Evaluation of Sex-Specific Differences in Lung Cancer Radiation Risks and Recommendations for Use in Transfer and Projection Models

March 2022

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National Council on Radiation Protection and Measurements
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Preface

The study of Japanese atomic bomb survivors exposed acutely to ionizing radiation in 1945, has reported the risk of radiation-related lung cancer to be nearly three times greater for females than for males (similar for both mortality and incidence) on a relative scale. Because radiation protection standards for flight crew members that take part in NASA human space-flight programs have been based on individual lifetime risk projections of cancer mortality, this sex-specific difference limits the time female flight crew members (compared with males) can spend on missions in space, as previously discussed in NCRP Commentary No. 23, Radiation Protection for Space Activities: Supplement to Previous Recommendations (2014). NASA requested that NCRP evaluate the risk of radiation-induced lung cancer in populations exposed to chronic, protracted, or fractionated exposure to radiation to investigate whether similar sex-specific differences in lung cancer risk occur when exposure occurs gradually over years contrasted with the acute exposure received by the Japanese atomic bomb survivors.

The purposes of this National Council on Radiation Protection and Measurements (NCRP) Commentary are to:

- Evaluate sex-specific (male versus female) differences in lung cancer radiation risk estimates in exposed human populations.
- Assess the use of these sex-specific risk estimates in lifetime risk-projection models, with particular attention to providing recommendations to the National Aeronautics and Space Administration (NASA) for application of the findings to space activities.

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Kathryn D. Held
President
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1. Executive Summary

1.1 Background

Previously, NASA limited total career radiation exposure to astronauts\(^1\) to doses that will not exceed a 3 % lifetime risk of fatal cancer at the upper bound of the 95 % confidence interval to account for the uncertainties in risk projection (NASA 2014). Currently, NASA limits the total career dose based on ensuring all astronauts (inclusive of all ages and sexes) remain below 3 % mean risk of cancer mortality based on that risk for a 35-year-old female (NASA 2022) (see also NASEM 2021). The operational risk model currently in use relies on data from the Life Span Study (LSS) of Japanese atomic bomb survivors. According to this model, radiation-induced lung cancer is the largest contributor to fatal cancer risk and females are at nearly three times greater risk of radiation-induced lung cancer than males on a relative scale. Lung cancer risk is a major constraint to long duration missions in deep space and the higher total mortality risk for females results in the time in space allowed for female astronauts being much less than the time allowed for male astronauts.

The goals of this Commentary are to:

- Review the epidemiologic, experimental, and biological information relevant to radiation-induced lung cancer.
- Evaluate the existing NASA model for lifetime risk projections for lung cancer mortality and quantification of associated uncertainties.
- Make recommendations to NASA with regard to sex-specific lung cancer risk and suggest modifications to the current lifetime risk projection model.
- Make recommendations for future research activities to improve the risk projection model and knowledge of sex-specific differences in radiation-induced lung cancer risk.

The key issues addressed are:

\(^1\) In this Commentary, the term astronaut refers to any flight crew member that takes part in a NASA space flight.
258 • Whether recent epidemiologic data on radiation-associated lung cancer risk indicate a
clear difference between males and females.
259 • Whether the existing NASA lifetime risk projection model for lung cancer should be
modified and, if so, how?

1.2 Review of Epidemiologic Studies Relevant to a Radiation-Related Sex-Specific
Difference in Lung Cancer Risk

Ideally, inferences about sex-specific lung cancer risks would be based on several studies
to enable evaluation of effects that population characteristics and other factors might have on
lung cancer risk. For astronauts, the most relevant studies would be those of populations with
large numbers of healthy, nonsmoker males and females who exercise regularly, with chronic
radiation exposure between the ages 35 and 55 y and with lengthy post-exposure follow-up.
Including studies that involve exposure to high linear-energy transfer (LET) radiation would
provide additional information to model risks for the various types of radiation that astronaut
flight crews are likely to encounter during space missions.

This Commentary reviews 18 epidemiologic studies relevant to assessing the sex-specific
lifetime radiation risk estimates for lung cancer. These studies and the criteria for including them
are discussed in Section 3.2 and listed in Table 3.2 along with summary information on the
characteristics of each study. Two of the studies provided information on both mortality and
incidence, thus there are 20 listings in Table 3.2. The exposed populations were wide ranging
and included medical patients, workers, members of the public, and the Japanese atomic bomb
survivors. The studies included populations that were exposed to either low-LET radiation (e.g.,
gamma rays), high-LET radiation (e.g., internally-deposited alpha-particle emitters), or both.
Except for the acute exposure of the atomic bomb survivors, all the other exposures were either
fractionated or chronic. The populations evaluated included subjects from over 20 countries,
including the United States, Canada, the United Kingdom, the Russian Federation, China, and
Japan. Based on the mixed and conflicting results for a sex-specific lung cancer risk from these
studies (Section 3.4.1), no firm conclusion on a sex difference in radiation risk for lung cancer can be supported based on the evidence available to date.

1.3 Biological Plausibility of a Radiation-Related Sex-Specific Difference in Lung Cancer Risk

The evidence for a greater radiation-induced lung cancer risk in females than males is observed in some epidemiologic studies. Grounding this finding with evidence from biological systems would lend confidence to the epidemiologic findings and might point to potential countermeasures against radiogenic lung cancer. Unfortunately, the available evidence from radiation biology studies is not sufficient to determine whether females would be at greater risk. While there are several tumorigenic mechanisms with the potential to place females at increased risk for radiation-induced lung cancer, none of them has been verified as playing a role in radiogenic lung cancer. The following mechanisms are currently considered plausible and are described more fully in Section 4.2. They are not mutually exclusive.

- Hormonal differences between males and females, particularly for estrogens, may place females at greater risk for both sporadic and radiation-induced lung cancer.
- There are differences between males and females in the frequencies of specific driver mutations in spontaneous lung cancers. A greater risk for radiation-induced lung cancer would be expected for females if radiation exposure drives tumorigenesis through pathways involving driver mutations that are more commonly found in female lung cancers than in male lung cancers.
- Females have two X chromosomes, one of which is inactivated in each cell. X-chromosome reactivation (or failure of inactivation) might result in the overexpression of a gene (or genes) that contributes to the development of lung cancer when dysregulated.
- Sex differences in immune system function strongly impacts other ailments of the lung such as asthma, chronic obstructive pulmonary disease, and infectious disease. These immune system differences may play a role in distinct sex-dependent outcomes of lung cancer following radiation exposure.
1.4 Animal Studies Relevant to a Radiation-Related Sex-Specific Difference in Lung Cancer Risk

Data from murine studies, though extensive, were not considered suitable for determining whether females are at greater risk of radiation-induced lung cancer than males. The mouse models used to date for the study of radiation-induced lung cancer do not recapitulate the sex difference observed in human epidemiologic studies, possibly because of the high radiosensitivity of the murine ovary.

1.5 Current NASA Modeling Approaches

The current NASA projections of cancer risk to astronauts for galactic cosmic radiation exposures for most cancer types are based on a multistep procedure involving:

- Cancer risk models for predominantly low-LET radiation derived from analyses of incidence data from the LSS of the Japanese atomic bomb survivors.
- Application of these models to data on baseline mortality rates for a target population of U.S. never-smokers.
- An adjustment to account for the dependence of risk at a unit dose on dose and dose rate.
- A sophisticated adjustment to account for the dependence of risk on radiation quality.

For low-LET radiation, the risk projections for U.S. never-smokers do not account for information from epidemiologic studies that provide useful radiation risk estimates in populations that involve chronic exposures. Furthermore, the NASA approach likely results in overestimates of lifetime lung cancer risk from low-LET radiation. This is because an underlying assumption in the application of the excess absolute risk (EAR) models (one of the models used for the NASA projections) is that excess cancer rates from exposure to radiation would be the same in a U.S. nonsmoking population as for the Japanese atomic bomb survivors. However, the EAR model was derived from a population that included smokers. Results from several epidemiologic studies (e.g., the LSS, the Mayak worker cohort, underground miners exposed to high levels of radon, and pooled residential case-control studies) establish that radiogenic lung cancer risks are several times greater for smokers than nonsmokers.
The source with the largest estimate of uncertainty in NASA projections is associated with the modeling of how risk from exposure to high atomic number, high-energy (HZE) particles relates to risk from low-LET radiation (i.e., the models for deriving the adjustment for radiation quality). Also important are:

- statistical uncertainties (e.g., corresponding to the width of confidence intervals for parameters in the risk models for the predominantly low-LET radiation exposure), and
- the problem of risk transport (e.g., how do excess cancer rates in the LSS and excess rates for astronauts depend on their respective baseline cancer rates).

More information is also needed on:

- how excess rates from exposure to low-LET radiation for never-smokers compares to those for ever-smokers within the LSS cohort, and
- how low-LET radiation risks depend on dose rate.

Other sources of uncertainty (e.g., dosimetry error) are likely less important.

It is very difficult to quantify uncertainties associated with several of the more important sources (e.g., associated with radiation quality and risk transport). Overall, the NASA approach for quantifying uncertainties appears reasonable. However:

- Standard deviations associated with excess relative risk (ERR) and EAR risk model parameters were subjectively chosen. An alternative approach based on the covariance matrix of the fitted parameters is preferred.
- The NASA evaluation of uncertainty associated with dosimetry error is incorrect.
- NASA did not quantify statistical uncertainties specific to never-smokers.
1.6 Proposed Bayesian Meta-Analysis Approach for Combining Results from Epidemiologic Studies

For this Commentary, lung cancer lifetime risk estimates were derived using radiation-effect estimates from major epidemiologic studies for which datasets are publicly available or for which estimates were obtained via customized requests to authors. These were studies of:

- incidence and mortality in the LSS;
- mortality in the Mayak worker cohort;
- mortality in four cohorts within the MWS; and
- incidence and mortality in the U.K. National Registry of Radiation Workers (NRRW) cohort.

The estimates of lifetime risk for never-smokers were sensitive to modeling choice. Lifetime risk estimates based on EAR models computed without smoking adjustment are overestimates for never-smokers and should not be used. While it is best to base lifetime risk estimates for a population of never-smokers on smoking-adjusted rate models, ERR models without smoking adjustment can provide more reasonable estimates of lifetime risk for never-smokers than unadjusted EAR models.

For some studies, (e.g., nuclear power plant workers and NRRW), smoking-data history is not available. For these studies, uncertainties associated with smoking-related effect modification and confounding are typically difficult to evaluate and can be sex-specific. For several MWS cohorts (e.g., Los Alamos National Laboratory, Tennessee Eastman Corporation and Hanford), there are reliable smoking-history data available from medical questionnaires or direct interviews that will be considered more directly in future analyses for those studies. Further, adjustments for socioeconomic status such as education, pay scale (hourly, salaried), or military rank (enlisted, officer) are made for all MWS cohorts as indirect surrogates for tobacco

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2 One Million U.S. Workers and Veterans Study of Low-Dose Radiation Health Effects (MWS).
use and other lifestyle factors. The NRRW used an industrial category as a similar surrogate for
tobacco use and other lifestyle factors.

A Bayesian meta-analytic method for combining results from these studies was proposed
and implemented on a select group of cohorts available for evaluation. The purpose was to
propose and demonstrate a method that could be used for assessing radiogenic lung cancer risks
between sexes. The specific results from the Bayesian meta-analysis presented in this
Commentary reflect the set of studies included, most notably the LSS and Mayak worker
investigations, which showed strong differences in sex-specific risks. Inclusion of other relevant
studies that show little or no difference in lung cancer risks by sex could be included in future
Bayesian meta-analyses and might lead to markedly different conclusions.

Lifetime risk estimates based on results from the Bayesian meta-analysis were also
presented. The meta-analysis indicates that upper uncertainty bound limits (e.g., 95th percentile
values of posterior distributions) for lifetime radiogenic lung cancer risk are highly dependent on
underlying assumptions. In contrast, central estimates of radiation risk (e.g., the median and
mean of posterior probability distributions) for both females and males are robust to underlying
assumptions (e.g., on study-to-study variation and the size of nonsampling error). The 75th
percentile posterior distribution values are also reasonably robust to underlying assumptions.

Results from the meta-analysis reflect the difficulty in assessing uncertainties associated
with projections of lung cancer risks for astronauts. For two of the study populations (LSS and
Mayak worker cohort), there were reasonably precise estimates of ERR and convincing evidence
that radiogenic lung cancer risks are greater for females than males. However, the Bayesian
meta-analysis did not include enough studies to draw reliable conclusions on how the lung
cancer risks vary by study population, and ultimately, the extent to which sex-specific
differences in lung cancer risk might differ for a target population of astronauts.
1.7 Recommendations

With regard to epidemiologic studies of lung cancer risk and female-male differences:

- Existing studies should be enhanced by obtaining smoking histories for both males and females.
- Additional epidemiologic studies should address chronic radiation exposure of the lung in relevant human populations to evaluate sex-specific differences in lung cancer risk. Emphasis should be on populations of nonsmokers.
- Studies of human populations with exposure to high-LET radiation experienced on Earth (such as alpha particles resulting from intakes of radionuclides) should be included. While such radiations are qualitatively different from galactic cosmic rays that are pervasive in space, studies where such radiations are present might provide useful insights.

With regard to biological data and animal experiments to assess female-male differences in lung cancer risk:

- Radiation biology studies and animal experiments should investigate whether the sex difference in radiogenic lung cancer risk observed in some epidemiologic studies is real and, if so, identify the biological mechanism(s) responsible for the difference. Recommended areas of such research are detailed in Sections 4.4 and 5.4, respectively, which include efforts to replicate the sex difference:
  - directly in carcinogenesis experiments in conventional and genetically modified animals; and
  - indirectly through experiments in animals, humanized animals, and engineered human lung tissue employing robust biomarkers specifically linked to lung carcinogenesis (bioindicators) as endpoints.
- These efforts should be informed by known molecular pathology differences between lung cancers arising in human males and females.
With regard to modeling lung cancer risk projections for astronauts:

- The NASA EAR models should be replaced with models that allow for smoking adjustment (Section 7.2). NASA’s current approach likely results in overestimates in lifetime risk projections (i.e., for both REIC and REID) because the NASA EAR model was derived from a population that included smokers.

- NASA should develop risk models for radiogenic lung cancer based on an approach that combines information from the LSS and other epidemiologic studies, particularly those for which the exposures include a chronic component. This Commentary suggests the Bayesian meta-analytic approach detailed in Section 7.4. It is stressed that the results given in Section 7.4 are for illustrative purposes only. The Bayesian meta-analysis should be based on updated results from the studies already considered in this Commentary and results from other studies as data become available. To the extent possible, NASA should reach out to researchers involved in the relevant studies to obtain sufficiently detailed information for risk estimation. The most informative studies would have estimates of lung dose for the individual subjects and quantitative estimates of the radiation dose response.
2. Introduction

Cumulative radiation exposure to astronaut flight crews going on long-term space missions, such as to Mars, is recognized as an important health consideration during and after such missions. Among the many hazards and risks faced are exposure to microgravity and associated bone loss and deconditioning, circadian rhythm disturbances and sleep deprivation, a potentially toxic and closed environment including elevated CO₂ in the atmosphere of the space vehicle, isolation, and behavioral issues related to close proximity to other flight crew members.

In addition, the cumulative radiation dose to flight crews for the duration of a Mars mission can reach the order of 1 Gy (weighted dose[^1]), and the potential health effects associated with the high atomic number, high-energy (HZE) particle component of galactic cosmic radiation are not fully known.

NASA has a radiation protection standard [in the form of Permissible Exposure Limits (NASA (2014))] to minimize the potential adverse health effects from the radiation encountered during space travel. As discussed in Section 2.1, the standard includes keeping the lifetime risk projection for cancer mortality to below an excess of 3 % (at the upper 95 % confidence limit).[^4]

There are two important issues related to the lifetime cancer risk projections. First, the projected lung cancer excess risk is the dominate contributor to the total cancer mortality risk. Second, from the Japanese atomic bomb survivor data, estimates of the radiation-related mortality risk for females due to lung cancer are nearly three times higher than that for males. These considerations determine the allowable time in space for astronaut flight crew members, and for the same amount of cumulative radiation dose, the higher total mortality risk for females results in the time in space allowed for female astronauts being much lower relative to the time allowed for male astronauts.

[^1]: In this Commentary, the weighted dose in an organ accounts for the increased biological effectiveness of high-LET components of radiation exposure. This quantity consists of the mean absorbed dose in the organ from low-LET components plus the weighted mean absorbed doses in the organ from high-LET components, where each high-LET mean absorbed dose component is multiplied by a judged weighting factor, as provided by the investigator. The quantity is expressed in gray.

[^4]: Recently, NASA superseded that standard with a limit for total career dose based on ensuring all astronauts (inclusive of all ages and sexes) remain below 3 % mean risk of cancer mortality based on that risk for a 35-year-old female (NASA 2022) (see also NASEM 2021).
NASA asked NCRP to address the issue of sex-specific lung cancer radiation risk as relevant to long-term NASA missions in space. The goals are to:

- Review the epidemiologic, experimental, and biological information relevant to radiation-induced lung cancer.
- Evaluate the existing NASA model for lifetime risk projections for lung cancer mortality and quantification of associated uncertainties.
- Make recommendations to NASA with regard to sex-specific lung cancer risk and suggest modifications to the current lifetime risk projection model.
- Make recommendations for future research activities to improve the risk projection model and knowledge of sex-specific differences in radiation-induced lung cancer risk.

2.1 Role of Risk Estimates in Setting Radiation Protection Guidance for NASA

For 40 y, NCRP has provided guidance to NASA on radiation protection issues associated with radiation received during space activities (NCRP 1989, 1997, 2000, 2002, 2006, 2010, 2014, 2016, 2019). NASA has incorporated the NCRP guidance to address the following specific issues:

- Use by NASA (2014) of the 95 % confidence level to account for uncertainties in radiation-induced cancer risk projections.\(^5\)
- Current evaluation of the potential for radiation-induced cardiovascular disease and central nervous system dysfunction.
- High priority research to address uncertainties in the estimation of radiation risk for NASA space missions, including the biological effectiveness of HZE particles.

This Commentary addresses the need for additional guidance on sex-specific radiation-induced lung cancer risk for astronaut flight crews embarking on long-term missions.

\(^5\) Recently, NASA superseded use of the 95 % confidence level with a limit for total career dose based on ensuring all astronauts (inclusive of all ages and sexes) remain below 3 % mean risk of cancer mortality based on that risk for a 35-year-old female (NASA 2022) (see also NASEM 2021).
2.2 Importance of Lung Cancer Sex Dependence on Lifetime Risk Projection Models

The greatest contributor to organ-specific radiation-induced lifetime risk projections is lung cancer. Because lung cancer is such a dominant factor, all factors and the necessary assumptions needed should be as valid as possible, such as:

- Optimum sex-specific radiation risk coefficients.
- Low dose-rate adjustments.
- Lung doses from HZE particles.
- Representative human populations with characteristics comparable to astronaut flight crews.

Incorrect or less optimum assumptions of the parameters needed for the lifetime risk projection model, in addition to the uncertainties associated with the projection models themselves, can substantially affect the time allowed in space for astronaut flight crews.

Currently, the risk projection approach relies heavily on the study of the Japanese atomic bomb survivors exposed acutely in 1945. In the Japanese study, for both excess relative risk (ERR) and excess absolute risk (EAR) models, estimates of age-specific radiation-related lung cancer mortality (and incidence) rates for females were found to be nearly three times higher than those for males. This substantially limits the time female crew members can spend in space missions under current guidelines. Thus, NASA requested that NCRP look at the evidence from all relevant epidemiologic studies that relates to radiation-related lung cancer and any differences between males and females. These study populations include those with chronic, protracted, or fractionated exposures. A review of relevant experimental studies and biological evidence is also included in this Commentary.
2.3 Brief Description of the Parameters Used in the Lifetime Risk Projection Model

The proposed NASA lifetime cancer risk projections (Cucinotta et al. 2013) for galactic cosmic radiation exposures for most cancer types are based on:

- Cancer risk models for predominantly low linear-energy transfer (LET) (low-LET) radiation derived from analyses of incidence data from the Life Span Study (LSS) of the Japanese atomic bomb survivors.
- Data on baseline incidence and mortality rates.
- An adjustment to account for the dependence of risk at a unit dose on dose and dose rate.
- An adjustment to account for the dependence of risk on radiation quality.

These lifetime risk projections were calculated for both the general U.S. population and a U.S. population of never-smokers more characteristic of the astronaut cohort. Although risk projections were calculated for both cancer incidence and mortality, the main emphasis is projections for cancer mortality.

The general approach for estimating risks for low-LET radiation is the same as that used in other authoritative reports on radiation risks (NCRP 1993, 2001; NA/NRC 2006; ICRP 2007; UNSCEAR 2008; EPA 2011). In brief, NASA’s proposed estimates of risk for most cancer sites are based upon models for both ERR and EAR, fit to the LSS data. ERR is the ratio of the age-specific increase in cancer rate attributable to a specific exposure to radiation to the baseline rate (i.e., the rate associated with other risk factors, including the natural background radiation level). EAR is the difference in cancer rates attributable to the specific radiation exposure. The modeled ERR and EAR for solid cancers are linear functions of dose for which the slope is modified by sex, age and temporal factors which may then be reduced by an appropriate dose and dose-rate effectiveness factor (DDREF). For leukemia, a linear-quadratic dose-response model is used, and no DDREF is applied. NASA applied standard formulae (Cucinotta et al. 2013), using a weighted average of the modeled ERRs and EARs and data on U.S. baseline rates for cancer and all-cause mortality, to estimate lifetime probabilities of an incident cancer (or cancer fatality) attributable to the specific exposure to radiation. A fuller description of the models is provided in Section 6.
2.4 Description of the Astronaut Cohort

Since the formation of the agency in 1958, NASA has selected 350 individuals for its elite Astronaut Corps, which includes 57 females. The first NASA astronaut class, chosen for the Mercury program, was an all-male group comprised of military test pilots selected to meet specific physical and educational requirements, which resulted in a relatively homogenous group (Voas 1960; Carpentier et al. 2018). The demographics of the NASA Astronaut Corps has changed over the decades since the selection of the Mercury Seven, reflecting societal changes with females and minorities earning more science and engineering degrees. The demographic shift also reflects changing agency mission requirements that started with the shuttle program when selection began for both mission specialists and pilots. Females joined the ranks in the late 1970s. Six females were selected as part of astronaut group 8 (Figure 2.1) including Sally Ride who would go on to become the first American female to venture into space (Ross-Nazzal and Lucid 2010). Anna Fisher, also a member of astronaut group 8, became the first mother to fly into space, just 14 months after the birth of her daughter (Contrera 2019).

In 2020, NASA had 48 active-duty astronauts, including 12 females (Mars 2020). The age range of these astronauts was 35 to 58 y and all share healthy lifestyle factors (normal weight, healthy diet, physically fit). While the majority of the astronaut corps are lifetime never-smokers, some of the early astronauts were smokers as was commonplace in the United States in the late 1950s and early 1960s (Scott and Jurek 2014).

The current space-based research platform is the International Space Station, orbiting approximately 200 miles above Earth in a region known as low-Earth orbit. The average mission length aboard the International Space Station is 6 to 12 months and flight crews are composed of 4 to 6 astronauts. Going back to the Moon is a major goal of the agency’s new Artemis program, with plans for landing the first female and next male on the lunar surface by 2024 (NASA 2020). The Artemis plan calls for sustainable lunar exploration and features development of an orbiting lunar space station (Gateway) and an outpost on the Moon’s surface known as the Artemis Base Camp. These will be stepping-stones to future destinations including Mars.
Fig. 2.1. (Left to right) NASA astronauts Shannon W. Lucid, Margaret Rhea Seddon, Kathryn D. Sullivan, Judith A. Resnik, Anna L. Fisher and Sally K. Ride. These six females were the first official female astronaut candidates, although 12 females underwent some astronaut training in the 1960s (Image: © NASA).
With plans for exploration to distances further away from Earth, the evaluation of how the sex of an astronaut influences space-flight health, social interaction, and team dynamics are increasingly important (Mark 2014). The interplay of radiation with the other human health hazards associated with space flight also escalates as missions extend beyond low-Earth orbit and for longer durations. These hazards are isolation and confinement, distance from Earth, altered gravity, and hostile and closed environments. Each of these hazards is associated with a variety of human health risks as identified by NASA’s Human Research Program (NASA 2021a), and each needs to be adequately understood and controlled in order to ensure safe and successful space missions. These health risks include, among others (Patel et al. 2020, NASA 2021b):

- spaceflight associated neuro-ocular syndrome, with symptoms such as swelling of the optic disc, wrinkling of the retinal layer, globe flattening and refractive error shifts;
- behavioral health and performance decrements, which may include decrements in performance, cognition, motor function, and alterations in psychological and behavioral health; and
- inadequate food and nutrition, which has the potential to impact all aspects of astronaut health.

### 2.4.1 Health Monitoring of Astronauts

In addition to extensive medical monitoring for active astronauts throughout the course of their career, NASA provides medical surveillance services to former NASA astronauts through an annual preventive exam and screening tests organized by the Lifetime Surveillance of Astronaut Health program at the NASA Johnson Space Center (NASA 2018). This program provides health screening and tracks astronauts for potential occurrence of occupationally related injury or diseases (Longnecker et al. 2004). Extending on this capability, the “To Research, Evaluate, Assess, and Treat Astronauts Act” (Lewis 2020) was signed into law in 2017 and provides authority to NASA for expansion of medical monitoring for former astronauts to include diagnosis and treatment, free of personal cost, for medical and psychological conditions that are considered to be associated with a flight crew’s time in space.
2.4.2 Epidemiologic Studies of Astronauts

In general, epidemiologic studies of the effects of space radiation and space flight on astronaut health are limited statistically by the small cohort size as well as the relatively low radiation exposure levels received by flight crews to date and short follow-up time. Nevertheless, several studies have been conducted and show increased longevity and reduced risk of cancer and cardiovascular disease in U.S. astronauts compared to the general U.S. population (Peterson et al. 1993; Reynolds and Day 2010; Reynolds et al. 2021). This finding is not unexpected given that the astronaut corps consists of extremely healthy individuals (healthy worker effect). This healthy worker effect, which is likely strong in the astronaut corps, makes identification of an appropriate comparison group difficult, hindering epidemiologic studies of this population. Reynolds and Day (2019) addressed this by comparing U.S. male astronaut mortality rates with those of professional athletes. Both groups in this study shared common features related to their health status (i.e., well-educated, excellent health, physical fitness, higher socioeconomic status than the average population, and top medical healthcare). In this evaluation, both astronauts and professional athletes had lower mortality compared to the general U.S. population. Also, there was no evidence of earlier deaths in the astronauts that might be related to exposure to hazards of space flight (Cucinotta et al. 2016; Elgart et al. 2018). Although, for radiation, the exposure levels received by earlier astronauts will likely be lower than what will be experienced by future astronaut flight crews traveling outside low-Earth orbit for longer duration missions. As more astronauts travel in space, some of the constraints associated with this cohort will lessen and future studies should produce more robust data (Peterson and Kovyrshina 2015; Ade et al. 2017; Elgart et al. 2018; Reynolds and Day 2018).

2.5 Specific Issues to be Addressed

The NASA-specific issues to be addressed in this Commentary are:

- First, does the recent epidemiologic data on radiation-associated lung cancer risk indicate a clear difference between males and females?
Second, should the existing NASA lifetime risk projection model for lung cancer be modified? And if so, how should it be modified?

An important corollary issue is whether lung cancer risk differs between chronic, protracted, or fractionated radiation exposure compared with acute radiation exposure. A mission to Mars will take at least 2.5 y so the exposure received will be chronic and prolonged. The unique exposure to space radiation includes the HZE-particle component of galactic cosmic radiation, and the impact on lung cancer risk from these HZE particles is not known. Also, the exposure is in a mixed field of low-LET and high-LET radiation (including a small neutron component). Do experimental studies of laboratory animals exposed to various forms of ionizing radiation provide relevant information to help in the judgment as to the sex-specific differences in lung cancer risk and the effect of fractionated or prolonged exposure on lung cancer risk?

While NASA has many important risk issues to deal with, in addition to those related to radiation exposure, this Commentary focuses on an evaluation of lung cancer risk from radiation exposure to a flight crew on any extended mission (an example being a long-duration mission to Mars).

2.5.1 What Epidemiologic Cohorts are Most Relevant to Estimate Sex-Specific Lung Cancer Rates for an Astronaut Flight Crew

The ideal epidemiologic cohort would have characteristics that are similar to the astronaut flight crews that will be engaged in long-term missions. Not just the personal characteristics such as age but also the exposure circumstances such as chronic low doses over years and in a mixed field of low-LET and high-LET radiation. As described in Section 2.4, the ideal population to study would have the following characteristics.

- Very healthy.
- Adults, age 35 to 50 y old at time-of-exposure.
- Exposed to chronic, protracted, or fractionated exposure over a period of several years.
• Exposed to both low-LET and high-LET radiation. Radiation exposures received from HZE particles would be ideal, but such Earth-bound populations do not exist.
• Exposures to other high-LET radiation experienced on Earth, such alpha particles resulting from intakes of radionuclides might provide useful insights.
• Include both females and males.
• Have long enough follow-up so that any adverse health effects occurring later in life could be observed.
• Be sufficiently large so there is a statistical ability to find adverse health effects had they occurred.
• Reasonable control of the major confounding factor for lung cancer, cigarette smoking. Astronauts are nonsmokers, so epidemiologic cohorts with large numbers of nonsmokers are ideal.

These characteristics for 31 epidemiologic studies relevant to radiation-related lung cancer are discussed in Section 3.2 (19 studies with sex-specific risk estimates) and Section 3.3 (14 studies not included in Section 3.2 because they did not include sex-specific estimates).

2.5.2 Approaches to Consider for Improving the NASA Lifetime Risk Projection Model for Lung Cancer

This Commentary also proposes recommendations to improve the NASA lifetime risk projection model for radiation-related lung cancer mortality by considering available epidemiologic, experimental, and biological information coupled with state-of-the art statistical modeling. The overarching goal is to suggest an optimum lifetime risk projection model for radiation-related sex-specific lung cancer mortality. Some of the issues to be addressed are listed below.

• Can the available epidemiologic, experimental, and biological information provide evidence for sex-specific difference in lung cancer risk, and address potential health effects from the HZE-particle component of galactic cosmic radiation (for which little to no human cancer data exist) in an integrated manner?
762 • Is there convincing evidence from epidemiologic and experimental studies that chronic,
763 protracted, or fractionated exposures result in sex-specific lung cancer risks that differ
764 from those following acute exposures?
765 • Does the recent and dramatic improvement in lung cancer survival (Ma et al. 2019;
766 Brawley 2020; Howlader et al. 2020a; Siegel et al. 2021) indicate a need to revise the
767 projected lifetime REID for radiation-induced cancer?
768 • How can the uncertainty in the lifetime risk projections for lung cancer be better defined
769 and reduced?
3. Epidemiology

Rationale: This Commentary evaluates sex-specific (female versus male) differences in lung cancer risk due to radiation exposure. For background, Section 3.1 describes the baseline distribution of lung cancer in the population before consideration of radiation exposure, including the age, sex and racial differences in incidence and mortality rates and the remarkable changes in recent decades. It is particularly important to review the lung cancer occurrence in nonsmokers, the population most applicable to astronauts. Other important inquiries are whether females are more susceptible to lung cancer than males for reasons other than a different prevalence of cigarette smoking and, similarly, whether racial differences in lung cancer risk can be related to factors other than cigarette smoking. It is unclear whether the observed sex-specific differences in baseline cancer rates are due to hormonal or genetic factors, or to the influence of occupational and lifestyle factors. The causes of lung cancer other than cigarette smoking are discussed as relevant to astronauts. Section 3.2 then reviews the major epidemiologic studies that provide information on radiation-related, sex-specific lung cancer risk. Section 3.3 reviews other epidemiologic studies that provide information on risk for radiation-related lung cancer but do not provide sex-specific estimates. The conclusions for Section 3 are provided in Section 3.4.

3.1 Epidemiologic Studies of Lung Cancer with a Focus on Nonsmokers

Lung cancer is the leading cause of cancer mortality in both males and females but is rare under the age of 40 y (Siegel et al. 2021). In 2021, an estimated 236,000 new lung cancer cases are expected (49% among females) and 136,000 deaths are expected (also 49% among females) (Siegel et al. 2021). These numbers are lower than previous years and reflect an accelerated decline in lung cancer mortality over the last decade. The annual decline changed from 3.1% during 2009 to 2013 to 5.5% during 2014 to 2018 in males, and from 1.8% to 4.4%, respectively, in females, including the largest ever single year drop in overall cancer mortality of 2.2% from 2016 to 2017. This remarkable decline in lung cancer mortality most likely reflects smoking cessation (and a concomitant decline in annual lung cancer incidence rates on average by 2.2% to 2.3% per year from 2008 to 2017) and general improvements in early detection and treatment (Brawley 2020; Howlader et al. 2020a; Siegel et al. 2021) which may have even more impact on lung cancer survival in the coming years (Hirsch 2020).
Historically, lung cancer rates have been higher in males than in females due to the higher smoking prevalence for males (Jemal et al. 2018; Fidler-Benaoudia et al. 2020). However, with smoking rates declining in the United States and other countries, incidence rates have reversed and now lung cancer incidence is higher in young females compared with young males aged 30 to 49 y. This crossover in sex-specific lung cancer rates is not completely explained by increasing rates of smoking among females, which have approached the smoking rates among males born after 1965 (Jemal et al. 2018).

Using U.S. data on smoking (1964 to 2015) and lung cancer mortality (1969 to 2010), Jeon et al. (2018) projected a decrease in age-adjusted lung cancer mortality by 79 % between 2015 and 2065, with a greater reduction in males (83 % versus 73 %). They also projected that the annual number of lung cancer deaths would decrease from 135,000 to 50,000 (63 % reduction overall, 68 % in males and 56 % in females). Owing to changing smoking habits in the population, the higher projected rate of lung cancer deaths in males compared with females would reverse by 2045 if current smoking trends continue.

Lung cancer survival rates have been historically low as lung cancer is often diagnosed at an advanced stage. Howlader et al. (2020b) report that a large proportion of patients (57 %) is diagnosed with metastatic disease, for which the 5 y relative survival rate is 5.8 %. The most recent data show a remarkable drop in lung cancer mortality suggesting that reduced smoking coupled with screening, early detection and new treatment regimens are starting to show tangible gains which may continue in the foreseeable future (Hirsch 2020).

Thun et al. (2006, 2008, 2013) conducted a number of pooling studies to evaluate trends in lung cancer mortality and cancer incidence rates in the United States. The Cancer Prevention Studies (CPS-I and CPS-II) directly measured the age-, sex-, and race-specific risks of lung cancer incidence and mortality among almost one million American never-smokers during 1959 to 1972 (CPS-I) and 1982 to 2000 (CPS-II), respectively (Thun et al. 2008). Both studies reported stable lung cancer death rates for nonsmokers by age (25 to 85+ y), calendar year and by sex (Thun et al. 2006). In a subsequent pooled analysis of 13 cohorts and 22 cancer registry studies, 1.8 million participants were followed for mortality and 630,000 for incidence during the
1980s and 1990s (Thun et al. 2008). Starting with age category 50 to 54 y, white male never-smokers had higher lung cancer mortality rates compared with white female never-smokers (significantly higher for ages 75+ y) (Thun et al. 2008). Although the number of observed cases increased for nonsmoking females, this was a natural consequence of there being more female nonsmokers than male nonsmokers of advanced age. The authors concluded that the lung cancer death rate was higher in nonsmoking males than in nonsmoking females, despite the prevailing clinical perception that the rate is increasing in females or that females have a higher incidence rate than males (Thun et al. 2008). Age-adjusted mortality rates for never-smokers also were found to be higher in African Americans and Asians living in Korea and Japan than in whites for both sexes.

In an update, Thun et al. (2013) pooled the data for those 55 y or older from contemporary cohorts followed up until the end of 2010. Age-standardized rates of death from lung cancer among nonsmokers remained constant for males over the last 5 decades (1960 to 2010) but increased for females during 1960 to 1980s, before decreasing in the contemporary period (1990 to 2010) (Thun et al. 2013). Figure 3.1 shows trends in lung cancer mortality for nonsmokers over the last 5 decades in the United States, separately for males and females, based on various historical and contemporary cohorts (Thun et al. 2008, 2013).

Overall, CPS-I and CPS-II provide useful data (Figure 3.2 provides incidence-rate and mortality-rate data for CPS II), but the years of last follow-up are not recent and any important lung cancer trends in nonsmokers in the last 5 to 10 y would be missed. Recently, the California Cancer Registry estimated lung cancer incidence rates among nonsmokers within the Sutter Health-Kaiser Hawaii lung cancer study (DeRouen et al. 2022). In this large dataset of more than 2.3 million individuals, lung cancer incidence rates among never-smokers were higher among females compared with males. The highest female-to-male ratios were observed among Chinese and non-Hispanic Whites, 1.23 for both groups, although not statistically significant [confidence intervals (CI) of 0.74, 2.11 and 0.99, 1.54, respectively]. Comparison of incidence rates from Thun et al. (2008) and DeRouen et al. (2022) suggests that the incidence rates of lung cancer among nonsmokers have dropped by ~15 to 20 % in the last decade for non-Hispanic White males and females but increased for Asian males and females (Table 3.1).
Fig. 3.1. Sex- and age-specific lung cancer mortality rates in white nonsmokers in the United States. Mortality follow-up from 1959 to 2004 in Thun et al. (2008) and from 1959 to 2010 in Thun et al. (2013).
Fig. 3.2. Sex-specific lung cancer incidence and mortality rates in the United States among nonsmokers of European descent in CPS-II cohort over time. Upper graph (incidence rates), lower graph (mortality rates). Age-standardized to the year 2000 International Agency for Research on Cancer world population, ages 40 to 79 y.
Table 3.1 -- Comparison of age-adjusted incidence rates (with 95% confidence interval) of lung cancer among never-smokers per 100,000 (Thun et al. 2008; DeRouen et al. 2022).

<table>
<thead>
<tr>
<th>Study</th>
<th>White</th>
<th>Asian</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>CPS-I and CPS-II * (Thun et al. 2008)</td>
<td>11.2 (9.8, 12.6)</td>
<td>12.4 (11.3, 13.5)</td>
</tr>
<tr>
<td>Cancer Registries Study (DeRouen et al. 2022)</td>
<td>8.2 (6.8, 9.7)</td>
<td>10.1 (9.0, 11.6)</td>
</tr>
</tbody>
</table>

* The Cancer Prevention Studies [CPS-I (1959 to 1972) and CPS-II (1982 to 2000)].
In summary, comprehensive epidemiologic descriptive and analytic investigations have provided insights into lung cancer risks among females and males that are relevant to lifetime risk projection models for astronauts. They also indicate the challenges in interpreting the complexities of rapidly changing lung cancer incidence and mortality rates over time coupled with changing patterns in cigarette smoking by age (birth cohort) and sex. Differences in lung cancer risk by race among nonsmokers might be considered for individual risk assessments.

Currently, there is an accelerated decline in lung cancer annual mortality rates that is unprecedented, among both males and females. Notably, the decline in males is two times higher than in females (Siegel et al. 2021). If this rapid decline continues (possibly reflecting changes in smoking prevalence, improvements in screening for lung cancer, effective treatments, and better survival due to early detection), the effect on changes in lifetime risk projections might be considerable. Notably, cigarette smoking is increasing among young females compared with young males, and a crossover (reversal) in the ratio of male-to-female lung cancer rates is seen with young females having higher rates. The prevalence of vaping is also increasing in those younger than 30 y. Mortality rates for lung cancer among nonsmokers are higher among African Americans and Asians (living in Asia) than among Whites. It is important to note that current safety guidelines for astronauts are based on lifetime risk projections of cancer mortality although cancer incidence is considered a more accurate metric to study the etiology of lung cancer.

### 3.1.1 Risk Factors

**Rationale:** To interpret the epidemiologic observations of lung cancer, it is helpful to understand the factors that contribute to the risk of this disease particularly among nonsmokers. The International Agency for Research on Cancer has designated 18 exposures and 11 occupations or occupational processes as lung carcinogens (Thun et al. 2017). Most of the etiologic factors, however, are not relevant to flight crews. Cigarette smoking (tobacco use) is by far the predominant cause of lung cancer worldwide. Among nonsmokers, secondhand smoke contributes to an increased risk, albeit small. Indoor radon is estimated to be the second most important cause of lung cancer with excess risks seen among males and females and nonsmokers. These and other notable causes of lung cancer are described in Sections 3.1.1.1 through 3.1.1.5, highlighting where sex-specific differences in etiology may be present.
3.1.1 Ionizing Radiation. Ionizing radiation has been convincingly linked to increases in lung cancer occurrence. Epidemiologic studies have found associations with exposure to x rays, gamma rays, plutonium, and radon and its decay products (NA/NRC 2006; UNSCEAR 2008; IARC 2012). Exposure to the noble gas radon and its short-lived radioactive decay products is considered the second leading cause of lung cancer in the United States. Some studies indicate that cigarette smoking and radiation may interact in a manner that is intermediate between additive (i.e., the separate risks add) and multiplicative (i.e., the separate risks multiply) (NA/NRC 1999; Thun et al. 2017). However, few astronauts have smoked in the past so this potential increase in risk due to interaction between radiation and smoking is of little concern, except in the transfer of radiation-related lung cancer risks from the Japanese atomic bomb survivors to a non-Japanese population (NA/NRC 2012). NA/NRC (2006) recommended a weight of 0.3 to the multiplicative transfer model, favoring an additive transfer model based on early analyses of the joint effect of smoking and radiation in the LSS (Cucinotta et al. 2013). The current NASA model uses a weight of 0.5 for the ERR lung cancer model. For never-smokers, this choice results in a lower lifetime risk estimate than a weight of 0.3. An even lower risk estimate would result if a weight of 0.7 were chosen, as is done for all other solid cancers.

The high prevalence of the medical uses of low-dose imaging procedures including computerized tomography has raised concern about patients who may receive frequent examinations over time. It is relevant to note that medical radiation screening examinations that are required for flight crews, any diagnostic and therapeutic medical procedure conducted on a flight crew member, or any natural background radiation received on Earth are not considered occupational doses and are not included in the lifetime risk projection models (NCRP 2014).

Exposure to ionizing radiation happens continually from natural and human-made sources. Natural sources include cosmic radiation from outer space and the sun as well as terrestrial sources including gamma rays and radon gas derived from natural sources of radioactive elements such as uranium. Acute, high-level exposure to ionizing radiation can kill a sufficient number of cells that organ and tissue damage can result. Exposures to levels of ionizing radiation at lower levels can cause damage to deoxyribonucleic acid (DNA) that may manifest later as cancer. Generally, cancers that occur after radiation exposure bear no “radiation
signature”. The period of expression of excess risk for solid cancers after ionizing radiation exposure is generally longer than 5 y and can be more than 50 y. Therefore, insights regarding possible associations and causes are often derived statistically by comparing, over long periods, populations with varying levels of radiation exposures. Observed risks are generally dependent upon radiation dose and type, age-at-exposure, and attained age (or time-since-exposure). The quality of the studies is dependent upon accurate, individual dosimetry, an awareness and control of confounding factors, and accurate follow-up data over long periods. Studies in humans have been performed for more than 100 y, and include populations exposed from medical applications of radiation, those living in locations with high natural background radiation, those exposed at their places of work and those exposed as a result of military circumstances. Flight crews on missions beyond Earth orbit will be exposed to galactic cosmic radiation [including HZE particles, low-energy protons (from the solar wind), helium nuclei, and neutrons and mesons (from collisions with shielding materials) at an absorbed dose rate of about 0.45 mGy d\(^{-1}\) (NCRP 2016).

3.1.1.2 Cigarette Smoking. Cigarette smoking is by far the primary cause of lung cancer in the United States and throughout the world (Thun et al. 2017). Tobacco use is estimated to cause 80% of all lung cancer deaths that occur each year in the United States. Involuntary exposure to tobacco smoke, or secondhand smoke, has been convincingly linked to lung cancer mortality and is considered the third leading cause of lung cancer mortality in the United States behind cigarette smoking and indoor radon. The decline in lung cancer incidence is faster among males than females, reflecting historical differences in tobacco cessation, as well as different patterns of smoking prevalence in some birth cohorts. As discussed in Section 3.1, differences in smoking patterns between males and females do not explain the higher lung cancer rates now occurring in young females compared with males (Jemal et al. 2018; Fidler-Benaoudia et al. 2020). Because practically all members of the astronaut corps are lifetime never-smokers (Section 2.4), this Commentary focuses on developing lifetime radiation risk estimates among never-smokers.

3.1.1.3 Workplace and Environmental Exposures. Lung cancer can be caused by relatively high exposures to occupational carcinogens, such as asbestos, arsenic, diesel exhaust, beryllium, nickel and chromium compounds, vinyl chloride, mustard gas, and silica dust (Field and Withers 2012; Thun et al. 2017). Today, government regulations have reduced such exposures in the
workplace. Some environmental contaminants, such as arsenic in drinking water have also been linked to lung cancer. Even with onboard air and water purification systems on spacecraft, chemicals will accumulate in the air and water as they recirculate or are recycled onboard. NASA has guidelines for measuring and reducing airborne contaminants such as vinyl chloride during space missions to levels unlikely to pose a health hazard (James 1997; NA/NRC 2012). Large numbers of people worldwide are exposed to polluted air that might contain particulate matter, diesel exhaust, and combustion products of coal used as household fuels (Thun et al. 2017). Outdoor air pollution is estimated to account for up to 5% of all lung cancer deaths. Diesel exhaust contains a complex mixture of chemicals such as polycyclic aromatic hydrocarbons, nitrogen dioxide, nitrogen oxides and particulate matter. The high risks of lung cancer reported among truck drivers and underground nonmetal miners suggest that polluted air might be a contributing cause for approximately 6% of annual lung cancer deaths (Thun et al. 2017). Astronaut crews are not likely to experience such air pollutants in space travel.

3.1.1.4 Host Factors. While the primary factors closely tied to lung cancer in never-smokers are radon, secondhand tobacco smoke, and indoor air pollutants, several predisposing medical conditions and inherited genetic susceptibility traits have been associated with increased or decreased lung cancer risk (Thun et al. 2017). Tuberculosis, chronic bronchitis, emphysema, pneumonia, and silicosis, for example, have been associated with an increased risk of lung cancer, possibly related to an inflammatory response (Brenner et al. 2012; Denholm et al. 2014), while asthma, hay fever, and eczema have been associated with a decreased risk (Rosenberger et al. 2012; Thun et al. 2017). The associations between chronic obstructive pulmonary disease, emphysema, chronic bronchitis and pneumonia could be due to misclassification of smoking or the effects of passive smoking, but the large size of the effect seen among never-smokers suggests a direct association between previous lung diseases and lung cancer risk, similar in males and females, most likely through an inflammatory pathway (Brenner et al. 2011).

Several small, but high quality, studies fail to confirm associations between nonmalignant lung disease and lung cancer (Alavanja et al. 1992; Samet et al. 2009). Several large cohort studies also fail to find an association between tuberculosis and lung cancer in the United States (Davis et al. 1989) and Canada (Howe 1995; Boice et al. 2019a) among males or females treated
with pneumothorax and monitored by repeated chest fluoroscopic x rays or among those given
other treatments not requiring fluoroscopic monitoring. The relevance of tuberculosis and other
nonmalignant lung diseases to astronaut crews is weak at best, but more research in this area is
suggested (Samet et al. 2009).

Inherited genetic susceptibility as a host factor for lung cancer is supported by studies
showing the aggregation of lung cancer in families, the linking of specific genes such as tumor
protein 53 (TP53) and retinoblastoma (Rb) in rare Mendelian cancer syndromes to lung cancer,
and in genome-wide association studies finding low penetrance germline variants associated with
lung cancer risk (Thun et al. 2017). Several recent reviews reported that females are more likely
than males to have nonsmoking-associated lung cancer and suggested that genetic predisposition
may play a role (Gazdar and Thun 2007; Kligerman and White 2011). In particular,
proportionally more females than males with lung cancer among nonsmokers have a mutation in
the epidermal growth factor receptor (EGFR) gene (Isla et al. 2017). EGFR mutations have been
shown to be more common in adenocarcinoma histology, nonsmokers, Asian populations and
females (Wakelee et al. 2007).

Genetic mutations in the Kirsten rat sarcoma viral oncogene homolog (KRAS) (Nelson et
al. 1999) and human epidermal growth factor receptor 2 (HER-2) (Guinee et al. 1995) genes
were also more prevalent in lung cancer tumor tissues of females compared with samples from
males. Mathematical models of lung cancer risk in the British Doctors’ Study and CPS-I and
CPS-II, suggest that cancer promotion events (rather than initiation) appear to dominate the
etiological mechanisms of lung cancer in nonsmokers (Hazelton et al. 2005). While there have
been major advances in understanding the role of inherited genetic susceptibility as a host factor
for lung cancer, the conclusions by NCRP (2010) on the impact of individual genetic
susceptibility on radiation risks in astronauts still holds, namely “… with the exception of a
relatively small fraction of the human population that is known to have innate genetic
susceptibility to cancer from radiation exposure, it is difficult if not impossible at this time to use
the available information to make predictions on the role of genetic factors for the small corps of
astronauts participating in space exploration”.

40
3.1.1.5 Hormones. A possible role of endogenous and exogenous hormones in lung carcinogenesis has been suggested because:

- lung cancer rates are increasing among nonsmoking females;
- lung cancer rates are generally higher among nonsmoking White females compared with nonsmoking White males (Table 3.1);
- adenocarcinoma occurs more frequently among nonsmoking females;
- mutations in the EGFR gene are more likely to be harbored in adenocarcinomas among nonsmoking females; and
- estrogen and progesterone receptors occur on human lung cancer cells (Brinton et al. 2011; Alberg et al. 2013; Tan et al. 2015; Cheng et al. 2018).

The epidemiologic evidence is inconsistent, however, and reproductive and hormonal factors are not listed as established risk factors for lung cancer (Thun et al. 2017; Siegel et al. 2021). Reproductive factors such as parity, menstrual history, age-at-menopause, and age-at-menarche are not consistently related to increased lung cancer risk (Baik et al. 2010; Brinton et al. 2011; Jeon et al. 2018; Jin and Lang 2019; Yin et al. 2020). Oral contraceptive use and hormonal replacement therapy also are not consistently found to increase lung cancer risk, and several studies report decreased risks among females taking hormonal replacement therapy (Brinton et al. 2011; Schwartz et al. 2015; Zeng et al. 2021). Women receiving hormonal treatments for infertility also have not been found to be at increased risk of lung cancer (Brinton et al. 2015). Of note are the clinical trial data from one of the largest studies in the United States, the Women’s Health Initiative, that failed to support the hypothesis that reproductive history or hormonal use (oral contraceptives or hormonal therapy) independently contributed to lung cancer development (Schwartz et al. 2015).

While the epidemiologic evidence for estrogens playing a role in lung carcinogenesis among nonsmoking females is equivocal and the applicability to female astronauts is tenuous at this time, because of the differences in lung cancer rates and the clinical and molecular characteristics of diagnosed tumors between nonsmoking females and males, detailed mechanistic studies and evaluation of risk factors in conjunction with estrogen receptor expression in the lung should continue (Schwartz et al. 2015). Additional studies addressing
biologic mechanisms associated with estrogen exposure of lung tissue would help resolve issues of the pathogenesis of lung cancers (Brinton et al. 2011).

3.1.2 Radiation and Histopathologic Subtypes

Rationale. The importance of knowing whether radiation exposure to lung tissue results in different distributions of histological subtypes than expected based on population rates relates to refinements in lifetime risk projection models that consider improved survival trends after diagnosis. The major histological subtypes of lung cancer are small cell, adenocarcinoma, squamous cell, and other. Survival differs appreciably by cell type, with small-cell cancers having the worst prognosis. The remarkable improvements in lung cancer survival over the past few years is concentrated among the 80% of incident non-small cell lung cancers (NSCLC). While there are epidemiologic evaluations of radiation-related lung cancer considering histologic subtype, there are few among nonsmokers. The study of Japanese atomic bomb survivors and studies of residential radon are the most informative with regard to radiation-related histologic subtypes of lung cancer among nonsmokers.

Lung cancer rates in the United States differ by smoking status, sex, race or ethnicity, and age (Section 3.1). Histological subtypes also vary by tobacco use with small-cell, squamous cell, and large-cell carcinomas more prevalent among smokers and adenocarcinomas among nonsmokers (McCarthy et al. 2012). The incidence of lung cancer in males of all races increased until 1980 and then decreased, but patterns varied by histology (Meza et al. 2015). Until about 1985, the incidence of small-cell and large-cell carcinoma increased and then decreased steadily. The incidence of squamous cell carcinoma increased until 1980, and then decreased until 2005. In 2005, the incidence of squamous cell carcinoma and adenocarcinomas, particularly in white males, began to increase. In contrast, overall lung cancer incidence rates for females increased until 2007, but patterns varied greatly by subtype. Around 2004, increasing rates for squamous cell carcinoma and adenocarcinomas were seen. These trends have resulted in lung adenocarcinoma being the most commonly diagnosed histological type in both males and females in the United States.
The study of Japanese atomic bomb survivors indicates significant differences in the risk of specific histological subtypes of lung cancer among never-smokers (Land et al. 1993; Egawa et al. 2012). The gender-averaged ERR at 1 Gy was 1.49 (95% CI 0.1, 4.6; n = 10) for small-cell carcinoma, 0.75 (95% CI 0.3, 1.3; n = 165) for adenocarcinoma, and 0.27 (95% CI 0.0, 1.5; n = 16) for squamous cell carcinoma. Although based on small numbers the female-to-male ratio of subtype risks was 0.35 for small-cell carcinoma and about 7 for NSCLC.

Darby et al. (2006) conducted a pooled analysis of European studies and included analyses of histological outcomes. Overall, the risk of radon-related lung cancer was significant only for small-cell lung cancer with risk estimates the same for males and females. The other types, combined and separately (squamous cell, adenocarcinoma, other), did not indicate significant association with radon concentration levels among either males or females. For small-cell carcinomas, the ERR at 100 Bq m\(^{-3}\) radon concentration was 1.40 (95% CI <0.031, >5.0; n = 84) for never-smokers, and for NSCLC it was 0.042 (95% CI <0.031, 0.203; n = 704). The comparable numbers for ex-smokers were 0.344 (95% CI 0.078, 0.876; n = 416) and 0.013 (95% CI <0.082, 0.146; n = 1,758). In two publications (Krewski et al. 2005, 2006) risks of radon exposure in residential settings in North America were estimated by gender and histological type. Small-cell carcinomas generally showed the largest dose response and were comparable in both males and females.

For workers exposed to plutonium at the Mayak Production Association facility, initial studies comparing risks of lung cancer due to plutonium exposures in males and females found two-fold significantly higher risks for females (Sokolnikov et al. 2008). However, more recent analyses considering smoking information available for 89% of the cohort found males to be at significantly higher risk than females, and there was no significant difference in radiation risks between males and females for nonsmokers (Labutina et al. 2013). Radiation risks of adenocarcinoma were higher than that for squamous cell carcinoma but only significantly so among males. The ERRs among nonsmokers were higher than among smokers, but the small number of cases among nonsmokers (n = 27) limited comparisons by histologic type. Data on small-cell carcinoma were not provided.
Overall, there is some evidence to suggest that small-cell carcinoma, which has the poorest survival characteristics, may have a higher radiation risk coefficient than other cell types, although the overall numbers of attributable cancers may be smaller in comparison. There is suggestive evidence, then, that the distribution of radiation-induced lung-cancer histologic subtypes may differ from the distribution occurring in the general population. More research and careful analyses on histologic type of radiation-induced lung cancers among nonsmokers is needed before definitive conclusions can be drawn.

### 3.2 Epidemiologic Studies of Sex-Specific Radiation-Related Lung Cancer

**Rationale and Summary:** Populations exposed to ionizing radiation can provide direct evidence on possible sex-specific differences in lung cancer risks. Exposures can occur gradually over years (such as in occupational or environmental settings) or acutely, as in the exposure received by the Japanese atomic bomb survivors or by some medically-exposed patients. In addition to the rate of exposure, various types of radiation differ in LET. Astronauts face a complicated mixed environment of exposure to both low-LET and high-LET radiation, and galactic cosmic radiation in particular.

Epidemiologic studies relevant to assessing the sex-specific lifetime radiation risk estimates for lung cancer are listed in Table 3.2 along with summary information. For each epidemiologic study, the following is provided in Table 3.2:

- References;
- Type of radiation [e.g., x rays, gamma rays, neutrons, radon (alpha particles), intakes of specific radionuclides];
- Type of exposure (acute or chronic; whole body or partial body);
- Number of subjects;
- Number of lung cancer deaths or cases;
- Years of follow-up;
- Radiation quantity [namely, absorbed dose in lung, weighted dose in lung (with weighting factor(s), personal dose equivalent, radon concentration)];
Mean and range values for the radiation quantity used (e.g., absorbed dose in lung);

Standardized Mortality Ratio (for lung cancer) (sex-specific, when available); and

Measure of radiation risk: excess relative risk or excess odds ratio (for lung cancer)

at 1 Gy, 100 mGy, 1 Sv or 100 Bq m$^{-3}$ (sex-specific, when available), with $P$ value for heterogeneity between female and male results, when available.

The general inclusion criteria for studies in Table 3.2 were:

Published in English and indexed in PubMed without regard for date of publication. When several publications were available for the same cohort, the results from the most recent and relevant publication(s) were reported.

Included individual estimates of the radiation quantity (e.g., absorbed dose in lung).

Included both males and females.

Included lung cancer mortality or incidence as an outcome.

Provided estimates of radiation risk per unit radiation quantity (e.g., absorbed dose in lung) for lung cancer separately for males and females or provided sex-specific estimates of Standardized Mortality Ratios.

The studies are grouped into the following categories (and each study is briefly described in the indicated subsection of Section 3.2):

Medical exposure of patients (Section 3.2.1).

Occupational exposure of workers (Section 3.2.2).

Environmental exposure of populations (Section 3.2.3).

The Japanese atomic bomb survivors (Section 3.2.4).

Following the subsections of Section 3.2, Section 3.3 discusses epidemiologic studies of radiation and lung cancer that were not included in Table 3.2 in large part because they provided sex-averaged estimates of lung cancer (i.e., no sex-specific estimates).
### Section 3.2.1: Medical Exposure of Patients

#### Canadian Tuberculosis Fluoroscopy

<table>
<thead>
<tr>
<th>Study (Section)</th>
<th>References</th>
<th>Type of Radiation</th>
<th>Type of Exposure</th>
<th>Number of Subjects</th>
<th>Number of Lung Cancer Deaths</th>
<th>Radiation Quantity</th>
<th>Absorbed dose in lung</th>
<th>Excess Odds Ratio</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>(3.2.1.1)</td>
<td>Boice et al. (1995)</td>
<td>Fluoroscopy</td>
<td>Chronic</td>
<td>T: 6,707 F: 3,787 M: 3,120</td>
<td>Deaths</td>
<td>Range: 0.37 - 0.84 Gy</td>
<td>T: 1.78 F: 0.64 M: 0.20</td>
<td>0.78 (1.04, 1.60)</td>
<td>Mean: T: 0.78 F: 0.15 M: 0.02 (Hewe 1995)</td>
</tr>
</tbody>
</table>

#### Massachusetts Tuberculosis Fluoroscopy

<table>
<thead>
<tr>
<th>Study (Section)</th>
<th>References</th>
<th>Type of Radiation</th>
<th>Type of Exposure</th>
<th>Number of Subjects</th>
<th>Number of Lung Cancer Deaths</th>
<th>Radiation Quantity</th>
<th>Absorbed dose in lung</th>
<th>Excess Odds Ratio</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>(3.2.1.2)</td>
<td>Davis et al. (1989)</td>
<td>Fluoroscopy</td>
<td>Chronic</td>
<td>T: 13,398 F: 6,637 M: 6,761</td>
<td>Deaths</td>
<td>Range: 0.50 - 0.84 Gy</td>
<td>T: 0.72 F: 0.41 M: 0.25</td>
<td>0.90 (1.04, 1.56)</td>
<td>Mean: T: 0.90 F: 0.04 M: 0.002 (Hewe 1995)</td>
</tr>
</tbody>
</table>

#### Hodgkin Lymphoma Patients

<table>
<thead>
<tr>
<th>Study (Section)</th>
<th>References</th>
<th>Type of Radiation</th>
<th>Type of Exposure</th>
<th>Number of Subjects</th>
<th>Number of Lung Cancer Deaths</th>
<th>Radiation Quantity</th>
<th>Absorbed dose in lung</th>
<th>Excess Odds Ratio</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>(3.2.1.3)</td>
<td>Gilbert et al. (2003)</td>
<td>Radiation therapy</td>
<td>Mainly high-energy photons</td>
<td>173 lung cancer cases controls</td>
<td>Cases and controls used in the radiation analyses were five-year survivors selected from 19,046 one-year survivors of Hodgkin lymphoma</td>
<td>Range: 0.50 - 0.84 Gy</td>
<td>Mean: T: 0.15 F: 0.04 M: 0.002 (Hewe 1995)</td>
<td>0.90 (1.04, 1.56)</td>
<td>Mean: T: 0.90 F: 0.04 M: 0.002 (Hewe 1995)</td>
</tr>
</tbody>
</table>

[NOT TO BE DISSEMINATED OR REFERENCED]
### Section 3.2.2: Occupational Exposure of Workers

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Authors</th>
<th>Data Source</th>
<th>Gamma rays (external), Plutonium ((^{239})Pu) intake</th>
<th>Full cohort</th>
<th>Deaths</th>
<th>Range 0.5-200 y</th>
<th>Mean Absorbed dose in lung</th>
<th>SMRs not provided</th>
<th>ERR at 1 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mayak Production Association (3.2.2.1)</td>
<td>Swan et al. 2021 (mortality study)</td>
<td>Gamma rays: Chronic exposure, usually at a low dose rate; Whole body Plutonium: Low dose rate, partial body (lung)</td>
<td>Full cohort: T: 25,757 F: 6,362 M: 19,395</td>
<td>25,757 F: 6,362 M: 19,395</td>
<td>8,315 F: 2,460 M: 5,855</td>
<td>0.25 Gy</td>
<td>F: 0.78 T: 0.78</td>
<td>M: 0.01 (&lt;0.00)</td>
<td>0.00</td>
</tr>
<tr>
<td>Mayak Production Association (3.2.2.1)</td>
<td>Gillies et al. 2017 (incidence study)</td>
<td>Gamma rays: Chronic exposure, usually at a low dose rate; Whole body Plutonium: Low dose rate, partial body (lung)</td>
<td>Full cohort: T: 22,374 F: 5,687 M: 16,687</td>
<td>22,374 F: 5,687 M: 16,687</td>
<td>6,989 F: 2,108 M: 4,881</td>
<td>0.46 Gy</td>
<td>F: 27.6 (15.4, 48.6) T: 7.8 (5.7, 10.7)</td>
<td>M: 5.2 (3.8, 7.1)</td>
<td>0.73</td>
</tr>
<tr>
<td>15 Country Study (3.2.2.2)</td>
<td>Cardis et al. 2007</td>
<td>Gamma rays: Chronic exposure, usually at a low dose rate, Whole body Plutonium: Intake of radionuclides were excluded</td>
<td>T: 407,391 F: 39,789 M: 367,602</td>
<td>407,391 F: 39,789 M: 367,602</td>
<td>1,457 F: 65 M: 1,392</td>
<td>1.4 Gy</td>
<td>T: 1.86 (0.93, 3.63) F: -0.94 (0.11, 1)</td>
<td>M: 1.88 (0.50, 3.66)</td>
<td>(heterogeneity): 0.73</td>
</tr>
<tr>
<td>Los Alamos National Laboratory (3.2.2.3)</td>
<td>Bocx et al. 2021a</td>
<td>Gamma rays: Chronic exposure, usually at a low dose rate; Whole body Plutonium: Intakes of radionuclides: prolonged exposure at a low-dose rate, partial body (lung)</td>
<td>T: 26,328 F: 6,524 M: 19,804</td>
<td>26,328 F: 6,524 M: 19,804</td>
<td>839 F: 186 M: 653</td>
<td>0.16 Gy</td>
<td>T: 0.54 (0.51, 0.58) F: 0.78 (0.67, 0.90)</td>
<td>M: 0.50 (0.46, 0.54)</td>
<td>0.88</td>
</tr>
</tbody>
</table>

**Note:** ERR at 1 Gy is the relative risk of dying at 1 Gy of effective dose, adjusted for smoking and other exposures. SMRs not provided: Smoking and other exposures were not considered in the analysis. ERR at 1 Gy at age 60 y (90% CI): Smoking and other exposures were considered in the analysis.
<table>
<thead>
<tr>
<th>Source/Location</th>
<th>Study</th>
<th>Intakes of radionuclides</th>
<th>Prolonged exposure and other factors</th>
<th>Deaths</th>
<th>Absorbed dose in lung (weighting factors)</th>
<th>Range</th>
<th>ERR at 100 mSv</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tennessee Eastman Corporation (3.2.2.4)</td>
<td>Boice et al. 2021b</td>
<td>Intakes of uranium</td>
<td>Prolonged exposure at a low dose rate, partial body (lung)</td>
<td>T: 26,650 F: 13,951 M: 12,699</td>
<td>Deaths: T: 1,654 F: 652 M: 1,002</td>
<td>Range 0.25-75 y</td>
<td>Absorbed dose in lung (weighting factor of 1 for uranium alpha particles)</td>
<td>T: 1.25 F: 1.20 M: 1.28</td>
</tr>
<tr>
<td>U.S. Nuclear Power Plant Workers (3.2.2.5)</td>
<td>Boice et al. 2022</td>
<td>Gamma rays</td>
<td>Chronic exposure usually at a low dose rate, whole body</td>
<td>T: 135,191 F: 4,420 M: 130,773</td>
<td>Deaths: T: 3,382 F: 48 M: 3,334</td>
<td>Range 0.08-60 y</td>
<td>Absorbed dose in lung</td>
<td>T: 0.10 F: 1.07 (0,14) M: 1.27 (0.94, 1.68)</td>
</tr>
<tr>
<td>U.S. Industrial Radiographers (3.2.2.6)</td>
<td>Boice et al. 2019a, 2021c</td>
<td>X rays, gamma rays</td>
<td>Chronic exposure usually at a low dose rate, whole body</td>
<td>T: 125,510 F: 55,577 M: 110,577</td>
<td>Deaths: T: 2,115 F: 48 M: 2,060</td>
<td>Range</td>
<td>Absorbed dose in lung</td>
<td>T: 1.10 F: 1.27 (0.94, 1.68) M: 1.10 (1.06, 1.16)</td>
</tr>
<tr>
<td>U.S. Medical Radiation Workers (3.2.2.7)</td>
<td>Boice et al. 2021d</td>
<td>X rays, gamma rays</td>
<td>Chronic exposure usually at a low dose rate, whole body</td>
<td>T: 109,039 F: 55,218 M: 55,521</td>
<td>Deaths: T: 370 F: 480 M: 40</td>
<td>Range 2-50 y</td>
<td>Absorbed dose in lung</td>
<td>T: 0.50 F: 0.68 (0.47, 0.54) M: 0.61 (0.38, 0.46)</td>
</tr>
<tr>
<td>Mound Nuclear Facility (3.2.2.8)</td>
<td>Boice et al. 2014, 2019a</td>
<td>Gamma rays, neutrons, tritium; intakes of polonium and plutonium</td>
<td>Gamma rays, neutrons, tritium; chronic exposure usually at a low dose rate, whole body</td>
<td>T: 4,994 F: 21 M: 182</td>
<td>Deaths: T: 509 F: 40 M: 470</td>
<td>Range 0.5-42 y</td>
<td>Nonuniform quantity reported in millisievert (mSv). Sum of personal dose equivalent for gamma rays; absorbed dose in lung for polonium, polonium and thorium (no weighting factors); weighted dose for neutrons (weighting factor of 10)</td>
<td>T: 0.85 (0.74, 0.98)</td>
</tr>
<tr>
<td>Hanford Site (3.2.2.9)</td>
<td>Gilbert et al. 1993a, 1993b</td>
<td>Gamma rays, neutrons, tritium; intakes of plutonium for 776 individuals (no estimates of lung dose made for plutonium)</td>
<td>Gamma rays, neutrons, tritium; chronic exposure usually at a low dose rate, whole body</td>
<td>T: 32,643 F: 7,971 M: 24,672</td>
<td>Deaths: T: 79 F: 39 M: 470</td>
<td>Range 0.5-42 y</td>
<td>Personal dose equivalent (gamma rays only)</td>
<td>T: 0.83 (0.72, 1.38) F: 0.84 (0.84, 1.01)</td>
</tr>
</tbody>
</table>
### Section 3.2.3: Environmental Exposure of Populations (Indoor Radon Studies)

<table>
<thead>
<tr>
<th>Region</th>
<th>Study Details</th>
<th>Chronic Exposure Characteristics</th>
<th>Lung Cancer Cases</th>
<th>The Disease-Related Exposure Time Window</th>
<th>Radon Concentration</th>
<th>Range</th>
<th>Not applicable since a pooled case-control study</th>
<th>Excess Odds Ratio (EOR) at 100 Bq m⁻³</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>China Case-Control</strong> (3.2.3.1)</td>
<td>Lubin et al. 2004 Wang et al. 2002</td>
<td>Alpha particles (radon progeny)</td>
<td>2 studies: T: 1,053 with lung cancer, 1,072 controls F: 400 with lung cancer, 755 controls M: 563 with lung cancer, 1,432 controls</td>
<td>All: T: 1,053 F: 400 M: 563</td>
<td>Gansu only: T: 768 F: 205 M: 563</td>
<td>&lt;400 - &lt;400 Bq m⁻³</td>
<td>Mean: Shenyang 122.4 Bq m⁻³</td>
<td>Mean: 105 Bq m⁻³</td>
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<td>For total, adjusted for smoking: T: 0.33 (0.01, 0.36) For Gansu (sex-specific estimates): CI not provided for sex, just for T: T: 0.19 (0.05, 0.47) F: 0.12 (CI not provided) M: 0.22 (CI not provided)</td>
</tr>
<tr>
<td><strong>Europe Case-Control</strong> (3.2.3.2)</td>
<td>Darby et al. 2006</td>
<td>Alpha particles (radon progeny)</td>
<td>3 studies: T: 7,148 persons with lung cancer, 14,208 controls</td>
<td>Lung cancer cases T: 7,148 F: 1,627 M: 5,521</td>
<td>Lifelong nonsmokers lung cancer cases T: 884 F: 616 M: 208 controls T: 5,418 F: 2,530 M: 2,888</td>
<td>&lt;200 - &lt;400 Bq m⁻³</td>
<td>Mean: Brussels 32.5 Bq m⁻³</td>
<td>Mean: 105 Bq m⁻³</td>
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<td>For total, adjusted for smoking: T: 0.08 (0.03, 0.16) F: 0.03 (0.04, 0.14)</td>
</tr>
<tr>
<td><strong>North America Case-Control</strong> (3.2.3.3)</td>
<td>Krewski et al. 2006</td>
<td>Alpha particles (radon progeny)</td>
<td>7 studies: T: 4,081 with lung cancer, 5,281 controls F: 2,766 with lung cancer, 3,779 controls M: 2,766 with lung cancer, 2,102 controls</td>
<td>Lung cancer cases T: 4,081 F: 2,655 M: 1,313</td>
<td>Cases with ≥2 residences and ≥20 y with alpha-particle track air monitors T: 1,810 F: 4,761 M: 3,655 controls T: 2,651 F: 1,956 M: 3,894</td>
<td>&lt;200 - &lt;400 Bq m⁻³</td>
<td>Mean: New Jersey 65.0 Bq m⁻³</td>
<td>Mean: 105 Bq m⁻³</td>
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<td></td>
<td></td>
<td>EOR at 100 Bq m⁻³</td>
</tr>
<tr>
<td><strong>Southwest Spain Case-Control</strong> (3.2.3.4)</td>
<td>Lorenzo-Gonzalez et al. 2019</td>
<td>Alpha particles (radon progeny)</td>
<td>4 studies (only nonsmokers): T: 523 with lung cancer, 892 controls F: 414 with lung cancer, 473 controls M: 109 with lung cancer, 419 controls</td>
<td>Lung cancer cases (only nonsmokers): T: 523 F: 414 M: 109</td>
<td>Median living in the measured dwelling (25th-75th percentiles): T: 30 y (15-44) F: 30 y (17-44)</td>
<td>&gt;200 Bq m⁻³ compared with 260 % for controls</td>
<td>Radon concentration [bequerel per cubic meter (Bq m⁻³)]</td>
<td>39.3 % of cases had residential radon concentration &gt;200 Bq m⁻³</td>
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<td></td>
<td>Odds ratio comparing those exposed to radon concentrations &gt;200 Bq m⁻³ compared with those exposed to &gt;100 Bq m⁻³ (only nonsmokers): T: 1.73 (1.27, 2.35) F: 1.44 (1.00, 2.09) M: 2.43 (1.40, 4.24)</td>
</tr>
</tbody>
</table>
Cheng et al. 2021

Alpha particles (radon progeny)

Comprised of 24 case-control studies, overall non-smokers

T: 2,341 with lung cancer, 8,967 controls

The sex-specific analyses consisted of 15 case-control studies

T: 1,360 with lung cancer, 6,074 controls

F: 990 with lung cancer, 2,898 controls

M: 370 with lung cancer, 3,176 controls

Lung cancer cases, overall

T: 4,801

Controls: T: 8,967

Lung cancer cases for sex-specific analyses

T: 1,360

F: 990

M: 370

Controls: T: 6,074

F: 2,898

M: 3,176

The disease-relevant exposure time window is over a 25 y period (i.e., the 30 y period ending 5 y prior to diagnosis of lung cancer or interview date for controls)

Radon concentration ([Bq m\(^{-3}\)]), not provided, although the highest radon concentration was reported to be >7,201 Bq m\(^{-3}\)

Not applicable since a case-control study

ERR at 100 Bq m\(^{-3}\)

Overall

T: 0.15 (0.06, 0.25)

Sex-specific subset

T: 0.13 (0.03, 0.25)

F: 0.09 (0.02, 0.20)

M: 0.46 (0.15, 0.76)

P(heterogeneity): 0.027

Section 3.2.4: The Japanese Atomic Bomb Survivors

Cahoon et al. 2017

Gamma rays and neutrons

Acute exposure at a high dose rate, Whole Body

T: 105,444

F: 62,534

M: 42,910

≥ 5 mGy

T: 44,227

F: 26,379

M: 17,848

Age-at-exposure ≥20 y

T: 59,657

F: 38,335

M: 21,322

Incidence

T: 2,446

F: 1,001

M: 1,445

Range 13.64 y

Mean: 29.2 y

Weighted dose in the lung, (with a weighting factor of 10 for neutrons)

For those ≥5 mGy

Mean

T: 214 mGy

F: 227 mGy

SMRs not provided

ERR at 1 Gy (never smokers):

T: 0.81 (0.51, 1.18)

F: 1.20 (0.74, 1.75)

M: 0.42 (0.16, 0.84)

F to M ratio: 2.83 (1.38, 7.23)

Japanese Atomic Bomb Survivor Study

(3.2.4)

Ozasa et al. 2012

Gamma rays and neutrons

Acute exposure at a high dose rate, Whole Body

T: 86,611

F: 50,924

M: 35,687

≥ 5 mGy

T: 48,102

F: 28,366

M: 19,736

Age-at-exposure ≥20 y

T: 51,215

Mortality

T: 1,558

F: 657

M: 901

Range 5-58 y

Mean: 38.0 y

Weighted dose in the lung, (with a weighting factor of 10 for neutrons)

For those ≥5 mGy

Mean

T: 200 mGy

SMRs not provided

ERR at 1 Gy (no adjustment for smoking):

T: 0.75 (0.51, 1.03)

F: 1.10 (0.68, 1.67)

M: 0.40 (0.17, 0.67)

F to M ratio: 2.7 (1.3, 6.8)
a For example, x rays, gamma rays, neutrons, intakes of radionuclides.

b For low linear-energy transfer (LET) radiation, a low absorbed dose is <100 mGy delivered acutely, and a low absorbed-dose rate is <5 mGy h⁻¹ for any accumulated absorbed dose (NCRP 2015).

c Chronic exposure: radiation exposure of long duration because of fractionation or protraction.

d Radiation quantities: absorbed dose in the lung (in gray); weighted dose in the lung (in gray) [with weighting factor(s)]; personal dose equivalent (at 10 mm) (in sievert); radon concentration (in becquerel per cubic meter).

e 95% confidence interval (CI). When no CI values were provided by the authors, that is indicted by (CI not provided).

f When available, sex-specific Standardized Mortality Ratios are presented. Standardized Mortality Ratio (SMR) is the ratio of the mortality rate from a disease in the population being studied to the comparable rate in a standard population.

g Excess relative risk (ERR) at specified units as given by the study authors: ERR at 1 Gy; ERR at 100 mGy; ERR at 1 Sv; ERR at 100 mSv; or ERR at 100 Bq m⁻³; also, excess odds ratio (EOR) at 100 Bq m⁻³ (see footnote p).

h P(heterogeneity) is a test of the difference between the female and male estimates of risk.

i A weighting factor for plutonium was not used. For gamma rays, personal dose equivalent was converted to absorbed dose in lung.

j Plutonium dose estimates came from different ICRP models using two different absorption rates, slow and fast.

k Plutonium dose via ICRP absorption models (see footnote j); external gamma-ray dose from personal dose equivalent (badge measurements) converted to absorbed dose in lung.

l Personal dose equivalent (at 10 mm) (recorded dose from low-LET radiation) was converted to absorbed dose in lung.

m In Table 3.2, the weighted dose in the lung accounts for the increased biological effectiveness of high-LET components of radiation exposure. The weighted dose consists of the mean absorbed dose in the lung from low-LET components plus the weighted mean absorbed doses in the lung from high-LET components, where each high-LET mean absorbed dose component is multiplied by a judged weighting factor, as provided by the investigator. The weighted dose is expressed in gray.

n The judged weighting factor described in footnote m.

o The indoor radon concentration [becquerel per cubic meter (Bq m⁻³)] is the time-weighted average residential radon concentration over a 25 y window (i.e., the 30 y period ending 5 y prior to diagnosis of lung cancer or interview date for controls). A conversion to lung dose was not attempted because of the multiple factors and assumptions involved.

p Excess odds ratio (EOR) is the odds ratio minus 1.0. Odds ratio is a measure of association in case-control studies [i.e., the odds of being exposed among diseased persons (cases) divided by the odds of being exposed among non-diseased persons (controls)].
3.2.1 Medical Exposure of Patients

Patient populations exposed to diagnostic or therapeutic radiation have provided quantitative evidence of cancer risks (NA/NRC 2006; UNSCEAR 2008; NCRP 2011; Gilbert et al. 2020). Of relevance to flight crews are studies of patients with tuberculosis receiving collapse therapy and monitored with frequent chest x-ray fluoroscopic examinations, and patients with Hodgkin lymphoma treated with radiation therapy (Table 3.2).

3.2.1.1 Canadian Tuberculosis-Fluoroscopy Cohort Study. A lung cancer mortality study was conducted of 63,707 Canadian tuberculosis patients (50 % females) who received multiple chest fluoroscopic examinations during the monitoring of lung collapse therapy between 1930 to 1969 (Howe 1995; Zablotska et al. 2014a; Boice et al. 2019a). The mean absorbed dose in the lung was 1.06 Gy (among exposed subjects) and the maximum was 9.6 Gy. There was no evidence for a radiation-related increase in lung cancer among either female or male patients. There was no difference between the sexes in the risk of radiation-related lung cancer.

3.2.1.2 Massachusetts Tuberculosis-Fluoroscopy Cohort Study. A cancer mortality study was conducted of 13,385 Massachusetts patients (49 % females) diagnosed with tuberculosis between 1925 and 1954 who received multiple chest fluoroscopic examinations during the monitoring of lung collapse therapy (Boice et al. 1978; Davis et al. 1989; Brenner 2010). Patients were examined bi-weekly over a period of several years. The average number of x-ray fluoroscopic imaging examinations was 77, and the mean absorbed dose in the lung was 0.84 Gy (among the exposed) and the maximum was 8 Gy. There was no evidence for a radiation-related increase in lung cancer among either female or male patients. For patients with minimal to moderate tuberculosis, large portions of the lung were healthy and not diseased. Adjustments for smoking and the amount of lung tissue at risk did not modify these observations.

3.2.1.3 Hodgkin Lymphoma Patients. Case-control studies of patients with Hodgkin lymphoma treated with radiation therapy provide evidence that very high lung doses (mean 25 Gy) cause lung cancer (Travis et al. 2002; Gilbert et al. 2003; NCRP 2011). In a cohort of 19,046 patients with Hodgkin lymphoma treated from 1965 to 1994, 173 lung cancer cases were diagnosed and
matched to 347 controls. The smoking-adjusted radiation risk of lung cancer for male patients was four times higher than for female patients, but this difference was not statistically significant.

3.2.2 Occupational Exposure of Workers

Occupational studies of radiation-exposed workers provide information on the level of lung cancer risk associated with low-dose fractionated exposures received over a period of years. This gradual exposure over time is relevant to flight crews on long-term missions in space. Table 3.2 summarizes studies of workers employed in medicine, nuclear fuel processing and weapons development, nuclear utility generation, and nondestructive testing (industrial radiographers). Few occupational studies include many female workers; notable exceptions with around 50% of the cohort being female are the MWS medical worker study (49% female) and the “girls of the atomic city” who worked at the Tennessee Eastman Corporation in Oak Ridge (52% female). Most occupational studies involve exposures to low-LET radiation (i.e., x rays or gamma rays), but several involve high-LET radiation to lung tissue following the inhalation of alpha-particle emitting radionuclides such as plutonium among Mayak workers, polonium among Mound workers and uranium among Tennessee Eastman Corporation workers.

3.2.2.1 Mayak Production Association. Workers at the Mayak Production Association facility in the Russian Federation were followed from 1948 through 2015 (Gilbert et al. 2004, 2013; Labutina et al. 2013; Gillies et al. 2017; Stram et al. 2021). In the most recent study for mortality (Stram et al. 2021), 25,757 (25% female) were included, and mean cumulative absorbed doses in the lung were reported for external exposure to gamma rays (0.42 Gy) and for intakes of 239Pu (0.55 Gy). In this analysis, adjusted for smoking, significant sex-specific differences in the ERRs for lung cancer mortality at 1 Gy (estimated at age 60 y) for gamma-ray exposure and for intakes of 239Pu were reported. For gamma-ray exposure, females had 3.4 times higher risk compared with males [not statistically significant, P(heterogeneity): 0.25]. For intakes of 239Pu, females were at 2.5 times higher risk compared with males (not statistically significant).
For incidence, 22,374 workers (25 % female) were followed until the end of 2008 (Gillies et al. 2017). Mean cumulative absorbed dose in the lung from gamma rays was 0.46 Gy (maximum 7.6 Gy). The mean cumulative absorbed dose in the lung from $^{239}$Pu was 0.13 Gy (assuming a fast solubility) or 0.18 Gy (assuming a slow solubility) with maximums of 16.5 Gy and 19.7 Gy, respectively. A statistically significant difference between the female and male ERR at 1 Gy for lung cancer for intakes from plutonium were reported with female ERR at 1 Gy being four times higher than for males. The authors suggested that differences between females and males could be due to a sub-multiplicative interaction between smoking and plutonium exposure, since the smoking rates in females and males were quite different (4 % and 74 %, respectively, among individuals with known smoking status). The estimates of plutonium dose were based on incomplete coverage of 42 % of the workers (Gillies et al. 2017; NCRP 2018a). When the analyses were restricted to workers who received an absorbed dose in the lung from plutonium of <0.2 Gy, the female and male estimates of risk remained the same and still statistically significantly different (Gillies et al. 2017).

3.2.2.2 15-Country Study. The 15-Country Study included 407,391 workers (~10 % females) and reported significantly increased risks of lung cancer overall, with a positive and statistically significant increase in males but no increased risk in females (Cardis et al. 2007). These findings need to be interpreted with caution because the overall radiation risk of lung cancer was substantially reduced and no longer statistically significant when Canadian data were excluded from the analyses (Cardis et al. 2007; Zablotska et al. 2014b). The U.K., French, Hanford, Oak Ridge National Laboratory, Idaho National Engineering and Environmental Laboratory cohorts in the 15-Country Study are included in the International Nuclear Workers Study (INWORKS) (Section 3.3.2.2), as are 49,346 U.S. nuclear power plant workers, (i.e., results of these pooled studies are not independent).

3.2.2.3 Los Alamos National Laboratory. The mortality experience of 26,328 workers (25 % females) employed during 1943 to 1980 at the Los Alamos National Laboratory (LANL) was determined through 2017 (Boice et al. 2021a). Lung doses were estimated for each worker from gamma rays, neutrons, tritium, $^{238}$Pu, and $^{239}$Pu. The mean cumulative weighted dose in the lung (assuming a weighting factor of 20 for the $^{238}$Pu and $^{239}$Pu alpha particles) was 28.6 mGy.
(maximum, 16.8 Gy). If a weighting factor of 10 is assumed, as presented in Section 7.3.1.2, the mean and maximum weighted doses are 20.6 mGy and 8.6 Gy, respectively. The sex-adjusted ERRs did not differ (except by a trivial amount) whether a weighting factor of 1, 10 or 20 was applied, indicating the relatively small contribution to lung dose from plutonium compared with the dose from gamma rays. There was little evidence that prolonged occupational exposure experienced over a period of years increased the risk of lung cancer, and there was no difference in radiation-related lung cancer risk between males and females. For female workers the lung doses were low, and no one received >50 mGy (weighted dose), precluding statistically meaningful comparisons.

3.2.2.4 Tennessee Eastman Corporation. A new study (Boice et al. 2021b) was conducted of 26,650 workers (52 % female) employed at the Tennessee Eastman Corporation uranium processing facility at Oak Ridge between 1943 and 1947 (Polednak and Frome 1981; Cookfair 1982; Cookfair et al. 1983; Beck et al. 1983; Dupree et al. 1995). The majority of workers had died (94 %) at last follow-up in 2019. The females employed at Tennessee Eastman Corporation were popularized in the novel The Girls of Atomic City (Kiernan 2013). Airborne measurements were used to estimate lung doses from the inhalation of uranium dust. The mean absorbed dose in the lung (assuming a weighting factor of 1 for uranium) was 32.7 mGy (maximum 1.05 Gy) for females and 18.5 mGy (maximum 0.5 Gy) for males. There was little evidence that radiation increased the risk of lung cancer. There was no statistically significant difference in the lung cancer risk estimates between males and females.

3.2.2.5 U.S. Nuclear Power Plant Workers. A new study was conducted of 135,193 nuclear power plant workers (3 % females) first monitored for radiation during 1957 to 1984 and followed through 2011 (Boice et al. 2022). The cohort was derived from the U.S. Nuclear Regulatory Commission's (NRC) Radiation Exposure Information and Reporting System (REIRS) (Hagemeyer et al. 2018; NRC 2018) and the Landauer, Inc. dosimetry database. The annual personal dose equivalent (at 10 mm) was available for each worker. The mean absorbed dose in lung was estimated by adjusting the personal dose equivalent by scaling factors, accounting for exposure geometry and energy of the incident gamma rays (Dauer et al. 2018; NCRP 2018a). The mean absorbed dose to the lung was 43.2 mGy (maximum 1.09 Gy).
sex-averaged ERR at 100 mGy for lung cancer was negative and of borderline significance. There was limited statistical power to discern a difference in sex-specific lung cancer rates because of the relatively small number of female workers and their relatively low estimated absorbed doses in the lung (Boice et al. 2019a, 2021c, 2022).

3.2.2.6 U.S. Industrial Radiographers. The NRC’s REIRS (Hagemeyer et al. 2018) and the Landauer Inc. dosimetry database identified 123,510 industrial radiographers (10 % females) who were first monitored for external radiation during 1939 to 2011 (Boice et al. 2019a, 2021c; Mumma et al. 2019). Over 26,000 radiographers worked in naval shipyards with the potential for asbestos exposure. For each worker, their personal dose equivalent (at 10 mm) was converted to lung-specific dose (Bouville et al. 2015; NCRP 2018a). The mean cumulative absorbed dose in the lung was 10.9 mGy (maximum 1.43 Gy). The sex-averaged lung cancer risk estimate (ERR at 100 mGy) was significantly elevated. Males were at significantly high risk for developing radiation-related lung cancers, but the dose response for females was negative. This sex-specific difference in radiation risk was not statistically significant in part due to the smaller number of females and their relatively lower lung doses.

The study of U.S. nuclear power plant workers (Section 3.2.2.5) and this study of U.S. industrial radiographers were constructed using the same methodologies and the source populations included both the NRC’s REIRS and the Landauer Inc. dosimetry databases. A pooled analysis of these two studies included 17,353 females and 241,350 males and attained educational level was adjusted for in the analysis as a surrogate for cigarette smoking (Boice et al. 2019a). There were no statistically significant increases overall (ERR at 100 mGy = 0.01; 95 % CI -0.04, 0.06; n = 5,550) or among female workers (ERR at 100 mGy = 0.16; 95 % CI -0.49, 0.81; n = 103) or male workers (ERR at 100 mGy = 0.01; 95 % CI -0.04, 0.06; n = 5,397). The difference in the sex-specific radiation lung cancer risk estimates was not statistically significant [P(heterogeneity): 0.86].

3.2.2.7 U.S. Medical Radiation Workers. A new study of 109,019 U.S. medical radiation workers (49 % females) was designed to evaluate sex-specific lung cancer risks following low-dose fractionated exposures (Boice et al. 2021d). The cohort was derived within the Landauer, Inc.
dosimetry data base (Bouville et al. 2015; NCRP 2018a; Dauer et al. 2018; Yoder et al. 2021). Mean cumulative absorbed dose in the lung was estimated by adjusting the personal dose equivalent (at 10 mm) available for all workers by scaling factors, accounting for exposure geometry, the energy of the incident photon radiation, the sex of the worker, and whether an apron was worn (Yoder et al. 2018, 2021; NCRP 2020a). The sex-averaged lung cancer risk estimate (ERR at 100 mGy) was significantly elevated. The risk among male workers was 1.8 times that of female workers and the difference approached statistical significance.

Recently, the U.S. medical radiation workers study was pooled with the U.S. nuclear power plant workers (Section 3.2.2.5) and U.S. industrial radiographers (Section 3.2.2.6) studies for a combined population size of 367,722 workers; 71,154 females and 296,568 males. Sex-specific risks for lung cancer were not provided but the overall sex-adjusted ERR estimate at 100 mGy was 0.02 (95% CI -0.03, 0.07; n = 6,400) (Boice and Dauer 2021; Boice et al. 2021c).

3.2.2.8 Mound Nuclear Facility. The Mound Nuclear Facility near Dayton, Ohio, employed 4,954 workers (20% females) first monitored for radiation exposure during 1944 to 1971 (Boice et al. 2014). Dose estimation for the lung included exposure to gamma rays, neutrons, tritium and intakes of polonium, plutonium. The cumulative mean reported dose for the lung (a nonuniform quantity expressed in millisieverts, see Table 3.2) was 96 mSv (maximum 17.5 Sv). The population included 2,235 workers with positive bioassays for polonium, a soft-tissue seeking alpha-particle emitter with a relatively short biological half-life of 30 d which accounted for most of the high lung doses. The sex-averaged lung cancer risk estimate (ERR at 100 mSv) was not significantly elevated. There was no difference in the sex-specific lung cancer risk estimates. Despite the relatively high estimates of lung doses for some workers, the study is limited by small numbers.

3.2.2.9 Hanford Site. There were 32,643 workers (24% females) employed at the Hanford plutonium production site during 1944 to 1978 and followed through 1989 (Gilbert et al. 1993a, 1993b). The mean cumulative film badge dose [personal dose equivalent (at 10 mm)] was 26.2 mSv (maximum > 400 mSv). Intakes of plutonium were recorded but associated organ doses were not evaluated. A small number of workers were exposed to neutrons. The sex-averaged
lung cancer risk estimate (ERR at 1 Sv) was not significantly increased. There was little evidence for heterogeneity of lung cancer risks between males and females in a pooled analysis of five nuclear facilities, including Hanford with a subsequent follow-up through 1994 (Schubauer-Berrigan et al. 2015). A small case-cohort study of white male Hanford workers reported a negative dose response after adjusting for tobacco use (Peterson et al. 1990).

3.2.3 Environmental Exposure of Populations (Indoor Radon Studies)

Radon exposure studies are relevant for lung cancer risk assessment among astronaut flight crews because the rate of exposure is low and over a period of many years, comparisons between males and females can be made, cigarette smoking on an individual basis was comprehensively assessed, exposure was to high-LET radiation (alpha-particle decay of radon progeny), and substantial numbers of never-smokers are available for sex-specific lung cancer comparisons. There have been three comprehensive pooling studies in China, Europe, and North America, and one comprehensive meta-analysis of never-smokers.

3.2.3.1 Indoor Radon Studies (China). Lubin et al. (2004) pooled two Chinese case-control studies with a total of 1,050 lung cancer cases (47 % females) and 1,997 controls. Radon concentrations in becquerel per cubic meter (Bq m$^{-3}$) were determined by one year alpha-particle track measurements in all homes occupied for two or more years during the 5 to 30 y prior to enrollment (generally taken as 5 y prior to the cancer diagnosis and comparable interview date for controls). Cases and controls were interviewed for lifestyle factors including cigarette smoking. A significant increase in lung cancer risk associated with radon concentration was found, adjusting for smoking. There was no difference in risk by sex. One of the studies was unique and involved populations that lived in underground dwellings with radon concentrations between normal residential homes and underground mines (Wang et al. 1996, 2002).

3.2.3.2 Indoor Radon Studies (Europe). Darby et al. (2005, 2006) pooled 13 European case-control studies with a total of 7,148 lung cancer cases (23 % females) and 14,208 controls. Lifetime nonsmokers included 884 cases (70 % females) and 5,418 controls. Measurements of radon concentrations in residents were made to estimate the exposures received during a 25 y
period (i.e., the 30 y period ending 5 y prior to diagnosis of lung cancer or index date for controls). A significant increase in lung cancer risk associated with radon concentration was found, adjusting for smoking. The radon-related lung cancer risk was 3.7 times higher in males than females, but the difference was not statistically significant. For lifetime nonsmokers, the radon-related lung cancer risk was 5.3 times higher in males than females, but the difference was not statistically significant.

3.2.3.3 Indoor Radon Studies (North America). Krewski et al. (2005, 2006) pooled seven North American case-control studies with a total of 4,081 lung cancer cases (68 % females) and 5,281 controls. Radon concentrations were measured in similar ways as described in the China and European studies (i.e., alpha-particle track radon measurements were made in most homes within the exposure time window of 5 to 30 y prior to the index date). Adjustment was made for smoking obtained from interviews. The association between radon exposure and lung cancer was not statistically significant for the entire dataset, but it was for the subset of subjects with the highest quality exposure data [i.e., for the subset of 1,910 lung cancer cases (72 % females) and 2,651 controls with ≤2 residences and ≥20 y with alpha-particle track air monitors]. For all subjects, sex-specific risks were 5.7 times higher in females than in males, but this difference was not statistically different. For the subjects characterized as having high quality exposure data, there was no difference between the sex-specific lung cancer risks.

3.2.3.4 Indoor Radon Studies (Northwest Spain). Lorenzo-González et al. (2019) pooled four case-control studies conducted in Northwest Spain of never-smokers with a total of 523 lung cancer cases (79 % females) and 892 controls (53 % females). Radon concentrations were measured somewhat differently than in the China, European, and North American studies (i.e., alpha-particle track radon detectors were placed only in the current home and not previous ones). The median years lived in the measured home was 30 y for both cases and controls and the 75 percentiles were 44 y for both cases and control. Residential radon concentration data was not available for everyone (i.e., available for 93.5 % of cases and 84.2 % of controls). Radon concentrations were higher among cases compared with controls: 39.3 % of cases had a residential radon concentration ≥200 Bq m⁻³ compared with 26.0 % for controls. A significant association between radon exposure and lung cancer for all never-smokers was reported at radon
concentrations $\geq 200$ Bq m$^{-3}$ compared with concentrations $\leq 100$ Bq m$^{-3}$ [odds ratio: 1.73 (95 % CI: 1.27, 2.35)]. The odds ratio for females was 1.44 (95 % CI: 1.00–2.09) and 2.43 (1.40, 4.24) for males. Males were at over three times higher radon-related risk for lung cancer than females, but no tests of heterogeneity were provided.

3.2.3 Indoor Radon Studies (Meta-analysis of Never-Smokers). Cheng et al. (2021) conducted a meta-analysis that included never-smoking subjects in the four pooled analyses presented in Sections 3.2.3.1 through 3.2.3.4 to evaluate radon-related lung cancer risk among never-smokers. The four pooled analyses comprised 24 independent studies. Overall, there were 2,341 lung cancer cases and 8,967 controls who were never-smokers. The adjusted ERR at 100 Bq m$^{-3}$ radon concentration was 0.15 (95 % CI 0.06, 0.25). For the sex-stratified meta-analyses, data were pooled for 15 case-control studies. There were 1,360 lung cancer cases (990 females and 370 males) and 6,074 controls (2,898 females and 3,176 males) who were never-smokers. The ERR at 100 Bq m$^{-3}$ was 5.1 times higher for the males than for the females. This difference was statistically significant [$P$(heterogeneity): 0.027]. However, the authors’ state that “A random-effects approach was not used because of the necessity to include pooled estimates from collaborative studies in our meta-analysis. Also, a measure of heterogeneity across the component studies in the pooled analysis, which is needed for an analysis using random effects, was not reported and could not be assessed”. Thus, while there is evidence that never-smokers are at increased risk of radon-related lung cancer, the significant difference between male and female risk should be interpreted cautiously.

3.2.4 The Japanese Atomic Bomb Survivors

The study of Japanese atomic bomb survivors provides strong evidence that acute exposures to ionizing radiation can lead to an increased risk of lung cancer. Females are reported to be at nearly three times higher risk of radiation-related lung cancer than males using ERR models (Furukawa et al. 2010; Ozasa et al. 2012; Cahoon et al. 2017). Lung cancer incidence analyses showed that lung cancer risk was modified by smoking intensity, with the risk highest for those smoking 10 cigarettes per day and approaching no risk at 20 cigarettes per day. The female-to-male incidence ratio of excess risk decreased with increasing radiation dose.
Recent analyses evaluated cancer incidence from 1958 to 2009 (Cahoon et al. 2017). There were 105,444 subjects evaluated, of whom 80,205 (76.1%) were within 10 km of the hypocenters with radiation dose estimates, and 25,239 subjects (23.9%) who were not in either city at the time of the bombings. Of the subjects with radiation dose estimates, 35,978 (44.9%) were distal survivors with weighted doses less than 5 mGy. Self-reported smoking information was available for 64,465 subjects (61.1%) of whom 14% of the men and 82% of the women were never-smokers. For never-smokers, the sex-averaged ERR at 1 Gy [weighted dose in the lung (sum of gamma-ray absorbed dose and 10 times the neutron absorbed dose)] for lung cancer was 0.81 (95% CI 0.15, 1.18) and the female-to-male ratio was 2.83. The estimate of risk was significantly high for low-to-moderate smokers and no radiation risk was apparent for heavy smokers. The authors mentioned that the results should be interpreted in the context of several limitations (e.g., smoking history was unknown for ~40% of the lung cancer cases and for ~60% of the follow-up time).

The mortality data (Ozasa et al. 2012) are more complete than the incidence data in the sense that the entire country of Japan after 1950 was covered for death determinations, whereas the two cancer registries in Hiroshima and Nagasaki began in 1958 and did not include the entire country for incidence determinations. The mortality analyses focused on the 86,611 LSS cohort members within 10 km of the hypocenters with dose estimates. There was no adjustment for smoking. The sex-averaged ERR at 1 Gy (weighted dose in the lung as defined above) was 0.75 (95% CI 0.51, 1.03). The ERR at 1 Gy (weighted dose) was greater among females (1.1; 95% CI 0.68, 1.6) compared with males (0.40; 95% CI 0.17, 0.67). The female-to-male ratio was 2.7 (95% CI 1.3, 6.8). The EAR ratio of females to males was 0.98 (95% CI 0.40, 1.8), indicating the importance of background rates of disease when making inferences on risk differences.

### 3.3 Other Epidemiologic Studies of Radiation-Related Lung Cancer

**Rationale and Summary:** Section 3.2 and Table 3.2 reviewed the epidemiologic studies that provide sex-specific estimates of radiation-related lung cancer risks. Other epidemiologic studies summarized in Section 3.3 and Table 3.3 include sex-only studies, such as male nuclear
weapons test participants, or report only sex-adjusted risks, such as the INWORKS investigation. These studies can be used in various modeling schemes for lifetime risk estimation. A few studies with sex-specific estimates had incomplete or inadequate estimation of absorbed dose in the lung and are included in this section. The format for Table 3.3 and the general criteria for inclusion are the same as for Table 3.2 and as listed in Section 3.2 except that sex-specific parameters are not available.

These other studies on lung cancer risk are grouped into the categories similar to those for the sex-specific studies. After Table 3.3, each study is briefly described:

- Medical exposure of patients (Section 3.3.1).
- Occupational exposure of workers (Section 3.3.2).
- Environmental exposure of populations (Section 3.3.3).
- Nuclear weapons test participants (Section 3.3.4).
Table 3.3 --- Other epidemiologic studies that provide information on risks for radiation-related lung cancer that are not included in Section 3.2. The reasons for listing a study in Table 3.3 are given in the introduction to Section 3.3. The following information (as provided by the authors in the cited references) is presented: epidemiologic study; references; type of radiation; type of exposure; number of subjects; number of lung cancer deaths or cases; years of follow-up; radiation quantity; mean and range values for radiation quantity; standardized mortality ratio (for lung cancer); excess relative risk (for lung cancer) at 1 Gy, 100 mGy, 1 Sv or 100 mSv.

| Study (Section) | References | Type of Radiation | Type of Exposure | Number of Subjects: Total (T) | Number of Lung Cancer Deaths (Mortality) or Cases (Incidence): Total (T) | Years of Follow-Up | Range | Radiation Quantity | For the Radiation Quantity Used | Standardized Mortality Ratio (SMR) (95 % CI)
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<td>Section 3.3.1: Medical Exposure of Patients</td>
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<tr>
<td>U.S. Scoliosis Study (3.3.1.1)</td>
<td>Ronckers et al. 2010</td>
<td>Diagnostic x rays</td>
<td>Chronic exposure, low dose fractions at a high dose rate, partial body (chest)</td>
<td>T (all F): 5,573</td>
<td>Mortality T (all F): 57</td>
<td>Range 0.91.5 y</td>
<td>Mean 46.8 y</td>
<td>Absorbed dose in lung</td>
<td>Range 0.576 mGy</td>
<td>Mean: For Total (T) For Females (F) For Males (M)</td>
<td>T (all F): 0.77 (0.57, 1.00)</td>
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<tr>
<td>Radiation Therapy for Peptic Ulcer (3.3.1.2)</td>
<td>Carr et al. 2002</td>
<td>Radiation therapy, orthovoltage x rays (250 kV)</td>
<td>High dose fractions at a high dose rate, partial body (abdomen); 1.5 Gy fractions to the stomach from 5 min exposures lasting 6 to 14 d</td>
<td>T: 3,710</td>
<td>Mortality: Exposed T: 1,859 Unexposed T: 1,860</td>
<td>Range 1.6 y</td>
<td>Mean 25 y</td>
<td>Absorbed dose in lung</td>
<td>Heterogeneous dose in lung</td>
<td>Range 0.1-17.4 Gy Mean (Gy) for T: left lung 1.8 right lung 0.6</td>
<td>Exposed: T: 1.99 (1.66, 2.37) Unexposed: T: 1.20 (0.96, 1.49)</td>
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<td>Section 3.3.2: Occupational Exposure of Workers</td>
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<tr>
<td>U.K. National Registry for Radiation Workers (3.3.2.1)</td>
<td>Haylock et al. 2018, Muirhead et al. 2009</td>
<td>X rays, gamma rays, neutrons, tritium; 23 % of workers monitored for intakes of radionuclides (plutonium, uranium) but does not included</td>
<td>External and internal: chronic exposure, usually at a low dose rate, whole body</td>
<td>T: 167,003</td>
<td>Mortality: T: 3,058 Incidence: T: 3,283</td>
<td>Range 10 - 32 y</td>
<td>Mean 32 y</td>
<td>Personal dose equivalent</td>
<td>Range: &lt;10 - &gt;400 mSv Mean (mSv) T: 25.3 F: 5.6 M: 27.5</td>
<td>T: 0.76 (0.75, 0.79) n =2,433 (Muirhead et al. 2009)</td>
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NOT TO BE DISSEMINATED OR REFERENCED
### International Nuclear Workers Study (3.3.2.2)

<table>
<thead>
<tr>
<th>Source</th>
<th>Richardson et al. 2018</th>
<th>X rays, gamma rays, neutrons, tritium, (neutron doses not estimated); monitoring of intakes of radionuclides (plutonium, uranium) was known but organ doses not estimated</th>
<th>External and tritium; chronic exposure, usually at a low dose rate, whole body</th>
<th>T: 108.297 F: 40.035 M: 268.262</th>
<th>Mortality T: 5.802</th>
<th>Range not provided and varied by country Mean 27 y</th>
<th>Absorbed dose in lung</th>
<th>Range T: 0 - &gt;700 mGy Mean (mGy) (95th percentile): M: 22.8 (106.3) F: 4.8 (18.8)</th>
<th>SMR not provided</th>
<th>ERR at 1 Gy (90 % CI) (not adjusted for smoking) T: 0.51 (0.00, 1.09)</th>
</tr>
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</table>

### Sellfield (U.K. Plutonium Production) (3.3.2.3)

| Source                        | Gilles et al. 2017 Omar et al. 1999 McGeoghegan et al. 2003 | Gamma rays; intakes of plutonium | External; chronic exposure, usually at a low dose rate, whole body | T: 23.443 F: 2.813 M: 20.630 | Mortality T: 406 F: 10 M: 396 | Mean 25.7 y | Absorbed dose in lung | External (mGy): Range: 0 - 1.848 Mean (T): 72.5 Internal (mGy): Range: 0 - 654 Mean (T): 1.9 or 5.5 (depending on solubility) | Omar et al. 1999 T: 0.89 (0.79, 0.99) n = 338 | McGeoghegan et al. 2003 (Fissionation workers) 0.68 (0.22, 1.58) n = 5 | F: Not explicitly provided but stated to be either 0.00 or < -1.00 depending upon the model parameters used. CIs not provided. |

### U.S. Radiological Technologists Study (3.3.2.4)

| Source                        | Velazquez-Kroesen et al. 2020 Mohan et al. 2002 | X rays | Chronic exposure, usually at a low dose rate, whole body | T: 106.068 F: 80.180 M: 25.888 | Mortality T: 1.090 F: 711 M: 379 | Range 2.62 y | Mean 23.8 y | Absorbed dose in lung | Range 0.810 mGy Mean (T): 25 mGy Mohan et al. 2002 T: 0.80 (0.64, 0.79) n = 781 F: 0.80 (0.73, 0.88) n = 423 M: 0.67 (0.61, 0.74) n = 358 | F: Not explicitly provided but stated to be either 0.00 or < -1.00 depending upon the model parameters used. CIs not provided. |

### Rocketdyne (Atomics International) (3.3.2.5)

| Source                        | Boice et al. 2011 | Gamma rays; neutrons; intakes of 14 radionuclides, primarily uranium | External; chronic exposure, usually at a low dose rate, whole body | T: 5.801 F: 466 M: 5.335 | Mortality T: 214 | Range 0.5-60 y | Mean 33.9 y | Weighted dose in the lung (in this case, the equivalent dose (lung) as defined by ICRP): 1 | Range 0.3-380 mSv (or mGy) T: 19 mSv (or mGy) McGeoghegan et al. 2003 (Fissionation workers) 1.40 (0.97, 1.94) n = 5 | F: Not explicitly provided but stated to be either 0.00 or < -1.00 depending upon the model parameters used. CIs not provided. |

### Mallinckrodt Chemical Works (3.3.2.6)

| Source                        | Golden et al. 2019 | Gamma rays; x rays; intakes of radium, uranium; ambient radon and radon progeny | External; chronic exposure, usually at a low dose rate, whole body | T: 2.514 | Mortality T: 157 | Range 0.1-79 y | Mean 43.3 y | Absorbed dose in lung | Range 0.485 mGy Mean (T): 69.9 mGy McGeoghegan et al. 2003 (Fissionation workers) 1.40 (0.97, 1.94) n = 5 | F: Not explicitly provided but stated to be either 0.00 or < -1.00 depending upon the model parameters used. CIs not provided. |

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<table>
<thead>
<tr>
<th>Location</th>
<th>Source(s)</th>
<th>Exposure</th>
<th>Dose (lung)</th>
<th>Dose (whole body)</th>
<th>Mortality</th>
<th>Range</th>
<th>Weighted Dose in the Lung</th>
<th>SMR</th>
<th>ERR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cotabrook Plant</td>
<td>Dupree et al. 1987</td>
<td>Gamma rays; intake of radium, uranium; ambient radon and radon progeny</td>
<td>Weighted dose (lung) (weighting factor of 10 for alpha-particle emitters)</td>
<td>Range: 0 &lt; 10 Gy to 100 Gy</td>
<td>1.0</td>
<td>0.3</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fernald Feed Materials</td>
<td>Silver et al. 2013</td>
<td>Gamma rays; intake of uranium; radon and radon decay products</td>
<td>Weighted dose (lung) (in this case, the equivalent dose (lung) as defined by ICRP)</td>
<td>Range: 0.13 Gy to 1.5 Gy</td>
<td>1.3</td>
<td>0.2</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Savannah River Site</td>
<td>Cragle et al. 1998</td>
<td>Gamma rays; intake of plutonium, uranium, fission products, americium,</td>
<td>Weighted dose (lung) (in this case, the equivalent dose (lung) as defined by ICRP)</td>
<td>Range: 0.13 Gy to 1.5 Gy</td>
<td>1.3</td>
<td>0.2</td>
<td>-</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Section 3.3.4: Nuclear Weapons Test Participants (Atomic Veterans)

<table>
<thead>
<tr>
<th>Nuclear Weapons Test Participants (Atomic Veterans) (3.3.4)</th>
<th>Boice et al. 2020</th>
<th>Gamma rays, intakes of radionuclides</th>
<th>External: chronic exposure, usually at a low dose rate, whole body</th>
<th>Internal: chronic low dose rate, partial body</th>
<th>Total M: 114,270</th>
<th>Mortality T: 7,978</th>
<th>Range 0.65 y</th>
<th>Mean 47.0 y</th>
<th>Absorbed dose in lung</th>
<th>Range 0.972 mGy</th>
<th>Mean 6.21 mGy</th>
<th>Total M: 1.08 (1.06, 1.11)</th>
<th>ERR at 100 mGy (not adjusted for smoking)</th>
<th>Total M: 0.08 (-0.06, 0.22)</th>
</tr>
</thead>
</table>

- For example, x rays, gamma rays, neutrons, intakes of radionuclides.
- For low linear-energy transfer (LET) radiation, a low absorbed dose is <100 mGy delivered acutely, and a low absorbed-dose rate is <5 mGy h⁻¹ for any accumulated absorbed dose (NCRP 2015).
- Chronic exposure: radiation exposure of long duration because of fractionation or protraction.
- Radiation quantities: absorbed dose in the lung (in gray); weighted dose in the lung (in gray) [with weighting factor(s)]; personal dose equivalent (at 10 mm) [with weighting factor(s)].
- Equivalent dose (lung) is a weighted dose in the lung (footnote b) where the weighting factors for the high-LET components plus the weighted mean absorbed doses in the lung from high-LET components, where each high-LET mean absorbed dose component is multiplied by a judged weighting factor, as provided by the investigator. The equivalent dose is expressed in gray.
- The judged weighting factor described in footnote b, as provided by the investigator.
3.3.1 Medical Exposure of Patients

Several patient populations exposed to diagnostic or therapeutic radiation provide informative estimates of lung cancer risk following fractionated exposures but not separately for females and males. These studies are of patients with scoliosis who received frequent spinal x-ray examinations, and patients with peptic ulcer treated with radiation therapy (Table 3.3).

3.3.1.1 U.S. Scoliosis Study. The U.S. Scoliosis Study included 5,573 female patients monitored with frequent spinal x rays for curvature changes during the adolescent growth spurt and before 20 y of age from 1912 to 1965 and followed through 2004 (Hoffman et al. 1989; Ronckers et al. 2010). The average follow-up was 46.8 y and ranged as high as 91.5 y. The average number of x rays was 22.9 and ranged up to 553. The average cumulative absorbed dose in the lung was 47 mGy and the maximum was 676 mGy. Smoking histories were obtained by questionnaire for 3,121 patients who survived until 1993, and there was suggestive evidence that patients with scoliosis smoked less than the general population. Lung cancer (SMR: 0.77; 95% CI 0.57, 1.00; n = 57) was not elevated, and there was no evidence of a dose response (ERR at 1 Gy: -1.4; 95% CI -7.1, 3.1).

3.3.1.2 Radiation Therapy for Peptic Ulcer. Radiation was used during 1940 to 1960s to treat nonmalignant disease (Ron 2003). Radiation therapy for peptic ulcer (Griem et al. 1994; Carr et al. 2002; Little et al. 2013) and ankylosing spondylitis (Weiss et al. 1994) provided information on radiation-related lung cancer risk. Among 3,719 patients with peptic ulcer (22 % females, 50 % treated with radiation) seen at the University of Chicago and followed through 1997, 209 deaths from lung cancer occurred. Among the 1,859 patients treated with radiation therapy, the mean treatment dose to the stomach was 14.8 Gy. The mean absorbed dose in the left lung was 1.8 Gy and to the right lung was 0.6 Gy. The distribution of absorbed dose in the lung, however, was very heterogeneous with ~15 % of the lung receiving 12 Gy. Smoking was adjusted for in the analyses. A sex-adjusted statistically significant risk of lung cancer was reported (ERR at 1 Gy: 0.56, 95% CI 0.22, 1.02) (Little et al. 2013). The excess risk based on the absorbed dose in exposed lung tissue was lower (ERR at 1 Gy: 0.24 (95% CI 0.07, 0.44) (Carr et al. 2002). A
multiplicative relationship between smoking and radiation was reported. Sex-specific lung cancer risks were not provided.

### 3.3.2 Occupational Exposure of Workers

Many occupational studies of radiation-exposed workers include only males or provide no estimates of risk for female workers. Nonetheless, they provide information on the level of lung cancer risk associated with low-dose fractionated exposures received over a period of years, which is relevant to flight crews on long-term missions in space. Table 3.3 summarizes studies of workers employed in medicine, nuclear fuel processing, and weapons development. Most occupational studies involve exposures to low-LET radiation (i.e., x rays or gamma rays), but several involve high-LET radiation to lung tissue following the inhalation of alpha-particle emitting radionuclides such as plutonium among Rocky Flats workers and uranium among Mallinckrodt workers.

#### 3.3.2.1 U.K. National Registry for Radiation Workers

The U.K. National Registry for Radiation Workers (NRRW) study includes 174,541 workers first employed 1947 to 1999 and followed through 2011 (Muirhead et al. 2009). Because of concerns that the data for the early years of radiation work, 1947 through 1954, may not have been reliable, follow-up before 1955 was excluded, which reduced the cohort to 167,003 workers (9.9 % females) (Haylock et al. 2018).

The overall mean lifetime dose from external exposure was 25.3 mSv [personal dose equivalent (at 10 mm)] and was higher among the 150,566 male workers (27.5 mSv) than among the 16,437 female workers (5.6 mSv). Nearly 25 % of the workers were monitored for tritium, and for intakes of radionuclides, including plutonium and uranium, but only the fact of monitoring was known; doses in the lung from these sources were not determined. Smoking was not adjusted for in the analyses. The sex-adjusted ERRs were not statistically significant, either for lung cancer mortality (ERR at 1 Sv: 0.028; 95 % CI -0.44, 0.63; n = 3,058) or lung cancer incidence (ERR at 1 Sv: 0.13; 95 % CI -0.35, 0.72; n = 3,263). No sex-specific analyses were provided.
3.3.2.2 International Nuclear Workers Study. The INWORKS occupational mortality study consists of 308,297 nuclear workers (13 % females) in France, the United Kingdom, and the United States followed until 2001 or through 2005 depending on country (Richardson et al. 2018). The U.K. data included the NRRW Third Analysis which also were included in the 15-Country Study as were data from France, Hanford, Oak Ridge National Laboratory, and Idaho National Engineering and Environmental Laboratory (Cardis et al. 2007). Thus, the results from various studies are not independent. Workers in France were hired as early as 1950 but because cause of death was not available until 1968 from the national registry, follow-up began in 1968 in contrast to 1944 and 1946 for the United States and United Kingdom, respectively. The mean (and 95th percentile) cumulative absorbed doses in lung from external gamma rays were 22.8 mGy (106.3 mGy) for males and 4.8 mGy (18.8 mGy) for females. Doses from intakes of radionuclides or from external exposure to neutrons were not determined. There were 5,802 lung cancer deaths. Smoking was not adjusted for in the analysis. The sex-adjusted ERR at 1 Gy was 0.51 (90 % CI 0.00, 1.09). Sex-specific estimates were not provided.

3.3.2.3 Sellafield (U.K. Plutonium Production). The Sellafield cohort includes 23,443 workers (12 % female) first employed during 1947 to 2002 and followed until the end of 2005 (Gillies et al. 2017). Non-radiation workers were excluded. It also forms a subset of the NRRW. There were 406 deaths due to lung cancer during 1947 to 2002 (8 in females) and 384 incident cases of lung cancer diagnosed during 1971 to 2002 (8 in females). The mean absorbed dose in the lung from external gamma-ray exposure was 72.5 mGy, while the absorbed dose in the lung from exposure to plutonium was lower (1.9 or 5.5 mGy, depending on solubility). Smoking was not adjusted for in the analysis. The Sellafield cohort showed no statistically significant associations between lung dose and lung cancer. Estimates of risk were provided for male workers but not explicitly for female workers. The authors stated, however, that the radiation risk estimate was lower among female workers than among male workers, although with large uncertainty.

An earlier study was conducted of 6,376 females who worked at the Sellafield Plant of British Nuclear Fuels and were followed through 1998 (McGeoghegan et al. 2003). For all female workers the SMR for lung cancer was 1.23 (95% CI 0.88, 1.68; n = 40). For the 2,527
female radiation workers the SMR was 0.68 (95% CI 0.22, 1.58; \( n = 5 \)). For the 3,849 female non-radiation workers the SMR was 1.40 (95% CI 0.97, 1.94; \( n = 35 \)). The SMR ratio of radiation workers to non-radiation workers was 0.46 (95% CI 0.19, 1.23). An earlier study of 14,319 workers (19% female) with follow-up through 1993 also was conducted (Omar et al. 1999). For all workers (males and females combined) the SMR for lung cancer was 0.89 (95% CI 0.79, 0.99; \( n = 338 \)). For the 10,382 radiation workers the SMR was 0.86 (95% CI 0.75, 0.97; \( n = 246 \)). For the 3,937 non-radiation workers the SMR was 0.97 (95% CI 0.79, 1.20; \( n = 92 \)). The SMR ratio of radiation workers to non-radiation workers was 0.88 (95% CI 0.69, 1.12).

Sex-specific SMRs were not provided.

### 3.3.2.4 U.S. Radiological Technologists Study

The U.S. radiological technologists study includes 106,068 workers (76% females) who were certified by the American Registry of Radiologic Technologists for at least 2 y from 1926 to 1982; responded to mailed questionnaires during 1983 to the 1990s about work history practices, medical history, smoking habits and other lifestyle and sociodemographic factors; were free from cancer at the start of follow-up in 1983; and were followed through 2012 (Boice et al. 1992; Velazquez-Kronen et al. 2020). Mean cumulative absorbed dose in the lung was estimated to be 25 mGy (range, 0 to 810 mGy).

Overall, 1,090 lung cancer death occurred (65% among females). Smoking was adjusted for in the analysis. Occupational radiation lung dose was not associated with lung cancer mortality. The ERR at 100 mGy was -0.02 (95% CI <0, 0.13). Uncertainty in the estimates of lung doses before 1960, the exclusion of possible high-dose workers who died before 1983, and the somewhat low participation rates are limitations (NCRP 2018b). Sex-specific estimates were not provided. An earlier study of the entire radiological technologist cohort, both questionnaire responders and non-responders, of 146,022 workers (73% female) followed through 1997 presented SMR estimates for lung cancer (Mohan et al. 2002). For all workers the SMR for lung cancer was 0.80 (95% CI 0.68, 0.79; \( n = 781 \)). For the 106,884 female workers the SMR was 0.80 (95% CI 0.73, 0.88; \( n = 423 \)). For the 39,031 male workers the SMR was 0.67 (95% CI 0.60, 0.74; \( n = 358 \)). Absorbed doses in the lung were not estimated for the SMR evaluations.

### 3.3.2.5 Rocketdyne (Atomics International)

2006a, 2006b, 2011). Overall, 5,801 workers (8% female) were monitored for radiation activities, of whom 2,284 (39%) had intakes of radionuclides, primarily uranium. The mean equivalent dose (lung) was estimated to be 19 mSv (or mGy) [maximum 3,580 mSv (or mGy)] \(^6\). The workers with the highest lung doses had the highest intakes of alpha-particle emitting radionuclides. A small interview survey indicated that pay category (hourly, salaried) was a reasonable surrogate for cigarette smoking. The ERR at 100 mSv (or mGy) for lung cancer was estimated to be -0.02 (-0.18, 0.17) (Boice et al. 2021c). Sex-specific estimates were not provided.

3.3.2.6 Mallinckrodt Chemical Works. The Mallinckrodt Chemical Works study evaluated 2,514 white male workers employed 1942 to 1966 and followed through 2012 (Boice et al. 2018; Ellis et al. 2018; Golden et al. 2019). The workers were exposed to external gamma rays, and internal radiation from intakes of pitchblende dust (uranium, radium, and silica). Occupational medical x-rays and ambient levels of radon and radon progeny were incorporated in the dose reconstruction. The mean absorbed dose in the lung was 69.9 mGy and ranged up to 885 mGy. Pay category (hourly, salaried) was used as an adjustment for smoking in the analysis. There were 157 lung cancer deaths. There was little evidence for a radiation dose response. The ERR at 100 mGy was -0.06 (95% CI -0.18, 0.06). One strength of the study is the comprehensive dose reconstruction and a broad dose distribution following high-LET alpha-particle exposure to lung tissue.

3.3.2.7 Linde Air Products Company Ceramics Plant. The Linde Air Products Company Ceramics Plant was a uranium processing facility that employed 995 white male workers during 1943 through 1947 and who were followed through 1979 (Dupree et al. 1987). Belgian Congo pitchblende and domestic ores were processed. Workers were exposed to uranium dust and compounds, radium, airborne radon and radon decay products. Historical air monitoring data indicated that the internal radiation exposure levels were similar to the Tennessee Eastman Corporation cohort (Section 3.2.2.4). The mean lung dose was approximately 100 mGy.

\(^6\) As noted at footnote \(^i\) in Table 3.3, equivalent dose (lung) is a weighted dose in the lung and could also be expressed in gray.
(weighted dose, applying a weighting factor of 10 for alpha-particle emitters). Nearly 40% of
the workers received lung doses >100 mGy. Based on 21 lung cancer deaths, the SMR was 0.97
(95% CI 0.60, 1.48). No statistically significant deviations from the expected values were
observed over categories of lung dose. Study strengths include relatively high lung doses from
the intake of uranium-emitting high-LET alpha particles, and a relatively short duration of
exposure of several years. Limitations include the small size and the absence of information on
smoking.

3.3.2.8 Rocky Flats Nuclear Weapons Plant. The Rocky Flats plant employed 9,490 workers
(20% females) during 1952 through 1979 and followed through 1992 (Wiggs 1993). Two cohort
studies of 5,413 white males have been published (Wilkinson et al. 1987; Gilbert et al. 1993a),
and one case-control study that included female workers (Brown et al. 2004). Worker exposure
was from mixed fields of external radiation (gamma rays and neutrons), and intakes of alpha-
particle emitting plutonium, americium, and uranium. The average external radiation dose was
41 mSv (or mGy) ranging to over 100 mSv (or mGy), and the mean lifetime plutonium dose was
350 mSv (or mGy) ranging to over 1 Sv (or Gy)\(^7\) [the body burden on average was 64.8 Bq (1.75
nCi)]. The SMR for lung cancer based on 30 deaths was 0.64 (95% CI 0.46, 0.87), and there
were no significant dose-response associations with lung dose (Wilkinson et al. 1987). The ERR
at 1 Sv (or Gy) was estimated as <0 (95% CI <0, 6.1) (Gilbert et al. 1993a). Preliminary results
from a follow-up through 2019 are consistent with these earlier studies and report the ERR at
100 mGy (absorbed dose in lung) to be 0.01 (95% CI -0.10, 0.11; \(n = 324\)) (Boice et al. 2021c).
Adjustment for smoking was not done. Sex-specific estimates were not provided.

3.3.2.9 Fernald Feed Materials Production Center. The Fernald Feed Materials Production
Center was a uranium processing plant that employed 6,403 workers (15% females) from 1951
to 1984 who were followed through 2004 (Hornung et al. 2008; Anderson et al. 2012; Silver et
were low and estimated to be 1.0 mGy for males and 0.24 mGy for females. Mean cumulative

\(^7\) These are equivalent doses (lung). As noted at footnote 1 in Table 3.3, equivalent dose (lung) is a
weighted dose in the lung and could also be expressed in gray.
absorbed doses in lung from external radiation were estimated to be 14.6 mGy for males and 1.3 mGy for females. The SMR for lung cancer was 1.14 (95 % CI 1.01, 1.28; n = 294) among all workers; 1.06 (95 % CI 0.93, 1.19; n = 272) among males; and 1.26 (95 % CI 0.79, 1.90; n = 22) among females. Pay category was a strong predictor of lung cancer with hourly workers having a significantly high SMR and salaried workers a significantly low SMR. Pay category (hourly, salaried) was adjusted for in the analysis as a surrogate for smoking. No statistically significant relationships between lung cancer and external exposure, intakes of uranium, or exposure to radon and its decay products were observed. The ERR at 100 mGy from external exposure among white males was estimated as 0.12 (95 % CI -0.32, 0.74). An ERR estimate for females was not provided.

3.3.2.10 Savannah River Site. The Savannah River Site in South Carolina has operated as a production facility for nuclear fuels and other materials since 1952. There were 9,860 white males employed during 1952 to 1974 and followed through 1986 (Cragle et al. 1988, 1998). Dose reconstruction focused on external exposure (gamma rays and neutrons) and tritium. Intakes of radionuclides were mainly from plutonium, although other intakes could include uranium, fission products, americium, curium, and californium (HAI 1996; Taylor 2000; Taylor et al. 1995). The mean cumulative equivalent dose (lung) was 40.5 mSv (or mGy) [maximum 476 mSv (or mGy)]. The SMR for lung cancer was 0.95 (95 % CI 0.81, 1.10; n = 175). The SMR was significantly low for the 2,561 salaried workers (SMR 0.60) and elevated for the hourly workers but not significantly (SMR 1.08). Adjustment for smoking was not made. The dose trend for lung cancer deaths over cumulative lung dose categories was not statistically significant. An extended study was conducted of 18,883 workers (19 % females) hired between 1950 and 1986 and followed through 2002 but did not include information on radiation exposure (Richardson et al. 2007). The SMRs for lung cancer were 0.93 (95 % CI 0.85, 1.01; n = 524) for all workers, 0.88 (95 % CI 0.82, 0.95; n = 497) for male workers, and 0.68 (95 % CI 0.48, 0.94; n = 27) for female workers. Salaried workers had a significantly low SMR for lung cancer, and hourly workers had a significantly high SMR. The SMRs for lung cancer were not associated

\(^1\) As noted at footnote 'i' in Table 3.3, equivalent dose (lung) is a weighted dose in the lung and could also be expressed in gray.
with duration of employment. A significant excess of cancer of the pleura suggested exposure to asbestos. A study of African-Americans who worked at the Savannah River Site was conducted but did not evaluate lung cancer risk (Wartenberg et al. 2001).

3.3.3 Environmental Exposure of Populations (Techa River Resident Cohort)

Between 1949 and 1956 the Mayak Production Association in the Russian Federation released radioactive waste into the Techa River (UNSCEAR 2018; NCRP 2018b). Nearly 30,000 individuals who lived in 41 villages along the river were exposed to multiple sources of external radiation and ingested radionuclides (Kossenko et al. 2005; Degteva et al. 2012). The incidence of lung cancer was evaluated in a subset of 17,435 individuals (57 % females) over the age of 20 y at initial exposure (Davis et al. 2015). Among 7,521 males, 292 cases of lung cancer were reported. Among 9,914 females, 47 cases of lung cancer were reported. The mean absorbed dose in lung was 50 mGy. Smoking was adjusted for in the analysis. There was little evidence for a lung cancer dose response [i.e., the sex-adjusted ERR at 1 Gy was 0.01 (95 % CI -0.02, 0.18)]. Sex-specific lung cancer risks were not provided.

3.3.4 Nuclear Weapons Test Participants (Atomic Veterans)

From 1946 to 1962 the United States conducted over 200 above-ground atmospheric weapons tests during the Cold War at the Nevada Test Site and the Pacific Proving Grounds (e.g., Bikini Atolls) (Caldwell et al. 2016; Boice et al. 2020). Among 114,270 male military personnel followed from 1946 through 2010, there were 7,978 deaths due to lung cancer. Dose reconstructions were comprehensive (Till et al. 2014, 2018; Beck et al. 2017). Absorbed dose in the lung was low, mean 6.21 mGy with a maximum of 972 mGy. Military pay grade (enlisted, officer) was used as a surrogate for smoking in the analysis. There was no statistical evidence for a radiation dose response over the estimated range of lung doses (ERR at 100 mGy = 0.04 (95 % CI -0.11, 0.19).
3.4 Summary and Conclusions

Section 3.1 presents epidemiologic descriptive characteristics of lung cancer by sex with a focus on nonsmokers. Of particular importance are the differences in the baseline mortality rates of lung cancer in male and female nonsmokers, and the remarkable improvements in survival over the last decade. Risk factors are discussed such as cigarette smoking, physical and chemical exposure in the workplace, host factors, and histopathological subtypes. These features provide a foundation for understanding the radiation epidemiologic studies of sex-specific differences in lung cancer (Table 3.2), and the additional epidemiologic studies relevant to radiation-associated lung cancer risk overall, but for which sex-specific differences were not available or informative (Table 3.3). Table 3.2 includes 18 studies, with 20 listings (the studies of Japanese atomic bomb survivors and Russian Federation Mayak workers each have 2 listings, one for mortality and one for incidence). Table 3.3 includes 14 studies. The total number of studies is 31 (with 33 listings). A qualitative summary of the studies reviewed in Section 3.2 (Table 3.2) and Section 3.3 (Table 3.3) is provided below.

3.4.1 Sex Differences in Lung Cancer Risk in Epidemiologic Studies of Radiation-Exposed Populations

Of the 18 studies included in Table 3.2 providing estimates of sex-specific lung cancer risks:

- On a relative scale, a statistically significant higher risk among females compared with males was seen in two studies (Japanese atomic bomb survivors and Russian Federation Mayak workers with intakes of plutonium). This was the case for both the mortality and incidence listings for each study.
- Males were at statistically significant higher risk than females in one study (the meta-analysis of radon-exposed never-smokers) and a higher risk of borderline significance in another (medical radiation workers).
- No statistically significant sex-specific differences were reported in the other 14 studies reviewed.
• Eleven of the 18 studies showed statistically significant increased radiation risk for lung cancer for the full study group. The other 7 studies did not show an increased lung cancer risk.

Accordingly, no firm conclusion on a sex difference in radiation risk for lung cancer can be supported based on the evidence available to date. While radiation-related lung cancer risk is observed in one or more studies in each of the exposure scenarios (medical, occupational, environmental, and the atomic bomb survivors), whether that risk is borne differentially by males and females remains unknown.

3.4.2 Other Epidemiologic Studies of Lung Cancer Risk in Radiation-Exposed Populations that Inform Lifetime Risk Estimates

In addition to the 18 studies that provided contrasts in risk estimates by sex, 14 studies summarized in Section 3.3 and Table 3.3 include single sex studies, or studies that did not provide separate male and female (or any) lung cancer risk estimates. These studies were included to provide additional information that may be useful for assessing radiation-related lifetime lung cancer risk. Of these 14 studies, two showed statistically significant elevated radiation-related lung cancer risk, while 10 showed no statistically significant increase in risk, and two provided no risk estimates.

3.4.3 Considerations for Further Epidemiologic Studies

The review of radiation epidemiologic studies did not provide an unequivocal answer as to whether females are at higher risk than males for radiation-related lung cancer. All studies have weaknesses which can include small numbers of females, narrow dose distributions, inadequate dose assessment, very different exposure scenarios from space radiation (e.g., high-dose radiation therapy to sections of the lung or acute exposures), less than optimal methodologies (such as high lost to follow-up rates or low participation rates), and inadequate information on smoking. Based on the published literature, an argument might be made that males and females have similar risks of radiation-related lung cancer. Also, since additional
studies are becoming available where the exposure is fractionated or chronic, there is a need to
further evaluate whether fractionated or chronic radiation exposure (such as experienced by
astronauts) carries a similar or a lower risk of lung cancer than when the exposure is acute.

None of the epidemiologic studies has an exposure scenario that is similar to a space
radiation environment, and no individual study is statistically powerful enough to provide an
unequivocal assessment of sex-specific lung cancer risk. Thus, there is a need to further pool or
combine epidemiologic studies. The concept of pooling or combining for statistical power is not
new as evident in a number of the epidemiologic investigations reviewed in Sections 3.2 and 3.3
(e.g., the INWORKS study, the 15-Country study, the four radon pooled analyses, the U.K.
Registry of Radiation Workers). Therefore:

- Pooling relevant epidemiologic studies would improve the statistical power of studies on
  sex-specific differences, particularly if large numbers of nonsmokers and females can be
  identified.
- Pooling studies with mixed-field exposures such as to gamma rays, neutrons, and intakes
  of radionuclides might represent a more similar environment to space than studies of low-
  LET exposures alone.

In addition, the last mortality follow-up for many of the epidemiologic studies evaluated
was 10 y ago, and for many it was 20 y or more ago. Continued follow-up to the present would
identify more lung cancer deaths and provide a more accurate assessment of lifetime risk.

An ideal epidemiologic cohort would have similar characteristics as astronaut flight
crews engaged in long-term missions. The cohort would include nonsmoking healthy males and
females at ages from 25 y to 50 y at time-of-exposure to chronic, protracted, or fractionated
radiation over a period of several years. The space environment includes exposure to both low-
LET and high-LET radiation (galactic cosmic rays). Since Earth-bound populations are not
exposed to galactic cosmic rays, internal intakes of radionuclides that expose lung tissue to high-LET alpha particles might contribute useful insight.
4. Biological Issues of Lung Cancer and Potential Differences Between Males and Females

Summary: Section 4 examines biological factors that might lead to a greater risk of radiation-induced lung cancer in females than males. Since lung cancer is not a single disease entity, the few reports available on molecular subtypes that are most likely to be radiation induced are reviewed. A similar review of which histopathological subtypes are most likely to be radiation induced was presented in Section 3.1.2. Also, tumorigenic mechanisms that have the potential to place females at increased risk are considered. In summary, a greater risk of radiation-induced lung cancer for females is biologically plausible but given the paucity of data it is only speculative.

4.1 Histopathology and Molecular Pathology of Radiation-Induced Lung Cancer

4.1.1 Histopathology of Radiation-Induced Lung Cancer

The most recent WHO classification of 2015 incorporates more immunohistochemical findings than previous classification schemes since these can impact the choice of therapy (Travis et al. 2015). Lung tumors are classified as adenocarcinoma, adenosquamous cell carcinoma, squamous cell carcinoma, large-cell carcinoma, sarcomatoid carcinoma, neuroendocrine carcinoma, and diffuse idiopathic pulmonary neuroendocrine cell hyperplasia. In the literature reviewed for this Commentary, the major forms of interest are adenocarcinoma, squamous cell carcinoma and small-cell lung cancer (neuroendocrine carcinoma in the WHO classification). Of these, adenocarcinoma is the form that occurs most frequently in nonsmokers. Adenocarcinoma, squamous cell carcinoma and large-cell carcinoma are grouped together as NSCLC.

Obviously, a first step in determining if females are more susceptible to radiation-induced lung cancer than males is to determine which histologic subtypes are associated with radiation exposure. However, as detailed in Section 3.1.2, it is challenging to determine whether radiation increases the risk of a specific histopathological subtype of lung cancer and there are inconsistent findings between exposed cohorts. The effects of radiation and smoking on the subtype of lung
tumors observed in the Japanese atomic bomb survivors have been studied. There was a
significant ERR at 1 Gy (1.34) for adenocarcinoma in female never-smokers. For male never-
smokers there was a significant ERR at 1 Gy (2.21) for small-cell lung cancer, though with large
confidence intervals (Egawa et al. 2012). Among patients treated for Hodgkin lymphoma with
radiation therapy and who subsequently developed lung cancer, the highest ERR at 1 Gy values
are for adenocarcinoma and large-cell carcinoma (Gilbert et al. 2003). However, because
Hodgkin lymphoma patients receive high radiation doses, are immunosuppressed, and are also
treated with chemotherapy, the authors of that report caution against extrapolating their findings
to other populations or to lower doses. Radiation therapy for breast cancer also increases lung
cancer risk (Prochazka et al. 2005), though only in smokers. In this study the increased risk was
for squamous cell carcinoma in the lung ipsilateral to the tumor. Once again, caution is needed in
generalizing this finding to lower doses.

4.1.2 Molecular Pathology

Besides histopathology, another approach to categorize lung tumors is by their driver
mutations. Sequencing data specific for human radiation-induced lung cancers are not available
because it is not possible to know if an individual lung cancer is radiation induced or not.
However, there are two reports that hint at which mutations may be most pertinent to radiation-
induced lung tumors. The first is Yoshida et al. (2009) and deals with a cytosine-adenine (CA)
dinucleotide repeat number polymorphism in the first intron of the EGFR gene. The number of
times CA is repeated at this position varies between alleles of EGFR, and EGFR transcription is
inversely correlated with the CA repeat number. Japanese atomic bomb survivors were divided
into two groups (short and long) based on the sum of the CA repeats in both their EGFR alleles.
Individuals with the long genotype were at higher risk of radiation-associated lung cancer and
that risk increased with dose. Yoshida et al. (2009) also report that in unexposed or negligibly
exposed individuals, the short allele was associated with increased risk of adenocarcinoma,
suggesting that increased levels of EGFR increase lung cancer risk. An interpretation of these
data is that of the long EGFR allele tamps down the EGFR signaling pathway and radiation
exposure overcomes this protective effect thus increasing the risk in individuals with the long
allele, but not the short allele. This points to a role for the EGFR signaling pathway in radiation-
induced lung cancer. Since this lung cancer pathway is more commonly used by tumors arising
in females than males (Rosell et al. 2009), females could be at greater risk than males of
radiation-induced lung cancer. It is also important to note that there are marked ethnicity-based
differences in frequencies of EGFR CA repeat polymorphisms. Long alleles are found in higher
prevalence in individuals of East Asian descent compared to those of European descent and
African Americans (Liu et al. 2003; Nomura et al. 2007), which is an important consideration as
it may impact risk coefficients used for radiation risk assessment in NASA astronauts.

The second report is from Castelletti et al. (2019) who, based on sequence and
histological data from a large collection of tumors (Campbell et al. 2016), propose dividing lung
adenocarcinomas into two molecular classes, those with driver mutations in genes encoding
receptor proteins (RMUT) and those with driver mutations in transducer proteins in signal
transduction pathways (TMUT). The RMUT group consists of tumors harboring mutations in
EGFR, ERRB2, MET, ALK, RET or ROS1.9 The TMUT group encompasses tumors with
mutations in KRAS, BRAF, ARHGAP35 or NF1.10 Patients with RMUT tumors are more
frequently female and, based on mutational signatures of tobacco exposure, have reduced
smoking exposure. RMUT and TMUT tumors can be distinguished on a number of characteristics.
Among these is that RMUT tumors have a higher ratio of insertion or deletion mutations (indels)
to single-nucleotide variants than TMUT tumors. A high indel to single-nucleotide variant ratio
may be a signature of radiation-induced tumors (Sherborne et al. 2015; Behjati et al. 2016;
Goerlitz et al. 2019; Lee et al. 2019; Rose et al. 2020). Also, the RMUT group of tumors includes
those with ALK, RET and ROS1 fusion genes.

One way to synthesize these observations is that radiation exposure drives tumorigenesis
in susceptible individuals through pathways in which indel and fusion gene mutations
predominate, and these happen to be pathways associated with tumors in nonsmokers and
females. Fusion genes are also characteristic of radiation-induced papillary thyroid carcinoma

9 Gene names not yet given: ERRB2 (v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2),
MET (MET proto-oncogene, receptor tyrosine kinase), ALK (anaplastic lymphoma kinase), RET
(rearranged during transfection), ROS1 (ROS proto-oncogene 1, receptor tyrosine kinase).
10 Gene names not yet given: BRAF (B-Raf proto-oncogene, serine/threonine kinase), ARHGAP35 (Rho
GTPase activating protein 35), NF1 (neurofibromin 1).
(PTC) (Ricarte-Filho et al. 2013; Santoro and Carlomagno 2013; Arndt et al. 2018). In fact, a recent genomic analysis of PTC arising after the Chernobyl accident showed that fusion gene driver events accounted for 41% of PTC cases, with the most frequent involving the RET gene and other receptor tyrosine kinases. Fusion gene drivers were more frequent at higher radiation doses (Morton et al. 2021). Interestingly, fusion genes are frequent driver mutations in lung cancer (Suda and Mitsudomi 2020) and the random breakpoint distribution in RET fusions in lung adenocarcinoma (not necessarily radiation associated) analyzed by Mizukami et al. (2014) was similar to that in PTC.

4.2 Plausible Mechanisms that Would Lead to a Greater Risk in Females

Based on current knowledge there are several plausible mechanisms that could result in females being at greater risk of radiation-induced lung cancer than males. These mechanisms are not mutually exclusive, and none is yet proven. It is certainly possible that there are other important processes yet to be described. With the recent increased emphasis on incorporation of sex-based factors in biomedical research it is likely that additional clarity on these and other important mechanisms will emerge in the future (Clayton and Collins 2014).

4.2.1 Mechanism 1. Hormonal Differences Between Males and Females

Hormonal differences between males and females could place females at greater risk for lung cancer generally and by extension to radiation-induced lung cancer. In particular, estrogens may be involved in lung carcinogenesis through their activation of cellular proliferation and through metabolic intermediates in their biosynthesis that produce DNA adducts resulting in DNA damage and oxidative stress. A role for estrogen in lung carcinogenesis is supported by epidemiologic studies and experimental studies with cells and with mice.

4.2.1.1 Estrogen Promotes Cell Proliferation and is Pro-Inflammatory. Estradiol, the major female estrogen, is a potent mitogen which binds to estrogen receptors alpha and beta (ER-α and ER-β). Ordinarily, ER-β is expressed in normal lung and bronchial epithelial cells whereas ER-α is generally absent or at low levels in normal lung and in tumor cells. Upon estradiol binding,
ER-β is translocated to the nucleus where it binds to estrogen response elements and forms active transcription complexes. Estrogen receptors also activate other cell and nuclear membrane proteins including EGFR and ERK/MAPK\(^{11}\) to further stimulate cell growth. When estrogen was exogenously added to lung cancer cell lines, cell proliferation was increased and there was an increase in phospho-EGFR and phospho-MAPK, likely through release of the EGFR ligands [tumor necrosis factor alpha (TNF-α), heparin binding-EGF and amphiregulin] (Stabile et al. 2005). Other pathways regulated by estrogen signaling include induction of tumor angiogenesis via vascular endothelial growth factor secretion (Marquez-Garban et al. 2011), secretion of hepatocyte growth factor, and stimulation of CXCR4\(^{12}\) expression (Rodriguez-Lara et al. 2017). In addition to activation of EGFR, ER-α is known to cause the transactivation of insulin-like growth factor 1 receptor resulting in the activation of both the ERK/MAPK and PI3K/AKT\(^{13}\) pathways (Razandi et al. 2003; Song et al. 2007). In a NSCLC xenograft model, tumor growth was decreased by the administration of the estrogen-receptor antagonist fulvestrant and further reduced with the combination of fulvestrant and the EGFR inhibitor gefitinib (Stabile et al. 2005). In addition, apoptosis was increased. Further support for a role of estrogen in lung cancer comes from a knockout mouse lung cancer model in which Kras was conditionally expressed and transformation related protein 53 (Trp53) was deleted. Female mice had twice the number of tumors which were larger and higher grade than tumors in their male counterparts. This effect was eliminated in ovariectomized females (Hammoud et al. 2008). The authors suggest that estrogen functions as a promoter of lung cancer in this oncogene-initiated mouse model.

Estrogen receptors are also broadly expressed on cells that make up the tumor microenvironment, including immune cells of myeloid lineage, tumor infiltrating lymphocytes and cancer-associated fibroblasts. Estrogen-associated signaling pathways in this context are thought to play important roles in immune surveillance functions that may contribute to the sex differences observed in NSCLC (Smida et al. 2020).

\(^{11}\) ERK (extracellular signal-regulated kinase); MAPK (mitogen-activated protein kinase).
\(^{12}\) CXCR4 (C-X-C chemokine receptor type 4).
\(^{13}\) PI3K (phosphatidylinositol 3-kinase); AKT, also known as PKB (protein kinase B).
Estradiol is pro-inflammatory. Physiological estradiol concentrations, corresponding to the menstrual peak in females, induce the formation of reactive oxygen species and the production of chemokines, including interleukin-8. This process does not require estrogen-receptor interaction, it leads to increased oxidative stress and may contribute to carcinogenesis.

Anti-inflammatory androgens (testosterone) can counteract these effects by blunting the response of cells to TNF-α and lipopolysaccharides, altering the CD4+/CD8+ ratio\textsuperscript{14} by increasing the number of CD8+ cells and reducing the number of CD4+ cells, reducing monocyte numbers, and reducing the proliferative response of lymphocytes (D’Agostino et al. 1999; Cutolo et al. 2002; Kissick et al. 2014). Testosterone also reduces the expression of pro-inflammatory mediators monocyte chemoattractant protein-1, interleukin-6, TNF-α and interleukin 1 beta (Huber et al. 1999; Yao et al. 2003; Gilliver 2010) suggesting that differing balances between estrogens and androgens in males and females may partially account for risk differences (Henderson and Feigelson 2000; Fuentes and Silveyra 2018).

\textbf{4.2.1.2 Clinical Evidence for the Role of Estrogen in Lung Cancer.} Some reports on the risk for lung cancer associated with estrogen replacement therapy point to an increased risk (Adami et al. 1989; Ganti et al. 2006) while others studies suggest the opposite (Schabath et al. 2004; Chen et al. 2007; Ramnath et al. 2007; Meinhold et al. 2011). Differences in the tumorigenic effects of estrogens may be related to the timing of their administration and the presence or not of disease (Brinton et al. 2011). Furthermore, females on postmenopausal hormone replacement therapy who have lung cancer have a much greater risk of death from lung cancer, whereas there was no statistically significant increased risk for death by lung cancer for the placebo group nor in females who did not have lung cancer or who had small-cell lung cancer. Hormone replacement therapy may not have caused new cancers; however, NSCLCs in those with hormone replacement therapy were considered more likely to be poorly differentiated and more likely to engender metastases (Chlebowski et al. 2009). The expression of ER-β is associated with a better prognosis while ER-α is associated with a poorer prognosis. ER-β overexpression is more common in tumors from nonsmokers (53.5 %) than tumors from smokers (36.6 %) and among

\textsuperscript{14} Ratio of T helper cells (with the surface marker CD4) to cytotoxic T cells (with the surface marker CD8).
nonsmokers, high expression of ER-β is more frequent in females (58.3 %) than in males (40.9 %) (Barrera-Rodriguez and Morales-Fuentes 2012).

Large randomized studies suggest that estrogen plus progestin therapy is associated with an increased risk of lung cancer. As part of the Women's Health Initiative trial (Chlebowski et al. 2009), 16,608 females were randomly assigned to estrogen-progestin therapy or placebo. There was a statistically nonsignificant trend toward an increased incidence of NSCLC in females taking estrogen-progestin therapy when compared with placebo. In a component of the Women's Health Initiative trial, 10,739 females who had previously undergone a hysterectomy were randomly assigned to estrogen alone or a placebo. However, after 8 y of follow-up, there was no statistically significant increase in the incidence of lung cancer (Chlebowski et al. 2009).

The prospective Vitamins and Lifestyle Study followed a cohort of over 36,000 peri- and postmenopausal females during 6 y of follow-up. After adjusting for smoking and other confounding factors, the risk of incident lung cancer was increased for those who used estrogen plus progestin and the risk was proportional to the duration of hormone exposure (Slatore et al. 2010) although a subsequent pooled analysis suggested no increased risk (Pesatori et al. 2013).

Expression of aromatase, a member of the P450 cytochrome superfamily responsible for estrogen synthesis, in lung tumors and surrounding tissue could support paracrine or autocrine estrogen-receptor signaling and augment circulating estrogen in promoting proliferation of lung tumors. This possibility is supported by experimental evidence using mouse xenograft models of lung adenocarcinoma in which treatment with an aromatase inhibitor significantly decreased lung tumor growth (Weinberg et al. 2005). Also, lower levels of aromatase gene expression in NSCLC tumor tissues were associated with a greater probability of survival in females 65 y and older (Mah et al. 2007), which supports a role for estrogen in enhanced pathogenesis of lung tumors in females. Another interesting result is the correlation between ER-α expression and EGFR mutations in lung adenocarcinoma (Raso et al. 2009).

4.2.1.3 Animal Studies on the Role of Estrogen. Rodent studies of radiation-induced lung cancer are described in Section 5. A quick synopsis is that sex differences in susceptibility to radiation-
induced lung cancer are not apparent in conventional rodent models, but that caution is needed in extrapolating results from mice to humans. The ovary is a major site of estrogen production and the primordial follicles in the murine ovary are more sensitive to destruction by radiation than human primordial follicles. While primordial follicles are quiescent and are not involved in steroid synthesis, they are nonrenewable precursors to later stages of follicle development and their loss leads to early onset ovarian failure thus diminishing estrogen production (Baker 1971; Adriaens et al. 2009).

Results from animal experiments on the effects of estrogen are mixed. Ovariectomy does not spare female RFM strain mice from either spontaneous or radiation-induced lung tumors (Storer et al. 1982). But, in that particular study, radiation exposure did not lead to a sizable increase in lung cancer incidence anyway. Also, the presence of estrogen receptors has not yet been demonstrated in lung tumors arising in RFM mice, which means the model itself might not be relevant for the study of estrogen effects on risk. A study in mice with engineered \textit{Kras} and \textit{TP53} alleles, which did not include radiation exposure, showed slight but nonsignificant protection against lung tumors by ovariectomy, but significant increases in tumor foci if the mice were implanted with a slow-release estradiol capsule. These results suggest that superphysiological levels of estrogen (for mice) can drive lung tumorigenesis in this model. How these results might translate to normal physiological levels of estrogen in humans is unknown.

\subsection{Mechanism 2. The Increased Risk from Radiation Exposure Arises Predominantly from One Lung Cancer Subtype (or a Limited Set of Subtypes) and Females have a Higher Background Rate for that Subtype}

Lung adenocarcinomas in nonsmokers exhibit broad sex differences in terms of clinicopathological, molecular characteristics and response to therapy. Nonsmoking females are more likely than nonsmoking males to develop lung cancer with adenocarcinomas as the histological subtype (Wakelee et al. 2007; Barta et al. 2019). Female patients tend to present with disease at an earlier age compared to males, and there are indications that females have more favorable prognostic outcomes (Ragavan and Patel 2020).
At the molecular level there are broad sex-based differences in NSCLCs (Yuan et al. 2016). Mutations in EGFR, a receptor tyrosine kinase, are more frequently observed in lung adenocarcinomas from nonsmoking females, which impacts treatment options as this protein is a target for receptor tyrosine kinase inhibitors (Pao et al. 2004; CGARN 2014). These sex differences have led to speculation that lung cancer in females is a distinct entity and has spurred examination of potential contributing factors which are discussed below (Pao et al. 2004; Sun et al. 2007). There are also unique ethnic differences in female lung adenocarcinomas that should be considered (Zhang et al. 2016). These may be due or partly due to ethnic differences related to indoor air pollution from cooking fumes, secondhand smoke, coal burning and differences in infectious factors.

As noted in Section 3.1, lung cancer in females differs in some regards from lung cancer in males. Females are more likely to present with adenocarcinoma, and EGFR mutations are more prevalent in lung cancers arising in females. There is some evidence for a greater prevalence of ER-β overexpression in NSCLC resected from female never-smokers than male never-smokers (Wu et al. 2005). In a study of lung cancer, aromatic DNA adducts were found to be higher in the normal lung tissue of female smokers compared to male smokers and this sex difference in adduct levels may be due to the higher expression levels of CYP1A1 seen in female smokers and is associated with greater lung cancer risk (Mollerup et al. 1999).

Mutations in EGFR were the first specific genetic mutation associated with adenocarcinoma histology in never-smokers (Pao et al. 2004). Furthermore, in an analysis of EGFR mutations in exons 18-21 from 9 separate studies that included over 2,000 NSCLCs, Shigematsu and Gazdar (2006) found EGFR mutation present: in adenocarcinomas versus other NSCLC histologies at a rate of 30 % versus 2 %; in never-smokers versus ever-smokers at a rate of 45 % versus 7 %; in East Asian versus non-Asian NSCLCs at a rate of 33 % versus 6 % and 48 % versus 12 % if confined to adenocarcinomas; and in female versus males at a rate of 38 % versus 10 %, all at a p < 0.001. A separate study of several hundred NSCLCs found similar differences (Shigematsu et al. 2005a). Nearly all EGFR mutations lead to increased tyrosine

\[ \text{CYP1A1} \] (cytochrome P450 family 1 subfamily A member 1)
kinase activity and while these tumors are sensitive to anti-EGFR therapy, a substitution
mutation (T790M) confers resistance to EGFR inhibitors (Kobayashi et al. 2005; Pao et al.
2005). T790M has also been found as a germline mutation in some families. The estimated lung
cancer risk in non-smoking individuals carrying a germline T790M mutation is greater than 30 %
in non-smokers (Yu et al. 2014). Female carriers appear to be a greater risk than male carriers.
The tumors that arise in patients carrying a germline T790M mutation frequently have an
additional, somatic activating mutation in EGFR (Gazdar et al. 2014; Yu et al. 2014).

Interestingly, some genetic polymorphisms influence lung cancer risk in females but not
males, which suggests there are some differences in tumorigenesis between the sexes. The
GSTM1\textsuperscript{16} null polymorphism increases risk in females more than in males. However, GSTM1
(and CYP1A1) act through the metabolism of chemical carcinogens and it is not apparent that
they would influence risk to radiation-induced lung cancer. DNA repair is a more likely process
in which sequence variants might influence radiation-induced lung cancer risk. Lower DNA
double strand break repair efficiency as measured by the low dose-rate \( \gamma \)H2AX assay has been
linked to an increased susceptibility to radiation-induced lung cancer in mice (Ochola et al.
2019). In humans, patients with early onset lung cancer have decreased DNA repair capacity
measured by the comet assay (single-cell gel electrophoresis), as do their first-degree relatives
(Rosenberger et al. 2012).

In that regard, polymorphisms in the excision repair cross-complementing group 2
(ERCC2) gene which encodes xeroderma pigmentosum group D protein are associated with
reduced DNA repair capacity. For example, reduced repair capacity to cyclobutane dimers
specific to ultraviolet irradiation have been noted for the Asp312An and Lys751Gln
polymorphisms in ERCC2 (Hemminki et al. 2001; Qiao et al. 2002). Of the two polymorphisms
only Lys751Gln was associated with limited repair of \( x \)-ray induced chromatid aberrations (Lunn
et al. 2000a). While a number of studies have found associations with polymorphisms in the
DNA repair gene families and NSCLC, there appears to be multiplicative effects with smoking
status (Dresler et al. 2000; Zhou et al. 2003) and suggested associations for lung cancer that vary

\textsuperscript{16}GSTM1 (glutathione S-transferase mu 1).
Lys751Gln polymorphism is a risk factor for Caucasian smokers and nonsmoking Chinese females (Zhang et al. 2010), and the x-ray repair cross complementing 3 (XRCC3) Thr241Met polymorphism is associated with a decreased risk of lung cancer in Caucasians but not Asians (Huang et al. 2013).

The KRAS oncogene is another of the most commonly mutated genes in lung cancer with most mutations in KRAS occurring in smokers; 80% to 90% of KRAS mutations occur at codon 12 as a G→T transversion and in adenocarcinoma, the protein is mainly overexpressed. Furthermore, these mutations are associated with therapeutic resistance and poor outcomes. The frequency of genetic alterations is greater in female smokers with lung cancer (26.2%) than in male smokers with lung cancer (17.4%). And although not well understood in terms of prognosis or therapy, there is the suggestion that there is a higher frequency of “nonclassical” KRAS mutations in nonsmokers. In this study of the spectrum of KRAS mutations, 15% of tumors from never-smokers had KRAS mutations compared to 22% of tumors from former smokers, and 25% of tumors from current smokers. Never-smokers were significantly more likely to have a G→A transversion mutation compared to former or current smokers instead of the smoking related transversion mutations, G→T or G→C suggesting that never-smokers with lung cancer may have a distinct KRAS mutation profile (Riely 2008).

There are other genes with a familial association with lung cancer. Families with breast cancer (BRCA) gene mutations have higher levels of lung cancer but there is no association with sex or age (Digennaro et al. 2017). Mutations in HER-2, a member of the EGFR family, are more frequent in nonsmokers, patients of Asian background and females (Shigematsu et al. 2005b). In patients with NSCLC, V600E BRAF mutations are more common in never-smokers and female lung cancer cases (Marchetti et al. 2011; Ding et al. 2017). This mutation is associated with an aggressive tumor histology and poor prognosis.

Gastrin-releasing peptide receptor (GRPR) stimulates proliferation and growth of bronchial epithelial cells and has been associated with the regulation of the development of the human lung in utero (Shriver et al. 2000; Shan et al. 2004). Activated GRPR acts as a growth factor in lung and other cancers (Patel et al. 2006) likely by mediating the activation of EGFR.
and AKT (Thomas et al. 2005; Liu et al. 2007). GRPR expression increases in airway cells exposed to estrogens, suggesting that the GRPR gene could be regulated by this hormone and, as GRPR is located on the X chromosome, there is the suggestion that two copies of the GRPR gene in females may play some role in increasing female susceptibility to lung cancer (Barrera-Rodriquez and Morales-Fuentes 2012). GRPR messenger ribonucleic acid (RNA) expression was seen in airway cells and tissues of 55% of female nonsmokers but none was detected in male nonsmokers and 75% of females who were short-term smokers (1 to 25 pack-years) had GRPR messenger RNA expression compared with 20% of male short-term smokers (Shriver et al. 2000).

Whether radiation drives lung tumorigenesis through steps that are more commonly associated with lung cancer in females is unknown. However, there is some evidence that radiation increases the risk of adenocarcinoma, and that the EGFR pathway is important in that process.

Twin studies do not detect a genetic component of lung cancer risk in males as determined by a greater concordance for lung cancer among monozygotic than among dizygotic twin pairs (Braun et al. 1994; Lichtenstein et al. 2000), but there is clear evidence for a genetic component in females (Lichtenstein et al. 2000). This may be relevant, if the genetic background controls risk to a greater extent in females than males. However, the data may simply be a function of the environmental effect of the greater smoking rates of males obscuring any genetic effect.

4.2.3 Mechanism 3. Chromosomal and Background Gene Expression Differences

Besides hormonal differences related to reproduction, there are other biological differences between males and females that could lead to a greater spontaneous lung cancer risk in females. About 60 genes are differentially expressed in the lung between males and females (Gershoni and Pietrokovski 2017). In mice, a number of radiation responses, including radiation-induced changes in the expression of specific genes differ between males and females.
(SSK 2009). Whether any of these sex-determined response differences would impact lung cancer risk is unknown.

Another possible susceptibility mechanism is based on the different complement of sex chromosomes between males and females. Somatic cells in females have two X chromosomes, one of which is inactivated to achieve comparable expression levels for X-chromosome genes between males and females. The X inactive specific transcript (XIST) gene encodes a non-coding RNA required for X-inactivation. Disruption of X-inactivation by a conditional knockout XIST allele in mouse hematopoietic stem cells leads to cancer in female mice with 100% penetrance, specifically chronic myelomonocytic leukemia, erythroleukemia and histiocytic sarcoma (Yildirim et al. 2013). This illustrates the carcinogenic potential of X-chromosome inactivation failure which, of course, would only affect females. A similar pro-carcinogenic effect has not yet been demonstrated in the lung, though the experiment is certainly doable.

Another window into the effects of X-chromosome number comes from observations of sex chromosomal aneuploidy in humans. Klinefelter syndrome, is a syndrome in which males have more than one X chromosome (generally, 47,XXY). One of the X chromosomes is randomly inactivated and presumably escape from X-chromosome inactivation can occur. Males with Klinefelter syndrome are at increased risk of lung cancer mortality (Swerdlow et al. 2005a, 2005b) which is particularly notable since they are at decreased risk for solid tumors in general (Ji et al. 2016). A cavate here is that Klinefelter syndrome patients have high estrogen levels compared to other males which could contribute to lung cancer risk. One X-chromosome gene of particular interest is GRPR. It can escape X-inactivation and its overexpression is linked to bronchial cell proliferation and the development of lung cancer. (Thomas et al. 2005; Kligerman and White 2011).

Challenging the X-chromosome number mechanism, there is also evidence that failure of X-chromosome inactivation or X-chromosome reactivation can result in females being less susceptible to some cancers than males. In males, loss of function of an X-linked tumor suppressor gene in the non-pseudoautosomal region of the X chromosome cannot be compensated by reactivation of its homolog on the inactive X chromosome since males have a single X chromosome. In females however, reactivation of the tumor suppressor gene on the
inactive X chromosome is possible and would be protective. In effect, biallelic inactivation of some X-linked tumor suppressor genes would be needed for tumorigenesis of some cancers in females, whereas only a single inactivation event would be needed in males. This is precisely what has been observed (Dunford et al. 2017). Escape from X-inactivation in this scenario would be protective against lung cancer, not a risk factor.

4.2.4 Mechanism 4. Sex Differences in Immune Function (and Relationship to Radiogenic Lung Cancers)

Sexual differences in immune system response are well documented and are known to influence manifestation, symptomology and clinical course of many diseases. In general, females exhibit higher rates of autoimmune diseases such as lupus, multiple sclerosis, and rheumatoid arthritis, while males have greater susceptibility to, and exhibit greater severity to diseases caused by infectious agents such as bacteria and viruses. The higher mortality of males observed in the current coronavirus disease 2019 pandemic is a prime example of this difference (Takahashi and Iwasaki 2021). These distinctions are not fully understood but may be related to the stronger cellular and humoral immune responses to antigenic stimulation observed in females compared to males, which are advantageous for fighting acute infectious agents but may also contribute to greater likelihood of developing diseases associated with aberrant immune responses and chronic inflammation (Kennedy et al. 2014; Klein and Flanagan 2016).

Sex differences in immune function are thought to be mediated at both the intrinsic, genetic level and through sex hormone action, as evidenced by alterations that occur both dependent and independent of an individual’s age and reproductive status (Brown and Su 2019). An example of this is the earlier occurrence of asthma in young males, a trend that switches to a higher incidence in females post-puberty, suggesting the influence of sex hormones in the disease process (González-Arenas and Agramonte-Hevia 2012; Townsend et al. 2012, Shah and Newcomb 2018). In contrast, the greater susceptibility of males to infection agents is present in early life and through adulthood and thus appears to be independent of hormone action. Interestingly, there is evidence that many genes involved in regulation of innate immunity are X-
chromosome linked, which could lead to greater diversity in immune responses of females (Fish, 2008; Spolarics et al. 2017; Fang et al. 2019).

It is established that the immune system plays a central role in cancer development and progression through innate and adaptive immune processes in the tumor microenvironment that modulate inflammation and anti-tumor immunity, and shape tumor development (Gonzalez et al. 2018; Rubin et al. 2020). As such, the ability to evade immune destruction is recognized as one of the hallmarks of cancer, while tumor promoting inflammation is an enabling characteristic that modifies multiple cancer development processes (Hanahan and Weinberg 2011). Sex differences in these immune responses have been noted in both chronic inflammatory and in cytotoxic innate and adaptive immune processes that participate in host anti-tumor defense (Jaillon et al. 2019; Klein and Morgan 2020). These differences may contribute to sex-dependent variation in cancer rates and the observed sex difference in response to therapeutic interventions. (Fish 2008; Pennell et al. 2012; Capone et al. 2018; Özdemir and Dotto 2019).

For example, investigations evaluating expression datasets from NSCLCs show enrichment in gene sets related to immune processes in tumors derived from females. A comprehensive study by Ye et al. (2020) focused specifically on this issue using molecular profiling data from immunotherapy clinical trials along with evaluation of multiple immune features from The Cancer Genome Atlas (NCI 2021) and independent patient datasets. Varying patterns of sex-based differences in patient response to therapy were observed based on tumor type. Female NSCLC patients exhibited longer overall survival and higher response rate to immune checkpoint therapies (Miao et al. 2018; Ye et al. 2020). Other investigations evaluating expression datasets from NSCLCs show enrichment in gene sets related to immune processes in tumors derived from females, which may play a role in clinical differences between males and females (Araujo et al. 2016; Pérez-Díez et al. 2021).

Finally, biological processes related to immune function are known to contribute to sex differences in incidence and morbidity of noncancer lung disease such as asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, pulmonary hypertension, and infectious disease (Townsend et al. 2012; Casimir et al. 2013). Males are more susceptible to infectious
diseases of the lung such as pneumonia; while females appear to be at greater risk of diseases associated with detrimental, chronic inflammation such as chronic obstructive pulmonary disease and asthma (Shim et al. 2013; Fuentes and Silveyra 2018; Yung et al. 2018). Similar to lung cancer, the incidence of chronic obstructive pulmonary disease has dramatically increased in females and is frequently associated with smoking (Houghton 2013; Stapelfeld et al. 2020). Similar immune function related processes may have a role in the observed sex differences in lung cancer, although this is speculative.

4.3 Conclusion

There are several tumorigenic mechanisms that have the potential to place females at increased risk for radiation-induced lung cancer. These mechanisms are described in depth in Section 4.2. However, the available evidence from radiation biology studies is not sufficient to make a determination on whether females are at greater risk.

4.4 Research Areas to Assess Potential Differences in Radiation-Related Lung Cancer Between Males and Females

Desirable areas of research to examine biological factors that might lead to a greater understanding of potential differences in radiation-induced lung cancer between females and males are listed below:

- Undertake studies on sex differences in radiation injury and response. Studies should be designed to develop an adequate understanding of the effects of radiation exposure (including radiation quality effects) on reproductive status and related endocrine function. Studies should also evaluate radiation effects on sex differences in immunity and the possible role of sex hormones in shaping the tissue microenvironment, and how this may influence radiation cancer initiation and progression in a sex-dependent manner.
- Locate and procure archival lung tumor tissue and normal tissue from irradiated humans and animals. Use these tissues for molecular and histological assays to detect sex
differences. NCRP Report No. 186 (NCRP 2020b) contains information on tissue repositories.

- Implement tissue-sharing arrangements with research teams outside of NASA studying irradiated non-human primates with the aim of obtaining lung tissues from irradiated and unirradiated male and female non-human primates used in these studies. These tissues can be assayed using a variety of methodologies to detect sex differences in radiation injury and response to that injury that may be relevant to humans. Though many non-human primate studies involve high doses and tissue harvests at very early post-irradiation timepoints, useful data on sex differences may nevertheless be obtained, and some studies are done at doses that are clearly relevant to potential space exposures.
5. Animal Experiments Relevant to Sex-Specific Differences in Lung Cancer Radiation Risk

Summary: Radiation carcinogenesis studies in rodents do not support a greater lung cancer risk for females. However, since lung tumors may be estrogen driven, so the greater radiosensitivity of the murine ovary needs to be considered when extrapolating rodent results to humans. Relative biological effectiveness (RBE) values for HZE-particle induced lung tumors have not yet been determined, but RBEs for fission neutrons in the range of 20 to >50 have been reported (Ullrich 1983; Lafuma et al. 1989). Results from low dose-rate neutron exposures suggest an inverse dose-rate effect for this tumor type.

Tables listing studies relevant to this Commentary are provided in Sections 5.1 and 5.2. Some inbred strains and non-inbred stocks of laboratory mice are susceptible to radiation-induced lung cancer, specifically pulmonary adenomas and adenocarcinomas (Section 5.1). Radiation carcinogenesis studies with mice have yielded valuable information on radiation quality effects and dose-rate effects on lung cancer incidence (Section 5.2). However, very few studies have compared susceptibilities between male and female mice in the same experiments and the tumors appear not to have been characterized in detail beyond basic histopathology.

Sequencing of a single lung tumor, to about 20x coverage, did not detect exonic mutations in Trp53, Egfr or Kras (Wang et al. 2016).

5.1 Sex Differences in Radiogenic Lung Cancer Risks in Conventional Laboratory Mice and Rats

Table 5.1 presents experimental details of animal studies with conventional laboratory mice and rats that evaluate radiogenic lung cancer.

Storer et al. (1988) irradiated both male and female C3Hf/Bd and C57BL/6Bd mice with 0, 0.5, 1.0 or 2.0 Gy absorbed doses of $^{137}$Cs gamma rays (0.4 Gy min$^{-1}$) and monitored them by tumor development. Male C3H mice were more susceptible than females at all absorbed doses, including 0 Gy. For the C57BL/6 strain, male mice had a higher risk, but only at the highest absorbed dose (2 Gy).
<table>
<thead>
<tr>
<th>Strain/Description</th>
<th>Age at First Exposure</th>
<th>Radiation Quality and Delivery</th>
<th>Total Dose</th>
<th>Period Post Exposure</th>
<th>Lung Cancer</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>C3H/Bl, C57Bl/6Bd, M and F</td>
<td>10 weeks</td>
<td>$^{137}$Cs gamma rays</td>
<td>0.4 Gy min$^{-1}$</td>
<td>0, 0.5, 1.0, 2.0 Gy</td>
<td>Lifetime</td>
<td>C3H males more susceptible than females at all doses. C57Bl/6 males at higher risk at 2 Gy.</td>
</tr>
<tr>
<td>B6CF1 (C57BL6 x BALB/c) mice, M and F</td>
<td>15 weeks</td>
<td>$^{60}$Co gamma rays, acute or fractionated (Janus archives)</td>
<td>Single 20 min, 1 exposure per week x 24 weeks, 1 exposure per week x 60 weeks, (10 - 378 mGy min$^{-1}$)</td>
<td>0.9 - 51 Gy</td>
<td>Lifetime</td>
<td>Janus experimental archives; two-step clonal expansion model. Females have a lower lung cancer risk. Lifetime relative risk for acute gamma-ray exposures at 1 Gy is 1.33 (M), 1.75 (F), and is ~ half for fractionated gamma-ray exposures at doses &lt;1 Gy. The RBE for acute neutrons at low doses is ~10 and decreases with dose and fractionation.</td>
</tr>
<tr>
<td>B6CF1 mice, M and F</td>
<td>13 - 25 weeks</td>
<td>$^{60}$Co gamma rays, acute or fractionated (NURA/Janus archive)</td>
<td>10 - 378 mGy min$^{-1}$</td>
<td>4 weekly fractions x 1.5 Gy</td>
<td>450 d</td>
<td>Observed strain dependent results: M &gt; F in 8 strains; F &gt; M in 5 strains.</td>
</tr>
<tr>
<td>Recombinant congenic mice (STS/A and BALB/c founders), M and F</td>
<td>5 - 6 weeks</td>
<td>$^{60}$Co gamma rays</td>
<td>unavailable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F344/N rats, M and F</td>
<td>12 weeks</td>
<td>Inhaled $^{14}$C02 aerosols (beta particle-emitting)</td>
<td>initial dose-rate variable</td>
<td>1.25 - 50 Gy</td>
<td>up to 900 d</td>
<td>Incidence of lung neoplasms increased linearly with increasing doses to the lungs, no difference in susceptibility between male and females.</td>
</tr>
<tr>
<td>F344/Crl rats, M and F</td>
<td>12 weeks</td>
<td>Inhaled $^{14}$C02 aerosols (beta particle-emitting)</td>
<td>single or bimonthly for 1 y</td>
<td>single</td>
<td>0.26 - --50 Gy, repeated 2.1 - 250 Gy</td>
<td>Lifetime</td>
</tr>
<tr>
<td>F344 rats, M and F</td>
<td>12 weeks</td>
<td>x rays (280 kV), whole body and thoracic</td>
<td>0.22 Gy min$^{-1}$, single (whole body) or daily fractions (thoracic and whole body)</td>
<td>whole body</td>
<td>5.76 Gy, thoracic 3.46 - 38.4 Gy</td>
<td>Lifetime</td>
</tr>
<tr>
<td>RFM and BALB/c mice, F after ovariectomy at 90 d</td>
<td>10 weeks</td>
<td>$^{137}$Cs gamma rays</td>
<td>0.4 Gy min$^{-1}$</td>
<td>0, 0.5, 2 Gy intact, 0.5, 1, 2, 4 Gy ovariectomized</td>
<td>Lifetime</td>
<td>No major differences between intact and ovariectomized mice in lung tumors.</td>
</tr>
</tbody>
</table>

* NURA (Northwestern University Radiation Tissue Archive).
Szymanska et al. (1999) monitored lung cancer induction in male and female mice from 20 recombinant congenic strains derived from the BALB/c and STS/A founder strains and from the BALB/c parental strain. The mice were exposed to four weekly fractions of 1.5 Gy absorbed dose from $^{137}$Cs gamma rays and monitored to 450 d of age. The study involved an average of 39 mice per strain (range 17 to 47 mice), and data on spontaneous lung tumors were not collected. Combining results from all of the strains, 28% of male mice and 25% of female mice developed lung tumors. Males had more lung tumors than females in 8 of the strains and females had more tumors than males in 5 of the strains.

Recently a new statistical approach was used to re-evaluate archival data from the Janus experiments, which was a series of large-scale rodent studies conducted at Argonne National Laboratory from 1972 to 1989 (Zander et al. 2020). Re-analysis of data from carefully matched control and gamma-ray irradiated animals concluded that female mice were at a higher overall risk for all causes of death, with the exception of lung tumors, while the risk for lung cancers was significantly higher for irradiated and control male animals. Similar results were found in an analysis by Heidenreich et al. (2006) using a two-step clonal expansion model.

F344/N rats exposed to beta-particle emitting $^{144}$CeO$_2$ aerosols developed pulmonary tumors histologically characterized as adenomas, adenocarcinomas, adenosquamous cell carcinomas, and squamous cell carcinomas. No difference in susceptibility was observed between male and female rats (Hahn and Lundgren 1992; Lundgren et al. 1996). Similarly, no apparent sex differences were observed in studies of F344/N rats exposed to whole-body or thoracic x rays at higher absorbed doses Hahn et al. 2010).

It should be noted that radiation leads to ovarian failure at lower doses in mice than in humans. If estrogen enhances radiation induction of lung cancer, ovarian failure with its associated reduction in estrogen production could be protective. Thus, if an increased lung cancer risk for females compared to males is due to higher estrogen levels, this difference would be more pronounced in irradiated humans than irradiated mice since estrogen levels are reduced at lower doses in mice than humans. As mentioned in section 4.2.1.3, a study by Storer et al.
(1982) using RFM and BALB/c mice showed no sparing effect of ovariectomy on lung tumor formation, either spontaneous or radiation induced, although the overall levels of radiation-induced lung tumors were low.

5.2 Radiation Quality and Dose-Rate Effects

Table 5.2 presents experimental details of animal studies evaluating radiation quality and dose-rate effects on radiogenic lung cancer.

Coggle (1988) irradiated SAS/4 mice to the thorax only with 200 kV (peak tube voltage) x rays (0.6 Gy min\(^{-1}\)) or 7.5 MeV neutrons (1.06 Gy min\(^{-1}\)). SAS/4 mice are an outbred stock with a high background incidence of pulmonary adenoma and adenocarcinoma. Unirradiated female mice had significantly fewer tumors than males. Male mice were at greater risk following irradiation, though the neutron RBE values for 7.5 MeV neutrons calculated from the linear fits of the low-dose regions of the dose responses were 7.4 for female and 4.5 for male SAS/4 mice. Other neutron RBES for radiogenic lung cancers were 18.5 measured in BALB/c female mice with fission neutrons compared to \(^{137}\)Cs gamma rays (Ullrich 1983), and in excess of 50 for lung tumors in male Sprague Dawley rats irradiated with fission neutrons compared to \(^{60}\)Co gamma rays (Lafuma et al. 1989).

Wang et al. (2015) studied radiation quality and fractionation effects on lung cancer prevalence 1.5 y post-exposure in C57BL/6 mice irradiated with 320 kV x rays, \(^{16}\)O ions (600 MeV n\(^{-1}\))\(^{17}\), \(^{28}\)Si ions (300 MeV n\(^{-1}\)), or \(^{56}\)Fe ions (600 MeV n\(^{-1}\)). The absorbed dose was 1 Gy delivered either as an acute exposure or as five 0.2 Gy fractions at 24 h intervals. No lung cancers were observed in 40 unirradiated mice and only one lung cancer was detected in the x-ray irradiated mice. Lung tumors did develop in the ion-irradiated mice (8.3 % to 10 %), but the group sizes were not large enough to detect sex effects or fractionation effects.

\(^{17}\)MeV n\(^{-1}\) is megaelectron volt per nucleon.
<table>
<thead>
<tr>
<th>Strain</th>
<th>Age at First Exposure</th>
<th>Radiation Quality and Delivery</th>
<th>Dose Rate</th>
<th>Total Dose</th>
<th>Period Post Exposure</th>
<th>Lung Cancer</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAS/4 outbred mice, M and F</td>
<td>12 weeks thoracic</td>
<td>x rays 200 kV x rays, 7.5 MeV fast neutrons</td>
<td>x rays 0.6 Gy min⁻¹; neutrons 1.06 Gy min⁻¹</td>
<td>x rays 0.25 - 7.5 Gy, neutrons 0.1 - 4.0 Gy</td>
<td>3, 6, 12, 18, 24 months</td>
<td>Females had fewer tumors than males at 0 Gy. Males at greater risk after exposure, though the neutron RBE was higher in females. Neutron RBE of 7.4 ± 2.3 female, 4.5 ± 1.8 males.</td>
<td>Coggle 1988</td>
</tr>
<tr>
<td>Sprague-Dawley rats, M only</td>
<td>3 months radon inhalation, fission neutrons (Nereid reactor), ⁶⁰Co gamma rays</td>
<td>radon 2x weekly 1 h for up to ~6 months, neutron 20-22 h, ⁶⁰Co gamma rays 14 h</td>
<td>radon daughters 25, 50 working level months, neutrons 0.012 - 0.49 Gy, gamma rays 1, 3 Gy</td>
<td>Lifetime</td>
<td>Neutron RBE in excess of 50 at doses of a few cGy, RBE of radon daughters ~4 to 8.</td>
<td>Lafuma et al. 1989</td>
<td></td>
</tr>
<tr>
<td>Balb/c mice, F only</td>
<td>12 weeks ¹³⁷Cs gamma rays, fission neutrons (Health Physics Research Reactor, ORNL)</td>
<td>¹³⁷Cs gamma rays 40 cGy min⁻¹; neutrons 5-25 cGy min⁻¹</td>
<td>gamma rays 10 -200 cGy; neutrons 2.5 - 200 cGy</td>
<td>Lifetime</td>
<td>Neutron RBE estimates of 18.5 for lung tumors.</td>
<td>Ullrich 1983</td>
<td></td>
</tr>
<tr>
<td>C57BL/6 mice, M and F</td>
<td>6 weeks ³²⁰kV x ray, ¹⁴O 600 MeV n⁻¹, ⁵⁶Ni 300 MeV n⁻¹, ⁶⁰Fe 600 MeV n⁻¹</td>
<td>1 Gy single dose or (0.2 Gy x 5) at 24 h intervals</td>
<td>1 Gy</td>
<td>1.5 y</td>
<td>No lung cancers in controls, one lung cancer in x-ray irradiated, more in ion irradiated. No sex differences or fractionation effects.</td>
<td>Wang et al. 2015</td>
<td></td>
</tr>
<tr>
<td>129S2 KruzLA1 mice, M and F</td>
<td>5 - 15 weeks ⁵⁶Fe ions 1 GeV n⁻¹</td>
<td>x rays 0.14 Gy min⁻¹, ⁵⁶Fe ions 0.2 Gy min⁻¹</td>
<td>x rays 1, 2 Gy, ⁵⁶Fe ions 0.1, 0.2, 0.5, 1 Gy</td>
<td>Lifetime</td>
<td>No consistent radiation quality or fractionation effect, no sex effect on progression noted.</td>
<td>Delgado et al. 2014</td>
<td></td>
</tr>
<tr>
<td>129S2 KruzLA1 mice, M and F</td>
<td>8 - 15 weeks protons 50 MeV n⁻¹ or 150 MeV n⁻¹, x rays (250 kV)</td>
<td>protons 20 cGy min⁻¹, x rays 20 cGy min⁻¹</td>
<td>2 Gy</td>
<td>Lifetime</td>
<td>Protons more effective than x rays in enhancing progression, no sex effects reported.</td>
<td>Luitel et al. 2018</td>
<td></td>
</tr>
<tr>
<td>129S2 KruzLA1 mice, M and F</td>
<td>8 - 12 weeks protons 120 MeV n⁻¹, helium 250 MeV n⁻¹, ⁵⁶Ni ions 300 MeV n⁻¹</td>
<td>0.5 cGy min⁻¹</td>
<td>30 cGy</td>
<td>1 y</td>
<td>Order of ion delivery effected tumor progression, no sex effects reported.</td>
<td>Luitel et al. 2020</td>
<td></td>
</tr>
<tr>
<td>RFM and BALB/c mice, F only</td>
<td>10 weeks ¹⁷⁷Cs gamma rays</td>
<td>high dose rate 0.45 Gy min⁻¹, low dose rate 0.083 Gy day⁻¹</td>
<td>0, 0.5, 2 Gy</td>
<td>Lifetime</td>
<td>Reduced effectiveness for tumorigenesis at lower dose rate.</td>
<td>Ullrich and Storer 1979</td>
<td></td>
</tr>
<tr>
<td>SAS/4 mice, F only</td>
<td>No entry ⁶⁰Co gamma rays</td>
<td>high dose rate 1.0 Gy min⁻¹, low dose rate 0.1 Gy h⁻¹</td>
<td>0 - 4 Gy</td>
<td>No entry</td>
<td>3 - 4-fold reduction in effectiveness for lung tumor induction at low dose rate.</td>
<td>Coggle 1991</td>
<td></td>
</tr>
<tr>
<td>Study</td>
<td>Species</td>
<td>Exposure Details</td>
<td>Radiation Type</td>
<td>Dose Details</td>
<td>Effect</td>
<td>Reference</td>
<td></td>
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<tr>
<td>Ullrich 1984</td>
<td>BALB/c mice, F only</td>
<td>12 weeks</td>
<td>acute, fractionated fission neutrons (Health Physics Research Reactor, ORNL), chronic neutrons $^{255}$Cf</td>
<td>high dose rate (1-25 rad min$^{-1}$) single or split 24 h or 30 d interval, chronic 0.1 Gy d$^{-1}$ (20 h) and 0.01 Gy d$^{-1}$ (20 h)</td>
<td>reactor neutrons, 0 to 0.5 Gy $^{252}$Cf 0 to 0.4 Gy</td>
<td>Enhanced tumor formation at low dose rate (inverse dose-rate effect) or with fractionation at higher doses, no dose-rate or fractionation effect in the range 0-20 cGy.</td>
<td></td>
</tr>
<tr>
<td>Ullrich et al. 1987</td>
<td>BALB/c mice, F only</td>
<td>12 weeks</td>
<td>$^{137}$Cs gamma rays, high dose rate single and fractionation over 2 to 30 d, chronic low dose rate 24 d</td>
<td>high dose rate 0.35 Gy min$^{-1}$, low dose rate 0.083 Gy d$^{-1}$</td>
<td>2 Gy</td>
<td>Lifetime</td>
<td>Tumor response was dependent on dose per fraction. Acute daily fractions of 0.1 Gy were similar to low dose-rate exposure.</td>
</tr>
<tr>
<td>Grahn et al. 1992</td>
<td>B6CF1 mice, M and F</td>
<td>16 weeks</td>
<td>single, 24 or 60 weekly doses of fission neutrons (Janus reactor) or $^{60}$Co gamma rays, highly protracted gamma rays (M only)</td>
<td>10 - 378 mGy min$^{-1}$</td>
<td>gamma rays 0 - 25 Gy, neutrons 0 - 2.4 Gy</td>
<td>Lifetime</td>
<td>Males show higher rates throughout life for both lung and liver tumors. Prevalence of lung tumors greater in irradiated mice depending on sex and radiation quality. Inverse dose-rate effect.</td>
</tr>
<tr>
<td>Zander et al. 2021</td>
<td>B6CF1 mice, M and F</td>
<td>16 weeks</td>
<td>single, 24 or 60 weekly doses of fission neutrons (Janus reactor)</td>
<td>10 - 378 mGy min$^{-1}$</td>
<td>neutrons 0.94 - 301 cGy</td>
<td>Lifetime</td>
<td>Re-evaluation of Janus experimental archives. Fractionation was protective against tumor deaths in mice exposed either to neutrons or gamma rays, fractionation was not protective for lung tumors in either case$^6$. Females had lower incidence of lung tumors.</td>
</tr>
</tbody>
</table>
Delgado et al. (2014) irradiated male and female Kras\textsuperscript{G12D} mice with various absorbed doses and fractionation schedules of 250 kV x rays or \textsuperscript{56}Fe ions (1 GeV n\textsuperscript{-1})\textsuperscript{18}. This engineered strain develops lung adenomas as a result of the spontaneous activation of a genetically-engineered latent \textit{Kras} G12D allele. The adenomas will progress to invasive carcinomas in \approx18\% of the mice. All fractionated schedules, whether x ray or \textsuperscript{56}Fe ions, increased the rate of invasive carcinomas relative to unirradiated controls, although not always with statistical significance when adjusted for age, while the consequences of single doses of either x rays or \textsuperscript{56}Fe ions are not consistent. A gene signature generated by transcriptome analysis of those tumors from fractionated exposures was capable of risk stratifying human lung and breast adenocarcinoma patients but not patients with squamous cell carcinomas. These data suggest that fractionated radiation exposures, including those of heavy ions, are highly effective at promotion and progression of lung cancer. Sex effects on progression were not noted.

Using the same model, protons were found to be more effective than x rays in enhancing progression (Luitel et al. 2018). A single 0.3 Gy total absorbed dose delivered by sequential multiple beams (120 MeV n\textsuperscript{-1} protons, 250 MeV n\textsuperscript{-1} helium ions and 300 MeV n\textsuperscript{-1} silicon ions) was also tested. Without dose-response data or gamma-ray exposed controls, an RBE value could not be established. The experiment was designed to detect an effect of the order in which the ions were delivered. Curiously, there was an increase in adenomas with atypia and adenocarcinomas over unirradiated controls if protons were delivered first, but not if silicon ions were delivered first (Luitel et al. 2020).

Dose-rate effects on lung tumorigenesis have been studied using BALB/c mice and B6CF1 hybrids, (but no study has included both sexes). Fractionated or chronic low-LET exposure induced fewer lung tumors than acute exposure in BALB/c and SAS/4 female mice (Ullrich and Storer, 1979; Ullrich et al. 1987; Coggle 1991; Fry 1996; NA/NRC 2006). However, chronic exposure to fission spectrum neutrons at an absorbed dose rate of 10 mGy d\textsuperscript{-1} resulted in more lung tumors at a unit absorbed dose than acute neutron exposure in female BALB/c mice, the inverse dose-rate effect (Ullrich 1984). A similar inverse dose-rate effect was

\textsuperscript{18} GeV n\textsuperscript{-1} is gigaelectron volt per nucleon.
obtained by spreading the absorbed dose over 24 or 60 weekly fractions in neutron-irradiated B6CF1 mice (Grahn et al. 1992); however, a subsequent study of incidence of lung cancer as a cause-specific hazard using the same dataset did not support this notion (Zander et al. 2021). In that study the interaction term between fractionation and total dose was not significant ($p = 0.73$) for lung tumors.

### 5.3 Conclusion

Currently available mouse models do not recapitulate the sex difference in radiogenic lung cancer risk observed in human epidemiologic studies, possibly because of the greater radiosensitivity of the murine ovary. Consequently, currently available data from murine studies cannot be used to make a determination on whether females are at greater risk of radiation-induced lung cancer than males.

### 5.4 Research Areas to Assess Potential Differences in Radiation-Related Lung Cancer Between Males and Females

Data from rodent radiation carcinogenesis studies are used to set parameters for radiation quality and dose-rate effects in the NASA space radiation cancer risk model (Cucinotta et al. 2013). However, data from current rodent models are not useful for quantifying sex differences in lung cancer risks because they do not recapitulate the sex difference in radiogenic lung cancer risk observed in human epidemiologic studies. The development of new rodent models that replicate the sex differences in humans is needed to accomplish the following:

- Confirm that the risk difference detected in epidemiologic studies is real. If a model that reproduces greater risk in females can be created by manipulating known biological differences between human males and females in mice, it will increase confidence in and further validate the use of the epidemiologic data.
- Identify the mechanism that underlies sex difference in risk. If, for example, manipulating estrogen levels or EGFR signaling in mice places females at greater risk of
radiogenic lung cancer, that finding would support a similar role for those factors in human sex-dependent risks.

The identification of the relevant mechanism is of import because it can be incorporated into a biologically based model that enhances or supplants the current risk model. Furthermore, knowledge of the mechanism enables the rational development of countermeasures designed to reduce the greater risk for females or even reduce risk for both sexes. Finally, the model that is developed can be used to test the efficacy of candidate countermeasures.

The development of rodent models should not be restricted to specific experimental systems (e.g., inbred or genetically-modified mice); multiple complimentary models should be employed. Of particular interest would be models in which radiation-induced lung cancers express estrogen receptors, models in which reproductive hormone levels can be manipulated over protracted periods of time, and models in which carcinogenesis can be directed down specific pathways by a range of driver mutations, particularly those most likely to be associated with nonsmoking lung cancers [e.g., EGFR, ALK].

It would also be desirable to undertake research involving human lung tissue or engineered human lung tissue irradiated ex vivo or as transplants in immunosuppressed rodents or rodents with “humanized” immune systems. These tissues can be assayed for changes in transcriptional profiles or for fusion genes related to carcinogenesis. The findings would be relevant to sex differences in risk because some of the transcriptional or mutational changes that will potentially be found occur in tumors that arise predominantly in females, thus pointing to an increased risk of radiogenic lung cancer in females and highlighting the underlying mechanism behind it. Note that conventional ex vivo studies will not detect sex differences that only occur in an intact organism, but strategies such as hormonal supplementation could be employed to overcome this limitation and even narrow down a mechanistic underpinning to a sex difference.

6.1 Introduction

Section 6 presents and reviews NASA’s approach for projecting radiogenic cancer risks to astronauts, with a focus on lung cancer. Other organizations such as NA/NAS (2006), UNSCEAR (2008), ICRP (2007) and EPA (2011) have used the same well-established general approach for projecting radiogenic cancer risk to large (often diverse) target populations (e.g., U.S. population, and the mixed European, U.S. and Asian population). The approach relies on:

- radiation risk models derived from data from the LSS of Japanese atomic bomb survivors;
- risk transport assumptions on how radiogenic risks observed in the LSS relate to radiogenic risks in the target population; and
- assumptions about how risks depend on dose rate and type of radiation.

Two major issues that set apart the problem of projecting risks for astronauts are:

1. Most astronauts are generally in excellent health and do not smoke.
2. The problem of assessing RBE for the types of radiation exposure associated with space travel.

Section 6.2 outlines the NASA approach for projecting radiogenic cancer risks to astronauts. Section 6.3 provides a brief discussion of the problem of risk transport. Sections 6.4 through 6.6 then describe the specific risk models and data sources (e.g., for baseline cancer rates) that underlie NASA’s risk projections. Section 6.7 evaluates the appropriateness of NASA’s method for projecting risks to a nonsmoking population, and Sections 6.8 and 6.9 provide a very brief description of NASA’s approach for accounting for radiation quality. Finally, Section 6.10 discusses NASA’s treatment of uncertainties associated with their risk projections.
6.2 NASA Lifetime Risk Projection Model for Solid Cancer

Lifetime risk projections are computed by applying sex \((s)\), age-at-exposure \((e)\), and attained-age \((a)\) dependent estimates of the cause-specific radiation-associated excess cancer rates \([\overline{EAR}_c(s, e, a)]\) derived from a source population to cause-specific rates in the target population of interest. The cause-specific excess rates\(^{19}\) used for NASA’s lifetime risk estimates are based on risk models fit to the LSS cancer incidence \((I)\) data described in Preston et al. (2007). The target population was U.S. nonsmokers. The \(\overline{EAR}_c\) estimates used by NASA were computed as a weighted average of the LSS excess relative risk (ERR) estimate times the cause-specific rate in the target population (relative risk transport) and an excess absolute risk (EAR) estimate for the LSS population (absolute rate transport) with an adjustment for the dose and dose-rate effectiveness factor \((DDREF)\). This can be written as:

\[
\overline{EAR}_c^{(i)}(D_T, s, e, a) = \frac{1}{DDREF} \left[ v_c FERR_c(D_T, s, e, a) \lambda^{(i)}_{i0}(s, a) + (1 - v_c) EAR_c^{(i)}(D_T, s, e, a) \right] \quad (6.1)
\]

where:

- \(ERR_c^{(i)}(D_T, s, e, a)\) is the estimated cause-specific ERR for a target-tissue dose of \(D_T\) from the LSS incidence data.
- \(EAR_c^{(i)}(D_T, s, e, a)\) is the estimated cause-specific EAR from the LSS data.
- \(\lambda^{(i)}_{i0}(s, a)\) is the sex- and age-specific incidence \((I)\) rate for this cause in the target population \((0)\) (e.g., U.S. never-smokers).
- \(v_c\) is the cause-specific weight assigned to relative risk transport.

To estimate excess cancer mortality, a similar approach is often used. For the NA/NRC (2006) and UNSCEAR (2008) reports, site-specific cancer ERR models derived from LSS incidence data are used (for solid cancers), but they are applied to baseline cancer mortality data.

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\(^{19}\)Excess rate refers to the rate of cancer incidence or mortality in an exposed population minus the corresponding rate in an unexposed population, for the particular model conditions being discussed. In this Commentary, the focus is on the excess rate for lung cancer.
The EARs that had been fit to LSS incidence data are multiplied by the age-specific ratio of baseline incidence \( I \) to mortality \( M \) rates:

\[
\overline{\text{EAR}}_c^{(M)}(D_T, s, e, a) = \frac{1}{\text{DDREF}} \left[ v_c \overline{\text{ERR}}_c^{(I)}(D_T, s, e, a) \lambda_c^{(M)}(s, a) + \left(1 - v_c \right) \frac{\lambda_c^{(M)}(s, a)}{\lambda_c^{(I)}(s, a)} \overline{\text{EAR}}_c^{(M)}(D_T, s, e, a) \right] \tag{6.2}
\]

The lifetime risk of exposure-induced cancer (incidence) (REIC) for cause \( c \) is:

\[
\overline{\text{REIC}}_c(D_T, s, e) = \frac{1}{S'(e)} \int_0^{\infty} \overline{\text{EAR}}_c^{(I)}(D_T(a), s, e, a) S'(D_T, s, a) \, da \tag{6.3}
\]

where:

\[
S'(D_T, s, a) \text{ denotes the probability that an exposed person survives and is cancer-free to age } a.
\]

A similar formula is used to calculate risk of exposure-induced death (REID).

### 6.3 Risk Transport

One source of uncertainty, particularly for cancer sites (e.g., stomach, liver and prostate cancers) for which baseline rates differ greatly in a Japanese population exposed in 1945 versus the present-day U.S. population regards the assigned weights \( (v_c) \) for the ERR-based projections. This relates to the problem of risk transport (i.e., how the estimated risks for the Japanese atomic bomb survivor cohort are to be used to estimate risks for another population for which baseline cancer risks differ). The underlying assumption for using an ERR-based model derived from the LSS to estimate radiogenic risks in the United States is that ERR estimates derived from the LSS data are directly applicable to U.S. baseline rates. For EAR-based projections it is assumed that EAR estimates from the LSS are directly applicable. When, as in the case of lung cancer, the U.S. baseline rates differ from those for Japan, lifetime risk estimates based on ERR and EAR transport will differ. The REIC and REID estimates for a given target population can differ markedly when the baseline rates in the target population differ from those in the population on which the ERR or EAR estimates were based.
Information on how radiogenic risks differ between populations is limited, and the choice of weights assigned to the competing (ERR versus EAR) risk-model estimates clearly involves subjective judgment (NA/NRC 2006). NASA proposes to use a weight of 0.5 for lung cancer. This differs from the weight for lung cancer adopted by NA/NRC (2006) and ICRP (2007) of 0.3.

6.4 ERR and EAR Models

Another consideration is the parametric form of the tissue-specific ERR and EAR models. In NA/NRC (2006) and for the most recent ICRP (2007) risk models, the models for ERR for most solid cancer sites are of the following form:

\[ ERR(D_T, s, e, a) \text{ or } EAR(D_T, s, e, a) = \beta_s D_T \exp(\gamma e^*) \left( \frac{a}{60} \right)^\eta \]  

(6.4)

where:

- \( \beta_s \) is the sex-dependent slope of the linear dose response.
- \( e^* \) represents a function of age-at-exposure (e) [e.g., in NA/NRC (2006)]; \( e^* = \frac{\min(e,30)-30}{10} \)
- \( \gamma \) is a parameter which governs how steeply ERR or EAR fall with age-at-exposure. For NA/NRC (2006) models \( \gamma = -0.3 \) for cancers of the lung and seven other specified sites. This indicates that excess rates decrease by \( \sim 25\% \) for each decade increase in age-at-exposure up to age 30 y.
- \( \eta \) is a parameter which governs how steeply ERR or EAR changes with attained age (a). In both NA/NRC (2006) and the most recent ICRP (2007) models, ERR decreases with attained age whereas EAR increases with attained age (i.e., excess rates increase with attained age but not as steeply as baseline rates).

For the models recommended by NA/NRC (2006) and ICRP (2007), the default assumption is that the parameter values \((\gamma, \eta)\) associated with age-at-exposure and attained age are identical for solid cancer sites. Separate estimates for these parameters were obtained only for cancer sites for which there was a statistically significant difference in fitted values.
The risk models recommended by UNSCEAR (2008) differed in that many of them include a term for modification of the dose response by time-since-exposure. As illustrated in Table 6.1, terms included in the risk models depended to a much greater extent on cancer type than the site-specific models recommended by NA/NRC (2006). For cancer sites other than lung cancer, NASA proposes to use the same risk models as those recommended by UNSCEAR (2008), noting that for individual sites, the UNSCEAR (2008) models tend to provide a better fit to the LSS data. However, the difference in the parameters and their values for many of the cancers introduces an added complexity and raises questions as to how these differences in the types of risk models (e.g., models which include a term for age-at-exposure versus those which do not) should properly be interpreted.

In fitting models to the LSS data, there is a tension between ensuring that results do not depend on unrealistic assumptions (e.g., age and temporal patterns are the same for all solid cancers) and unrealistic expectations (e.g., data is sufficient to reliably estimate how an excess prostate cancer risk depends on age-at-exposure). ICRP (2007), NA/NRC (2006) and UNSCEAR (2008) derived linear dose-response models for solid cancer sites [with the exception of UNSCEAR (2008) for bone cancer and nonmelanoma skin cancer, for which upward curving dose responses were produced, and linear-quadratic dose-response models for leukemia]. It should be noted that UNSCEAR (2008) found that for all solid cancers combined a linear-quadratic dose-response model provided a slightly better fit than a linear model, and there is still considerable uncertainty concerning the shape of the dose response for solid cancers. A more recent analysis (Grant et al. 2017) found some indication for all solid cancers of a linear-quadratic dose response for males but not for females; for lung cancer the dose response appears to be linear for both males and females. Most noteworthy, a recent analysis of LSS mortality (Little et al. 2020) suggested a pronounced upward curvature in the dose response for lung cancer.
<table>
<thead>
<tr>
<th>Cancer</th>
<th>Dose Response</th>
<th>Effect Modifiers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stomach</td>
<td>Linear</td>
<td>Attained age</td>
</tr>
<tr>
<td>Colon</td>
<td>Linear</td>
<td>ERR: attained age</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EAR: time-since-exposure</td>
</tr>
<tr>
<td>Liver</td>
<td>Linear</td>
<td>ERR: none</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EAR: attained age</td>
</tr>
<tr>
<td>Lung</td>
<td>Linear</td>
<td>ERR: sex</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EAR: sex, attained age</td>
</tr>
<tr>
<td>Female breast</td>
<td>Linear</td>
<td>ERR: attained age</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EAR: time-since-exposure</td>
</tr>
<tr>
<td>Bladder</td>
<td>Linear</td>
<td>ERR: none</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EAR: attained age</td>
</tr>
<tr>
<td>Thyroid</td>
<td>Linear</td>
<td>ERR: age-at-exposure, attained age</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EAR: sex, age-at-exposure</td>
</tr>
</tbody>
</table>
6.5 Dose and Dose Rate Effectiveness Factor

For low dose or low dose-rate exposures, a DDREF is applied to the slope parameter in the ICRP (2007) and UNSCEAR (2008) solid cancer models. In other words, the slopes derived from the LSS data for moderate to high doses received at a high dose rate are reduced when applied to circumstances of low-level exposure (i.e., the assumption is that the slope of the underlying dose response is greater at higher doses and that the slope at low doses is appropriate for low dose-rate exposures). In its proposal, NASA applies a DDREF of 1.5 to most UNSCEAR (2008) models for which, for almost all cancers other than leukemia, the fitted dose response is linear (Table 6.1). It should be noted that ICRP (2007) adopted a DDREF of 2.0 for solid cancers.

6.6 Baseline Rates

For NASA’s proposed ERR-based model projections for the general (i.e., average) U.S. population, estimates of ERR are applied to baseline cancer incidence and mortality data for U.S. populations to estimate REIC and REID [see Equation 6.3]. The baseline cancer rates were obtained via the Center for Disease Control and Prevention (CDC) database called WONDER (CDC 2020) and the National Cancer Institute (NCI) software DevCan (NIH 2020) that contains Surveillance, Epidemiology and End Results (SEER) data (NIH 2021).

Baseline lung cancer rates for never-smokers are derived from data on the baseline cancer rates for the general U.S. population; current smoker, former smoker, and never-smoker prevalence; and cancer-specific estimates of relative risk (Chappell 2015).

6.7 Risk Projections for Never-smokers

NASA calculated REIC and REID for never-smokers using a similar approach to the one used to calculate risks for the general population. For the ERR model-based projections, ERR models were applied to baseline cancer rates and survival functions derived for never-smokers. NASA then calculated a weighted average of these ERRs and EARs (the latter are the same as
for the general population) to obtain estimates of excess cancer rates (see Equations 6.1 and 6.2).

For lung cancer, an equal weight (0.5) was assigned to the ERR and EAR models. An estimate of REIC obtained is calculated via Equation 6.3. A similar equation is used for REID.

However, for lung cancer in never-smokers, NASA’s approach likely results in overestimates for both REIC and REID. This is illustrated in Table 6.2, which gives preliminary NASA excess lung cancer risk estimates [percent REID at 1 Gy (absorbed dose in the lung)] for both the general U.S. population (includes both smokers and never-smokers) and a U.S. never-smoker population. For the general population, the NASA additive (EAR) estimate for a 45 y old female was 1.3 % REID at 1 Gy; the corresponding multiplicative model (ERR) estimate was 3.5 % REID at 1 Gy.

The mixture model, based on an average of the two types of models, naturally results in an estimate (2.39 % REID at 1 Gy) about midway between the EAR- and ERR-based estimates. The mixture-model estimate represents a reasonable compromise between competing assumptions. For the EAR model, radiogenic risks in the general U.S. population are assumed to be similar to the radiogenic risk observed for Japanese atomic bomb survivors.

For the ERR model, the radiogenic risks are assumed to be (approximately) proportional to baseline lung cancer rates (for the respective populations). However, for never-smokers, the estimates given in Table 6.2 do not reflect the same logic.

The never-smoker mixture model estimates of 0.95 % REID at 1 Gy (females) and 0.45 % REID at 1 Gy (males) are roughly equal to the average of EAR model-based estimates for the general population (1.27 % REID at 1 Gy and 0.71 % REID at 1 Gy) and an ERR model-based estimate for never-smokers (0.57 % REID at 1 Gy and 0.15 % REID at 1 Gy). One of the reasons for the difference between the EAR and ERR model-based estimates is that they are estimates for two very different types of populations (the general population versus the population of never-smokers).
Table 6.2 -- Dependence of preliminary NASA projections of lung cancer mortality risks on target population and model type. a

<table>
<thead>
<tr>
<th>Model Type</th>
<th>Target Population</th>
<th>Percent REID at 1 Gy</th>
<th>Percent REID at 1 Gy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Females</td>
<td>Males</td>
</tr>
<tr>
<td>Additive (EAR)</td>
<td>General United States b</td>
<td>1.27</td>
<td>0.71</td>
</tr>
<tr>
<td>Multiplicative (ERR)</td>
<td>General United States</td>
<td>3.50</td>
<td>1.17</td>
</tr>
<tr>
<td>Mixture</td>
<td>General United States</td>
<td>2.39</td>
<td>0.94</td>
</tr>
<tr>
<td>Multiplicative (ERR)</td>
<td>U.S. never-smokers</td>
<td>0.57</td>
<td>0.15</td>
</tr>
<tr>
<td>Mixture</td>
<td>U.S. never-smokers</td>
<td>0.95</td>
<td>0.45</td>
</tr>
<tr>
<td>Generalized multiplicative</td>
<td>U.S. never-smokers</td>
<td>0.47</td>
<td>0.17</td>
</tr>
</tbody>
</table>

a Estimates (percent REID at 1 Gy) in Table 6.2 are abstracted from Cucinotta et al. (2013) and are based on models derived by UNSCEAR (2008) at age-at-exposure 45 y.

b Includes current, former, and never-smokers.
For never-smokers, a more appropriate mixture model-based estimate of the radiogenic risk in the United States would be a weighted average of:

- an estimate of the radiogenic risk (REID) for Japanese atomic bomb survivors that were never-smokers, and
- the same estimate of the radiogenic risk in the LSS multiplied by the ratio of baseline never-smoker lung cancer rates in the United States versus the corresponding baseline cancer rates for the LSS cohort. A better alternative might be to base this latter projection on an EAR model fit directly to the LSS data.

There are at least two ways to estimate risk for LSS never-smokers. One is to use estimates of ERRs from LSS data assuming a multiplicative model (i.e., that the ERRs are the same for smokers and never-smokers) and then apply these ERR estimates to baseline lung cancer rates observed among LSS never-smokers. An alternative is to use a more flexible model, such as the model fit to LSS data by Furukawa et al. (2010) for which radiation and smoking effects on the lung cancer ERR are multiplicative but with smoking intensity as a radiation-effect modifier.

Furukawa et al. (2010) found the more flexible model provided a significantly better description of how risk depends on smoking and radiation on lung cancer risk than, for example, a multiplicative model for which ERR associated with radiation is independent of smoking intensity. Results indicated that the sex-averaged ERR at 1 Gy²⁰ associated with radiation is 0.59 for never-smokers (at age-at-exposure 30 y and attained age 70 y) increases for light to moderate smokers with the number of cigarettes smoked per day until it reaches a peak value of ~2, and then steadily decreases to a value of almost 0 for very heavy smokers who smoke more than 20 cigarettes per day. Furukawa et al. (2010) also fit the simpler multiplicative model which yielded a very similar sex-averaged estimate for ERR at 1 Gy of 0.68. Section 7 provides a detailed examination of how lung cancer risk-estimate projections derived from the LSS depend on the modeling of smoking-related effect-modification. An alternative model, similar in concept

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²⁰The lung dose in the LSS is a weighted dose expressed in gray, computed as the absorbed dose from low-LET photons plus 10 times the absorbed dose from neutrons.
to the that introduced by Furukawa et al (2010), but for which EARs are directly modeled, is
found to provide a better fit to the LSS data.

6.8 Cancer Risks and Radiation Quality

Based on results given in Cucinotta et al. (2013) (see also NA/NRC 2012), the largest
quantified source of uncertainty in NASA projections is associated with the modeling of how
risk from exposure to HZE particles relates to risk from low-LET radiation. To estimate risk
associated with the variety of charged particles from galactic cosmic radiation exposure, NASA
scales sex- and age-specific risk estimates for low-LET radiation by a quality factor. Quality
factors are subjective judgments of experimental determinations of maximum RBEs determined
as the ratio of initial slopes for linear dose-response curves for HZE particles compared to
gamma rays (Cucinotta et al. 2013). In contrast to quality factors recommended in the context of
radiation protection by ICRP for terrestrial radiation, which depend on LET, the proposed NASA
quality factors depend on parameters such as $Z^{*2}/\beta^2$, where $Z^*$ is effective charge number and $\beta$
is speed relative to the speed of light. The rationale for this approach is concisely described in the
NA/NRC (2012) technical evaluation; that is, LET is a poor descriptor of track structure and
energy disposition in biomolecules. NASA did a series of Monte Carlo simulations of energy
disposition patterns from radiation tracks, including secondary electron tracks, which indicated
that $Z^{*2}/\beta^2$ is a better indicator than LET of the energy disposition in small nanometer volumes.
Furthermore, NASA identified several published studies which showed that observed biological
effects (e.g., mutations) of the same LET differ depending on the HZE particle, and that there is
a much better correspondence with $Z^{*2}/\beta^2$. Other parameters used to determine quality factor
describe characteristics of a risk cross section (e.g., how maximum values compare to that for
gamma-ray exposure).

6.9 Integrated Model

The NASA model (NA/NRC 2012; Cucinotta et al. 2013) for calculating excess cancer
rates $[\text{EAR}^{(z)}_{\text{ZE}}]$ for HZE-particle exposure divides the excess rate into both low-LET
\[
[\overline{\text{EAR}}_c^{(M)}(D_T, s, e, a)]\text{ and high-LET (HLC) components with relative proportions, } P(Z, E),
\]

which depend on particle charge \((Z)\) and energy \((E)\):

\[
\overline{\text{EAR}}_c^{(M)}(D_T, s, e, a) = [1 - P(Z, E)] \overline{\text{EAR}}_c^{(M)}(D_T, s, e, a) + P(Z, E) \text{ HLC} \quad (6.5)
\]

The low-LET component is obtained using the standard formula for low-LET radiation

given in Equation 6.2; the high-LET component depends more directly on tissue fluence,

\[
F_T(Z, E):
\]

\[
\text{HLC} = \overline{\text{EAR}}_c^{(M)}(D_T, s, e, a) \frac{\Sigma_0}{\alpha_y} F_T(Z, E) \quad (6.6)
\]

Here, \(\frac{\Sigma_0}{\alpha_y}\) is an empirically derived parameter which represents the ratio of the maximum value of the risk cross section compared to that for gamma rays. From Equations 6.2, 6.5 and 6.6, the corresponding quality factor \((QF)\) for HZE-particle exposure, obtained as the ratio of excess rates for high-LET radiation \([\overline{\text{EAR}}_c^{(M)}]\) versus low-LET radiation \([\overline{\text{EAR}}_c^{(M)}]\) is given by:

\[
QF = 1 - P(Z, E) + \frac{\Sigma_0}{\alpha_y} \frac{F_T(Z, E)}{D_T(Z, E)} \quad (6.7)
\]

6.10 NASA Treatment of Uncertainties

NASA used a Monte Carlo approach for evaluating uncertainties associated with their projections of excess risk. The general approach is based on recommendations made by NCRP (2000; 2006). Specifics\(^{21}\) of the current NASA approach regarding treatment of uncertainties are outlined here.\(^{22}\) The central estimates of REID and REIC are modified by replacing terms in the model with random variables; for most terms, the random variables are represented as products of a central estimate multiplied by an uncertainty factor with a normal or lognormal distribution.

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\(^{22}\) For the future, NASA is evaluating the use of ensemble models for treatment of uncertainties (Simonsen and Slaba 2020, 2021).
An exception is the DDREF, for which NASA used a t-distribution. Probability distributions for REID and REIC can then be obtained via sampling the random variables associated with each of these terms. For example, to calculate REIC, one needs to first calculate the tissue-specific ERRs associated with low-LET exposure. For the uncertainty analysis, NASA multiplied the central estimate of ERR derived from LSS data by uncertainty factors for: 1) sampling (or “statistical”) uncertainty for tissue-specific estimates of ERR, and 2) errors associated with Japanese atomic bomb survivor dose estimates (DS02).

Thus, in Equation 6.2, \( \text{ERR}_T(D_T, s, e, a) \) is multiplied by the product of random (uncertainty) factors, associated with statistical or sampling uncertainty \( x_{stat} \) and dosimetric errors \( x_{DS02} \). For the statistical uncertainties, the \( x_{stat} \) were assigned normal distributions with mean equal to 1 and with standard deviation \( \sigma \) dependent on cancer site (e.g., for lung cancer \( \sigma = 0.6 \)); for the LSS dosimetric uncertainties, a lognormal distribution with geometric standard deviation of 1.3 was used.

Overall, the approach used by NASA for quantifying uncertainties is reasonable. However, it is noted that:

- In the current NASA cancer risk models, the so called “tissue-specific statistical error (\( \beta \))” represents uncertainties only in the central estimate of the sex-specific main radiation risk effect of the dose response (i.e., excess risk at a unit dose). Uncertainties associated with attained age and age-at-exposure risk effect modifiers for \( \beta \) are not explicitly accounted for (Simonsen and Slaba, 2021). The uncertainty distributions and standard deviations for the distributions of \( \beta \) in the NASA cancer risk models were subjectively chosen (Cucinotta et al. 2013) to be Gaussian with a mean of 1.0 and tissue-specific standard deviations ranging from 0.2 to 1.0. These subjective choices were intended to represent the intervals for \( \beta \) collectively ascertained from the published sources from which the risk models were taken [UNSCEAR 2008 (where the uncertainties in the risk model parameters are not given); NA/NRC 2006; Preston et al. 2007; Simonsen and Slaba 2021].

---

\(^{23}\) DS02 refers to Dosimetry System 2002 (Radiation Effects Research Foundation) (Young and Kerr, 2005).
It is recommended that in the future all the major sources of uncertainty should be accounted for as far as possible in these “tissue-specific statistical errors” including the excess risk effect modifiers of age attained and age-at-exposure, and the correlations between these parameters. This can be done by taking the central estimate of excess risk at a unit dose, often given for age attained 70 y and age-at-exposure 30 y, and then for other ages in the integrals for the REID or REIC calculations. These central excess risk estimates are then recomputed using the risk effect modifiers (for age attained and age-at-exposure). The associated errors should come from a Monte Carlo simulation using the errors on the central estimate of excess risk at a unit dose, the risk effect modification of attained age and the risk effect modification of age-at-exposure, accounting for the correlations between estimates of these parameters (Hafner et al. 2021; Walsh et al. 2021).

Separate estimates of statistical uncertainties should also be provided for nonsmokers. For lung cancer and other smoking-related cancers, these uncertainties would tend to be greater.

The uncertainty factor (\(\chi_{DSS}^2\)) associated with dosimetry error is inappropriate for the purpose of this analysis. The lognormal distribution reflects uncertainty in individual dose estimates, for which the geometric standard deviation is about 1.4 (e.g., Pierce et al. 2008). The uncertainty factor that should be used should reflect effects of both random and systematic dosimetry errors on ERR and EAR estimates.

### 6.11 Summary and Conclusions

NASA’s approach for projecting radiogenic cancer risks to astronauts relies on:

- radiation risk models derived from data from the LSS of the Japanese atomic bomb survivors;
- risk transport assumptions on how radiogenic risks observed in the LSS relate to radiogenic risks in the target population; and
- assumptions about how risks depend on dose rate and type of radiation.
In broad outline, NASA first applied the risk models derived from the LSS (e.g., an ERR model to baseline rates for U.S. nonsmokers) to estimate excess cancer rates for nonsmokers for exposure to low-LET radiation. NASA then adjusted the excess cancer rates to account for radiation quality associated with exposures in space. Finally, NASA calculated lifetime probabilities based on formulas for REID, as outlined in Section 6.2.

Conclusions:

• Overall, NASA is to be commended for the methodology it developed for projecting cancer risk to astronauts.

• However, for lung cancer among never-smokers, NASA’s approach likely results in overestimates for both REIC and REID. This is because the NASA EAR model was derived from a population that included smokers.

• Overall, the NASA approach for quantifying uncertainties associated with low-LET radiation is reasonable. However, the uncertainty distributions and standard deviations for the tissue-specific and sex-specific main effect of the dose response in the NASA cancer risk models were subjectively chosen. In the future, it is suggested that these be based on Monte Carlo simulations which account for covariances in risk model parameter estimates.

• The uncertainty factor associated with dosimetry error does not reflect the effect of dosimetry error on estimates of ERR or EAR.

• NASA’s risk projections are based on a model derived from one study (i.e., the LSS). Section 7 will discuss how information may be combined for several studies with relevant information on lung cancer risks.
7. Alternative Approaches for Modeling Risks

7.1 Introduction

Section 6 outlined NASA’s current approach for estimating radiogenic lung cancer risk for the astronaut population of never-smokers. The primary goal of Section 7 is to describe and illustrate a procedure that could be used by NASA to develop sex-specific lifetime risk estimates for radiation-associated lung cancer mortality in astronauts on lengthy deep space missions. In contrast to the current NASA methodology in which lifetime risks are estimated using radiation-effect estimates derived from the Japanese atomic bomb survivors in the LSS, this section describes a Bayesian hierarchical modeling approach that makes use of results from multiple study populations to provide sex-specific lifetime risk estimates and information about the uncertainty of these estimates.

While the results presented later in this section include sex-specific lifetime risk estimates for lung cancer in an astronaut-like population of nonsmokers, the results are for illustrative purposes and are not intended to be definitive risk estimates for NASA’s use in formulating time-on-mission limits. The estimates were not based on a more comprehensive set of relevant studies that have adequate radiation-effect estimates, but the available studies used help to illustrate the proposed procedures.

As will be discussed in Section 8, this Commentary suggests that NASA researchers should reach out to those responsible for the studies to glean source-population information beyond basic model parameter estimates in order to develop lifetime risk estimates for astronauts. Prior to describing and illustrating the suggested meta-analytical method in Section 7.3, Section 7.2 presents and discusses some examples describing issues in developing source-population radiation-effect models appropriate for use in the computation and characterization of risks of radiation-associated deaths for lung cancer.
7.2 Issues in the Development of Useful Risk Models

7.2.1 ERR and EAR Models for Source-Population Radiation Effects

As indicated in Section 6, lifetime risk estimates for a target population are a function of excess rates that are estimated for some source population (or populations) and then adjusted for important risk factors (e.g., smoking), along with the relevant cause-specific and total mortality rates in the target population. Since it is generally unknown how radiation-effect estimates from one population should be applied to another population with different disease or death rates, it is common (e.g., ICRP 2007; UNSCEAR 2008; NA/NRC 2006) to consider target population excess rate estimates computed from the source-population excess risk estimates in two ways.

For what is called relative risk (RR) transport, the excess rate ($\overline{ERR}_R$) is computed as the product of the estimated age(a)-dependent, age-at-exposure(e) dependent, and sex(s)-dependent cause-specific $ERR^S$ for a source population and the target (T) population background rates ($\lambda^T_0$):

$$\overline{ERR}^R(a,s,e,x_0,z_0) = ERR^S(a,s,e,x_0) \lambda^T_0(a,s,z_0) \quad (7.1)$$

where $x_0$ represents radiation-effect modifiers and $z_0$ represents (baseline) risk factors. For absolute risk (AR) transport, the excess rate ($\overline{EAR}_A$) is computed as the estimated age(a)-dependent, age-at-exposure(e) dependent and sex(s)-dependent cause-specific $EAR^S$ from the source population:

$$\overline{EAR}^A(a,s,e,x_0,z_0) = EAR^S(a,s,e,x_0, z_0). \quad (7.2)$$

As noted elsewhere, if the cause-specific rates for the source and target populations differ, these excess rate estimates, and hence the lifetime risk estimates will depend on the cause-specific transportation weights used in lifetime risk estimation.

Within a study population, a given ERR (EAR) model has an equivalent EAR (ERR) model determined by the relationships:

$$EAR_{ERR}(a,s,e,x_0,z_0) = \lambda_0(a,s,x_0) \overline{ERR}(a,s,e) \quad (7.3)$$

and
As in the lifetime risk computations carried out in ICRP (2007), UNSCEAR (2008) and NA/NRC (2006), NASA independently developed ERR and EAR models for the relative and absolute transport computations. In principle, due to the relationships noted above, lifetime risk estimates computed using separately developed source-population ERR and EAR models should provide similar lifetime risk estimates. However, this is not necessarily the case, and one of the models may describe the data markedly better than the other.

Section 7.2.2 examines how lifetime risk estimates using separate or equivalent source-population ERR and EAR models affects lifetime risk estimates. The results presented here use smoking-adjusted low-LET ERR and EAR models of lung cancer mortality rates from recent analyses of the LSS lung cancer mortality data\(^{24}\) (Brenner et al. 2021) and the Mayak worker cohort (Stram et al. 2021) to compute lifetime risk estimates for U.S. nonsmokers. Section 7.2.3 concludes with some comments on the choice of source-population ERR and EAR models.

7.2.1.1 Lifespan Study Lung Cancer Mortality 1958-2009. Working with the Radiation Effects Research Foundation scientists responsible for a recent smoking-adjusted analysis of lung cancer mortality rates for the period from 1958 through 2009, separate ERR and EAR radiation-effect models were developed that include fully parametric models for the baseline rates and smoking effects\(^{25}\). The ERR model assumed that the joint effects of smoking and radiation were multiplicative with smoking intensity also acting as a radiation-effect modifier. In the EAR model, radiation was assumed not to be a smoking-effect modifier, while the radiation EAR was taken to depend on smoking duration, intensity, and time since quitting. The radiation-effect estimates, and the lifetime risk estimates presented here are those for nonsmokers and were computed by setting smoking duration and intensity to 0 in the fitted smoking-adjusted radiation-effect models. Since the computation of the derived ERR (EAR) models depends on the background rates, the baseline rate and radiation-effect parameters for nonsmokers are presented.


Table 7.1 presents the sex-specific model nonsmoker baseline and radiation-effect parameter estimates for ERR and EAR models fit to the LSS mortality data. In addition to the primary estimates from each model, Table 7.1 also includes an EAR estimate indirectly derived from an ERR model (attained age 70 y following exposure at age 40 y) and an ERR estimate indirectly derived from an EAR model (same ages). For males, the direct and indirect ERR and EAR estimates at age 70 y are similar. For females, the direct and indirect EAR estimates are similar, but the indirect estimate of the ERR at age 70 y (2.197) is about 70% greater than the direct estimate (1.276).

Figure 7.1 illustrates how the estimated baseline rates, ERRs, and EARs for nonsmokers vary with attained age. The radiation-effect plots include both the direct and indirect estimates of the radiation effects. The ERR and EAR model-based estimates of the nonsmoker baseline rates are similar for females at all ages. For males, the baseline rates derived from the EAR model were dramatically lower than estimates derived from the ERR model. As noted above, the EAR model-based ERR estimates for females are consistently higher than the direct ERR estimates.

Table 7.2 presents lung cancer mortality [risk of exposure-induced death (REID)] estimates for males and females following a weighted dose\(^{26}\) (lung) of 1 Gy using the LSS ERR and EAR models described above applied to U.S. nonsmoker baseline rates. The REID estimates for males are similar regardless of the transportation method (i.e., the ERR-based and EAR-based REID estimates are similar). However, for females, the EAR-based REID estimates are notably higher than the ERR-based estimates. Regardless of the source-population risk model used, the choice of transport method makes larger differences for females than males. This is a consequence of the fact that for males the estimated nonsmoker baseline rates in the LSS are closer to the U.S. nonsmoker rates used in these calculations than are those for females.

7.2.1.2 Mayak Lung Cancer Mortality 1950-2015. Analyses of Mayak lung cancer have focused exclusively on ERR models for the effects of low-LET external and high-LET internal (plutonium) doses on lung cancer risks. Working with the authors of the most recent paper (Stram et al. 2021) an EAR model fit to the data used for the analyses in that paper was developed\(^{27}\). Table 7.3 shows baseline and radiation risk estimates from models fit using both ERR-based and EAR-based models.

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\(^{26}\) As in all routine dose-response analyses in the LSS, weighted dose is defined as the gamma-ray absorbed dose plus 10 times the neutron absorbed dose, expressed in gray. LSS survivor dose estimates are also routinely adjusted for the effects of dose-measurement error.

\(^{27}\) Stram DO. 2021. Personal communication. Los Angeles, California: University of Southern California.
Table 7.1 -- *LSS 1958-2009 lung cancer mortality ERR and EAR model parameter estimates for smoking-adjusted excess rates.*

| Non-smoker Baseline \(^a\) | ERR Model | | | EAR Model | | |
|-----------------|-----------|-----------|-----------|-----------|-----------|
|                  | Male      | Female    | Male      | Female    |
| Cases per 10,000 PY at age 70 y | 4.592 | 2.676 | 3.459 | 3.76 |
| 1905 birth cohort | log(age/70) | 5.960 | 5.458 | 6.008 | 6.926 |
|                   | [log(age/70)]\(^2\) | -2.082 | 0.550 | 0.003 | 2.564 |
|                   | [log(age/70)]\(^2\) (age > 70 y) | -7.612 | 2.823 | -3.054 | -4.778 |
| (birthdate – 1905)/10 | 0.106 | 0.109 | 0.094 | 0.002 |
| Non-smoker Radiation Effect \(^b\) | | | | | |
| ERR at 1 Gy | 0.528 | 1.276 | \(0.557\)\(^d\) | 2.197\(^d\) |
| (age 70 y; exposure at age 40 y) \(^c\) | (0.226) | (0.286) | (0.162) | (0.298) |
| EAR at 1 Gy | 2.425\(^e\) | 4.414\(^e\) | 2.094 | 5.880 |
| (age 70 y; exposure at age 40 y) \(^c\) | (1.046) | (0.920) | (1.419) | (1.189) |
| log(age/70) | -2.33 | -1.026 | 2.393 | 4.513 |
| (age-at-exposure – 40)/10 | 0.111 | 0.099 | 0.002 | 0.115 |

\(^a\) Age effects in the baseline rate model were modeled using sex-specific log-linear splines in log(age) with a single knot at age 70 y. The model also included smoking effects and sex-specific birth cohort effects. The smoking-effect parameters are not shown since the interest was in the risks for nonsmokers. To reflect more recent rates, rates for the 1950 birth cohort were used. The baseline rate model includes birth cohort effects and age-at-exposure is determined by birthdate; since the intercept is given for age-at-exposure 40 y the relevant birth cohort is 1905.

\(^b\) Effect modification was modeled as a log-linear function of attained age and age-at-exposure parameterized as indicated. There were statistically significant sex differences in the age-effect modification while the age-at-exposure effect modification did not differ significantly by sex. The full model also included effect modification by smoking intensity. These effects are not shown since the primary interest was in the risks for nonsmokers.

\(^c\) Asymptotic standard errors for directly estimated dose-effect estimates are given in parentheses.

\(^d\) ERR computed from EAR model parameters as the ratio of the EAR at age 70 y for a person exposed at age 40 y born in 1905 to the EAR model baseline cases per 10,000 PY at age 70 y.

\(^e\) EAR computed from ERR model parameters as product of ERR at age 70 y for a person exposed at age 40 y born in 1905 times the ERR baseline cases per 10,000 PY at age 70 y.
Fig. 7.1. Nonsmoker baseline rate, ERR and EAR estimates for age-at-exposure 40 y based on smoking-adjusted ERR and EAR models fit to the LSS 1958 through 2009 lung cancer mortality data. Estimates for males are shown using green curves while orange curves are used for females. Estimates based on the fitted ERR model are shown as solid curves while those based on the fitted EAR model as dashed curves. The ERR and EAR estimates were computed for exposure at age 40 y.
Table 7.2 -- Estimates of the risk of exposure-induced death (REID)$^*$ for selected ages-at-exposure based on Life Span Study lung cancer mortality risk models applied to current U.S. population nonsmoker death rates.

<table>
<thead>
<tr>
<th>Age-at-Exposure (y)</th>
<th>Males</th>
<th></th>
<th>Females</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ERR-Based</td>
<td>EAR-Based</td>
<td>ERR-Based</td>
</tr>
<tr>
<td></td>
<td>RR</td>
<td>AR</td>
<td>RR</td>
<td>AR</td>
</tr>
<tr>
<td>Transport</td>
<td>0.36</td>
<td>0.39</td>
<td>0.40</td>
<td>0.46</td>
</tr>
<tr>
<td>Transport</td>
<td>0.32</td>
<td>0.34</td>
<td>0.34</td>
<td>0.42</td>
</tr>
<tr>
<td>Transport</td>
<td>0.29</td>
<td>0.28</td>
<td>0.28</td>
<td>0.37</td>
</tr>
</tbody>
</table>

* REID estimates are given in units of radiation-associated deaths per 100 people exposed to 1 Gy with a dose rate effectiveness factor of 1.5 assuming a 5 y latent period with follow-up from the age-at-exposure until age 100 y.
Table 7.3 -- Mayak worker cohort 1950-2015 lung cancer mortality ERR and EAR model

Parameter estimates for smoking-adjusted excess. Estimates were derived using both an ERR model and an EAR model.

<table>
<thead>
<tr>
<th></th>
<th>ERR</th>
<th></th>
<th>EAR</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>Cases per 10,000 PY at age 70 y</td>
<td>6.228</td>
<td>3.695</td>
<td>5.306</td>
<td>3.568</td>
</tr>
<tr>
<td>log(age/70)</td>
<td>2.509</td>
<td>2.509</td>
<td>2.567</td>
<td>2.567</td>
</tr>
<tr>
<td>[log(age/70)]²</td>
<td>-7.560</td>
<td>-7.560</td>
<td>-7.546</td>
<td>-7.546</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>ERR</th>
<th></th>
<th>EAR</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonsmoker Baseline</td>
<td></td>
<td>Nonsmoker External Radiation Effect</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
<td>Female</td>
</tr>
<tr>
<td>ERR at 1 Gy (at age 70 y)</td>
<td>0.164</td>
<td>0.550</td>
<td>0.438</td>
<td>0.659</td>
</tr>
<tr>
<td></td>
<td>(0.062)</td>
<td>(0.332)</td>
<td>(0.395)</td>
<td>(0.405)</td>
</tr>
<tr>
<td>EAR cases per 10,000 PY (at 1 Gy)</td>
<td>1.019</td>
<td>2.014</td>
<td>2.298</td>
<td>2.355</td>
</tr>
<tr>
<td></td>
<td>(1.065)</td>
<td>(1.748)</td>
<td>(1.241)</td>
<td></td>
</tr>
<tr>
<td>log(age/70)</td>
<td>--</td>
<td>--</td>
<td>1.224</td>
<td>1.718</td>
</tr>
<tr>
<td>[log(age/70)]²</td>
<td>--</td>
<td>--</td>
<td>-7.586</td>
<td>-7.130</td>
</tr>
</tbody>
</table>

a Age effects in the baseline rate model were modeled using a log-linear quadratic function of log(age) and sex-dependent intercepts (rates at age 70 y). The model also included smoking effects and plutonium effects. The smoking and plutonium dose-response parameters are not shown since the interest was in the risks for nonsmokers.
b There was no evidence of significant variation in the ERR with time or smoking. For the EAR model the effect modification by age was described using sex-dependent log-quadratic functions of log(age). The EAR model also included both smoking and plutonium dose/exposure status effect modifiers. For both the ERR and EAR models the effect modification by smoking was described using an ERR-like function that was linear in pack-years. These smoking and plutonium effects are not shown since the primary interest here concerns the external gamma-ray absorbed dose effects in the lung for nonsmokers.
c Asymptotic standard errors for directly estimated dose-effect estimates are given in parentheses.
d ERR computed from EAR model parameters as the ratio of the EAR at age 70 y for a person exposed at age 40 y born in 1905 to the EAR model baseline cases per 10,000 PY at age 70 y.
e EAR computed from ERR model parameters as product of ERR at age 70 y for a person exposed at age 40 y born in 1905 times the ERR baseline cases per 10,000 PY at age 70 y.
Figure 7.2 presents the fitted baseline rates (left panel), ERR-based model estimates (center panel), and EAR-based model estimates (right panel) for nonsmokers (parameter estimates shown in Table 7.3). As with the LSS analyses presented earlier and despite the theoretical equivalence of the excess rate estimates based on fitted ERR and EAR models, the EAR and ERR estimates for nonsmokers (which are a subset of the full population) based on the fitted models are quite different. In particular, the sex difference in excess rates is different for the ERR-based model (female greater than male). The EAR-based model also predicts slightly higher excess risks for females compared to males, particularly at later ages. After allowing for the number of parameters used in each of the models, the relative fit of the models was nearly identical.

Table 7.4 summarizes the external exposure lifetime risk estimates for the Mayak worker cohort ERR-based and EAR-based models (both direct and indirect estimates) using relative and absolute rate transport methods. The RR-transport based REID estimates are slightly larger than the AR-transport based estimates for both the ERR and EAR models. This reflects differences between the U.S. nonsmoker baseline rates and the estimated baseline rates in the Mayak worker cohort data. Also, the EAR-model based REID estimates decrease somewhat more rapidly with increasing age-at-exposure than ERR-model based estimates. Also, as suggested by the ERR- and EAR-model based EAR estimates shown in Figure 7.2, the sex differences in the REID estimates differ depending on whether one uses the ERR-model-based estimates (female lifetime risks greater than males) or EAR model-based estimates (males greater than females).

For females the ERR- and EAR-model based REID estimates are similar and the differences between the RR- and AR-based transport estimates are not large. However, for males, the EAR-model based lifetime risk estimates are more than twice those obtained using the ERR model. As with the LSS data, these results highlight the fact that despite the theoretical equivalence of ERR and EAR models in describing the excess rates, the two types of models can result in striking differences in excess risk estimates.
Fig. 7.2. Nonsmoker baseline rate, ERR and EAR estimates for age-at-exposure 40 y based on smoking-adjusted ERR and EAR models fit to the Mayak 1950 through 2015 lung cancer mortality data. Estimates for males are shown using green curves while orange curves are used for females. Estimates based on the fitted ERR model are shown as solid curves while those based on the fitted EAR model as dashed curves. The Mayak models do not include age-at-exposure effects so the ERR and EAR estimates are applicable, over an appropriate age range, for any age-at-exposure.
Table 7.4 --- *Estimates of the risk of exposure-induced death (REID)*\(^a\) for selected ages-at-exposure based on Mayak worker cohort lung cancer mortality risk models applied to current U.S. population nonsmoker death rates.

<table>
<thead>
<tr>
<th>Age-at-Exposure (y)</th>
<th>Males Risk Model</th>
<th>Females Risk Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ERR</td>
<td>EAR</td>
</tr>
<tr>
<td>Transport RR</td>
<td>Transport AR</td>
<td>Transport RR</td>
</tr>
<tr>
<td>40</td>
<td>0.12</td>
<td>0.17</td>
</tr>
<tr>
<td>50</td>
<td>0.12</td>
<td>0.16</td>
</tr>
<tr>
<td>60</td>
<td>0.11</td>
<td>0.13</td>
</tr>
</tbody>
</table>

\(^a\) REID estimates are given in units of radiation-associated deaths per 100 people exposed to 1 Gy assuming a 5 y latent period with follow-up from the age-at-exposure until age 100 y.
7.2.2 Smoking Adjustment and Lifetime Risk Estimates

Since the astronauts are physically fit and health conscious, the lifetime radiation risk estimates of primary interest are those for nonsmokers. While some of the studies, such as the LSS and Mayak worker cohort, have rather extensive and detailed information on smoking, other studies may have less extensive or even no information on smoking. In this section the LSS data are used to illustrate how lifetime risk estimates are affected if the source-population risk estimates are unadjusted for smoking or if they are adjusted using only ever-smoking and never-smoking indicators rather than more detailed information on individual smoking histories. A similar set of sensitivity analysis calculations (to evaluate the effect incomplete smoking information has on lifetime risk estimates) was made for the Mayak worker cohort data. Although the results of those calculations are not presented in this Commentary (i.e., in Section 7.2.2.2), the patterns seen in the REID estimates were qualitatively similar to those seen for the LSS.

7.2.2.1 Smoking Adjustment and Lifetime Risk Estimates. To investigate how lifetime risk estimates depend on the nature of the smoking adjustment in the Japanese atomic bomb survivor lung cancer mortality data, REID estimates were computed for the U.S. nonsmoker population for ERR and EAR models with smoking effects handled in three ways:

1. The pack-year and duration adjusted model (pack-year adjusted)
2. A model with no adjustment for smoking (unadjusted)
3. A model with adjustment for smoking using a sex-specific ever-smoker indicators (ever-smoker adjusted).

The plots in Figure 7.3 compare the fitted nonsmoker baseline rate, ERR and EAR estimates for the pack-year adjusted ERR model (solid curves) with those for an ERR model that is not adjusted for smoking (top row dashed curves) and for an ERR model adjusted using only sex-specific ever-smoking and unknown smoking indicators (bottom row dashed curves). Since most of the males and few of the females in this cohort were smokers the fitted baseline rates for the unadjusted model for males are considerably higher than those from the fully adjusted model. The unadjusted and pack-year adjusted baseline rate difference for females is considerably
Fig. 7.3. Comparison of fitted LSS nonsmoker lung cancer mortality baseline, ERR, and EAR estimates for multiplicative ERR models with baseline rates adjusted for smoking using detailed smoking history data (solid lines) to those for models without adjustment for smoking (dashed curves top row) or adjusted using only an ever-smoker indicator (dashed curves bottom row). Green curves represent the estimates for males and orange curves the estimates for females. EAR estimates were computed as the product the nonsmoker baseline rate and ERR estimates. In the middle graph of the top row (for ERR), the green solid curve (males, adjusted for smoking) and the green dashed curve (males, without adjustment for smoking) are almost identical and overlay each other.
smaller than that for males, largely because few females in this cohort smoked and female
smokers tended to smoke less than males. The differences in the sex-specific baseline rate
estimates are much less pronounced when comparing the pack-year adjusted and ever-smoker
adjusted fits, though the ever-smoker adjusted model baseline rates are noticeably greater than
those for the fully adjusted model.

Figure 7.4 presents a similar comparison of baseline rate, ERR, and EAR estimates based
on EAR models fit to the LSS data.

The ERR estimates from the unadjusted ERR model are similar to those for the pack-year
adjusted model for both males and females. However, the sex-specific EAR estimates for both
males and females derived from the unadjusted ERR estimates are much greater than those from
the fully adjusted model since the unadjusted baseline rates, especially those for males, are much
greater than those for the pack-year adjusted model. For the unadjusted EAR model both the
fitted ERR and EAR estimates are strikingly different than those from the pack-year adjusted
model. The fitted ERR and EAR estimates from the ever-smoker adjusted ERR model are like
those for the fully adjusted model. However, for the EAR model, there is a striking difference
between the pack-year adjusted and ever-smoker adjusted EAR estimates for males.

As noted earlier, the pack-year adjusted EAR model fit these data better than the
corresponding ERR model. However, for both the unadjusted and ever-smoker adjusted analyses,
the ERR models fit somewhat better than the EAR models.

Table 7.5 presents lifetime risk estimates for U.S. nonsmokers following an acute
absorbed dose in the lung of 1 Gy at age 40 y for the six models considered in this section.

7.2.2.2 Smoking Adjustment in the Mayak Worker Cohort and Lifetime Risk Estimates. As with
the LSS data, REID estimates were computed for the U.S. nonsmoker population for unadjusted,
ever-smoker adjusted, and pack-year adjusted ERR and EAR models fit to the Mayak worker
cohort lung cancer mortality data. Figures 7.5 and 7.6 compare nonsmoker baseline rate, ERR
and EAR estimates for ERR (Figure 7.5) and EAR (Figure 7.6) models. As with the LSS, most
Fig. 7.4. Comparison of fitted LSS nonsmoker lung cancer mortality baseline, ERR, and EAR estimates for multiplicative EAR models with baseline rates adjusted for smoking using detailed smoking history data (solid lines) to those for models without adjustment for smoking (dashed curves top row) or adjusted using only an ever-smoker indicator (dashed curves bottom row). Green curves represent the estimates for males and orange curves the estimates for females. ERR estimates were computed as the ratio of the fitted EAR to the nonsmoker baseline rate estimates.
### Table 7.5 -- Comparison of low-LET REID estimates (excess deaths per 100 people) for U.S. nonsmokers at 1 Gy for age 40 y based on LSS ERR and EAR models\(^a\) with different types of smoking adjustment.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Transport (^b)</th>
<th>Pack-Year Adjusted (^c)</th>
<th>No Smoking Adjustment (^d)</th>
<th>Sex-Specific Ever-Smoker Adjustment (^e)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ERR</td>
<td>EAR</td>
<td>ERR</td>
</tr>
<tr>
<td>Male</td>
<td>RR</td>
<td>0.36</td>
<td>0.40</td>
<td>0.36</td>
</tr>
<tr>
<td></td>
<td>AR</td>
<td>0.39</td>
<td>0.46</td>
<td>1.65</td>
</tr>
<tr>
<td>Female</td>
<td>RR</td>
<td>0.70</td>
<td>1.25</td>
<td>0.80</td>
</tr>
<tr>
<td></td>
<td>AR</td>
<td>1.04</td>
<td>1.60</td>
<td>1.87</td>
</tr>
</tbody>
</table>

\(^a\) The LSS ERR and EAR models were fit using estimates of weighted dose in the lung computed as the gamma-ray absorbed dose plus 10 times the neutron absorbed dose, adjusted to allow for the effects of dose uncertainty.

\(^b\) Method for using the LSS risk estimates to estimate the radiation-associated cases in the target, U.S. nonsmoker, population. For relative risk transport (RR) the LSS nonsmoker relative risk was applied to the sex- and age-specific U.S. nonsmoker risk estimates. For absolute risk transport (AR) the EAR estimate for LSS nonsmokers was applied directly to the U.S. nonsmoker rates.

\(^c\) The source-population pack-year adjusted risk models used were the ERR and EAR models fit to the LSS lung cancer mortality data for the 1958 through 2009 period. In these models the smoking effect was described as linear in pack-years with an additional effect proportional to smoking intensity (packs per day) to a power, and, for past smokers, time since. The models also included an indicator for males with unknown smoking status.

\(^d\) LSS ERR or EAR models fit without any adjustment for smoking.

\(^e\) LSS ERR or EAR models fit with the smoking effect replaced by sex-specific ever-smoker effects for males and females and an effect for males with unknown smoking status.
Fig. 7.5. Comparison of fitted Mayak worker cohort nonsmoker lung cancer mortality baseline, ERR, and EAR estimates for multiplicative ERR models with baseline rates adjusted for smoking using detailed smoking history data (solid lines) to those for models without adjustment for smoking (dashed curves top row) or adjusted using only an ever-smoker indicator (dashed curves bottom row). Green curves represent the estimates for males and orange curves the estimates for females. EAR estimates were computed as the product the nonsmoker baseline rate and ERR estimates.
Fig. 7.6. Comparison of fitted Mayak worker cohort nonsmoker lung cancer mortality baseline, ERR, and EAR estimates for multiplicative EAR models with baseline rates adjusted for smoking using detailed smoking history data (solid lines) to those for models without adjustment for smoking (dashed curves top row) or adjusted using only an ever-smoker indicator (dashed curves bottom row). Green curves represent the estimates for males and orange curves the estimates for females. ERR estimates were computed as the ratio of the fitted EAR to the nonsmoker baseline rate estimates.
of the males and few of the females in this cohort were smokers and among smokers the females
smoked less than males. As a result, the unadjusted model baseline rates model for males are
about seven times those from the fully adjusted model. The unadjusted /pack-year adjusted
baseline rate difference for females is considerably smaller than for males. The differences in the
sex-specific baseline rate estimates are much less pronounced when comparing the ever-smoker
and pack-year adjusted models though age-specific rates for the ever-smoker adjusted model are
noticeably greater than those for the fully adjusted model. The ERR estimates from the
unadjusted model are much higher than those for the fully adjusted model for both males and
females. As a result of this the sex-specific EAR estimates for males from the unadjusted models
are more than ten times those from the fully adjusted mode. The sex-specific ERR differences
are greatly reduced for the ever-smoker adjusted model. However, because of the greater
estimated baseline rates at older ages in the ever-smoker model, the estimated EARs for this
model are biased upward at older ages most relevant to lifetime risk estimation.

Table 7.6 presents the lifetime risk estimates following exposure at age 40 y based on the
Mayak worker cohort multiplicative ERR and EAR radiation-effect models applied to U.S.
nonsmoker background rates. The male relative-risk transport REID estimates for the unadjusted
model are slightly greater than those based on the pack-year adjusted model while, as with the
LSS models, the absolute-risk transport unadjusted model estimates are biased upwards. While
there are some differences, the REID estimates based on the ever-smoker adjusted Mayak worker
cohort model are often similar to those from the fully adjusted model.

These results suggest that, while not without some bias, REID estimates based on models with a
relatively simple smoking adjustment can be useful. These results indicate that unadjusted EAR models
are of little use in the estimation of lifetime risks, especially for AR-transport REID estimates.

7.2.3 Source-Population Radiation-Effect Modeling and Model Selection Issues

The examples presented earlier in Sections 7.2.1 and 7.2.2 illustrate several issues that arise in
These issues and suggestions for addressing them discussed in the next few paragraphs are also applicable
to lifetime risk calculations for outcomes other than lung cancer.
Table 7.6 -- Comparison of low-LET REID estimates (excess deaths per 100 people) for U.S. nonsmokers at 1 Gy for age 40 y based on Mayak worker cohort ERR and EAR models with different types of smoking adjustment.

<table>
<thead>
<tr>
<th>Sex</th>
<th>Transport</th>
<th>Pack-Year Adjusted</th>
<th>No Smoking Adjustment</th>
<th>Sex-Specific Ever-Smoker Adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>ERR</td>
<td>EAR</td>
<td>ERR</td>
</tr>
<tr>
<td>Male</td>
<td>RR</td>
<td>0.12</td>
<td>0.29</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>AR</td>
<td>0.17</td>
<td>0.38</td>
<td>1.68</td>
</tr>
<tr>
<td>Female</td>
<td>RR</td>
<td>0.32</td>
<td>0.37</td>
<td>0.33</td>
</tr>
<tr>
<td></td>
<td>AR</td>
<td>0.39</td>
<td>0.45</td>
<td>0.48</td>
</tr>
</tbody>
</table>

a The low-LET REID estimates in this table are based on the Mayak external gamma-ray absorbed dose risk estimates derived from models that included plutonium exposure and dose effects. For these computations it was assumed that the plutonium dose was zero.

b Method for using the Mayak worker cohort radiation-effect estimates to estimate the radiation-associated cases in the target, U.S. nonsmoker, population. For relative risk transport (RR) the Mayak nonsmoker relative risk was applied to the sex- and age-specific U.S. nonsmoker risk estimates. For absolute risk transport (AR) the EAR estimate for Mayak nonsmokers was applied directly to the U.S. nonsmoker rates.

c The source-population pack-year adjusted risk models used were the ERR and EAR models fit to the Mayak lung cancer mortality data for the 1958 through 2009 period. In these models the smoking effect was described as linear in pack-years with an additional effect proportional to smoking intensity (packs per day) to a power. There was no adjustment for smoking cessation. The models also included an indicator for males with unknown smoking status.

d Mayak ERR or EAR models fit without any adjustment for smoking.

e Mayak ERR or EAR models fit with the smoking effect replaced by sex-specific ever-smoker effects for males and females and an effect for males with unknown smoking status.
It is common practice in lifetime risk computations (ICRP 2007; UNSCEAR 2008; NA/NRC 2006; EPA 2011; Cucinotta et al. 2013) to use source-population ERR models for RR transport and source-population EAR models for AR transport. However, as previously noted, both RR and AR transport can be carried out using either type of model, provided that one has a fully parametric (unstratified) model for the baseline rates. In practical terms this means that Poisson regression methods for rate modeling are preferable to partial likelihood methods (such as Cox regression) when developing rate models for cohort survival data. It should not be difficult to develop reasonable parametric baseline rate models for most outcomes of interest. In particular, good baseline rate models can be developed fairly easily using log-linear quadratic functions or quadratic splines in \( \log(\text{age}) \) with main effects and, as needed, simple interactions for sex, birth cohort, and period effects.

For any fitted ERR (EAR) model there is, in principle, an equivalent EAR (ERR) model. However, with existing tools for the specification and fitting models for the radiation effect on rates, it can be difficult (or impossible) to directly fit these equivalent models. Developing well-fitting EAR models can be quite challenging, especially when one is dealing with multiple risk factors (such as smoking and radiation). As the examples presented in Section 7.2.1 illustrate, the target population lifetime risks computed using ERR and EAR source-population models can differ rather markedly.

When both ERR and EAR models are available, model averaging (Burnham and Anderson 2002) is a useful method for developing a single radiation-effect model for use in the lifetime risk computations. This method, which is used in the ProZes software for assigned share computations (Ulanowski et al. 2020), involves weighting the alternative models using weights that are a function of differences in a goodness-of-fit measure called the Akaike Information Criterion (AIC) (Akaike 1974), which can be defined as the deviance (or minus twice the log-likelihood) for the fitted model plus twice the number of parameters in the model. If one has \( n \) models and defines \( \Delta AIC_i \) as the difference between the AIC for the model \( i \) and that for the model with smallest AIC value, the model-specific weights are defined as:
With only two alternative models and if $\Delta AIC$ for the poorer fitting model is 6, the weight for this model is 0.047 and decreases by about 60% for each unit increase in $\Delta AIC$. In practical terms, when comparing an ERR and an EAR model, if $\Delta AIC$ is more than 5 one could simply use the better fitting model. For the LSS ERR and EAR models given in Section 7.2.1.1, the ERR model is a poorer fitting model with $\Delta AIC_{ERR} = 22.2$ so it is reasonable to use the EAR model for both RR and AR transport in the lifetime risk computations. For the Mayak worker cohort models given in Section 7.2.1.2 the ERR model has the smallest AIC, but $\Delta AIC_{EAR} = 3.3$ which would result in modeling averaging weights for 0.84 and 0.16 for the ERR and EAR models, respectively.

While it is preferable to have both ERR and EAR source-population radiation-effect models, it may be that both types of models are not available. In such cases it is most likely that one would have only an ERR model since the development of EAR models is generally more challenging (at least with currently available software). In this case, it is better to use the available model to compute both the RR-transport based and AR-transport based lifetime estimates for the target population than to use only RR transport (for ERR models) or AR transport (for EAR models).

The studies considered in this review were cohort studies, but case-control study results might also provide information on radiation effects on population rates that could be useful for lifetime risk estimation. It is possible to develop ERR models from case-control data. As with ERR estimates from cohort studies, case-control study based ERR estimates can be used for lifetime risk computations based on RR transport. However, AR transport is not possible without information on baseline rates in the source population. Ideally this information would consist of sex- and age-specific source-population rates, but if such detailed information is not available, one might use estimates of the sex-specific ratio of population rates in the source and target populations to develop lifetime risks based on AR transport.
The above discussion of smoking adjustment of source-population radiation-effect estimates indicates that target population lifetime risk estimates for never-smokers are biased upward, especially for AR transport. This distortion appears to be least pronounced for ERR models with RR transport, but even in this case, the resulting lifetime risk estimates for nonsmokers are likely to be biased upward. Adjustment of the source-population rates using sex-specific ever-smoker indicators is better than using unadjusted rates, but the resulting non-smoker lifetime risk estimates are still likely to be distorted. It should also be noted that, while smoking effects on lung cancer relative risks are larger than those for other specific causes of death, smoking impacts the rates for other types of cancer deaths and for noncancer deaths (particularly heart disease) that are important when considering the lifetime post-mission mortality risk associated with mission-related radiation exposure.

7.3 Risk Models for Other Populations for Use in Bayesian Meta-Analysis

7.3.1 MWS Cohort Models and REID Estimates

The MWS includes data on almost 30 cohorts of U.S. workers with occupational radiation exposures (Boice et al. 2019b, 2021c). For this Commentary, lung cancer risks in four of these cohorts were considered. Each of these four cohorts include both male and female workers, and their dosimetry and mortality follow-up are complete. These cohorts include medical radiation workers, industrial radiographers, nuclear power plant workers, and workers at Los Alamos National Laboratory (LANL). The medical radiation workers, industrial radiographers, and nuclear power plant workers received primarily low-LET exposures while LANL workers had both external low-LET exposures and internal high-LET exposures from plutonium aerosols. The results presented here were obtained in a pooled analysis of the medical radiation workers, industrial radiographers, and nuclear power plant workers, and a separate analysis of the LANL cohort.

These analyses were adjusted for birth cohort and socioeconomic status using categorical variables, but since smoking history information was not currently available for these cohorts there is no adjustment for smoking. The baseline rate parameters and ERR-based excess rate computations described below were carried out based on the highest socioeconomic status categories using later birth cohorts as indicated in the model descriptions below.
7.3.1.1 MWS Pooled Cohort Mortality Unadjusted for Smoking. Table 7.7 and Figure 7.7 present the baseline rate parameter estimates and ERR estimates for models with and without allowance for a sex difference in the ERR. While the estimated sex difference in the ERR is quite large, it was not statistically significant, and its size is most likely a consequence of the limited information on the female dose response in this cohort.

Table 7.8 presents lifetime lung cancer risk estimates for U.S. nonsmokers based on the common and sex-specific ERR model excess risk estimates given in Table 7.7. The small difference between the two types of estimates for males indicate the limited information on female risks in this cohort. In view of the limited information on the sex difference in the excess risk estimates for this cohort, the REID estimates in Table 7.8 based on the common ERR model are preferred.

7.3.1.2 MWS Los Alamos National Laboratory Cohort Mortality Unadjusted for Smoking. LANL workers could receive exposure to gamma rays (low LET) and neutrons (high LET) from external sources, and exposure to alpha particles (high LET) due to plutonium intake. The data do not support the estimation of sex-specific excess risk estimates, so only models with common ERR or EAR estimates in which baseline rates were adjusted using categorical effects for birth cohort and education were considered. The radiation effects were evaluated using models with weighted dose (for all sources) and models with separate (jointly estimated) effects for external sources and plutonium intake. For the Bayesian meta-analysis, the weighted dose in the lung was computed as the sum of the gamma-ray absorbed dose (from external exposure), 10 times the neutron absorbed dose (from external exposure), and 10 times the absorbed dose from plutonium intake. Table 7.9 presents the baseline rate parameter estimates for the latest birth cohort (after 1940) and most highly educated group. Table 7.9 presents the ERR and EAR estimates for all sources of exposure, and separately for external sources and plutonium intake.

These risk estimates are quite uncertain, especially the separate estimates for low-LET (external sources) and high-LET (plutonium intake) doses. However, the Mayak worker cohort data suggest that the level and temporal pattern of the excess risks for these different types of exposure are likely to differ (Stram et al. 2021).
Table 7.7 -- MWS pooled cohort lung cancer mortality ERR model parameter with no smoking adjustment.

<table>
<thead>
<tr>
<th>Baseline Rates</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases per 10,000 PY at age 70 y</td>
<td>11.145</td>
<td>10.738</td>
</tr>
<tr>
<td>( \log(\text{age}/70) )</td>
<td>5.378</td>
<td>5.671</td>
</tr>
<tr>
<td>( [\log(\text{age}/70)]^2 )</td>
<td>-3.822</td>
<td>-2.499</td>
</tr>
<tr>
<td>( [\log(\text{age}/70)]^2 ) (age &gt; 70 y)</td>
<td>-13.55</td>
<td>-11.45</td>
</tr>
<tr>
<td>( \text{year of birth} - 1960/10 )</td>
<td>-0.093</td>
<td>-0.093</td>
</tr>
</tbody>
</table>

Radiation Effect – No Sex Difference

<table>
<thead>
<tr>
<th>ERR at 1 Gy</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{ERR at 1 Gy} )</td>
<td>0.137</td>
<td>0.137</td>
</tr>
<tr>
<td>( \text{ERR at 1 Gy} ) (year of birth – 1960) ( \text{ERR at 1 Gy} )</td>
<td>(0.243) ( b )</td>
<td>(0.243) ( b )</td>
</tr>
</tbody>
</table>

Radiation Effect – With Sex Difference

<table>
<thead>
<tr>
<th>ERR at 1 Gy</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>( \text{ERR at 1 Gy} )</td>
<td>0.155</td>
<td>-0.515</td>
</tr>
<tr>
<td>( \text{ERR at 1 Gy} ) (year of birth – 1960) ( \text{ERR at 1 Gy} )</td>
<td>(0.247) ( b )</td>
<td>(1.10) ( b )</td>
</tr>
</tbody>
</table>

\( a \) The age effects in the baseline rate model were modeled using sex-specific log-linear splines in log(age) with a single knot at age 70 y. There is no adjustment for smoking. The model also included a categorical education category variable and a log-linear birth cohort effect. The baseline rates at age 70 y are for the highest education category and the 1960 birth cohort. The baseline rate parameters shown are those for the ERR model with no sex effect on the ERR. The parameters for the model with sex-dependent ERRs were virtually identical.

\( b \) Asymptotic standard errors of the maximum likelihood estimate of ERR at 1 Gy absorbed dose in the lung.
Fig. 7.7. Baseline rate, ERR and EAR estimates for age-at-exposure 40 y based on ERR models without smoking adjustment fit to a pooled analysis of lung cancer mortality in three of the cohorts in the MWS (medical radiation workers, industrial radiographers and nuclear power plant workers). Estimates for males are shown using green curves while orange curves are used for females. Estimates based on a fitted ERR model with no sex effect on the dose response are shown as solid curves while those based on a sex-dependent ERR model are shown as dashed curves.
Table 7.8 -- Estimates of the risk of exposure-induced death (REID)\(^a\) for selected ages-at-exposure based on MWS pooled cohort lung cancer mortality ERR risk models applied to current U.S. population nonsmoker death rates.

<table>
<thead>
<tr>
<th>Age-at-Exposure (y)</th>
<th>Males</th>
<th>Females</th>
<th>Sex-specific ERR Model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Transport</td>
<td>RR</td>
<td>AR</td>
</tr>
<tr>
<td>Common ERR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>0.15</td>
<td>0.41</td>
<td>0.12</td>
</tr>
<tr>
<td>50</td>
<td>0.15</td>
<td>0.42</td>
<td>0.12</td>
</tr>
<tr>
<td>60</td>
<td>0.15</td>
<td>0.41</td>
<td>0.11</td>
</tr>
<tr>
<td>Sex-specific ERR Model</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>0.17</td>
<td>0.47</td>
<td>-0.46</td>
</tr>
<tr>
<td>50</td>
<td>0.17</td>
<td>0.47</td>
<td>-0.45</td>
</tr>
<tr>
<td>60</td>
<td>0.17</td>
<td>0.46</td>
<td>-0.43</td>
</tr>
</tbody>
</table>

\(\text{REID estimates are given in units of radiation-associated deaths per 100 people exposed to 1 Gy absorbed dose in the lung, assuming a 5 y latent period with follow-up from the age-at-exposure until age 100 y.}\)
Table 7.9 -- *MWS LANL cohort lung cancer mortality ERR and EAR models parameter no sex effects without adjustment for smoking.*

<table>
<thead>
<tr>
<th></th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Rates</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases per 10,000 PY at age 70 y</td>
<td>2.60</td>
<td>4.02</td>
</tr>
<tr>
<td>log(age/70)</td>
<td>6.00</td>
<td>6.00</td>
</tr>
<tr>
<td>[log(age/70)]²</td>
<td>-1.04</td>
<td>-1.04</td>
</tr>
<tr>
<td>[log(age/70)]² (age &gt; 70 y)</td>
<td>-16.0</td>
<td>-16.0</td>
</tr>
</tbody>
</table>

|                                |           |           |
| All exposure sources           |           |           |
| ERR at 1 Gy                    | 0.121     |           |
| (0.869)                        |           |           |
| EAR cases per 10,000 PY (at 1 Gy)| 0.118   |           |
| (3.583)                        |           |           |

|                                |           |           |
| External sources               |           |           |
| ERR at 1 Gy                    | -0.012    |           |
| (0.921)                        |           |           |
| EAR cases per 10,000 PY (at 1 Gy)| 0.584   |           |
| (6.256)                        |           |           |

|                                |           |           |
| Plutonium intake               |           |           |
| ERR at 1 Gy                    | 2.722     |           |
| (4.673)                        |           |           |
| EAR cases per 10,000 PY (at 1 Gy)| -1.485 |           |
| (34.8)                         |           |           |

---

*Age effects in the baseline rate model were modeled using sex-specific log-linear splines in log(age) with a single knot at age 70 y. The model also included a categorical education category variable and a categorical birth cohort effect. The baseline rates at age 70 y are for the highest education category and the post 1940 birth cohort. The baseline rate parameters shown are those for the ERR model with separate internal and external dose effects. The baseline parameter estimates for the ERR and EAR models with either weighted dose or separate internal and external dose effects were virtually identical.*

*Weighted dose for all exposure sources was computed as the sum of the gamma-ray absorbed dose (from external exposure), 10 times the neutron absorbed dose (from external exposure), and 10 times the absorbed dose from plutonium intake.*

*Parenthesized values are the asymptotic standard errors of the maximum likelihood estimates.*

*Dose computed as the sum of the gamma-ray absorbed dose (from external exposure) and ten times the neutron absorbed dose (from external exposure).*

*Dose computed as 10 times the absorbed dose from plutonium intake.*
The lifetime risk estimates based on the LANL risk models in Table 7.10 are based on the excess risk parameters given in Table 7.9. The estimates for all exposure sources do not depend on the transport method and the EAR-based estimates are slightly lower than the ERR-based estimates. The separate lifetime risk estimates (for external sources and plutonium intake) reflect the striking difference in the excess risk parameters for the ERR and EAR models. It is unclear how useful these estimates would be for risk prediction.

### 7.3.2 NRRW Incidence Models

The U.K. National Registry of Radiation Workers (NRRW) is an important source of information on occupational radiation exposures. The most recent published analyses of radiation effects on cancer mortality and incidence in the NRRW had follow-up from 1955 through 2011 (Haylock et al. 2018). Supplementary analyses of lung cancer incidence rates in this cohort are nearing completion. The primary results presented here were provided by the researchers carrying out these analyses. Since data on smoking are not available for this cohort, the models described below are unadjusted for smoking.

In the NRRW ERR model, the logarithm-transformed baseline rates were modeled as sex-dependent quadratic functions of log attained age with sex-dependent effects for birth cohort, duration of employment, occupation type (industrial worker or not) and, for males, facility first employed. The baseline model parameter estimates for long duration, long-term non-industrial workers are presented in the upper portion of Table 7.11.

As indicated in the lower portion of Table 7.11, the model provided for use by the analysts included a statistically significant rapid attenuation of the ERR for males but not for females. The linear ERR estimates for males and females were similar and were considerably larger than those seen in the other cohorts. However, because of the large log-linear attenuation of the male ERR with increasing dose the fitted male ERR at 0.1 Gy and 1 Gy are 0.004 and 0.25,

---

Table 7.10 -- Estimates of the risk of exposure-induced death (REID)* for selected ages-at-exposure based on MWS LANL cohort lung cancer mortality ERR and EAR risk models applied to current U.S. population nonsmoker death rates.

<table>
<thead>
<tr>
<th>Age-at-Exposure (y)</th>
<th>Weighted Dose</th>
<th>External Dose</th>
<th>Internal Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>ERR Model</td>
<td>EAR Model</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Males</td>
<td>Females</td>
<td>Males</td>
</tr>
<tr>
<td></td>
<td>Transport</td>
<td>Transport</td>
<td>Transport</td>
</tr>
<tr>
<td>RR</td>
<td>AR</td>
<td>RR</td>
<td>AR</td>
</tr>
<tr>
<td>40</td>
<td>0.13</td>
<td>0.13</td>
<td>0.11</td>
</tr>
<tr>
<td>50</td>
<td>0.13</td>
<td>0.13</td>
<td>0.10</td>
</tr>
<tr>
<td>60</td>
<td>0.13</td>
<td>0.13</td>
<td>0.10</td>
</tr>
<tr>
<td>40</td>
<td>-0.01</td>
<td>-0.01</td>
<td>-0.01</td>
</tr>
<tr>
<td>50</td>
<td>-0.01</td>
<td>-0.01</td>
<td>-0.01</td>
</tr>
<tr>
<td>60</td>
<td>-0.01</td>
<td>-0.01</td>
<td>-0.01</td>
</tr>
<tr>
<td>40</td>
<td>2.95</td>
<td>2.83</td>
<td>2.34</td>
</tr>
<tr>
<td>50</td>
<td>2.86</td>
<td>2.86</td>
<td>2.33</td>
</tr>
<tr>
<td>60</td>
<td>2.81</td>
<td>2.81</td>
<td>2.23</td>
</tr>
</tbody>
</table>

*REID estimates are given in units of radiation-associated deaths per 100 people exposed to 1 Gy assuming a 5 y latent period with follow-up from the age-at-exposure until age 100 y.
Table 7.11 -- *Sex-specific ERR model parameter estimates for lung cancer incidence in the NRRW cohort.*

<table>
<thead>
<tr>
<th></th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Baseline Rates Unadjusted for Smoking</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases per 10,000 PY at age 70 y</td>
<td>2.56</td>
<td>1.21</td>
</tr>
<tr>
<td>log(age/60)</td>
<td>6.760</td>
<td>6.465</td>
</tr>
<tr>
<td>[log(age/60)]</td>
<td>-1.396</td>
<td>-11.57</td>
</tr>
<tr>
<td>[log(age/60)]² (age &gt; 60 y)</td>
<td>-7.804</td>
<td>-</td>
</tr>
<tr>
<td>(birth year – 1915)/10</td>
<td>-0.25</td>
<td>-0.02</td>
</tr>
</tbody>
</table>

**Radiation ERR with High Dose Attenuation for Males**<sup>b</sup>

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ERR at 1 Gy</td>
<td>0.004</td>
<td>4.763</td>
</tr>
<tr>
<td></td>
<td>(0.064)</td>
<td>(5.001)</td>
</tr>
<tr>
<td>ERR attenuation (e^β dose)</td>
<td>-7.138</td>
<td>0</td>
</tr>
</tbody>
</table>

**Radiation ERR Extrapolated from 0.1 Gy Risk**<sup>c</sup>

<p>| | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>ERR at 1 Gy</td>
<td>2.516</td>
<td>4.763</td>
</tr>
<tr>
<td></td>
<td>(1.586)</td>
<td>(5.001)</td>
</tr>
</tbody>
</table>

<sup>a</sup> The logarithm of the baseline rates was modeled as sex-specific quadratic splines in age with a sex-specific birth cohort effect, duration of employment, and adjustment for job classification with “professionals” as the reference category.

<sup>b</sup> The ERR males was described using a linear model with log linear attenuation in dose. The estimate shown here is equal to 5.137 exp(-7.138). The standard error for the male linear dose parameter is 1.910. Since there was no evidence for attenuation of the linear ERR with increasing dose for females, a simple linear dose-response model was used. The standard errors for the dose response at 1 Gy are given in parentheses. The standard error for the estimated male ERR at 1 Gy was computed using the delta method. The standard error for the estimated ERR at 1 Gy for females is the usual asymptotic standard error obtained directly from the fitted linear dose-response model.

<sup>c</sup> The male ERR was computed as ten times the fitted ERR at a dose of 0.1 Gy. The standard error for this estimate was computed using the delta method applied to the parameter estimates and the asymptotic standard errors from the fitted risk model.
respectively. On the other hand, the fitted ERRs for females at 0.1 Gy and 1 Gy are 0.51 and 5.1,
respectively. The apparent, and rather implausible, attenuation in the male dose response is likely to
reflect the outsize influence of the small group of workers with doses above 400 mGy with no cases on
the fitted male dose response. The apparent attenuation is not seen for females since none of them
received these relatively large doses. Because of skepticism about the male ERR estimate, in addition to
considering radiation effects for males based on the fitted model, a model in which the ERR at 1 Gy for
males was taken to be ten times that at 0.1 Gy or 2.51 was also considered.

Figure 7.8 illustrates the fitted baseline rates for the NRRW incidence ERR model, together with
ERR and EAR estimates for the fitted model and the model described above in which the male ERR at 1
Gy was taken to be 10 times that fitted ERR at 0.1 Gy. The sex difference in the baseline rates largely
reflects the fact that this analysis is unadjusted for smoking and males were more likely to be smokers
than females.

Table 7.12 presents sex-specific and age-at-exposure specific lifetime risk estimates for the
NRRW ERR models with and without the male dose-response attenuation. For females and in the
imputed linear model for males, the lifetime risk estimates based on the NRRW are higher than those seen
in most of the other cohorts. Of course, the male lifetime risks are essentially zero for the high-dose
attenuation model. Because this analysis is not adjusted for smoking and because these are based on
incidence data, the lifetime risk estimates based on AR transport are overestimates of the nonsmoker
mortality lifetime risks. The model with the imputed ERR for males is probably the best model for use in
the lifetime risk computations for the astronauts.

7.4 Methodology for Combining Information from Selected Studies

This section details a meta-analytic approach for combining information for evaluating sex-
specific differences in excess lung cancer risk and constructing REID projections for the astronauts. The
approach was applied to the results presented in Sections 7.1 to 7.3, which had been derived using the
following datasets on lung cancer mortality rates in populations with exposure to low-LET radiation, or a
combination of low-LET and high-LET radiations:

- LSS mortality data with smoking covariables with follow-up 1958 through 2009.
- Mayak worker cohort mortality data (1948 through 2015) for external and internal (plutonium)
exposures with smoking information (1948 through 2015).
Fig. 7.8. Baseline rates, ERR, and ERR-based EAR estimates for a sex-specific linear ERR model fit to the NRRW lung cancer mortality data with follow-up through 2011. Estimates are given for males (green curves) and females (orange curves). The estimates for the fitted model are shown using solid curves. The fitted baseline is that for nonindustrial workers born in 1950. As discussed in the text, because of the unrealistic attenuation factor male dose response, also considered was an alternative model for males (dashed curves), in which the male ERR at 1 Gy was equal to 10 times the fitted male ERR at 100 mGy.
Table 7.12 -- *Estimates of the risk of exposure-induced death (REID)* for selected ages-at-exposure based on NRRW lung cancer incidence ERR risk models applied to current U.S. population nonsmoker death rates.

<table>
<thead>
<tr>
<th>Age-at-Exposure (y)</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Transport</td>
<td>RR</td>
</tr>
<tr>
<td>Sex-specific ERRs with high Dose Attenuation for Males</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>0.00</td>
<td>0.01</td>
</tr>
<tr>
<td>50</td>
<td>0.00</td>
<td>0.01</td>
</tr>
<tr>
<td>60</td>
<td>0.00</td>
<td>0.01</td>
</tr>
<tr>
<td>Sex-Specific Linear ERRs for Both Males and Females</td>
<td></td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>2.73</td>
<td>7.36</td>
</tr>
<tr>
<td>50</td>
<td>2.71</td>
<td>7.44</td>
</tr>
<tr>
<td>60</td>
<td>2.68</td>
<td>7.24</td>
</tr>
</tbody>
</table>

* REID estimates are given in units of radiation-associated deaths per 100 people exposed to 1 Gy assuming a 5 y latent period with follow-up from the age-at-exposure until age 100 y.
• MWS data from a pooled cohort of medical radiation workers; industrial radiographers and nuclear power plant workers.
• MWS data from a cohort of LANL workers.
• NRRW data with follow-up from 1955 through 2011.

Table 7.13 provides summary information about the studies used in this meta-analysis. Additional information on these studies is given in Sections 3.2 or 3.3.

Each of the selected studies satisfied the requirement that either:

• The radiation epidemiologic data used to fit risk models was available; or
• Arrangements could be made to obtain needed information from the primary investigators.

Due to time constraints and data-protection laws (which often restrict access to cohort specific work groups responsible for data collection, analyses, and publications), it was not feasible to select a more “representative” set of relevant studies with accessible source-population information beyond basic model parameter estimates. Thus, the results of the meta-analyses are not meant to be definitive and are presented here for illustrative purposes only.

Access to underlying data and/or other needed information would allow for the:

• Refit of risk models with model parameters adjusted to the age-at-exposure and attained age characteristics of astronauts.
• Refit of published excess risk models with no information on the mathematical form of the baseline cancer rates with parametric baseline models. This is an important feature when comparing contemporary U.S. baseline rates for nonsmokers to the corresponding baseline rates in the epidemiologic cohort used to fit the risk models.
• Refit of excess risk models (that present the risk at a unit weighted dose based on assumptions on biological effectiveness for high-LET radiation components) with separate organ dose contributions (e.g., high-LET and low-LET organ dose components).
• Testing of alternative risk models for suitability.
• Obtaining of information required for uncertainty analyses for excess risk models, such as the parameter correlation matrix (which is often not published with risk models), by refitting published and/or alternative models.
Table 7.13 -- *Characteristics of studies used in the Bayesian meta-analysis.*

<table>
<thead>
<tr>
<th>Study</th>
<th>Male</th>
<th></th>
<th></th>
<th>Female</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>People</td>
<td>Person Years</td>
<td>Lung Cancers</td>
<td>Dose (mGy) $^a$</td>
<td>People</td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>Max.</td>
<td>Mean</td>
<td>Max.</td>
<td>Mean</td>
</tr>
<tr>
<td>Life Span Study $^b$</td>
<td>45,864</td>
<td>1,218,431</td>
<td>1,569</td>
<td>95</td>
<td>3,444</td>
</tr>
<tr>
<td>Mayak Worker Cohort $^c$</td>
<td>19,635</td>
<td>721,683</td>
<td>837</td>
<td>416</td>
<td>7,835</td>
</tr>
<tr>
<td>MWS Pooled Cohort $^d$</td>
<td>296,568</td>
<td>778,177</td>
<td>6,009</td>
<td>17</td>
<td>1,435</td>
</tr>
<tr>
<td>MWS LANL $^e$</td>
<td>19,804</td>
<td>871,859</td>
<td>653</td>
<td>7</td>
<td>1,127</td>
</tr>
<tr>
<td>NRRW $^f$</td>
<td>150,566</td>
<td>3,253,530</td>
<td>3,163</td>
<td>28</td>
<td>1,748</td>
</tr>
</tbody>
</table>

$^a$ Two of the cohorts listed (Life Span Study and LANL) have mixtures of low-LET and high-LET exposures. The high-LET components were weighted to provide estimates for an equivalent low-LET absorbed dose in the lung (*i.e.*, the weighted dose, expressed in milligray). See footnotes $^b$ through $^f$.

$^b$ Weighted dose in the lung, computed as gamma-ray absorbed dose plus 10 times the neutron absorbed dose, adjusted for dose uncertainty.

$^c$ 5 y lagged cumulative external gamma-ray absorbed dose in the lung.

$^d$ 10 y lagged cumulative (person-year weighted) absorbed dose in the lung. This population includes members of three MWS subcohorts: medical workers, nuclear power plant workers, and industrial radiographers.

$^e$ 10 y lagged cumulative (person-year weighted) absorbed dose in the lung.

$^f$ 10 y lagged cumulative absorbed dose (based on personal dose equivalent, the recorded dose, in milliseivert).
Ideally, inferences and projections would be based on models derived from a pooled analyses of data from selected studies. This approach was applied for the Biological Effects of Ionizing Radiation (BEIR VI) report to obtain lung cancer risk projections for residential radon based on results from 11 underground miner cohorts (NA/NRC 1999). Two “preferred” risk models (the “age-concentration” and “age-duration” models) were fit to data from 11 underground miner cohorts. In both models, ERR is proportional to exposure (i.e., working level months). For the age-concentration model, risk modifiers include time-since-exposure, attained age, tobacco use (ever-smoker or never-smoker), and (average) radon level. The slope of the dose response depends on cohort, but parameter values were assumed to be the same for all cohorts for all risk modifiers. After the model was fit, an overall estimate of the dose response was obtained using standard (random-effects) meta-analysis techniques (NA/NRC 1999). The process was repeated using the alternative “age-duration” model of almost identical form, but for which the risk modifier for average radon level is replaced by duration of occupational exposure. EPA (2003) then calculated separate risk projections for the U.S. population for each of the two models using standard lifetable methods. A final estimate was obtained as the geometric mean of the two projections. Another example of a pooled analysis used to project radiogenic risks was the pooled analysis of data from residential case-control studies which formed the basis of risk projections given in the WHO Handbook for Radon (WHO 2009).

A pooled analysis analogous to the analysis underlying the risk projections in NA/NRC (1999) is beyond the scope of this Commentary. Such an approach is most easily applied to studies of the same design type, of populations which share common characteristics, and for which high quality data is available for a common set of risk factors. However, that is not the case for the five sets of available studies considered here, and it is not entirely clear whether such a pooled analysis would be feasible. For example, can a common set of independent variables be identified? How would partial information for the MWS or dose-rate effects (e.g., which may account for differences in excess cancer rates in the LSS versus other studies) be incorporated in a pooled analysis?

As an alternative, a Bayesian meta-analytic approach which combines the results obtained through separate analyses of the five datasets (representing seven cohorts) is described in Sections 7.2 and 7.3. The approach is based on two assumptions that:

1) For each study population the ERR (at a unit dose) is equal to a reference value ($\beta_{sex,study}$) multiplied by a function that depends on sex, age-at-exposure and attained age $[g_{sex,study}(e, a)]$.

Reference ERR values are defined here as the ERR at 1 Gy (low-LET absorbed dose in the lung)
for age-at-exposure 40 y and attained age 70 y (a “central” value for cancer death commonly used, for example, in analyses of LSS data). The reference ERR values depend on sex and study population. However, the risk-modifier function \( g_{sex,study}(e,e) \) does not and is the same for each of the five studies and for the target population of astronauts:

\[
ERR_{sex,study}(D_T,e,a) = \beta_{sex,study} g(e,a) D_T
\] (7.6)

Although it is certainly not strictly true, it is assumed that deviations from the assumption of a common risk-modifier function are relatively small, and that any resulting bias in estimates of REID would be relatively small.

2) Parameter estimates derived from the LSS can be used to estimate this common age-at-exposure and attained age pattern in ERR.

From 1) and 2), it follows that REID at 1 Gy for the astronauts can be approximated as:

\[
REID_{sex,astronauts}(at 1 Gy) = \frac{1}{S(e)} \int_{a}^{\infty} \hat{\beta}_{sex,astronauts} g(e,a) S^*[D_T(a,s,a)] da
\] (7.7)

where the values for \( \hat{\beta}_{sex,astronauts} \) are obtained from a meta-analysis based on the estimates of ERR (for \( e = 40 \) y, \( a = 70 \) y), their standard errors, and (as explained below) the baseline rates for the study cohorts given in Table 7.14. Inputs into the meta-analysis also include baseline lung cancer rates (at age 70 y) for astronauts (3.154 and 2.431 per 10,000 PY for males and females, respectively).

Typically, the estimates would be based on an overall summary estimate of risk obtained using standard fixed-effects or random-effects formulas. Among these is the DerSimonian and Laird (1986) random-effects estimate [see also DerSimonian and Kacker (2007)] for an updated review of leading meta-analytic approaches), which for astronauts might be:

\[
\hat{\beta}_{sex,astronauts} = \frac{\sum_{study=1}^{5} \hat{\beta}_{sex,study} / [se(\hat{\beta}_{sex,study})^2 + \Delta^2]}{\sum_{sex,study=1}^{5} 1 / [se(\hat{\beta}_{sex,study})^2 + \Delta^2]}. \] (7.8)
Table 7.1 -- Summary statistics for external low-LET lung dose risk estimates used as inputs to the Bayesian meta-analysis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Model</th>
<th>Sex</th>
<th>ERR at 1 Gy Estimate</th>
<th>Standard Error</th>
<th>Baseline Rate (per 10,000 PY)</th>
<th>Baseline Rate Used (per 10,000 PY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>LSS</td>
<td>EAR</td>
<td>Male</td>
<td>0.557</td>
<td>0.162</td>
<td>3.459</td>
<td>3.459</td>
</tr>
<tr>
<td></td>
<td>Smoking adjusted</td>
<td>Female</td>
<td>2.197</td>
<td>0.298</td>
<td>3.760</td>
<td>3.760</td>
</tr>
<tr>
<td>Mayak worker cohort</td>
<td>ERR</td>
<td>Male</td>
<td>0.164</td>
<td>0.062</td>
<td>6.228</td>
<td>6.228</td>
</tr>
<tr>
<td></td>
<td>Smoking adjusted</td>
<td>Female</td>
<td>0.550</td>
<td>0.332</td>
<td>3.695</td>
<td>3.695</td>
</tr>
<tr>
<td>MWS pooled b</td>
<td>ERR</td>
<td>Male</td>
<td>0.155</td>
<td>0.247</td>
<td>11.15</td>
<td>3.154 a</td>
</tr>
<tr>
<td></td>
<td>No smoking adjusted</td>
<td>Female</td>
<td>-0.51</td>
<td>1.10</td>
<td>10.74</td>
<td>2.431 a</td>
</tr>
<tr>
<td>LANL</td>
<td>ERR</td>
<td>Sex-averaged</td>
<td>-0.012</td>
<td>0.92</td>
<td>2.6</td>
<td>3.154 a</td>
</tr>
<tr>
<td></td>
<td>No smoking adjusted</td>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Female</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NRRW</td>
<td>ERR</td>
<td>Male</td>
<td>2.516</td>
<td>1.586</td>
<td>2.56</td>
<td>2.56</td>
</tr>
<tr>
<td></td>
<td>Smoking adjusted</td>
<td>Female</td>
<td>4.763</td>
<td>5.001</td>
<td>1.21</td>
<td>1.21</td>
</tr>
</tbody>
</table>

*For MWS and LANL cohorts, baseline rates were not given for nonsmokers. U.S. nonsmoker baseline rates were used instead as inputs to the Bayesian meta-analysis.

b Pooled cohorts were nuclear power plant workers, industrial radiographers, and medical radiation workers.
For the random-effects approach, the sex and study-specific ERRs ($\beta_{sex,study}$) depend on study (conceptually, the estimates $\hat{\beta}_{study}$ are thought of as random quantities) and $\Delta^2$ denotes an estimate of the between-study variance (for the $\beta_j$). In contrast, for the fixed-effects approach, it is assumed that ERR does not depend on study; the corresponding formula can be obtained by setting $\Delta^2 = 0$. It is readily seen (Equation 7.8) that the DerSimonian and Laird (1986) estimates of ERR for the astronauts would be a weighted average of study-specific estimates. For the fixed-effects model, the weights are inversely proportional to the variance associated with sampling error for each of the study-specific estimates; for the random-effects model, the weights are inversely proportional to the sum of the sampling error and between study variance estimates.

This approach is based on some of the same concepts underlying the traditional meta-analysis approach. Most fundamentally, these projections of risk for astronauts are derived first as summary estimates of risk across all of the studies and the concept that study-specific ERRs can be thought of as random quantities which may tend to be similar (i.e., if $\Delta^2 = 0$ or is small). However, adjustment to these traditional methods is needed to account for four items:

1. What is already known or hypothesized about how risks depend on dose rate.
2. What is already known or hypothesized about how risks depend on other population characteristics.
3. Potential bias in the study-specific estimates associated with nonsampling errors, (e.g., dosimetry uncertainties, residual confounding, model misspecification).
4. With only two studies (LSS and Mayak worker cohort) with reasonably precise estimates of ERR, traditional maximum likelihood estimates for $\Delta^2$ are likely to fail (even if adjustments are made to accommodate 1) and 2). However, it may be unrealistic to assume a fixed-effects type model (i.e., $\Delta^2 = 0$).

Finally, the approach should incorporate methods for making inferences on how risks depend on sex.
7.4.1 Models for Combining Study-Specific Estimates of Excess Risk

The proposed meta-analysis for projecting lung cancer risks to the target astronaut population is based on the contention that the problem can be simplified by considering only the summary estimates of risk for the specific ages ($e = 40 \text{ y}, a = 70 \text{ y}$), and fixed-effects and random-effects type models which divide into several components.

The first component describes an assumed relationship between sex and study-specific estimates of excess risk and their estimates. Let $\beta_{sex,study}$ be the sex-specific ERR (per unit dose) for a specific study population ($e = 40 \text{ y}, a = 70 \text{ y}$). For each study there are estimates:

$$\hat{\beta}_{sex,study} = \omega_{sex,study} \beta_{sex,study} + e_{sex,study}$$  \hspace{1cm} (7.9)

where $\omega_{sex,study}$ represents the relative bias associated with nonsampling error sources (e.g., dose uncertainties, residual confounding) and $e_{sex,study}$ represents sampling error (assumed for our purposes to be normally distributed). If an estimate, $\hat{\beta}_{sex,study}$, is unbiased, then the corresponding factor $\omega_{sex,study} = 1$. Alternatively, lognormal distributions can be assigned to the $\omega_{sex,study}$ to investigate how study and sex-specific bias associated with nonsampling errors might impact results. The precision of the estimates and the potential for bias (reflected in the distributions for $\omega_{sex,study}$), relate to characteristics such as the number of males and females, the dose range, quality of the dose assessment, and information collected on smoking (Section 3.4.3).

The second component describes how study-specific ERRs relate to one another, and ultimately to the ERR for the target population of astronauts. For this, consider two alternatives:

1. A model analogous to the traditional fixed-effects meta-analysis model; and
2. A random-effects model.
### 7.4.1.1 Fixed-Effects Type Model

Consider first the conceptual model:

\[
\beta_{\text{sex,study}} = \mu \gamma_{\text{sex}} f(r_{\text{study}}, z_{\text{sex,study}}) \quad (7.10)
\]

Here, \( \mu \) is a sex-averaged central value for ERR associated with a “standard” population, for now simply assumed to be the population of astronauts, \( \gamma_{\text{sex}} \) is a multiplicative sex-effect, and \( r_{\text{study}} \) are study-specific dose-rate effects (equal to 1 except for the LSS). The \( z_{\text{sex,study}} \) would be vectors of summary study-specific population characteristics (e.g., that explain why the ERR for the same type of radiation might be different for members of the LSS versus employees at Mayak). Hypothetically, the \( z_{\text{sex,study}} \) might include study-specific information collected on genetic, environmental and lifestyle factors, assuming there is also information on how such factors modify radiation risk.

In fact, for the five studies considered, the ideal detailed information on population characteristics (as represented by \( z_{\text{sex,study}} \) in Equation 7.10) is not available and, even if such information were available, how this information would affect excess lung cancer rates is not known. Nevertheless, study-specific baseline cancer rates can serve as a surrogate, leading to the following adaptation of Equation 7.10:

\[
\beta_{\text{sex,study}} = \mu_{\text{sex}} \left[ w + (1 - w) \frac{h_{0,\text{sex}}(70)}{h_{\text{study,sex}}(70)} \right] r_{\text{study}} \quad (7.11)
\]

where:

- \( \mu_{\text{sex}} = \mu \gamma_{\text{sex}} \)
- \( h_{0,\text{sex}}(70), h_{\text{study,sex}}(70) \) are the baseline rates at age 70 y for the standard and study populations
- \( r_{\text{study}} = DDREF \) for the LSS and 1 for other studies.

The middle term in Equation 7.11 is consistent with the traditional risk projection approach in which the EAR in the study population is a weighted average of projections based on competing assumptions that ERR \( (w = 1) \) versus EAR \( (w = 0) \) are independent of study.
Let \( k_{\text{sex,study}}(w) = w + (1 - w) \frac{h_{0,\text{sex}(70)}}{h_{\text{study,sex}(70)}} \) \hspace{1cm} (7.12)

Then, Equation 7.11 can be re-expressed as:

\[
\hat{\beta}_{\text{sex,study}} = \mu_{\text{sex}} k_{\text{sex,study}}(w) r_{\text{study}} \hspace{1cm} (7.13)
\]

Furthermore, it is readily seen that Equation 7.13 is a simplification of Equation 7.10 for which \( f(r_{\text{study}}, z_{\text{sex,study}}) \) is assumed to be equal to \( k_{\text{sex,study}}(w) r_{\text{study}} \).

In fact, the model defined by Equations 7.9 and 7.13 is analogous to the traditional fixed-effects meta-analysis model. If \( w \) and the dose-rate effect factor are known, study-specific estimates of ERR could each be adjusted accordingly to provide unbiased estimates of a common ERR, assumed to be equal to the ERR for the astronaut population. More specifically:

\[
\hat{\mu}_{\text{sex,study}} = \frac{\hat{\beta}_{\text{sex,study}}}{k_{\text{sex,study}}(w) r_{\text{study}}} \hspace{1cm} (7.14)
\]

are estimates of ERR for the astronaut population based on the ERR estimate (\( \hat{\beta}_{\text{sex,study}} \)). Here \( \hat{r}_{\text{study}} \) might be set to 1.5 for the LSS (and would be equal to 1 for the other studies). The estimates given in Equation 7.14 represent adjustments to the raw ERR estimates that one might consider as inputs into a variant of the traditional DerSimonian and Laird (1986) fixed-effects formulas.

### 7.4.1.2 Random-Effects Type Model

A proposed random-effects model is based on the recognition that two populations with identical (or almost identical) baseline lung cancer rates may have nonnegligible differences in excess rates associated with the same exposure to radiation. The random-effects model attempts to accommodate this through a generalization of Equation 7.11:
\[ \beta_{\text{sex,study}} = \mu_{\text{sex}} \left[ w + (1 - w) \frac{h_{\text{sex} (70)}}{h_{\text{study,sex} (70)}} \right] r_{\text{study}} (\varphi_{\text{study}} \delta_{\text{sex,study}}) \] (7.15)

Here \( \varphi_{\text{study}} \) and \( \delta_{\text{sex,study}} \) represent multiplicative random components of population-specific variation in the ERR not attributable to \( z_{\text{sex,study}} \). The multiplicative random components might incorporate, for example, the modifying effects associated with environmental and genetic characteristics not assessed in the study and not fully captured in the baseline rates. If values for these components can be assumed to be close to 1, then the fixed-effects model would be a close approximation.

A subtle point is that for the random-effects model, the term standard population and the parameter \( \mu_{\text{sex}} \) need to be more clearly defined. The standard population is defined here as a hypothetical population with the same baseline lung cancer rates as the astronauts. \( \mu_{\text{sex}} \) is then defined as the ERR for the hypothetical standard population.

The next component of the random-effects model relates the excess rates for the standard population to the excess rates for the target population of astronauts. For this, the reference population is specified as a hypothetical population with the same baseline cancer rates as the astronauts. Note, though, that two populations with similar baseline rates do not necessarily have similar excess risks. In this model, the sex-specific excess cancer rates for the astronauts differ from the sex-specific rates for the hypothetical reference population by the product \( \varphi_{\text{astronauts}} \delta_{\text{sex,astronauts}} \) so that:

\[ \beta_{\text{sex,astronauts}} = \mu_{\text{sex}} (\varphi_{\text{astronauts}} \delta_{\text{sex,astronauts}}) \] (7.16)

Probability distributions for \( \varphi_{\text{astronauts}} \) and \( \delta_{\text{sex,astronauts}} \) are assumed to be the same as the prior distributions assigned to \( \varphi_{\text{study}} \) and \( \delta_{\text{sex,study}} \) (i.e., the random components associated with the study populations).
7.4.2 Bayesian Meta-Analysis

As was stated previously, there is a lack of methods to adapt standard meta-analysis methods to account for many of the issues described above (e.g., effects of nonsampling error and the small number of studies for estimating between-study variability in random effects). Bayesian methodology provides a useful alternative. In this approach, $\mu$, $\gamma_{sex}$, $r_{LSS}$, $w$, $\omega_{sex,study}$, $\psi_{study}$, and $\delta_{sex,study}$ are all assigned prior probability distributions; these are then updated using the results in Table 7.1 to obtain posterior distributions. The assigned prior distributions reflect subjective judgement about the likely range of values for each parameter, without consideration of the information provided in Table 7.1. The posterior distributions reflect both the subjective information about the ERRs inherent in the prior distributions and what can be extracted from the results given in Table 7.1.

To provide a brief illustration to explain some of the terminology: suppose based on one of the models described above, the prior probability = 0.2 for $\mu_{female} > 1$, and the corresponding posterior probability = 0.05. Then, prior to consideration of the data, the ERR for females in a population with the same background rates as astronauts was assumed to be >1 with probability of 0.2. However, with information from the studies, the probability would be reduced to 0.05, or equivalently, the 95% value for $\mu_{female} = 1$.

For some parameters in the model, it is relatively easy to decide on an appropriate prior distribution. For example, a highly dispersed (weakly informative) prior is assumed for $\mu \sim N(0, sd = 5)$, (i.e., a normal distribution with mean 0 and standard deviation 5). With the prior distribution centered at 0 and a wide range of likely values (>95% prior probability that $\mu < 10$), this distribution assures that results will not be unduly influenced by subjective judgement about that parameter value. Ideally, if data from several studies were rich enough to obtain reasonable estimates, for example, of between-study variation in ERRs, highly dispersed priors could also be assigned to the parameters associated with random effects associated with sex and between-study variation in ERR. With only two studies with reasonably precise estimates of ERR, this is clearly not the case. For these parameters, prior distributions would ideally reflect, for example, how much ERR is likely to vary by study. Since such information, if
it exists, is limited and subjective, a sensitivity analysis was performed to evaluate the
dependence of results on choice of prior distributions. For the main analysis, prior probabilities
for associated sex and study-specific values for ERR could differ by 1 or 2 orders of magnitude
(the prior distribution for the random study effect is shown in Figure 7.9). The analysis is
repeated using more informative priors for which likely study and differences are restricted to
factors no greater than about 5. The analysis was repeated once again using the fixed-effects
model for which it is assumed there is no variation in study-specific ERRs after adjustment for
dose rate and baseline cancer rate.

Reflecting the lack of information as to whether absolute or relative risks are more
closely preserved across populations, a uniform distribution is assigned to the risk transport
method weight \([w \sim U(0, 1)]\). As in NA/NRC (2006), the lognormal distribution LN (geometric
mean = 1.5, geometric standard deviation = 1.35) is assigned to the DDREF (applicable for the
LSS study only).

Finally, for the main analysis, it is assumed that effects of nonsampling error can be ignored (i.e.,
\([\omega_{sex,study} = 1]\). For a sensitivity analysis, \(\omega_{sex,study} \) is assigned a lognormal probability distribution
such that the relative bias is between 0.5 and 2 with probability of about 70%.

A detailed description of the model parameters and their assigned prior distributions are given in
Tables 7.15 and 7.16.

Results presented in Section 7.4.3 on posterior distributions for parameters such as \(\mu_{sex} \) were
obtained through simulation using a complex sampling technique [Markov Chain Monte Carlo (MCMC)].
This was accomplished using the software program WinBUGS (Lunn et al. 2000b).\(^29\) For each of the
models, three separate chains of 500,000 samples each were simulated using MCMC. The first 250,000
samples from each chain were discarded, and the results presented in Section 7.4.3 are summary statistics
based on the combined (750,000) remaining samples from each of three chains. Gelman-Rubin statistics
were calculated to confirm convergence. A description of Bayesian methods and computational methods
such as MCMC can be found in textbooks such as Gelman et al. (2013).

\(^{29}\) The WinBUGS program used to obtain the main analysis results in this Commentary is available from
Fig. 7.9. Prior probability density for $\log_{10}(\gamma_{\text{female}})$. For example, the area under the curve for $\log_{10}(\gamma_{\text{female}})$ between 1 and 2 equals the prior probability that the ERR in the standard population is between 1 and 2 orders of magnitude greater for females than males.
Table 7.1 – Fixed-effects model parameters and assigned prior distributions.

<table>
<thead>
<tr>
<th>Parameter(s)</th>
<th>Description</th>
<th>Prior Distribution</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_{\text{sex,study}}$</td>
<td>Sex and study-specific ERR for exposure age 40 y and attained age 70 y. Direct estimates for these parameters are $\hat{\beta}<em>{\text{sex,study}}$. The relationship between $\beta</em>{\text{sex,study}}$ and other parameters is given in Equations 7.11 and 7.15.</td>
<td>A prior distribution is not directly assigned to $\beta_{\text{sex,study}}$.</td>
</tr>
<tr>
<td>$\omega_{\text{sex,study}}$</td>
<td>Relative bias for the estimates $\beta_{\text{sex,study}}$. If $\omega_{\text{sex,study}} = 1$, then the estimates are unbiased. More generally, if $\omega_{\text{sex,study}} = k$, the $\beta_{\text{sex,study}}$ are expected to be on average $k$ times as large as $\beta_{\text{sex,study}}$.</td>
<td>Main analysis: $\omega_{\text{sex,study}} = 1$</td>
</tr>
<tr>
<td>$\mu$</td>
<td>Sex-averaged ERR for a population with the same baseline lung cancer rates as the astronauts.</td>
<td>$\mu \sim N(0, \text{sd} = 5)$ Although widely dispersed, the prior probability, $P(\mu &gt; 10) &lt; 0.03$</td>
</tr>
<tr>
<td>$\mu_{\text{sex}}, \gamma_{\text{sex}}$</td>
<td>$\mu_{\text{sex}}$ are the sex-specific ERR for the reference population: $\gamma_{\text{sex}}$ are the corresponding main sex effects: $\mu_{\text{sex}} = \mu \gamma_{\text{sex}}$, and $\gamma_{\text{male}} = 1/\gamma_{\text{female}}$</td>
<td>Main analysis: Prior distributions are assigned directly only to $\gamma_{\text{female}}$: $\gamma_{\text{female}}$ is assigned a mixture of lognormal distributions, $\ln (\gamma_{\text{female}}) \sim N(0, \text{sd} = \tau_{\text{sex}})$, $\tau_{\text{female}} \sim U[0,\ln(10)]$ Informative prior (for sensitivity analysis): Same as main analysis except: $\tau_{\text{female}} \sim U[0,\ln(2)]$</td>
</tr>
</tbody>
</table>


$w$ Weight assigned to relative risk transport.

- If $w = 1$, relative risks for a study population are expected to be the same (on average) as for the reference population.
- If $w = 0$, study population absolute risks are expected to be the same as for the reference population.

$w \sim U(0,1)$

<table>
<thead>
<tr>
<th>$r_{study}$</th>
<th>Dose-rate effect parameter</th>
</tr>
</thead>
<tbody>
<tr>
<td>$LS5$: $\ln (r_{study}) \sim N[\ln (1.5), sd = 0.3]$</td>
<td></td>
</tr>
<tr>
<td>All other studies: $r_{study} = 1$</td>
<td></td>
</tr>
</tbody>
</table>
Table 7.1 -- Parameters exclusive to the random-effects model and corresponding prior distributions.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Main analysis:</th>
<th>Informative prior (for sensitivity analysis):</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\phi_{\text{study}}$</td>
<td>Random multiplicative study effects: When multiplied by $\mu$, the products, $\mu \phi_{\text{study}}$, are adjusted sex-averaged excess cancer rates associated with the study. The adjustment accounts for differences in excess rates between the study and the standard population associated with dose rate (LSS only) and baseline cancer rates.</td>
<td>$\phi_{\text{study}}$ are assigned a mixture of lognormal distributions. [\ln(\phi_{\text{study}}) \sim N(0, \text{sd} = \tau_{\text{study}})] $\tau_{\text{study}} \sim U[0, \ln(10)]$</td>
<td>Same as main analysis except $\tau_{\text{study}} \sim U[0, \ln(2)]$</td>
</tr>
<tr>
<td>$\delta_{\text{sex,study}}$</td>
<td>Random multiplicative study-specific sex effects: When multiplied by $\mu$ and $\phi_{\text{study}}$, the resulting products, $\mu \phi_{\text{study}} \delta_{\text{sex,study}}$, are adjusted sex-specific excess cancer rates associated with the study. The adjustment accounts for differences in excess rates between the study and the standard population associated with dose rate (LSS only) and baseline cancer rates.</td>
<td>$\ln(\delta_{\text{female,study}}) \sim N(0, \text{sd} = \tau_{\text{sex,study}})$ $\tau_{\text{study}} \sim U[0, \ln(10)]$ $\delta_{\text{male}} = 1/\delta_{\text{female}}$</td>
<td>Same as main analysis except $\tau_{\text{study}} \sim U[0, \ln(2)/2]$</td>
</tr>
</tbody>
</table>

Not used for fixed-effects model, or equivalently:
- $\phi_{\text{study}} = 1$
- $\delta_{\text{female,study}} = 1$
7.4.3 Results

The results given in this section address the following:

- What inferences can be made about differences in lung cancer risks for females versus males?
- How large are ERRs for females and males in a standard nonsmoking population with the same baseline rates as astronauts? How large are excess relative radiation risks for the population of astronauts?
- What can be said about lifetime risks for astronauts?

For the main analysis, ERR and the male-to-female ratio of ERR depend on study, even after the ERRs are adjusted for differences in baseline cancer rates and effects associated with dose rates. The main analysis allowed for considerable (e.g., as great as an order of magnitude) variation in study-specific ERRs. The main analysis also assumed that bias associated with nonsampling error is negligible. The analysis was repeated based on a variety of assumptions. These include:

- Analyses based on informative priors: Random variation in study-specific ERRs was greater than 0 but was generally assumed to be smaller than for the main analysis. A smaller range of likely values was also assumed for the ratio of female-to-male ERRs.
- Analyses based on a fixed-effects model: Assumes no variation in ERR that is not associated with baseline cancer rate or dose rate.
- Analyses that incorporated potential bias associated with nonsampling error: Assumes a lognormal distribution for the relative bias with likely (probability of 0.68) range of (0.5 to 2).

Results are also presented to show the effects of excluding each study one-at-a-time.

7.4.3.1 Are Lung Cancer Risks from Chronic Low-LET Radiation Exposures Greater for Females than Males? First, one can examine what might be inferred about differences between the radiation risks for females and males, based on results restricted to the selected studies.
Table 7.1 gives results for posterior distributions for the ratio $\mu_{female}/\mu_{male}$. The ratio represents the ERR at 1 Gy (low-LET radiation to the lung) for a standard population representative of astronauts (i.e., with the same baseline cancer rates).

The first row gives results for the main analysis. Central estimates for the ratio are given by the mean and median of the posterior distribution, 4.3 and 3.3, respectively. The 10th and 90th percentile results indicate a likely range for the ratio between 1.26 and 7.4. The probability that the ERR for females is greater than for males is estimated to be 0.95.

It is, however, important to note that results depend on model assumptions and associated prior distributions assigned to the parameter values. The more informative prior, for which the range of likely ERR values is more constrained, yields a narrower posterior distribution; the mean is smaller (3.7), the 90th percentile value drops to 5.9, and the probability that the ERR is greater for females than for males is 0.99. If one can assume that true ERRs do not depend on study (after adjustment for baseline cancer and dose rates), the underlying fixed-effects model, then the estimated probability that ERR is greatest for females approaches 1.

Conversely, introducing the possibility of bias associated with sampling error increases the uncertainty as to whether the ERR is greater for females than males. When the model allows for a moderate amount of bias (for any study, a 68% probability that the bias is between 0.5 and 2), the probability for a greater female ERR drops to 0.89.

Table 7.1 also shows how the posterior distribution derived via the main analysis changes when each study is excluded one-at-a-time. Not surprisingly, the sensitivity analysis indicates that results from the LSS and Mayak worker cohort had the most influence on the posterior distribution. For example, the probability that the ratio is $>1$ decreases to 0.63 (from 0.95 when results from the LSS are excluded; the probability is 0.92 without results from Mayak). There is essentially no change when results from MWS or NRRW are excluded.

Overall, the data from the selected studies indicate radiogenic lung cancer risks are greater for females than males, with most central estimates for the sex ratio of about 2.5 to 5. Results range from definitive (fixed-effects model) or suggestive (random-effects models with moderate nonsampling error),
Table 7.1 -- Posterior distribution for the female-to-male ratio in ERR at 1 Gy at attained age 70 y for an exposure age 40 y. Results are for a standard population of nonsmokers with the same baseline cancer rates as assumed for the astronauts.

<table>
<thead>
<tr>
<th>Method</th>
<th>Mean</th>
<th>Median</th>
<th>5 %</th>
<th>10 %</th>
<th>90 %</th>
<th>P(Ratio&gt;1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main analysis (MA)</td>
<td>4.3</td>
<td>3.3</td>
<td>1.00</td>
<td>1.26</td>
<td>7.4</td>
<td>0.95</td>
</tr>
<tr>
<td>Fixed-Effects</td>
<td>5.7</td>
<td>5.0</td>
<td>3.1</td>
<td>3.4</td>
<td>8.4</td>
<td>1.00</td>
</tr>
<tr>
<td>No nonsampling error, informative prior</td>
<td>3.7</td>
<td>3.3</td>
<td>1.44</td>
<td>1.80</td>
<td>5.9</td>
<td>0.99</td>
</tr>
<tr>
<td>Nonsampling error</td>
<td>3.8</td>
<td>2.5</td>
<td>0.81</td>
<td>0.99</td>
<td>7.3</td>
<td>0.89</td>
</tr>
<tr>
<td>MA without LSS</td>
<td>2.4</td>
<td>1.3</td>
<td>0.22</td>
<td>0.40</td>
<td>4.3</td>
<td>0.63</td>
</tr>
<tr>
<td>MA without Mayak</td>
<td>8.1</td>
<td>3.3</td>
<td>0.89</td>
<td>1.08</td>
<td>10.6</td>
<td>0.92</td>
</tr>
<tr>
<td>MA without MWS</td>
<td>4.5</td>
<td>3.4</td>
<td>0.99</td>
<td>1.25</td>
<td>7.9</td>
<td>0.95</td>
</tr>
<tr>
<td>MA without NRRW</td>
<td>4.5</td>
<td>3.5</td>
<td>1.02</td>
<td>1.32</td>
<td>8.0</td>
<td>0.95</td>
</tr>
</tbody>
</table>
depending on underlying assumptions. However, the results of the meta-analysis given in Table 7.17 also
depend on which studies are included. Bias associated with the selection of these five datasets may be
substantial, and caution is advised in interpreting the results given in Table 7.17. The results are for
illustrative purposes and are not intended to be definitive risk estimates for NASA’s use in formulating
time-on-mission limits.

Table 7.18 provides complementary information on the posterior distribution for the difference
(female minus male) ERRs. Central estimates, when all 5 studies are included, ranged from 0.40 to 0.89.

7.4.3.2 What are the Excess Relative Risks for Females and Males from Chronic Exposure to Low-LET
radiation? Table 7.19 presents posterior distributions for ERR at 1 Gy for females and males from
chronic low-LET exposures. The results are for a (hypothetical) standard population with the same
baseline rates as assumed for the population of astronauts at attained age 70 y and exposure age 40 y.
Note that, for random-effects models, the excess risks could be different for the astronauts than for the
standard population. In general, central estimates (median and mean of the posterior distribution) are
remarkably robust to modeling assumptions and prior distributions assigned to the parameters. The 75th
percentile values are also somewhat robust to modeling assumptions. In contrast, the 95th percentile
values can differ by a factor of more than 2 depending on whether a fixed-effects model is assumed or,
alternatively, both random study and sex effects and nonsampling error are included in the model.

Table 7.20 also provides posterior distributions for the ERR at 1 Gy for low-LET chronic
exposures, but for the population of astronauts. The difference in what results in Tables 7.19 and 7.20
represent is a subtle one:

- Table 7.19 provides posterior distribution results for ERRs associated with a standard population
  which has the same baseline cancer rates as the astronauts.
- Table 7.20 provides results for the population of astronauts.

The results in Table 7.20, most notably at the 95th percentile, differ (from the results in Table
7.19) because it is at least conceivable that populations with the same baseline cancer rates might not have
the same excess radiogenic cancer risks. Note also, that median values are insensitive to what is assumed
(i.e., with respect to variation associated with study population and bias associated with nonsampling
error); 95 % values are even more volatile than those given in Table 7.19 for the standard nonsmoking
population.
Table 7.1 -- Posterior distribution for the difference in ERR at 1 Gy (female minus male) at attained age 70 y for an exposure age 40 y. Results are for a standard population of nonsmokers with the same baseline cancer rates as assumed for the astronauts.

<table>
<thead>
<tr>
<th>Method</th>
<th>Mean</th>
<th>Median</th>
<th>5 %</th>
<th>10 %</th>
<th>90 %</th>
<th>P(Diff&gt;0)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Main analysis (MA)</td>
<td>0.74</td>
<td>0.58</td>
<td>0.00</td>
<td>0.08</td>
<td>1.46</td>
<td>0.95</td>
</tr>
<tr>
<td>Fixed-Effects</td>
<td>0.89</td>
<td>0.87</td>
<td>0.53</td>
<td>0.60</td>
<td>1.21</td>
<td>1.00</td>
</tr>
<tr>
<td>No nonsampling error, informative prior</td>
<td>0.66</td>
<td>0.62</td>
<td>0.15</td>
<td>0.25</td>
<td>1.10</td>
<td>0.99</td>
</tr>
<tr>
<td>Nonsampling error</td>
<td>0.61</td>
<td>0.40</td>
<td>-0.09</td>
<td>-0.00</td>
<td>1.43</td>
<td>0.89</td>
</tr>
<tr>
<td>MA without LSS</td>
<td>0.20</td>
<td>0.06</td>
<td>-0.40</td>
<td>-0.22</td>
<td>0.74</td>
<td>0.63</td>
</tr>
<tr>
<td>MA without Mayak</td>
<td>1.04</td>
<td>0.68</td>
<td>-0.06</td>
<td>0.03</td>
<td>3.33</td>
<td>0.92</td>
</tr>
<tr>
<td>MA without MWS</td>
<td>1.62</td>
<td>1.03</td>
<td>-0.01</td>
<td>0.14</td>
<td>3.61</td>
<td>0.95</td>
</tr>
<tr>
<td>MA without NRRW</td>
<td>0.78</td>
<td>0.57</td>
<td>0.00</td>
<td>0.08</td>
<td>1.54</td>
<td>0.95</td>
</tr>
</tbody>
</table>
Table 7.1 -- Posterior distribution for ERR at 1 Gy at attained age 70 y after exposure at age 40 y for a standard population of nonsmokers with the same baseline cancer rates as assumed for the astronauts.

<table>
<thead>
<tr>
<th>Estimate Type</th>
<th>Percentile 5</th>
<th>Percentile 50</th>
<th>Percentile 75</th>
<th>Percentile 95</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main analysis (MA)</td>
<td>0.24</td>
<td>0.86</td>
<td>1.30</td>
<td>2.70</td>
<td>1.10</td>
</tr>
<tr>
<td>Fixed-effects</td>
<td>0.74</td>
<td>1.09</td>
<td>1.27</td>
<td>1.56</td>
<td>1.11</td>
</tr>
<tr>
<td>Informative prior</td>
<td>0.43</td>
<td>0.90</td>
<td>1.15</td>
<td>1.64</td>
<td>0.95</td>
</tr>
<tr>
<td>Nonsampling error</td>
<td>0.19</td>
<td>0.74</td>
<td>1.23</td>
<td>2.72</td>
<td>1.02</td>
</tr>
<tr>
<td>MA without LSS</td>
<td>0.04</td>
<td>0.37</td>
<td>0.72</td>
<td>2.04</td>
<td>0.63</td>
</tr>
<tr>
<td>MA without Mayak</td>
<td>0.23</td>
<td>1.07</td>
<td>1.79</td>
<td>4.49</td>
<td>1.55</td>
</tr>
<tr>
<td>MA without MWS</td>
<td>0.43</td>
<td>1.55</td>
<td>2.75</td>
<td>7.37</td>
<td>2.39</td>
</tr>
<tr>
<td>MA without NRRW</td>
<td>0.22</td>
<td>0.84</td>
<td>1.28</td>
<td>3.00</td>
<td>1.13</td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main analysis (MA)</td>
<td>0.07</td>
<td>0.26</td>
<td>0.42</td>
<td>0.96</td>
<td>0.36</td>
</tr>
<tr>
<td>Fixed-effects</td>
<td>0.11</td>
<td>0.22</td>
<td>0.27</td>
<td>0.35</td>
<td>0.22</td>
</tr>
<tr>
<td>Informative prior</td>
<td>0.13</td>
<td>0.27</td>
<td>0.36</td>
<td>0.54</td>
<td>0.29</td>
</tr>
<tr>
<td>Nonsampling error</td>
<td>0.07</td>
<td>0.29</td>
<td>0.49</td>
<td>1.12</td>
<td>0.41</td>
</tr>
<tr>
<td>MA without LSS</td>
<td>0.05</td>
<td>0.26</td>
<td>0.47</td>
<td>1.36</td>
<td>0.43</td>
</tr>
<tr>
<td>MA without Mayak</td>
<td>0.04</td>
<td>0.32</td>
<td>0.60</td>
<td>1.61</td>
<td>0.51</td>
</tr>
<tr>
<td>MA without MWS</td>
<td>0.11</td>
<td>0.47</td>
<td>0.90</td>
<td>2.48</td>
<td>0.77</td>
</tr>
<tr>
<td>MA without NRRW</td>
<td>0.06</td>
<td>0.24</td>
<td>0.39</td>
<td>0.98</td>
<td>0.34</td>
</tr>
</tbody>
</table>
Table 7.20 -- Posterior distribution for ERR at 1 Gy attained age 70 y after exposure at age 40 y.

Results are for a population of astronauts.

<table>
<thead>
<tr>
<th>Estimate Type</th>
<th>Percentile</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5</td>
<td>50</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main analysis (MA)</td>
<td>0.08</td>
<td>0.86</td>
</tr>
<tr>
<td>Informative prior</td>
<td>0.29</td>
<td>0.90</td>
</tr>
<tr>
<td>Nonsampling error</td>
<td>0.07</td>
<td>0.73</td>
</tr>
<tr>
<td>MA without LSS</td>
<td>0.02</td>
<td>0.34</td>
</tr>
<tr>
<td>MA without Mayak</td>
<td>0.07</td>
<td>1.06</td>
</tr>
<tr>
<td>MA without MWS</td>
<td>0.15</td>
<td>1.47</td>
</tr>
<tr>
<td>MA without NRRW</td>
<td>0.07</td>
<td>0.84</td>
</tr>
<tr>
<td>Males</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main analysis (MA)</td>
<td>0.02</td>
<td>0.25</td>
</tr>
<tr>
<td>Informative prior</td>
<td>0.09</td>
<td>0.26</td>
</tr>
<tr>
<td>Nonsampling error</td>
<td>0.03</td>
<td>0.28</td>
</tr>
<tr>
<td>MA without LSS</td>
<td>0.02</td>
<td>0.25</td>
</tr>
<tr>
<td>MA without Mayak</td>
<td>0.02</td>
<td>0.30</td>
</tr>
<tr>
<td>MA without MWS</td>
<td>0.04</td>
<td>0.43</td>
</tr>
<tr>
<td>MA without NRRW</td>
<td>0.02</td>
<td>0.23</td>
</tr>
</tbody>
</table>
7.4.3.3 What are the Lifetime Risks for Females and Males from Chronic Exposure to Low-LET radiation? Posterior distributions for the lifetime mortality risk (REID) associated with an exposure at age 40 y are given in Table 7.21. The risk values pertain to a hypothetical population of nonsmokers with the same baseline rates as assumed for the astronauts. The calculations (Equation 7.7) are based on the posterior distributions for ERR for exposure age 40 y and attained age 70 y (Table 7.19) and age patterns observed in LSS mortality data (see EAR model results given in Table 7.1). Results in Table 7.21 are given for models which are based on differing assumptions on how ERR varies by population and on the magnitude of the potential effects associated with nonsampling error. Central estimates are robust to these assumptions; in contrast, calculated 95% upper uncertainty bounds differ by as much as a factor of 2.

7.4.4 Limitations of Meta-Analysis Associated with the Selection of Studies

As stated previously, the results are for illustrative purposes and caution is advised in interpretation of the meta-analysis results due to limitations associated with the selection of available studies. This section describes features of studies that would most ideally be included in a meta-analysis.

Studies useful for astronaut risk assessment ideally include both males and females. For example, of the 6,484 lung cancer cases in the MWS pooled cohort (medical radiation workers + industrial radiographers + nuclear power plant workers), 475 were seen in females. Another study aspect important to consider for astronaut risk assessment is the degree of suitability for contemporary application (i.e., are the baseline rates on which the models are based directly applicable to contemporary occupational space radiation risk assessments?). Unfortunately, none of the considered cohorts have people from birth cohorts comparable to the astronauts. For example, Japanese atomic bomb survivors who were exposed at age 40 y in 1945 were born in 1905, as opposed to a typical birth cohort of 1980 or later for Mars astronauts. Given the secular trends in lung cancer rates, the LSS baseline rates will not cover the calendar years that are required for astronaut risk assessment, therefore assumptions and/or projections need to be made in the application of the risk models. These birth cohort issues pertain also to the MWS and Mayak worker cohorts.
Table 7.21 -- Posterior distribution for REID at 1 Gy for exposure at age 40 y. Results are for a standard population of nonsmokers with the same baseline cancer rates as assumed for the astronauts. Results given in Table 7.21 are based on the ERR at 1 Gy for attained age 70 y and exposure age 40 y (Table 7.19) and age patterns in ERR observed in LSS for mortality.

<table>
<thead>
<tr>
<th>Estimate Type</th>
<th>Percentile</th>
<th>5</th>
<th>50</th>
<th>75</th>
<th>95</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main analysis</td>
<td></td>
<td>0.10</td>
<td>0.35</td>
<td>0.57</td>
<td>1.30</td>
<td>0.49</td>
</tr>
<tr>
<td>Informative prior</td>
<td></td>
<td>0.18</td>
<td>0.37</td>
<td>0.49</td>
<td>0.73</td>
<td>0.39</td>
</tr>
<tr>
<td>Nonsampling error</td>
<td></td>
<td>0.10</td>
<td>0.39</td>
<td>0.66</td>
<td>1.51</td>
<td>0.56</td>
</tr>
<tr>
<td>Females</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Main analysis</td>
<td></td>
<td>0.19</td>
<td>0.65</td>
<td>0.99</td>
<td>2.04</td>
<td>0.84</td>
</tr>
<tr>
<td>Informative prior</td>
<td></td>
<td>0.33</td>
<td>0.68</td>
<td>0.87</td>
<td>1.24</td>
<td>0.72</td>
</tr>
<tr>
<td>Nonsampling error</td>
<td></td>
<td>0.14</td>
<td>0.56</td>
<td>0.93</td>
<td>2.05</td>
<td>0.77</td>
</tr>
</tbody>
</table>
At least equally important is the ability to adjust cohort lung cancer risks at a unit dose of radiation for the impact of smoking. Smoking history data are available for many members of the LSS and most members of the Mayak worker cohort but currently not for all of the MWS cohorts or the NRRW cohorts.

Some cohorts are based on mainly low-LET exposures [MWS pooled cohort (medical radiation workers + industrial radiographers + nuclear power plant workers)] and others have high-LET and low-LET exposures (LSS, Mayak workers, MWS LANL). Since, for astronaut risk assessment, it is advantageous to include risks at a unit high-LET dose and at a unit low-LET dose, two of the latter mentioned cohorts (Mayak workers, MWS LANL) are suitable for providing risk at a unit high-LET dose. A further consideration is that astronauts are continuously exposed to space radiation during missions, and not instantaneously exposed as the LSS cohort members were. From the point of view of suitable dose-rate conditions, all cohorts mentioned here except the LSS have the advantage of protracted exposure conditions.

7.5 Summary and Conclusions

Summary: NASA’s current risk models were derived from a single study (i.e., the LSS). This constrains inferences that can be made about health effects for chronic radiation exposures to a population of astronauts who differ from the atomic bomb survivors with respect to genetic, environmental, and lifestyle factors that might be potential modifiers of risk. Publicly available datasets (or estimates from customized requests to the authors of the original papers) were used to derive ERR and EAR estimates.

- The Life Span Study (mortality and incidence) [Section 3.2.4]
- Mayak Production Association [Section 3.2.2.1]
- MWS pooled estimates based on the cohorts of medical radiation workers, industrial radiographers, and nuclear power plant workers [Section 3.2.2.7.6]
- Los Alamos nuclear power plant workers [Section 3.2.2.7.1]
- U.K. National Registry for Radiation Workers [Section 3.2.2.2]
A Bayesian meta-analysis for combining information from these five datasets was described, and estimates were presented of ERR and lifetime risk for chronic low-LET radiation exposures for nonsmoker populations. The estimates (mean, median and other percentile values) were given for two types of populations: 1) a standard population with the same baseline cancer rates as is assumed for the astronauts, and 2) the population of astronauts. It is noted that two populations with the same baseline rates can have different excess risks associated with radiation exposure. Also examined was whether the studies provide evidence that radiogenic lung cancer risk for nonsmokers is greater for females than males.

Conclusions:

- The LSS and Mayak worker cohort provide reasonably precise estimates of ERR and EAR for nonsmokers, and data from these studies have the most influence on the meta-analysis. However, information from the pooled MWS cohorts and LANL also had a noticeable effect on some of the meta-analysis outcomes.
- Estimates of lifetime risk for never-smokers are sensitive to modeling choices. Lifetime risk estimates based on EAR models computed without smoking adjustment are overestimates for never-smokers and should not be used. While it is best to base lifetime risk estimates for a population of never-smokers on smoking-adjusted rate models, ERR models without smoking adjustment can provide more reasonable estimates of lifetime risk for never-smokers than unadjusted EAR models.
- For some studies (e.g., MWS and NRRW), reliable smoking data history is not currently available. For these studies, uncertainties associated with smoking-related effect modification and confounding are typically difficult to evaluate and can be sex-specific. Surrogates for smoking in the MWS cohorts have included education level, pay category (hourly, salaried), and job category.
- Results from the meta-analysis indicate a greater risk of radiogenic lung cancer for female nonsmokers than for male nonsmokers. A “main” analysis indicated a 94% probability that the radiogenic lung cancer risk is greater for females than males.

However, caution is advised regarding interpretation of results.
The strength of the evidence for a greater female risk depends on the set of studies selected for the analysis. Data from the LSS and Mayak worker cohort had the most influence on results from the meta-analysis. When the LSS (or Mayak) study was excluded from the analysis, the probability decreased to 65% (or 92%).

Inclusion of other suitable datasets in an expanded meta-analysis, once the datasets become available, may further influence the results for sex-specific lung cancer risks.

Results can also be sensitive to assumptions about study-to-study variation in risk and bias associated with nonsampling errors. Depending on underlying assumptions, probabilities range from about 0.88 to almost 1 that radiogenic lung cancer risk is greater for females than males; corresponding median estimates of the female-to-male ratio in excess risk range from about 3 to 5.

- Lifetime risk estimates (i.e., of REID), based on results from the Bayesian meta-analysis were also presented.
  - Central estimates of radiation risk (e.g., the median and mean of posterior probability distributions) for both females and males are robust to underlying assumptions (e.g., on study-to-study variation and the size of nonsampling error). The 75th percentile posterior distribution values are also reasonably robust to underlying assumptions.
  - The meta-analysis indicates that upper uncertainty bound limits (e.g., 95th percentile values of posterior distributions) for lifetime radiogenic lung cancer risk are highly dependent on underlying assumptions. These results can also depend on how the target population is defined. The target population might be defined as a “standard” population of U.S. never-smokers with mortality rates determined from surveys such as those conducted by the American Cancer Society (e.g., the Cancer Prevention Study CPS-II). Alternatively, the target population might be defined as the population of astronauts, for whom baseline mortality rates are assumed to be equal to rates for U.S. never-smokers, but for whom radiogenic risk may differ.
8. Recommendations

8.1 Epidemiologic Studies of Lung Cancer Risk and Female-Male Differences

- Existing studies should be enhanced by obtaining smoking histories for both males and females.
- Additional epidemiologic studies should address chronic radiation exposure of the lung in relevant human populations to evaluate sex-specific differences in lung cancer risk. Emphasis should be on populations of nonsmokers.
- Studies of human populations with exposure to high-LET radiation experienced on Earth (such as alpha particles resulting from intakes of radionuclides) should be included. While such radiations are qualitatively different from galactic cosmic rays that are pervasive in space, studies where such radiations are present might provide useful insights.

8.2 Biological Data and Animal Experiments to Assess Female-Male Differences in Lung Cancer Risk

- Radiation biology studies and animal experiments should investigate whether the sex difference in radiogenic lung cancer risk observed in some epidemiologic studies is real and, if so, identify the biological mechanism(s) responsible for the difference. Recommended areas of such research are detailed in Sections 4.4 and 5.4, respectively, which include efforts to replicate the sex difference:
  - directly in carcinogenesis experiments in conventional and genetically modified animals; and
  - indirectly through experiments in animals, humanized animals, and engineered human lung tissue employing robust biomarkers specifically linked to lung carcinogenesis (bioindicators) as endpoints.

These efforts should be informed by known molecular pathology differences between lung cancers arising in human males and females.
8.3 Modeling Lung Cancer Risk Projections for Astronauts

- The NASA EAR models should be replaced with models that allow for smoking adjustment (Section 7.2). NASA’s current approach likely results in overestimates in lifetime risk projections (i.e., for both REIC and REID) because the NASA EAR model was derived from a population that included smokers.

- NASA should develop risk models for radiogenic lung cancer based on an approach that combines information from the LSS and other epidemiologic studies, particularly those for which the exposures include a chronic component. This Commentary suggests the Bayesian meta-analytic approach detailed in Section 7.4. It is stressed that the results given in Section 7.4 are for illustrative purposes only. The Bayesian meta-analysis should be based on updated results from the studies already considered in this Commentary and results from other studies as data become available. To the extent possible, NASA should reach out to researchers involved in the relevant studies to obtain sufficiently detailed information for risk estimation. The most informative studies would have estimates of lung dose for the individual subjects and quantitative estimates of the radiation dose response.
Glossary

95 % confidence level: In this Commentary, refers to the 95 % confidence level on the standard of 3 % risk of exposure-induced death (REID) for cancer, as implemented in NASA (2014).

absorbed dose (D): The quotient of \( d_e \) by \( dn \), where \( d_e \) is the mean energy imparted to matter of mass \( dn \) (i.e., \( D = d_e/dn \)). The unit for \( D \) is joule per kilogram (J kg\(^{-1}\)) with the special name gray (Gy).

astronaut: In this Commentary, any flight crew member that takes part in a NASA space flight.

background radiation: (see natural background radiation).

cancer: A general term for more than 100 diseases characterized by abnormal and uncontrolled growth of cells.

carcinogenesis: Induction of cancer by radiation or any other agent (a somatic effect).

CA repeat (cytosine-adenine dinucleotide repeat): A short sequence of DNA consisting of multiple repetitions of a set of two to nine base pairs, used as a genetic marker when individuals differ in the number of repetitions.

CD4+/CD8+ ratio: Ratio of T helper cells (with the surface marker CD4) to cytotoxic T cells (with the surface marker CD8).

charged particle: An atomic or subatomic quantity of matter (e.g., electron, proton, alpha particle, ionized atom) having a net positive or negative electrical charge of one or more elementary units of charge.

confidence interval (CI): A measure of the extent to which an estimate of risk, dose or other parameter is expected to lie within a specified interval (e.g., a 95 % CI of a risk estimate means that, based on available information, the probability is 0.95 that the true but unknown risk lies within the specified interval).

crew member: (see astronaut).

current smoker: An adult who has smoked 100 cigarettes in his or her lifetime and who currently smokes cigarettes.

deoxyribonucleic acid (DNA): Genetic material of cells; a complex molecule of high molecular weight consisting of deoxyribose, phosphoric acid, and four bases which are arranged as two long chains that twist around each other to form a double helix joined by hydrogen bonds between the complementary components.

dose: A general term used when the context is not specific to a particular dose quantity. When the context is specific, the name for the quantity is used (e.g., absorbed dose in the lung).
dose and dose-rate effectiveness factor (DDREF): A judged factor that generalizes the usually lower biological effectiveness (at a unit dose) of radiation exposures at low doses and low dose rates as compared with exposures at high doses and high dose rates.

dose rate: Dose delivered per unit time. Can refer to any dose quantity (e.g., absorbed dose in the lung).

ever-smoker: A person who has smoked at least one hundred cigarettes and cigars during the course of his or her life.

excess absolute risk (EAR): The rate of disease in an exposed population minus the rate of disease in an unexposed population.

excess rate (cancer): Refers to the rate of cancer incidence or mortality in an exposed population minus the corresponding rate in an unexposed population, for the particular model conditions being discussed. In this Commentary, the focus is on the excess rate for lung cancer. The excess absolute risk (EAR) also describes an excess rate [see excess absolute risk (EAR)].

excess relative risk (ERR): The rate of disease in an exposed population divided by the rate of disease in an unexposed population minus 1.0.

exposure: In this Commentary, exposure is used in a general sense meaning to be irradiated.

former smoker: An adult who has smoked at least 100 cigarettes in his or her lifetime but who had quit smoking at the time of interview.

fluence: The quotient of the number of particles incident on a sphere of cross-sectional area. The unit for fluence is m⁻², commonly given in cm⁻².

galactic cosmic radiation: The charged-particle radiation outside the magnetosphere comprised of 2% electrons and positrons, and 98% nuclei, the latter component consisting (by fluence) of 87% protons, 12% helium ions, and 1% high atomic number, high-energy (HZE) particles.

gamma ray: Short-wavelength electromagnetic radiation of nuclear origin (approximate range of energy: 10 keV to 9 MeV).

gray (Gy): The special name for the SI unit J kg⁻¹ (i.e., energy imparted per mass of a material) (see absorbed dose). 1 Gy = 1 J kg⁻¹.

high atomic number, high-energy (HZE) particles: Ions with an atomic number greater than that of helium (e.g., boron, carbon, nitrogen, neon, argon, or iron ions) that are positively charged and have high kinetic energy.

incidence: The rate of occurrence of a disease, usually expressed in number of cases per million.

inverse dose-rate effect: A more efficient inactivation of cells at lower rather than at higher dose rates.

ionizing radiation: Any electromagnetic or particulate radiation capable of producing ions, directly or indirectly, in its passage through matter.
Life Span Study (LSS): Life-span study of the Japanese atomic bomb survivors; the sample consists of 93,741 persons (in city) of whom 86,572 survivors have a defined dose assigned to them.

lifetime risk: The probability during one’s lifetime of expressing a given health outcome.

linear-energy transfer (LET): Mean energy lost per unit of particle track length, usually expressed in keV μm⁻¹.

low-LET: Radiation having a low linear-energy transfer (e.g., electrons, x rays, gamma rays).

high-LET: Radiation having a high linear-energy transfer (e.g., energetic protons, alpha particles, ions with an atomic number greater than that of helium, interaction products of fast neutrons).

low-Earth orbit (LEO): An Earth-centered orbit with an altitude of 2,000 km (1,200 mi) or less.

mean absorbed dose: The mean absorbed dose in an organ or tissue, obtained by integrating or averaging absorbed doses at points in the organ or tissue.

messenger RNA: A large family of RNA molecules that convey genetic information from DNA to the ribosome, where they specify the amino acid sequence of the protein products of gene expression.

natural background radiation: The amount of radiation to which a member of the population is exposed from natural sources, such as terrestrial radiation from naturally occurring radionuclides in the soil, cosmic radiation originating in outer space, and naturally occurring radionuclides deposited in the human body. The natural background radiation received by an individual depends on geographic location and living habits.

neutron: A particle with a mass similar to that of a proton, but with no electrical charge. Because a neutron is electrically neutral, it cannot be accelerated in an electrical field.

never-smoker: An adult who has never smoked, or who has smoked <100 cigarettes in his or her lifetime.

nonsmoker: In this Commentary nonsmoker is synonymous with never-smoker (see never-smoker).

personal dose equivalent (at 10 mm): An operational quantity used in personal monitoring. In this case, measured at a depth of 10 mm. Expressed in sievert (Sv), the special name of the SI unit for operational quantities. 1 Sv = 1 J kg⁻¹.

polymorphism (genetics): The presence of genetic variation within a population, upon which natural selection can operate.

protons: The nucleus of the hydrogen atom. A proton is positively charged.

quality factor (for HZE particles): In this Commentary, subjective judgments of experimental determinations of maximum RBE factors determined as the ratio of initial slopes for linear dose-response curves for HZE particles compared to gamma rays. [see relative biological effectiveness (RBE)].
radiation: (1) The energy propagated as waves; radiation or radiant energy, when unqualified, usually refers to electromagnetic radiation; commonly classified by frequency (e.g., infrared, visible, ultraviolet, x rays, and gamma rays), and (2) corpuscular emission, such as alpha and beta particles, or galactic cosmic radiation (see galactic cosmic radiation).

radiation quality: A general term referring to the spatial distribution of absorbed dose. For example, an exposure to neutron radiation may be quantitatively the same as an exposure to gamma rays, in the sense that, for large volumes of tissue on the order of 1 cm$^3$, the absorbed energy is the same, yet at resolutions of a few micrometers the ionizing events will be more uniformly dispersed for the gamma-ray radiation than for the neutron radiation, producing quantitatively different biological effects (see relative biological effectiveness).

relative biological effectiveness (RBE): A factor used to compare the biological effectiveness of absorbed doses from different types of ionizing radiation, determined experimentally. RBE is the ratio of the absorbed dose of a reference radiation to the absorbed dose of the radiation in question required to produce an identical biological effect in a particular experimental organism or tissue.

relative risk: The ratio of the risk of a given disease in those exposed to the risk of that disease in those not exposed.

risk: The probability of a specified effect or response occurring.

risk estimate: The number of cases (or deaths) that are projected to occur in a specified exposed population at a unit dose for a defined exposure regime and expression period.

standardized mortality ratio: The ratio of the mortality rate from a disease in the population being studied to the comparable rate in a standard population.

upper 95% confidence limit: In this Commentary, the upper bound of the 95% confidence interval of the probability distribution function for the cancer risk projection for space missions (see confidence interval).

weighted dose (in an organ): In this Commentary, the weighted dose accounts for the increased biological effectiveness of high-LET components of radiation exposure. This quantity consists of the mean absorbed dose in the organ from low-LET components plus the weighted mean absorbed doses in the organ from high-LET components, where each high-LET mean absorbed dose component is multiplied by a judged weighting factor, as provided by the investigator. The quantity is expressed in gray.
Abbreviations, Acronyms and Symbols

- $\beta$  tissue-specific statistical error
- AIC  Akaike Information Criterion
- AKT  also known as PKB (protein kinase B)
- ALK, ALK  anaplastic lymphoma kinase (gene, protein) (human)
- AR  absolute rate (transport)
- ARHGAP35  Rho GTPase activating protein 35 (gene) (human)
- BRAF  B-Raf proto-oncogene, serine/threonine kinase (gene) (human)
- BRCA  breast cancer (gene) (human)
- CA  cytosine-adenine (dinucleotide)
- CI  confidence interval
- CPS  Cancer Prevention Studies [CPS-I (1959 to 1972); CPS-II (1982 to 2000)]
- CXCR4  C-X-C chemokine receptor type 4
- CYP1A1  cytochrome P450 family 1 subfamily A member 1 (gene) (human)
- CYP1A1  cytochrome P450 family 1 subfamily A member 1 (protein) (human)
- DDREF  dose and dose-rate effectiveness factor
- DNA  deoxyribonucleic acid
- EAR  excess absolute risk
- EAR$_c$  cause-specific radiation-associated excess cancer rate
- EGF  epidermal growth factor
- EGFR, EGFR  epidermal growth factor receptor (gene, protein) (human)
- Egfr  epidermal growth factor receptor (gene) (mouse)
- ER-$\alpha$  estrogen receptor alpha
- ER-$\beta$  estrogen receptor beta
- ERCC2  excision repair cross-complementing group 2 (gene) (human)
- ERK  extracellular signal-regulated kinase
- ERR  excess relative risk
- ERRB2  v-erb-b2 avian erythroblastic leukemia viral oncogene homolog 2 (gene) (human)
- GRPR, GRPR  gastrin-releasing peptide receptor (gene, protein) (human)
- GSTM1  glutathione S-transferase mu 1 (gene) (human)
- HER-2  human epidermal growth factor receptor 2 (gene) (human)
- HZE  high atomic number ($Z$), high-energy
- indel  insertion or deletion mutation
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<tr>
<td>INWORKS</td>
<td>International Nuclear Workers Study</td>
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<tr>
<td>KRAS, KRAS</td>
<td>Kirsten rat sarcoma viral oncogene homolog (gene, protein) (human)</td>
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<tr>
<td>Kras, Kras</td>
<td>Kirsten rat sarcoma viral oncogene homolog (gene, protein) (mouse)</td>
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<td>LANL</td>
<td>Los Alamos National Laboratory</td>
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<td>SMT</td>
<td>linear-energy transfer</td>
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<td>LSS</td>
<td>Life Span Study (Japanese atomic bomb survivors)</td>
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<td>MA</td>
<td>main analysis</td>
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<td>MAPK</td>
<td>mitogen-activated protein kinase</td>
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<td>MCMC</td>
<td>Markov Chain Monte Carlo (sampling technique)</td>
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<td>MET</td>
<td>MET proto-oncogene, receptor tyrosine kinase (gene) (human)</td>
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<td>MWS</td>
<td>One Million U.S. Workers and Veterans Study of Low-Dose Radiation Health Effects</td>
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<td>RBE</td>
<td>relative biological effectiveness</td>
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<td>REIRS</td>
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<td>RMUT</td>
<td>driver mutations in genes encoding receptor proteins</td>
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