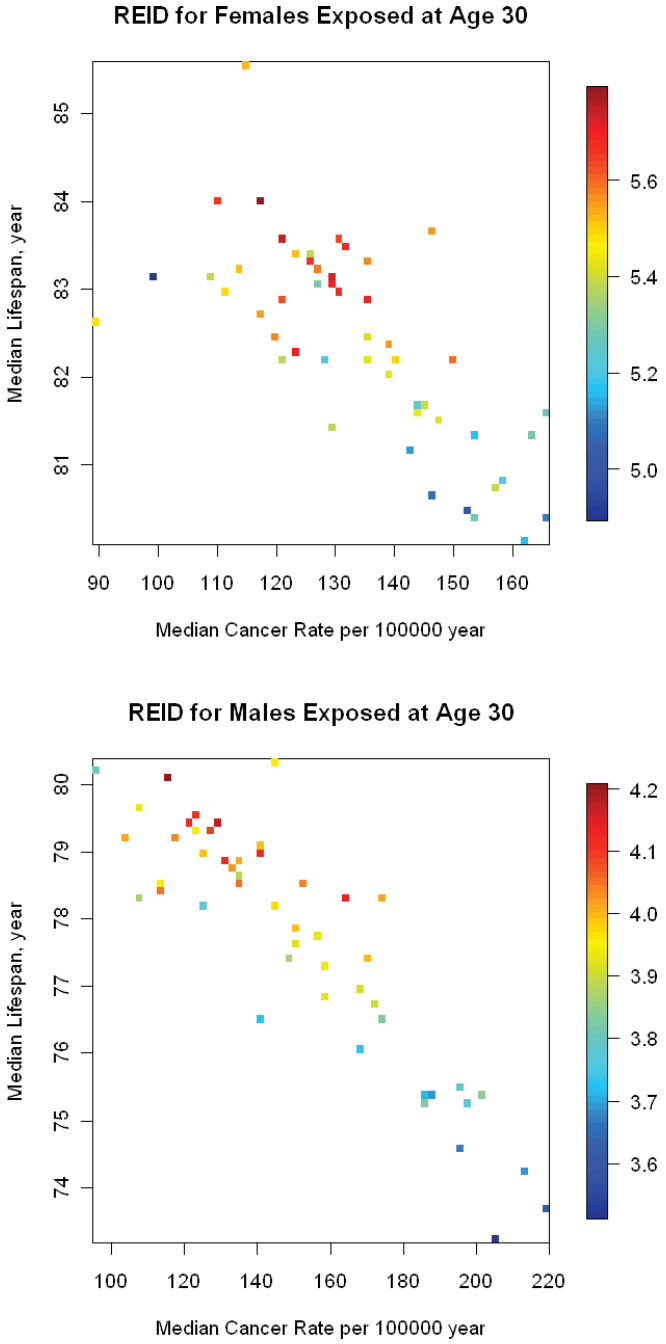

FIG. 3. REID per Sv estimates in the BEIR VII model with a DDREF of 1.5 for each state and Washington, DC as a function of median life span and fatal cancer rates for females (upper panel) and males (lower panel) exposed at age 30 years. The color scale represents variation in %REID. Calculations were made using age and gender-specific rates for all causes of death and cancer mortality for each of the 50 states and Washington, DC.

DDREF and Transfer Weights

To recommend a preferred model for use at NASA for point estimates of risk projections and dose limits, the DDREF and tissue transfer weights are needed. DDREF values are based on subjective assessment of various data sets (human epidemiology, animal studies and cell culture studies). Table 5 compares various DDREF estimates in other reports (*24–27*). The analysis of available human data supports a small DDREF value, below 2; however, the available human data are limited, especially at the low dose rates needed to make a direct comparison to data for acute exposures in a similar population. Mouse carcinogenesis studies show a range of values from 1 to 10, as has been reviewed previously (*25*). Also, cell culture studies or mutation, transformation or other likely oncogenesis-related events show even more variability. For uncertainty assessments, the impact of a wide range of DDREF values can be evaluated as will be done in part 2 of this study through error assessment methods. Here we will use a probability distribution function (PDF) for the DDREF similar to the NIH Working Group analysis (*24*) with a median value of DDREF = 1.75, which is at the high end of human data sets for solid cancers and near the lower values found for mouse tumor induction studies for solid cancer (*25*) relevant to human risk assessments.

For transfer weight assignments, there have been very few new findings to make changes since the NCRP Report 132 was published (*6*). The UNSCEAR 2006 report (*2*) did not make specific recommendations on transfer weights. Table 6 compares tissue-specific transfer weights assumed by different models. The BEIR VII report (*1*) argued for multiplicative weights for digestive cancers and several other cancers of $v_T = 0.7$ compared to the NCRP and other reports' usage of 0.5. For lung cancer estimates, BEIR VII made arguments for lung cancer having a higher weight for additive risk transfer with $v_T = 0.3$, based on the study of smoking effects in the LSS cohort by Pierce *et al.* (*28*) where additive effects were found. However, this study has been overcome by the recent reanalysis of the LSS lung data, where multiplicative effects between smoking and radiation are suggested, at least at low to moderate levels of cigarette use (*15*). Thus we are using the NCRP value of $v_T = 0.5$ for lung. Of less consequence is the choice for leukemia risk transfer, because the projections of the additive and multiplicative transfer model lead to similar results; however, the BEIR VII choice of $v_T = 0.7$ is very far from the NCRP Report 132 choice of additive transfer ($v_T = 0$) (*6*).

Table 7 compares estimates of REID per Sv and 3% REID limits in the NCRP, BEIR VII and our preferred model, denoted as NASA 2010. This model uses the UNSCEAR fits to the LSS data for most tissues except breast and thyroid cancers, for which the BEIR VII recommendation is followed to use meta-analysis results from several exposed cohorts. For several minor cancers not considered by UNSCEAR, we use the fits of Preston *et al.* (*3*), which are cancer risks for the oral cavity, prostate, ovary and uterus. Non-melanoma skin and bone cancers are not included in the present analysis. We

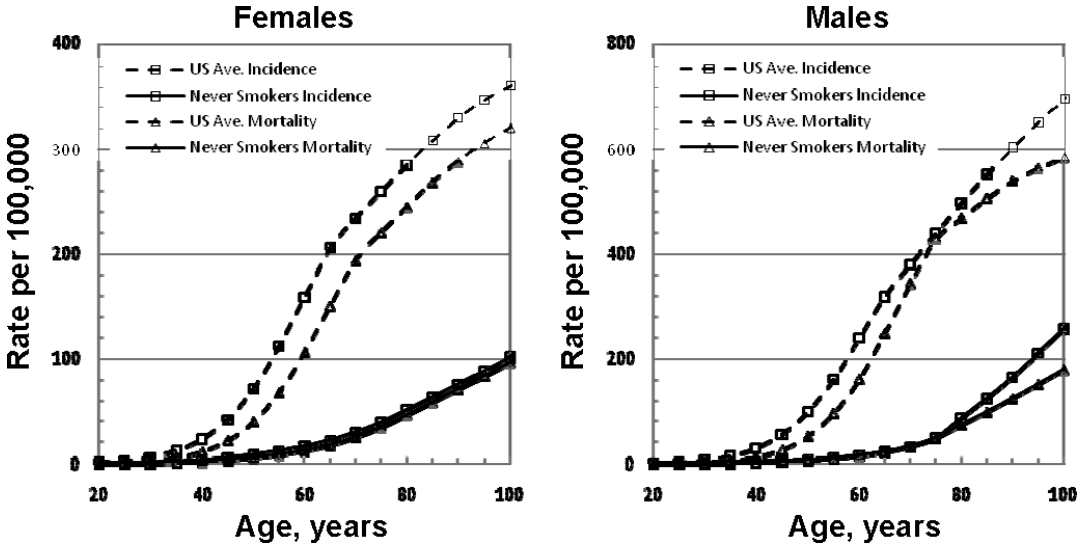

FIG. 4. Comparison on age-specific cancer incidence and mortality rates for the 2005 U.S. average population and recent analysis for never-smokers by Thun *et al.* (*14*).

also assume incidence base risk transfer to the U.S. population, including adjustments for never-smokers. The values listed for BEIR VII in Table 7 are directly from the report with DDREF = 1.5 and geometric averaging of transfer models. The transfer weights assumed by BEIR VII for lung ($v_T = 0.3$) and assumed here ($v_T = 0.5$) make up a larger part of the difference between BEIR VII result and the NASA 2010 model for the average U.S. population, because the multiplicative transfer model leads to a much higher risk than additive transfer, especially for females. The results in Table 7 estimate that female and male never-smokers are, respectively, at 30% and 20% less radiation cancer risk than the average person in the U.S. These differences are small compared to the uncertainties that enter into REID models (*1, 2, 8–10*); however, in a regulatory framework, a point estimate must be made and could potentially have large impacts. The 3-fold decrease in

TABLE 4
Risk of Exposure Induced Death (REID) for Lung Cancer per Sv in Several Models[a] with Dose and Dose-Rate Reduction Effectiveness Factor (DDREF) of 2

	Age at exposure (years)	% REID, females			% REID, males		
		35	45	55	35	45	55
Model type	Model rates	Average U.S. population, 2005					
Additive	BEIR VII	1.20	1.20	1.18	0.65	0.66	0.66
	UNSCEAR	1.28	1.27	1.22	0.71	0.71	0.69
	RERF	1.33	1.34	1.32	0.72	0.73	0.73
Multiplicative	BEIR VII	2.88	2.74	2.38	0.95	0.92	0.83
	UNSCEAR	3.56	3.50	3.23	1.17	1.17	1.11
	RERF	3.71	4.16	4.21	1.13	1.30	1.37
Mixture	BEIR VII	2.04	1.97	2.78	0.80	0.79	0.74
	UNSCEAR	2.43	2.39	2.23	0.94	0.94	0.89
	RERF	2.53	2.77	2.78	0.92	1.02	1.05
		Projections for never-smokers					
Multiplicative	BEIR VII	0.44	0.41	0.37	0.15	0.15	0.14
	UNSCEAR	0.57	0.57	0.54	0.15	0.15	0.14
	RERF	0.55	0.61	0.66	0.14	0.15	0.16
Mixture	BEIR VII	0.85	0.84	0.81	0.40	0.40	0.38
	UNSCEAR	0.96	0.95	0.91	0.46	0.45	0.42
	RERF	0.98	1.01	1.02	0.46	0.47	0.45
Generalized multiplicative	RERF, generalized multiplicative for never-smokers	0.39	0.47	0.53	0.16	0.17	0.20

[a] Calculations are made with the model rates from the BEIR VII report (*1*), UNSCEAR report (*2*) or Radiation Effects Research Foundation (RERF) report (*3*).

TABLE 5
Summary of Various Estimates of the Dose and Dose-Rate Reduction Effectiveness Factor (DDREF) for Estimating Solid Cancer Risks by Different Panels or Other Reviews of Human Data, such as the Japanese Atomic Bomb Survivor Life-Span Study (LSS), or Experimental Studies with Cells and Animals

Estimate or recommended value	DDREF estimate
NCRP Report No. 98[a] (*5*)	2.5
NCRP Report No. 132 (*6*)	2
BEIR VII: selected mouse tumor studies	1.5 [1.0, 4.4]
BEIR VII: LSS data analysis	1.3 [0.8, 2.6]
BEIR VII: Combined Bayesian Analysis	1.5 [1.1, 2.3]
ICRP (*26*)	2
UNSCEAR 2006[b] (by comparison of their fitted LQ and linear dose response models to LSS data)	1.22
NCI (*24*)	1.75
Jacob *et al.* (*27*) Rad Worker studies vs LSS	0.83 [0.53, 1.96]
Oncogenic changes in cell culture models	~1 to > 10
Solid tumors in mice from NCRP Report No. 64 (*25*)	3.48
NASA 2010 model	1.75

[a] NCRP used the related quantity DREF instead of DDREF.
[b] UNSCEAR did not make a DDREF recommendation.

fatal cancer risk from age 30 to 60 years in the NCRP model is reduced to less than 50% in the revised estimates.

DISCUSSION

The types of radiation in space, notably HZE nuclei and secondary high-LET radiation such as neutrons and recoil nuclei, are an ongoing concern, including the appropriateness of the use of epidemiology data from low-LET radiation and radiation quality factors to estimate space radiation risks. New methods and understanding of risks are an active area of research (*11–13, 29*); however, in the near term, the scaling of space radiation risks to human data for low-LET radiation must be used. In this report, we considered the most recent analysis of the LSS data in comparison to the older ones used by the NCRP (*6*), which is the basis for NASA's current dose limits and risk assessments. NASA uses estimates of the upper 95% confidence level of risk projection models as part of their mission readiness and design trade studies. The current report considered updates for the point or median projection based on new analysis since 2000; part 2 will consider updates to uncertainty evaluations for space radiation risk estimation. Estimates of cancer risk from low-LET radiation, such as X rays and γ rays, have been reviewed several times in recent years and indicate that the major uncertainty is the extrapolation of cancer effects data from high to low dose rates (*1, 2, 8*). Other uncertainties include the transfer of risk across populations and sources of error in epidemiology data

TABLE 6
Tissue-Specific Transfer Weight v_T for Multiplicative Risk Transfer

Tissue	NCRP No. 132	BEIR VII	NASA 2010
Lung	0.5	0.3	0.5
Breast	0.5	0[a]	0[a]
Thyroid	0.5	1.0[a]	1.0[a]
Stomach, colon, kidney, esophagus	0.5	0.7	0.7
Leukemia	0.0	0.7	0.5
All others	0.5	0.7	0.5

Notes. Additive risk transfer weight is then given by $1 - v_T$. Values described on page 126 of NCRP Report No. 132 (*6*), and from pages 275–276 of BEIR VII (*1*).
[a] Based on meta-analysis results described in BEIR VII (*1*).

including dosimetry, bias and statistical assumptions. Additional uncertainties contribute to estimates of the cancer risks from the protons and heavy ions and secondary radiation in space and in space dosimetry (*7, 9–13*). The limited understanding of heavy-ion radiobiology has been estimated to be the largest contributor to the uncertainty for space radiation effects (*6–9*). For low-LET radiation, the upper 95% CL is estimated at about two times the point estimate in most studies (*1, 2, 8*). For space radiation effects, the U.S. National Research Council (NRC) estimated an uncertainty range of 5- to 10-fold (*7*), and more detailed analyses (*9–11*) found the range to be 4- to 5-fold for GCR and about 3-fold for SPEs. These estimates will be re-examined in part 2 of this study. The dose limits estimates in Table 7 would then be reduced by the upper 95% CL uncertainty factor to consider maximum mission length or crew selection. Although not an absolute limit, such as the point estimate, the use of a 95% CL places important focus on uncertainty reduction through research and new knowledge in ensuring astronaut and mission safety.

The various approaches described above for fitting the most recent data set from the LSS study are based on stratified dose groups with the follow-up time from 1958–1998. Each report uses the recent DS02 organ dose estimates (*4*) and assumed a dose-independent neutron relative biological effectiveness (RBE) factor of 10. The UNSCEAR report introduced a Bayesian approach to consider dosimetry errors (*2, 19*). The UNSCEAR and RERF models used REIC or REID as the basic risk quantity, while BEIR VII used LAR. The use of LAR can result in an overestimation of REIC or REID at high dose levels and leads to errors in uncertainty analysis where for example some Monte Carlo trials lead to high risk probabilities (*8–10*). Tissue-specific doses were approximated by colon doses for solid cancers and bone marrow doses for leukemia risks. Not all of the specific tissues considered in each report were identical, which leads to differences in the definition of the remainder terms representing all cancer types excluded from tissue-specific analysis. The BEIR VII specifically

TABLE 7
Risk of Exposure-Induced Death (REID) per Sievert and 3% Effective Doses for Females in Different Models

	% Risk (REID) per Sv				Effective dose (Sv) for 3% REID			
Age at exposure, years	NCRP 132	BEIR VII	NASA 2010, average population	NASA 2010, never-smokers[a]	NCRP 132	BEIR VII	NASA 2010, average population	NASA 2010, never-smokers[a]
Females								
30	5.61	5.42	6.14	4.41 (4.51)	0.53	0.55	0.49	0.68 (0.67)
40	4.3	5.07	5.72	4.0 (4.09)	0.7	0.59	0.52	0.76 (0.74)
50	2.97	4.69	5.26	3.6 (3.69)	1.01	0.64	0.57	0.84 (0.82)
60	1.91	4.09	4.56	3.13 (3.22)	1.57	0.73	0.66	0.97 (0.94)
Males								
30	3.87	3.81	4.09	3.23 (3.57)	0.78	0.79	0.73	0.93 (0.85)
40	2.79	3.77	3.78	2.91 (3.25)	1.08	0.80	0.79	1.04 (0.93)
50	1.96	3.6	3.46	2.59 (2.92)	1.53	0.83	0.87	1.17 (1.04)
60	1.28	3.19	3.01	2.21 (2.51)	2.35	0.94	1.0	1.38 (1.21)

[a] Values in parentheses include corrections for lung risk for never-smokers but not other tissues.

assumed that radiation-related cancer risk did not vary by exposure age above age 30 years, which was included in the RERF and UNSCEAR approaches. Tests of goodness of fit to the LSS cancer mortality and incidence data were made by the UNSCEAR committee (*2*) using both the BEIR VII preferred model and the model of Eq. (6) and suggested that the UNSCEAR model as described by Eq. (6) provided the better fit to these data sets. The recommended model for use at NASA is based on the BEIR VII recommendation for tissue-specific, incidence-based risk transfer, however, uses the UNSCEAR analysis for most EAR and ERR functions and the analysis of Preston *et al.* (*3*) for several tissues not considered by UNSCEAR.

The largest difference between the NCRP estimates from 2000 (*6*) compared to the BEIR VII approach is the reduction of the age-at-exposure dependence of cancer risk estimates and dose limits, with a more than a 3-fold change over the possible ages of astronauts in the NCRP model compared to a less than a 50% change using an incidence-based risk transfer model. This observation is found for each of the models of tissue-specific incidence rates considered [BEIR VII (*1*), UNSCEAR (*2*) or Preston *et al.* (*3*)]. These assumptions have much larger impacts than those that would result from suggested changes to DDREF values recommended by the BEIR VII Report, where a DDREF of 1.5 increases the solid cancer risk estimate by 33% compared to a DDREF of 2 used in the past, and a smaller overall change when leukemia risk is included for the overall cancer risk. The incidence-based transfer model makes good sense when one considers the changing rates for incidence and mortality over time since 1945 and differences between LSS and U.S. background rates. Cancer mortality rates in the U.S. are reported to be decreasing, while incidence rates remain more stable except for lung cancer due to the reductions in tobacco use (*30*).

The statistical and bias errors in overall cancer incidence data are estimated to be smaller than mortality data by the NCRP (*8*). The LSS data for incidence starts in 1958, while mortality data were collected beginning in 1950. The classifications of cause of death or identification of type of primary cancer for incidence are also considered as sources of bias. Statistical errors for total cancer incidence should be smaller than those for mortality data because the number of cases is approximately 2-fold higher, while statistical errors for specific cancer sites should be higher because of fewer counts. However, recently Bayesian analysis has been used to show that statistical errors from individual tissues are much smaller than estimates from classical regression analysis when the correlations between different tissues in data sets are considered (*31*).

The biological basis for the age-at-exposure dependence of cancer risks needs to be considered with regard to the age dependences of radiation risks for astronauts with typical ages between 30 and 60 years. Radiation action as either a cancer initiator or promoter could be suggested to lead to differences in the age-at-exposure dependence of risk, and there are other competing biological factors to consider. Adults likely contain a much higher number of premalignant cells (*1, 2*). The differences in such ''cell numbers'' for different ages for astronauts or between the average population and a population of healthy workers such as astronauts is not known. The probability of such a smaller population of cells being modified at low dose and dose rate compared to normal cell populations should be considered relative to their probability of transformation. Aberrant changes to the tissue microenvironment (*32*) could increase with age, perhaps acting as a promotional effect for cells damaged from radiation exposure. The role of age in relationship to changing numbers of senescent cells, stem cells or other susceptible cells and possible reduced DNA repair capacity are all possible factors that could

influence the age-at-exposure dependence of radiation cancer risk.

A strong age dependence of cancer risks in children and adolescents is well known (*1, 2*), but a recent analysis by Little (*33*) suggests very little evidence for increased risk with age at exposure in adults for most tissues including lung. Preston *et al.* (*3*) reported increasing lung cancer risk with age of exposure; however, tobacco usage is an important confounder that was not considered in their analysis. The results in Tables 3 and 4 suggest that although the fits of Preston *et al.* (*3*) for lung cancer EAR and ERR increased with age at exposure, there was very small differences in REID or REIC estimates with the BEIR VII (*1*) and UNSCEAR 2006 (*2*) models when all other factors that enter into calculations are made the same. Of note is the similarity between the different models for lung and leukemia risk estimates and the differences between models for overall cancer risks, which indicates that larger differences between these models for fits of EAR and ERR functions for other tissues.

The risk estimates described for never-smokers are sensitive to the transfer model weights assumed in the calculations. Additive risk transfer models suggest that radiation acts independently of promotional effects in the population under study. Multiplicative risk transfer models suggest that radiation acts independently of other cancer initiators in the population under study (*1, 8*). Larger differences between the average U.S. population and a population of never-smokers than indicated in Table 7 would be found when a multiplicative transfer model is used and smaller differences when additive risk transfer is used. Multiplicative transfer models are supported by studies of solid cancers in mice (*34*) but are limited in describing human lung cancer histology or interactions with tobacco. The role of second-hand smoke is another confounder; however, it should be viewed as one of many in population-based risk estimates. We considered adjustments of population rates for cancers of the lung, esophagus, bladder and oral cavity in our estimates for never-smokers. There are other possible tissue-specific risks that could be adjusted for never-smokers; however, they are likely smaller adjustments than the tissues considered. Epidemiology data on breast cancer risks and tobacco are inconsistent (*35*), and the U.S. Centers for Disease Control and Prevention (CDC) does not include breast cancer as a smoking-attributable cancer (*22*). Other healthy worker effects related to obesity, nutrition, etc. would be more difficult to assess to adjust U.S. average rates compared to tobacco effects and would likely lead to smaller adjustments. Individual radiation sensitivity due to genetic makeup is likely a larger determinant of radiation risk and lung cancer (*36, 37*). However there are scientific, ethical and legal questions to be overcome before such assessments can be made for astronauts. The approach used here stays within the bounds of population-based risk assessments; however, it makes adjustments for never-smokers as appropriate for astronauts.

There are differences in the histology of cancers for smoking and ionizing radiation that need to be considered in radiation risk assessments. Very little information has been reported for the percentages of different types such as small cell lung carcinoma (SCLC) and non-small cell lung cancer (NSCLC) associated with radiation exposure, in part due to statistical limitations. Much more is known about the histology of lung cancers associated with tobacco use (*36, 37*). Land *et al.* (*38*) reported that radiation-induced lung cancer mortality risk was mostly associated with SCLC in the A-bomb survivors and uranium miners that received doses from α particles. A study of Hodgkin's disease patients treated with high doses of radiation in Europe and the U.S. indicated that NSCLC was associated with radiation exposure, and no significant risks for never-smokers were seen (*39, 40*). For high-LET α particles, the BEIR VI committee found that sub-multiplicative models fitted data for Uranium miners the best and ruled out additive risk models (*41*). This is a major uncertainty because never-smokers have a very small incidence of SCLC in the U.S., suggesting that additive risk transfer should be used to transfer the LSS data to the U.S. for SCLC risks or else no risk of SCLC cancer would be predicted for never-smokers. The additive transfer model leads to a risk estimate of about three times less than the multiplicative risk transfer model applied to the average U.S. population and about two times higher when applied to never-smokers. We recommend that the additive and multiplicative model rates applied to never-smokers be averaged for point risk estimates and dose limits for astronauts until better information and data to make an improved estimate are available.

The use of incidence-based risk transfer models allows for a great range of flexibility to introduce potentially tissue-specific risk assessment factors, such as tissue-specific DDREFs, quality factors and transfer models. Unfortunately not much is known to make informed choices for most tissues (*6, 8*). Also, individual organ doses vary by more than 2-fold for most SPEs and in some cases by more than 5-fold (*28, 42, 43*) depending on the shape of the proton energy spectra and the level of shielding. Skin and thyroid dose equivalents can be much larger than deep-seated organ doses causing large effective doses, which are weighted sums of various tissue dose equivalents (*6, 26*), although the cancer mortality risk for these tissues is very small. Therefore, the use of effective doses for SPEs is problematic for estimating cancer risks, with the summation of tissue-specific cancer estimates providing a more accurate approach for risk estimation. Calculations of attributable risks require tissue-specific cancer incidence esti-

mates (*24*), which is another advantage of the approach recommended in this report. Attributable risks estimates will be reported elsewhere for ISS and exploration missions of interest at NASA.

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