A historical survey of key epidemiological studies of ionizing radiation exposure

Mark P. Little[a b 1], Dimitry Bazyka[c], Amy Berrington de Gonzalez[d], Alina V. Brenner[e], Vadim V. Chumak[c], Harry Cullings[e], Robert D. Daniels[f], Benjamin French[g], Eric Grant[e], Nobuyuki Hamada[h], Michael Hauptmann[i], Gerald M. Kendall[j], Dominique Laurier[k], Choonsik Lee[a], Won Jin Lee[l], Martha S. Linet[a], Kiyohiko Mabuchi[a], Lindsay M. Morton[a], Colin R. Muirhead[m], Dale L. Preston[n], Preetha Rajaraman[e], David B. Richardson[o], Ritsu Sakata[e], Jonathan M. Samet[p], Steven L. Simon[a], Hiromi Sugiyama[e], Richard Wakeford[q], Lydia B. Zablotska[r]

[a]Radiation Epidemiology Branch, National Cancer Institute, Bethesda, MD 20892-9778, USA

[b]Faculty of Health and Life Sciences, Oxford Brookes University, Headington Campus, Oxford, OX3 0BP, UK

[c]National Research Center for Radiation Medicine, 53 Melnikov Street, Kyiv 04050, Ukraine

[d]Division of Genetics and Epidemiology, Institute of Cancer Research, London, UK

[e]Radiation Effects Research Foundation, 5-2 Hijiyama Park, Minami-ku, Hiroshima 732-0815, Japan

[f]National Institute for Occupational Safety and Health, Cincinnati, OH, USA

[g]Department of Biostatistics, Vanderbilt University Medical Center, Nashville, Tennessee, USA

[h]–Biology and Environmental Chemistry Division, Sustainable System Research Laboratory, Central Research Institute of Electric Power Industry (CRIEPI), 1646 Abiko, Chiba 270-1194, Japan

[i]Institute of Biostatistics and Registry Research, Brandenburg Medical School Theodor Fontane, Fehrbelliner Strasse 38, 16816 Neuruppin, Germany

[j]Cancer Epidemiology Unit, Nuffield Department of Population Health, University of Oxford,

Richard Doll Building, Old Road Campus, Headington, Oxford, OX3 7LF, UK.

[k]Institute for Radiological Protection and Nuclear Safety, Fontenay aux Roses France

[l]Department of Preventive Medicine, Korea University College of Medicine, Seoul, South Korea

[m]Newcastle upon Tyne, UK.

[n]Hirosoft International, Eureka, California 95501, USA

[o]Environmental and Occupational Health, 653 East Peltason, University California, Irvine, Irvine, CA 92697-3957 USA

[p]Department of Epidemiology, Colorado School of Public Health, Aurora, Colorado, USA

[q]Centre for Occupational and Environmental Health, The University of Manchester, Ellen Wilkinson Building, Oxford Road, Manchester, M13 9PL, UK

[r]Department of Epidemiology and Biostatistics, School of Medicine, University of California, San Francisco, 550 16th Street, 2nd floor, San Francisco, CA 94143, USA

Running title: Review of radiation epidemiology

[1]**Address for correspondence:** Radiation Epidemiology Branch, National Cancer Institute, 9609 Medical Center Drive, Bethesda, MD 20892-9778, USA, email mark.little@nih.gov, tel +1 240 276 7375, fax +1 240 276 7874

Abstract

Little, M.P., Bazyka, D., Berrington de Gonzalez, A., Brenner, A.V., Chumak, V.V., Cullings, H., Daniels, R.D., French, B., Grant, E., Hamada, N., Hauptmann, M., Kendall, G.M., Laurier, D., Lee, C., Lee, W.J., Linet, M.S., Mabuchi, K., Morton, L.M., Muirhead, C.R., Preston, D.L., Rajaraman, P., Richardson, D.B., Sakata, R., Samet, J.M., Simon, S.L., Sugiyama, H., Wakeford, R., Zablotska, L.B., A historical survey of key epidemiological studies of ionizing radiation exposure. *Radiat. Res.*

In this article we review the history of key epidemiological studies of populations exposed to ionizing radiation. We highlight historical and recent findings regarding radiation-associated risks for incidence and mortality of cancer and non-cancer outcomes with emphasis on study design and methods of exposure assessment and dose estimation along with brief consideration of sources of bias for a few of the more important studies. We examine the findings from the epidemiological studies of the Japanese atomic bomb survivors, persons exposed to radiation for diagnostic or therapeutic purposes, those exposed to environmental sources including Chornobyl and other reactor accidents, and occupationally exposed cohorts. We also summarize results of pooled studies. These summaries are necessarily brief, but we provide references to more detailed information. We discuss possible future directions of study, to include assessment of susceptible populations, and possible new populations, data sources, study designs and methods of analysis.

INTRODUCTION

Within a year of the discovery of X-rays in 1895, the first few cases of radiation-associated erythemal and other acute effects of radiation exposure were documented (one case being Thomas Edison) (*1*, *2*) and a few years later a radiation induced skin cancer was reported in a worker at a factory making X-ray tubes (*3*). A few years after its discovery radiation was being used for medical diagnosis and therapy, and after World War II there was an increasingly large number of workers exposed at various steps of the nuclear fuel production and use cycle, including uranium mining and processing, nuclear weapons production and power generation. While the growth in exposures from artificial sources of radiation exposure attracts most attention, naturally occurring radiation, in particular, the inhalation of radon and its decay products is a common source of exposure to the general population. Many of the exposed populations have been studied to assess risks of a variety of cancers and other serious health effects, and these studies, particularly of the survivors of the two atomic bombings in Japan have been instrumental in establishing radiation safety standards (*4*).

The present article surveys the history of the major epidemiological studies of radiation-exposed groups. We shall concentrate attention on studies in which risks can be assessed in relation to dose, generally organ dose. However, we also include studies of groups exposed to radon and certain exposures to high LET radiation, where risks have been evaluated in relation to time integrated activity (e.g., Bq m^{-3} y^{-1}) or in the case of miners exposed to radon, working level months. In particular we do not consider the various studies of radium dial workers (*5*, *6*) or the studies of persons who received the diagnostic contrast medium Thorotrast (*7*), in which generally risks have been estimated in relation only to administered activity. A critical part of many of the~~se~~

studies that we include in the review is the assessment of radiation dose to the relevant organs or tissues, which we discuss first. We then consider the findings from epidemiological studies of the Japanese atomic bomb survivors, persons exposed medically to radiation for diagnostic or therapeutic purposes, those exposed to environmental sources including Chornobyl and other reactor accidents, and occupationally exposed cohorts. We also summarize results of pooled studies. In all sections we provide a historical overview of the field and concentrate attention on the most current and informative studies, whilst calling attention where relevant, for the more important studies, to possible sources of bias; more detailed assessments of study strengths and weaknesses are given elsewhere (*8-11*). We conclude with discussion of possible future directions of study, to include assessment of susceptible populations, persons exposed to radiation sources not previously or well-studied, and new data sources and methods of analysis. In all that follows, unless stated to the contrary all quoted results are statistically significant (2-sided $p \leq 0.05$). In a few cases we refer to borderline significant findings (2-sided $0.05 < p \leq 0.1$).

IONIZING RADIATION DOSIMETRY FOR EPIDEMIOLOGICAL STUDIES

Radiation dose is of fundamental importance to radiation epidemiology because of the interest in quantifying the relationship between organ dose and occurrence of radiation associated disease. Radiation *absorbed dose* is defined as the absorbed energy per unit mass of the irradiated material where tissues and body organs are of primary interest to epidemiology. To support radiation protection as well as radiation epidemiology, the discipline of *dosimetry* has evolved which is based on our understanding of the physics of radiation interactions with matter. The application of dosimetry is usually termed *dose assessment* or *dose reconstruction*. The scientific underpinnings of radiation dosimetry (*12-16*) and application of dosimetry to organ dose estimation for exposed individuals are described in detail elsewhere (*16, 17*). Briefly, radiation dosimetry is based on the theories of energy transfer from indirectly ionizing radiation to directly ionizing radiation which occurs through a cascade of interactions in tissue by the release of photoelectrons followed by Compton scattering. Through those processes, the incident energy is dissipated in the tissue and is the basis for organ radiation dose and radiation damage. Given that it is impossible to directly measure the deposition of radiation energy in human tissue, quantifying these processes, which is based on our understanding of physics, necessarily involves calculation, although calculations are often supported by measurements. Those measurements may be individualized to persons, such as person~~ane~~l dosimeters worn on the outside of the body to estimate dose from external radiations that penetrate tissue, or bioassay measurements of radionuclides deposited in the body, such as measurements of excreted radionuclides in urine or feces. Another type of measurement of radiations emitted by internally deposited radionuclides is a bioassay of γ-rays emitted by various radionuclides (e.g., ^{137}Cs) using whole-body monitoring or by radioiodines in the thyroid using radiation detectors placed near the neck of the subject. Estimates of absorbed energy in tissue (i.e., dose) may also be derived from calculations that first quantify the intake rate of radioactive materials, ~~generally~~ through ingestion~~, but also through~~ and inhalation. Calculations at the whole-body or organ level for internal and external dose are accomplished with mathematical descriptions of the geometry and composition of the human body (phantoms), again using principles of radiation physics described by probabilities of various interactions that radiations undergo as they pass through air and penetrate human tissue. In the case of internally deposited radionuclides, the calculations must track units of radionuclide as they enter the body and are metabolized by the body, up to the point of excretion, if this happens, bearing in mind that radionuclides reside in the body for characteristic times, using data on the metabolism of the element and chemical form involved in a particular radionuclide. Although some calculations are done with deterministic methods using equations, many~~most~~ modern calculations are done with Monte Carlo methods that probabilistically track theoretical individual particles as they propagate. In this section, we discuss how dosimetry has been applied for purposes of epidemiology for ionizing radiation.

Dosimetry for the Japanese Atomic Bomb Survivors

Dose estimation for survivors of the atomic bombs in Japan in 1945 has played a crucial role in epidemiological studies whose findings have laid the foundation for radiological~~ation~~ protection in many countries. Dose estimation for atomic bomb survivors is primarily based on self-reported information on location in conjunction with estimate~~ion~~s of air kerma (a close approximation of the dose to air) at the location of each exposed person because of prompt γ-rays and neutrons released in the detonation, also slightly later arising radiation (mostly within about 1 min) from the fireball (*18*, *19*). Accounting for building and body shielding allows the estimation of whole-body dose.

Because location of survivors at the time of the detonation is critical to dose estimation, many of the survivors from the bombings were interviewed from the late 1940s onwards, and especially during the 1950s, to establish their exact position in the two cities (Hiroshima and Nagasaki), as well as the direction they were facing relative to the bombs and location on drawings of neighboring shielding structures (shielding histories). A number of initial individual dose estimates were constructed based on this information, beginning in the late 1950s using the Tentative 1957 Dosimetry (T57D) system (*20*), and in the mid-1960s the Tentative 1965 Dosimetry (T65D) and a slightly revised T65DR dosimetry (*21*). The T65DR doses implied a substantial neutron component of the dose, particularly in Hiroshima, and this in turn led to the realization in the late 1970s that T65DR neutron doses were too high, implying that neutron relative biological effectiveness (RBE) was higher than had been previously assumed. Partly as a result, a revised set of estimates via the Dosimetry System 1986 (DS86), were produced (*18*) which yielded very much lower estimates of neutron dose. DS86 used new calculations of radiation emission and transport in an air-over-ground environment based on first principles of radiation physics (*18, 22*). DS86 created model house clusters and detailed calculations of shielding at a number of positions inside and outside the houses that could be adapted by combinatorics to the shielding history data that had been collected on survivors. DS86 also calculated body self-shielding for the first time, using a set of three phantoms (infant, child, adult) constructed of basic geometrical shapes and calculating dose to 15 different organs (*18, 22*). Due primarily to a controversy about neutron activation measurements in environmental samples in Hiroshima and Nagasaki, a further refinement was Dosimetry System 2002 (DS02) (*19*). DS02 recalculated the source term and radiation transport with the latest methods, including changes in the estimated yields and heights of burst of the bombs, and took account of measurements of environmental samples that had been made in Hiroshima and Nagasaki by thermoluminescent dosimetry (γ-ray dose) and neutron activation analysis (*18*). DS02 in turn was modified by an extensive review and collation of various versions of survivor shielding data, resulting in DS02R1, the version representing the largest source of changes in dosimetry resulting from improved assessment of terrain shielding (*23*). Recent work using updated (and more realistic) phantoms in the Life Span Study (LSS) cohort suggested doses could be up to 20% different for certain organs, with more substantial changes in neutron dose (*24*).

There is so little neutron exposure in the LSS from DS86 onwards that inference on neutron relative biological effectiveness (RBE) is quite problematic. Little (*25*) and Cordova and Cullings (*26*) highlight the quite large central estimates of RBE, albeit with substantial uncertainties, that can be obtained. Care has to be taken, as was done in both these studies, to make sure that inferences on neutron RBE are not confounded by city differences. Hafner *et al* (*27*) illustrate how very high assumed neutron RBEs can lower the risk estimate, and also change the shape of the dose response for certain cancer endpoints. In most current analyses weighted absorbed dose (gamma dose + 10 x neutron dose) is used (*23*, *28-39*).

Dosimetry Methods for Medical Radiation Procedures

Patient exposure from diagnostic radiation procedures.

External diagnostic x-ray procedures include radiography, fluoroscopy (both diagnostic and interventional), and computed tomography (CT). Calculating organ doses for patients undergoing these diagnostic and therapeutic procedures relies heavily on pre-calculated organ dose conversion coefficients. The coefficients are applied to simplified dose descriptors commonly used as operational quantities in clinical settings: dose or kerma area product (DAP or KAP) for radiography and fluoroscopy, and CT dose index (CTDI) for CT scans. For patients undergoing diagnostic or therapeutic procedures more recently, the necessary dose descriptors can be obtained from medical records or from patient electronic files. Monte Carlo radiation transport techniques, coupled with computerized human anatomy models (*40*) are employed to derive conversion coefficients for various exposure scenarios and geometries (*41-44*) and CT (*40*, *45-49*). More complicated methods with higher associated uncertainties in individual doses need to be applied for estimation of doses from diagnostic radiation procedures in historical cohorts (*50*). The Massachusetts tuberculosis (TB) fluoroscopy study (*51*) included medical record abstraction, physician interview, patient contact, and calendar year specific machine exposure measurements. The methodology considered breast size and composition, patient orientation, X-ray field size and location, beam quality, type of examination, machine exposure rate, and exposure time during fluoroscopic examinations (*51*). Computerized human anatomy models could be used with adjustments for specific conditions of exposed populations (*52-54*).

Patient exposure from therapeutic radiation procedures.

External beam radiotherapy (RT) planning involves calculating radiation doses for tumor and nearby tissues. Two crucial components in dose reconstruction for RT patients are (i) dose calculation algorithms and (ii) human anatomy models. Dose calculation algorithms fall into three categories: measurement-based dose matrix, analytical dose calculation algorithms, and Monte Carlo radiation transport algorithms. The first involves physical dose measurements in water or air-irradiated radiation produced by linear accelerators (LINACs) (*55, 56*). The second is analytical dose calculation methods (*57, 58*) which are widely used in treatment planning but may not be suitable for regions far from treatment fields. The third is Monte Carlo radiation transport techniques (*59-61*). The second component of dosimetry for RT patients involves patient anatomy models, ranging from simplistic mathematical models (*55, 56*) to realistic image-based computational human models (*40, 60*) and patient-specific CT images used for treatment planning. In recent decades, a range of combinations involving dose calculation algorithms and patient anatomy models, as mentioned earlier, have been utilized in epidemiological investigations following up patients who underwent RT for cancer and other late serious health effects.

Patient exposure from diagnostic and therapeutic nuclear medicine procedures.

Dosimetry methods for patients undergoing nuclear medicine procedures derive from the Medical Internal Radiation Dose (MIRD) formalism for radionuclide energy spectra, which was first introduced in the 1960s (*62*) and has been continuously updated (*63-66*) nuclide energy spectrum. Biokinetic data, outlining the radionuclide distribution in the human anatomy, is derived from multi-compartmental models and a system of linear differential equations that are provided by the

International Commission on Radiological Protection (ICRP) publications (*67-69*). Energy transfer data within the human anatomy are obtained from computational human anatomy models, employing Monte Carlo radiation transport techniques (*70, 71*). The third component, radionuclide energy spectra, is established in ICRP Publication 107 (*72*). Various tools for organ dose calculations, based on these three dosimetry components, are available for dosimetrists to utilize in epidemiological studies of nuclear medicine patients (*73-79*).

Dosimetry for Medical Workers Studies

Occupational exposure to medical radiation primarily occurs during diagnostic radiology, although particularly high doses are incurred via interventional fluoroscopy and nuclear medicine procedures, where physicians, nurses or radiological technologists work in close proximity to radiation sources (*80*). The reconstruction of organ doses for medical radiological personnel relies on several factors, including work history, personal dose~~i~~meters, and organ dose conversion coefficients. Work history information can be gathered through surveys administered to study subjects while measurements using thermoluminescent dose~~i~~meters (TLDs), film badges, and electronic personal dose~~i~~meters (EPDs) are often placed on the worker's body to assess radiation exposure. Organ dose conversion coefficients for occupational exposure (*81-83*) are determined through computer simulations that consider various exposure geometries and X-ray characteristics distinct from those encountered in diagnostic X-ray patients. Simon *et al* (*84*) describes in detail the application of work history, use of personal dose~~i~~meters, organ dose coefficients, and shielding provided by protective lead aprons to a cohort of radiological technologists, as does Yoder *et al* (*85, 86*) in another group of medical radiation workers.

Dosimetry for Nuclear Workers Studies

Dose estimation for workers in nuclear industries is also an important application of dose reconstruction techniques and in ways similar to dose estimation for other radiation sources, it embodies calculations necessary to characterize both external and internal exposures. Nuclear worker studies are often advantaged by having individual measurements of radiation exposure via personal dose~~i~~meters (external exposure) and, in some cases, bioassay or whole-body counting data (internal exposure) (*87*). In general, most but not all historical studies (*88*) have used recorded doses as a ~~reasonable~~ proxy for organ absorbed dose (*87*). Bioassay information is sometimes available, though usually only for the most highly exposed workers. When bioassay data are available, dose estimates are derived from generalized radionuclide-specific biokinetic models that are published by international authorities or are developed in special occupational circumstances using bioassays, biokinetic models, and autopsy evaluations of radiation workers (*89*, *90*). In ways similar to dose reconstruction for medical workers, the main considerations for dose estimation include work history, data from personal dose~~i~~meters, and organ dose conversion coefficients. Work history would include job type(s), the possible exposure modalities (external vs. internal), time spent exposed, worker orientation (for some studies) and the type and degree of safety precautions utilized. A recent National Council on Radiation Protection and Measurements (NCRP) report details how dose calculations in two workforces with exposure to a mixture of low LET and high LET radiation can be used to evaluate radiation risk (*88*).

Dosimetry for Exposures from Naturally Occurring Radiation.

Naturally occurring radiation which potentially exposes people~~man~~ includes (i) γ-rays emitted from the decay of radionuclides in the earth’s crust and from within our own bodies, in particular, from radionuclides that are part of the well-known uranium and thorium decay chains and from potassium-40 (*91*), (ii) from the radioactive gases radon and thoron, which are created when other naturally occurring elements undergo radioactive decay, and from (iii) space, i.e., cosmic radiation. Exposure to naturally occurring radiation (*92, 93*) occurs for most people during normal living and working situations though exposures can also be enhanced by participation in certain occupations, e.g., enhanced doses to the lungs from radon and its progeny can be received by uranium miners, and enhanced whole-body doses from cosmic rays can be received by those working at higher-than-typical altitudes, e.g., aircrew and spacecrew (astronauts) (*94*).

Radon

The causal association of radon with lung cancer results from alpha particles released by the decay of two of its progeny, ^{218}Po (half-life ~3 minutes) and ^{214}Po (half-life ~0.0002 seconds) (*95*). While radon is a gas, these progeny are particulate and a variable proportion bind with other matter in the air in the so-called "attached fraction" (*95*). The critical malignancy-causing dose of α energy is delivered by progeny that have deposited on the bronchial epithelium. The α particles released by the two polonium progeny have sufficient energy to penetrate to cells in the basal layer of the epithelium and damage their DNA. The pattern of deposition varies with the size of the particles in the attached fraction, along with the rate and depth of breathing. Deposition varies between children and adults (*95*). Lung dosimetry models have long been available to calculate the dose of α energy delivered to the lung, given the concentration of inhaled radon progeny. Consideration of lung dosimetry is critical in extrapolating risks from studies of underground miners to exposures indoors; however, there are more direct estimates of risks from indoor radon exposure (*96, 97*).

Cosmic and other non-radon terrestrial radiation

The variations of doses received by the public primarily reflect the variations in the intensity of the sources at the location of exposure. For external dose from terrestrial radiation the sources include the local or regional concentrations of uranium and thoron in the soil and in the construction materials of residences (e.g., bricks made from earthen materials). For lung dose from domestic radon the source is the local concentration of radium and thoron in the soil coupled with the ventilation characteristics of home. For cosmic rays the source is primarily the altitude of residence, but also latitude on the earth's surface and the episodic occurrence of solar flares. Proportionally greater intensity of the radiation environment generally leads to proportionately greater doses. Assessments need to account for factors such as age, location, building ventilation rates, and construction types. Assessment of exposures to radiation from naturally occurring sources, is enhanced by substantial measurements which are possible using numerous types of monitoring devices. In terms of complexity of assessing doses from natural radiation, external dose is clearly the simplest. Determination of internal dose is complicated by attributes of ventilation, particle sizes in the air, and more complex radioactive decay schemes. Estimation of doses from cosmic rays, in contrast, is significantly more complex because of the interactions of high energy particles from space with the components of the earth's atmosphere (*94*) (https://www.epa.gov/radtown/cosmic-radiation).

Dosimetry for People Exposed due to Releases of Radioactivity to the Environment

Since the beginning of the atomic era (1945-) there have been three~~wo~~ large-scale ~~accidental~~ releases of radioactivity from reactor accidents into the environment - Kyshtym (i.e., Mayak, 1957) (*98*), Chornobyl (1986) (*99*) and Fukushima (2011) (*100*) while there have been other, less substantial accidental releases of radioactivity at sites including Windscale (1957) (*101*) and Three Mile Island (1979) (*102*). There were also other major~~significant~~ releases~~ not associated with reactor accidents~~, e.g., Hanford (1944-1957) (*103*), and Techa river (1949-1956) (*104*, *105*)~~ and Kyshtym (1957) (98)~~.

The dosimetry methods used to evaluate doses received by populations exposed to radioactivity released to the environment from sites~~facilities~~ such as nuclear reactors must account for attributes of the radioactive material released (e.g., particle sizes, solubility), and attributes of the population (e.g., lifestyle, age distribution) and wind direction and weather conditions. Details of the dose assessments, i.e., models and parameter values, are largely determined by the important modes of exposure and pathways, e.g., external exposure and internal exposure due to inhalation and/or ingestion including contamination of the food chain. The opportunities for collection of data about the exposed population will determine, in part, the level of detail which can be built into exposure assessment models.

The Chornobyl accident~~, like most reactor accidents,~~ released a broad mix of fission products including heavy and large particles which were deposited in the near vicinity of the reactor while volatile elements like iodine or cesium migrated for thousands of kilometers. These various attributes are accounted for in the dose assessment models by radionuclide-specific parameter values.

An important study cohort for the Chornobyl accident, as well as for releases at other facilities, are children exposed to radioactive iodine released to the atmosphere. The main pathway of intake was consumption of contaminated milk and fresh dairy products because of contamination of pasture grass eaten by dairy animals. A reconstruction of individual thyroid doses was based on thyroid activity measurements and application of ecological models of transfer of iodine radioisotopes, both of which are used to estimate the concentration of radioactivity in foods ingested by children (*106*). Those data combined with individual estimates of the consumption rates of milk and other foodstuffs collected through personal interviews with the subjects or their parents, allowed for dose estimation. Models to estimate the ingested radioactivity by children were calibrated and validated using measurement data of the radiation emitted from the thyroid of children who had consumed contaminated food products.

Dose assessment for the subjects of the nested case-control studies of leukemia and related disorders (*107, 108*) and of thyroid cancer (*109*) in the Ukrainian Chornobyl cleanup workers, and in the studies of germline mutations in offspring of occupationally exposed (Ukrainian cleanup workers) parents (*110*) was performed using analytical (“time-and-motion”) methods (*111*), where subjects’ whereabouts were accounted for by use of data derived from personal interviews with subjects,~~ or~~ next-of-kin or colleague proxies and superimposed with data on dose rates attributed to particular workplaces and time periods.

One of the more important groups studied in relation to man-made environmental exposure is the Techa River cohort residing downstream of Mayak in the Southern Urals in Russia. The dosimetry of the persons exposed living near the Techa River in the 1950s and subsequently followed up for mortality and cancer incidence have been subject to a number of increasingly sophisticated (and more individualized) assessments, which make use of various types of environmental measurement data, combined with whole-~~–~~body counter measures of cohort members and questionnaire data on residence (*104, 112*). A potentially important source of radiation exposure is medical diagnostic exposure, which is more intensive among those known to have larger environmental doses, and is not taken into account in the dosimetry (*112*).

Dosimetry for Exposures from Detonation and Testing of Nuclear Weapons in the Atmosphere

Exposures of the public from regional and global fallout deposition from nuclear testing occurred worldwide from 1945 through 1980 *(113, 114)*. Radiation dose estimations to populations living near to nuclear test sites in Nevada, Utah, and New Mexico, Kazakhstan and elsewhere have been conducted by accounting for exposure from external irradiation due to deposited radioactive fallout and from ingestion of food contaminated with radioactive fallout.

External radiation exposure and ingestion have been widely demonstrated to be the most important dose pathways. The less important pathways such as inhalation and immersion in contaminated air are discussed elsewhere (*115-117*). Because for most individuals exposed to fallout, there were no direct personal measurements of dose and because exposure rates from deposited fallout were sparse at most locations of residence, although there was monitoring at regular intervals at various locations (e.g. towns, ranches and roads), calculations rely both on the basic physics of radioactive decay as well as the use of extrapolation and interpolation of environmental measurement data and sometimes, atmospheric modeling.

The primary steps in the estimation of external and internal dose from fallout and the data required are diagrammed in Fig. 1 of Beck *et al* (*118*). The essential elements for external dose estimation are a time-integration of the exposure-rate at the location of interest while the essential elements for internal dose estimation are accounting for radionuclide ingestion rates requiring measurement data or calculated values of radionuclide concentrations in plant and animal foods. Several publications illustrate variations of the methods for assessing doses from fallout exposures from aboveground nuclear testing to the populations of Nevada, the Marshall Islands, and New Mexico (*115-117, 119-124*).

Several important factors for fallout exposure models have been developed and are either essential for a realistic fallout dose assessment, e.g., conversion factors from exposure rate to radionuclide ground deposition (*125-127*) or have served to improve the quality and reliability of fallout dose assessments, e.g., quantitative transfer factor for ^{131}I to mother's breast milk (*128*). Interception of particulate fallout on plants varies with distance from the detonation site (*117*), resuspension and inhalation models (*117*). These factors and others are presented in a comprehensive dosimetry methodology for radioactive fallout (*117*, *129*-*133*).

Uncertainty.

Uncertainty in dosimetry is a manifestation of the limitations of our knowledge of the true values of doses received or of values of parameters that are used in dose estimation. The root causes of uncertainty in estimated doses are lack of knowledge about the numerous factors required to estimate doses including individual~~random~~ variations (e.g. in biophysical clearance rates), measurement imprecision, the absence of relevant or specific information (e.g. the specific type of radionuclide people were exposed to), reliance on less than perfect information, and the necessity of making assumptions. While sources of uncertainty are usually described in conceptual terms, magnitudes of uncertainties are usually described using statistical formulations. Uncertainty is generally of two distinct types. Classical error is that in which the nominal (observed) dose is obtained by adding an error to the (unknown) true dose, with the error independent of the true dose (*134*). Berkson error is obtained when (unobserved) true dose is assumed obtained by adding an error to the nominal (observed) dose, the error in this case being independent of the nominal dose (*134*). Classical error generally results in the trend of effect with dose being biased towards the null, whereas Berkson error will generally not have any biasing effect on dose-effect trend, but will inflate confidence intervals for~~on~~ trend estimates (*134*). Both classical and Berkson errors can be shared (with some component of error common between individuals) or unshared (with no such error component in common).

The practical side to the theory of dosimetric uncertainty is *uncertainty analysis* which is the process of assessing the sources and magnitudes of the uncertainty of individual dose-rated factors and a determination of the total (combined) uncertainty of either individual organ or whole-body doses or the distribution of estimated doses to a cohort or a subgroup of a cohort. Uncertainty analysis today is an accepted component of dose estimation for epidemiological studies as it is key to understanding the limitations of the dose estimates used for risk analysis. There are many treatises available on mathematical uncertainty analysis and error propagation with several focused specifically on radiation dose and radiation risk assessment (*11, 16, 88, 135-137*). A significant component of uncertainty in epidemiology is associated with the exposure conditions and attributes of the exposed population in addition to pathways of exposure and the principles of physics. For these reasons, uncertainties must also reflect unknowns about human attributes, e.g., lifestyle and diet.

The basic methodology for estimating uncertainties in radiation dosimetry is to (i) catalog the sources of uncertainty with particular attention given to those which most significantly affect the estimated doses, (ii) characterize the uncertainty of each of those sources in mathematical terms, and (iii) propagate uncertainty through the dose algorithm in a similar way to the dose calculation itself. The most common methods to implement error propagation have been analytical error propagation and in more recent decades, Monte Carlo simulations. There are subtleties in Monte Carlo sampling that pertain to properly sampling dose model parameter distributions depending on whether they represent random or systematic errors. The Two-Dimensional Monte Carlo (2DMC) method (*138*) presents the required sampling strategies for both random ~~(unshared) errors~~ and systematic ~~(shared)~~ errors. [We discuss this and other methods for dealing with the effects of measurement errors in the "Future Statistical Methods" section below.]

Some generalizations are possible about the magnitude of uncertainties found in studies of different sources of exposure. In general, three factors largely determine the relative magnitude of dosimetric uncertainties: (i) whether the exposure was controlled, (ii) whether any monitoring of exposure was conducted, and (iii) the complexity of the exposure pathways. Controlled exposures occur, for example in medicine, resulting in relatively small uncertainties, while uncontrolled exposures in environmental releases and accidents result in relatively large uncertainties. Simple exposure pathways require simpler dose assessment models which result in smaller uncertainties, e.g., external dose for single instantaneous exposures that occur in diagnostic medicine. The converse is also true, i.e., complex exposure scenarios require more complex modeling and result in larger uncertainties, an example being environmental dose reconstructions for reactor releases and atmospheric nuclear testing. For these various reasons, uncertainty of estimated external doses is almost always smaller than uncertainty of estimated internal doses. A brief summary follows of dosimetric uncertainties found in estimating doses for the sources of radiation exposure discussed in above sub-sections.

Atomic bomb survivors. The sources of dosimetric uncertainty for the Japanese atomic bomb survivors have been discussed extensively in Chapter 13 of DS02 (*19*). Although some of the component uncertainties, such as those in the yields and heights of burst of the bombs, are shared by all survivors, the dominating uncertainties are individual uncertainties in location and shielding. The adjustments~~corrections~~ for uncertainty of atomic bomb dose estimates have been done with factors obtained by regression calibration using a single overall estimate of uncertainty. For many years a correction based on 35% classical error was used (*139*) while more recently a correction based on 40% classical error and 20% Berkson error has been proposed (*140*).

*Medical radiation sources***.** An illustration of uncertainties in medical imaging is provided by the extensive uncertainty analysis conducted for the European epidemiological study on pediatric CT (*141*). The authors note coefficients of variation of dose received ranging from 20 to 30% for the brain and 20 to 40% for active bone marrow (ABM) (also called red bone marrow (RBM)) in pediatric and adolescent patients undergoing head CT. At the present, there are few detailed uncertainty analyses reported for cohorts involving RT patients though assuming the availability of treatment records, uncertainty should be smaller than for diagnostic medicine.

Natural radiation sources. Estimates of radiation doses from radon isotopes and their decay products are difficult. Nevertheless, epidemiological studies have not generally used doses, but rather estimates of exposure to the gas (indoor concentrations in Bq m^{-3}) or to the decay products ("Working Levels" in miners - see section on Occupational Exposures). The uncertainty in direct measurements of indoor dose rates from environmental γ-rays with the directly ionizing component of cosmic rays appears to be around 5% (*142*). However, uncertainties in modeled doses, which are often required for epidemiology are larger (*142*). Except in the case of solar flares, doses to aircrew from cosmic rays can be predicted with reasonable accuracy, i.e., within ±30% at a 95% confidence level (*80*). Dose rates from solar flares at high altitude and high latitude can be least a factor of 10 higher than normal (https://hps.org/publicinformation/ate/faqs/solarflare.html).

Nuclear worker studies. Many r~~R~~adiation workers over the decades were individually monitored for external exposure to ionizing radiation by ~~film badge type~~ personal dose~~i~~meters; ~~and~~ evaluations have shown that the dose~~i~~meters were limited in their ability to respond accurately to all radiation energies to which workers are exposed or to radiation from all directions *(143)*. Bias (B) and uncertainty (K) in reported exposures among study facilities and across time were found as result of differences in incident photon energy, exposure geometry, and dose~~i~~meter type *(144)*. The bias factor accounts for the sum of systematic error while the uncertainty is best described as a range of values lognormally distributed. Bias factors in the International Nuclear Workers Study, as an example, ranged between 1.22–2.05, with K ranging between 1.65–4.08 *(87)*.

Environmental releases and nuclear testing. Estimates of the uncertainty of calculated external plus internal doses from environmental releases including atmospheric nuclear testing are typically expressed as a geometric standard deviation (GSD) because the probability density functions describing the uncertainty range of possible dose either for a representative person or an identified person are approximately lognormal. These distributions reflect the combined random and non-shared errors. For example, GSDs for doses calculated for nonspecific individuals from ingestion of ^{131}I from NTS fallout typically ranged between 2.5 and 3.0 (*121*); GSDs for identified persons in other studies were similar with most GSD estimates below 3.5. To account for complex shared and unshared uncertainty sources, the ~~two-dimensional Monte Carlo (~~2DMC~~)~~ method~~ which generates multiple realizations of the population dose distribution~~ was applied to dose estimation for Mayak releases (*145*) and for exposures to radioactive fallout in Kazakhstan (*146*). Note that GSDs of 2.5 or more, as shown for this category of exposure, represent significantly greater uncertainties than for the other radiation sources discussed above.

The dosimetry methods described above represent a range of approaches described by many investigators and have been applied to many of the epidemiologic studies included in current review. We recognize that decisions need to be made about the approaches used that consider what is possible to achieve based on the time involved, the costs, and the urgency of need. These points are considered for occupational studies by Steenland *et al* (*147*) and in a recent NCRP report (*88*).

HISTORY AND KEY EPIDEMIOLOGICAL STUDIES OF IONIZING RADIATION AND CANCER AND NONCANCER RISKS~~ TO DATE~~

JAPANESE ATOMIC BOMB SURVIVORS

History, Development of the Cohort, Statistical Analysis Methods

Following the atomic bombings of Hiroshima on 6th August and Nagasaki on 9th August 1945, it is estimated that before the end of 1945 as many as 140,000 people in Hiroshima (out of a civilian population of ~330,000) and as many as 80,000 in Nagasaki (out of a civilian population of ~280,000) died as a consequence of the bombings (*148, 149*).

The most important early (and largely null) findings were reported from the large-scale clinical study of adverse pregnancy outcomes and malformations in ~75,000 children born to exposed and nonexposed parents in both cities (*150, 151*). This study was initiated because of previous fruitfly (*Drosophila melanogaster*) data which suggested that radiation-associated genetic effects might be significant sequelae of the bombings (*152*). Anecdotal clinical observations on cataract (*153*) and small head size and mental retardation among *in utero* exposed survivors (*154*) in early studies led to setting up of clinical studies without a clearly defined population sampling base. Early clinical observations (by Drs Kikuchi; Yamawaki), and a survey conducted in the late 1940s that reported excess leukemia cases in proximally exposed survivors in Hiroshima and Nagasaki (*155*) led to the establishment (in 1950) of the Leukemia Registry in the two cities.

Recommendations of an expert group in 1955 (the Francis committee) led to formulation of a “unified study program” of morbidity surveys, clinical studies, death certificate, autopsy studies, and establishment of a cohort with retrospective mortality follow-up from the October 1950 National Census of Japan and with continuing nationwide prospective follow-up subsequently. A total of ~284,000 survivors were identified, about 195,000 of them residing in Hiroshima and Nagasaki at the time of the census. All survivors within 2.5 km of the hypocenters in both cities , and an age/sex matched subset of survivors between 2.5 km and 10 km from the hypocenters in the two cities, as well as a subset of those not in city (>10 km from hypocenters) at the time of the bombings were selected and each matched to the group of inner proximal survivors (<2 km) on city, sex, and age (*156*); this sample, with minor modifications in later years, made up the ~~Life Span Study (~~LSS~~) cohort~~, which numbered 120,320 individuals (*149*). With the establishment of the population-based cancer registries in Hiroshima in 1957 and Nagasaki in 1958, ascertainment of cancer incidence cases became possible among the LSS members residing in the two cities. Also, beginning in 1958, the Adult Health Study (AHS) LSS subset of 24,358 Hiroshima/Nagasaki-resident survivors were invited for biennial clinical health examinations; details of selection criteria are given elsewhere (*156*). The LSS and AHS have been the basis of numerous analyses of cancer and non-cancer mortality and morbidity. An *in utero* exposed cohort of 3638 persons (born to mothers exposed to atomic bomb radiation during pregnancy and born after the bombings but before May 31 1946) was identified from birth records and other records and has been followed up clinically and via mortality (*157*).

As noted in the dosimetry section, many of the survivors or their surrogates were interviewed during the 1940s-1950s (*158*) and individual dose estimates were constructed for about 92% of persons in the LSS cohort (*148*), beginning in the late 1950s with the T57D system (*20*), and in the mid -1960s the T65D/T65DR dosimetry (*21*). Several early analyses were based on grouped estimates of T57D dose, also using distance from the hypocenters, all using chi-squared tests (*159-162*). The earliest finding of excess solid cancer was for thyroid carcinoma, using a distance-based analysis (*163*). In the early 1970s and later Mantel-Haenszel contingency table and related analyses (e.g., based on binomial tests) began to appear using individual T65D/T65DR doses (*164-167*). Contemporary with the introduction of the DS86 dosimetry in the mid-1980s (*18*) improved methods of analysis (*168-170*) began to be employed, using Poisson regression (*171*). Many recent

Radiation Effects Research Foundation (RERF) analyses adjust for classical dosimetric error using regression calibration methods (*134*); this correction results in ~5-15% increase in risk estimates compared with estimates not incorporating adjustment for classical dosimetric error (*139*). The current DS02/DS02R1 dosimetry, introduced in the mid-2000s, has been used to assess risk of major cancer and non-cancer mortality outcomes (*28-30*) as well as cancer incidence (*23, 31-39*).

Cancer Risks

To date, there have been three major sets of analyses of the cancer incidence data, those of solid cancer and hemopoietic malignancies which were published in 1994, using DS86 (*172, 173*); solid cancer published in 2007 using DS02 (*174*); and the current publications for solid cancer, in 2017 (and later) using DS02R1, and with successively longer periods of follow-up; we only describe the results of the most recent reports of incidence findings below. With increasing follow-up through 2009, many types of cancer have been associated with atomic bomb radiation in the LSS. Specifically for cancer incidence, there is radiation-associated excess risk of most types of leukemia (*175*) including acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML) and chronic myeloid leukemia (CML), also for chronic lymphocytic leukemia (CLL) although based on only 12 cases, and excess incidence risk for all solid cancer including cancers of the lung, thyroid (for exposure in childhood), male and female breast, liver, uterine corpus (but not uterine cervix), colon, central nervous system (CNS), salivary gland, stomach, urinary tract and prostate cancers ~~(*23, 31-34, 36-39, 172-174*)~~ (*23, 31-34, 36-39, 176-179*) (see Table 1). There are also excess mortality risks of leukemia, solid cancer, including cancers of the esophagus, stomach, liver, gallbladder, lung, male and female breast, ovary, bladder and renal pelvis/ureter (*28, 176*) (see Table 1). In general, there has been little~~weak~~ evidence of radiation-associated excess mortality or incidence risks for any type of lymphoma or multiple myeloma (*28, 175*) (see Table

1). Over the decades, investigators have specifically examined cancer incidence and mortality of those exposed *in utero* and reported significantly increased risks of solid cancer incidence (both males and females) and mortality (female but not male) for this population (*157*, *180*).

Dose response curvature

There is well documented upward curvature in the dose response for leukemia, with strong indications of such curvature (*p*=0.01) for ~~acute myeloid leukemia (~~AML~~)~~ and to a lesser extent (*p*=0.05) for ~~acute lymphocytic leukemia (~~ALL~~)~~ (*175*). Although previous analyses of all solid cancer reported a linear dose-response relationship, the most recent data indicate upward curvature in the male all solid cancer incidence data, although not for females (*23*). Possible departure from a linear dose-response was also noted for esophageal cancer, with the apparent curvature in males but not females when the dose-response shape was allowed to vary by sex (*177*). A recent reanalysis of the LSS all solid cancer incidence and mortality data by Brenner *et al* (*181*) using a common period of follow-up (1958-2009) demonstrated a borderline significant upward curvature in male mortality, as well as significant curvature for female mortality. Determining the effect of curvature in the dose response and its impact on low dose effects is sometimes assessed via a factor determining the effect of extrapolation of dose, the so-called low dose extrapolation factor (LDEF), which is one component of the dose and dose-rate effectiveness factor (DDREF) used by the ICRP (*182*). The paper of Brenner *et al* (*181*) implied estimates of LDEF up to 13 for some ranges of dose; however, alternative analyses using slightly less current LSS mortality data (with follow-up over the period 1950-2003) suggested much lower estimates of LDEF (*183*) as did later analysis of current LSS mortality and incidence datasets (*184*).

Various other forms of departure from a linear dose response have been assumed for particular analyses, in particular linear-exponential, ~~or~~ quadratic-exponential (*185*) or quartic-exponential (*186*) also linear-threshold or linear-quadratic-threshold (*187-189*), which have highlighted departures from linearity in some cases ~~(*181*)~~ (*185*, *186*)

Effect modification by age, time since exposure and sex

For many solid cancers there are significant effects of age at exposure, attained age, sex, and time since exposure. The excess relative risk (ERR) for a given dose generally decreased with increasing age at exposure, attained age and male sex (*23*) except for the notably different patterns of increasing ERR with increasing age at exposure for lung cancer (*32*), and increased sensitivity to radiation exposure during puberty for breast (*31*) and uterine cancer (*36*). The most recent reports indicated differences in ERR of solid cancers for males and females, both for incidence and mortality (statistically significant for lung cancer only, see Table 2). Generally, ERR were higher for females compared to males (with the exception of colon cancer incidence) and for incidence compared to mortality. The radiation-associated ERR for colon cancer decreased with increasing time since exposure (*34*). For leukemia excluding ~~chronic lymphocytic leukemia (~~CLL~~)~~ and adult T-cell leukemia (ATL) there are significant modifications of radiation risk with attained age and either time since exposure or age at exposure, ERR reducing significantly with increases in all three variables (*175*).

Non-Cancer Risks

Following the atomic bombings of Hiroshima and Nagasaki in 1945, the higher-dose exposed survivors suffered from acute non-cancer effects, including hematological changes, bleeding, oropharyngeal lesions, burns, nausea, vomiting, fever and diarrhea in the first few days to weeks, and epilation and acute lethality (the latter due mainly to bone marrow destruction) in the first months after exposure (*190-192*)~~(*186*)~~. *In utero* high-dose radiation exposure also resulted in various non-cancer effects, such as microcephaly, mental retardation and growth retardation, depending on the developmental stage at the time of bombing (*193-195*). In the following subsections we discuss the main late occurring non-cancer effects.

Genetic effects and untoward outcomes of pregnancy

As noted above, the Atomic Bomb Casualty Commission (ABCC) (which later became RERF) formed the first filial (F_1) cohort, subsequently extended to children of atomic bomb survivors born in 1946-1984, to study the heritable genetic effects of radiation. Studies have included cancer incidence, cause of death, and biochemical genetic studies. No compelling evidence of effects has been found to date (e.g., (*196*, *197*)). A recent study that reexamined the risk of congenital malformations and perinatal death, using refined dose estimates and analytical methods, found some indication of a radiation-related increase in adverse pregnancy outcomes (stillbirths, neonatal deaths, major malformations) but the risk estimates were imprecise and not statistically significant, and the authors noted that data were not available on the full range of possibly confounding factors that are known to affect pregnancy outcome (*198*).

Central nervous system exposed in utero

Otake and Schull (*195*) documented radiation-associated small head size among those exposed *in utero* to the atomic bombs in Hiroshima and Nagasaki, with effects particularly pronounced for those exposed 0-7 weeks or 8-15 weeks post-ovulation. There are also radiation-associated reductions of intelligence quotient (IQ) and increase in severe mental retardation, particularly among those *in utero* survivors exposed 8-25 weeks post-ovulation (*199*). There are (non-significant)~~weak~~ suggestions of upward curvature in the dose response for small head size, particularly during the second trimester (*199*), but somewhat ~~much~~ stronger (but still non-significant) indications of upward curvature in all trimesters for severe mental retardation (*199*, *200*).

Circulatory system

Evidence for an increased radiation risk associated with overall and subtypes of cardiovascular disease (CVD) mortality, particularly heart disease and stroke, emerged in the 1990s and has been seen in a number of recent analyses of the LSS mortality data (*29*, *201*-*203*), although less so in the AHS incidence data (*204*), perhaps reflecting the smaller number of cases (e.g. 1546 incidence ischemic heart disease (IHD) cases (*204*) vs 3556 IHD deaths (*29*)) and differently defined endpoints (see Table 1), and possibly more accurate diagnosis in the morbidity data. More recently, other forms of CVD, including valvular heart disease (in particular rheumatic heart disease), hypertensive organ damage and heart failure have been associated with radiation exposure in the atomic bomb survivors (*29*) (see Table 1).

Dose response curvature

There are few indications of departures from linearity for most CVD endpoints, with very weak (p=0.17) indications of upward curvature for stroke (*203*). The analysis of aggregate CVD mortality data has estimated LDEF of ≤1 when restricted to weighted colon dose <3 Gy, but with considerable uncertainties (*183*, *184*).

Effect modification by age, sex and other factors

Radiation-associated ERR for CVD mortality decreases with increasing age at exposure (*205*) and there are borderline significant decreasing trends with attained age (*203*, *205*); however, the ERR does not substantially vary by sex, or time since exposure (*203*, *205*). Analysis of a subset of the LSS cohort (*203*) that responded to a postal survey revealed that adjusting for smoking, alcohol intake, education, type of household occupation, body mass index, and diabetes made generally no more than modest (<20%) change in radiation-associated ERR for all CVD, stroke or heart disease mortality.

Eye

A paper on clinically diagnosed cataract reported an increased prevalence linked to radiation exposure, with significant excess radiation-associated risks of cortical and posterior subcapsular cataract (PSC), but not nuclear cataract (*206*). A subsequent publication reported an increased prevalence risk for cataract surgery (see Table 1) and evidence of a significant dose threshold (*207*), but no evidence for upward curvature using a linear-quadratic model (*207*); as noted elsewhere there are methodological problems with the fitting of threshold models (*208*).

In addition to cataracts, radiation-associated incidence risks have also been reported in the AHS for various type of retinal degeneration (*209*) (see Table 1). Excess risks have also been seen for normal-tension glaucoma, although not for any other type of glaucoma (*210*) nor for macular degeneration (*211*) (see Table 1). For all endpoints except normal-tension glaucoma, and early macular degeneration radiation risk estimates are based on quite small numbers of cases (<100). Dose-response curvature has not been assessed for ocular endpoints apart from cataract.

Other organs/tissues

There is significant ($p<0.05$) radiation excess mortality risk from non-malignant respiratory diseases, but much weaker indications ($p>0.05$) of excess risk for digestive diseases, and very little excess risk from any other type of non-cancer mortality (*28*) (see Table 1). There are radiation-related increased prevalence risks of non-malignant thyroid disease ($p<0.0001$), chronic liver disease and cirrhosis ($p=0.001$), uterine myoma ($p<0.00001$) (*204*), and chronic kidney disease (*212*) (see Table 1). A report assessing radiation-related risks for neurodegenerative diseases, specifically dementia, did not find significant associations (*213*, *214*);~~.~~ the earlier of these two studies also noted that “also low is the rate for dementia since examination attendance is hampered for those with severe affliction. In fact, incidence estimates for highly debilitating diseases are expected to be lower in the AHS than in the general population.” (*214*). However, this observation was not made for the later follow-up (*213*), so it is unclear how much weight should be attached to this.

Possible Selection Effects in the Atomic Bomb Survivors

The huge numbers of early casualties, between 30%-40% of the population of the two cities (*148*, *149*) suggest a potential selection bias in survivors. The atomic bomb survivors suffered from burns, epilation and other acute injuries caused by the radiation as well as heat and blast of the bombs, and these injuries, in addition to radiation, may have contributed to development of non-cancer diseases in later life. There is striking downward curvature in the non-cancer mortality dose response in the 1950-1967 follow-up period, contrasting with the absence of such curvature in the 1968-1997 follow-up, which suggests selection effects in the early follow-up period (*215*). Some further evidence of selection effects has been presented by Stewart and Kneale (*191*), who documented evidence of heterogeneity of radiation risk for various endpoints, in particular CVD mortality, among various acute injury groups. However, Stewart and Kneale (*191*) did not consider the effects of dose error. Analysis taking this into account found much reduced and generally not statistically significant associations for CVD (*190*). Other evidence of selection, in particular an inverse dose response for suicide has been presented (*216*), although later analysis of this data has not been confirmatory (*217*).

MEDICAL DIAGNOSTIC EXPOSURES

Studies of diagnostic medical radiation exposures have contributed to our understanding of the cancer and non-cancer risks from fractionated, partial body exposure to low to moderate doses. The study populations have included a wide range of ages at exposure and provide complementary evidence to occupational studies~~ especially for females~~. They have also been used to assess the transportability of risk coefficients from the LSS to non-Japanese populations. The strongest studies are based on organ-dose estimation from medical records because recall of diagnostic radiation exposures is poor. Confounding by indication related to the underlying condition needs to be evaluated carefully. Key studies include the early studies of abdominal X-rays in pregnant women (*218*), ~~tuberculosis (~~TB~~)~~ patients monitored with fluoroscopy (*219*, *220*), spinal X-rays in women with scoliosis (*221*, *222*) and most recently the studies of pediatric CT scans. Findings from these studies are summarized below according to the outcomes.

Cancer Risk

Studies of early life exposure

The first studies to suggest a relationship between diagnostic X-rays and cancer were of childhood cancers after *in utero* radiation exposures. The Oxford Survey of Childhood Cancers (OSCC) suggested this link as early as 1956 using a case-control study based on self-reported medical history by the mothers (*218*). The X-rays in this study were primarily pelvimetry to examine the size of a woman's pelvis to assess whether she would be able to give birth vaginally or not; these were usually performed near the end of pregnancy. When the findings were replicated in a large US case-cohort study based on medical records, rather than self-report, the potential risks began to be taken more seriously (*223*). A variety of concerns including discrepancies with findings from *in utero* exposure in the atomic bomb survivors have been carefully evaluated~~ (224)~~ (*224*, *225*). The general (if not quite universal) consensus is now that these studies support a causal association of childhood cancer with *in utero* exposures as low as ~0.01 Gy (*224*-*226*) (see Table 3). A problem with all these studies is the lack of individual dosimetry, although estimates of doses have taken into account dates of X-ray exams, the number of diagnostic films taken during pregnancy (based on general practitioner or X-ray department records and patient self-report), and calendar period specific estimates of fetal dose per film (*225*, *227*).

The main arguments opposing a causal interpretation of the OSCC findings have been set out in an NCRP report (*228*), and include a lack of clear confirmation of the statistical association in cohort studies, although statistical power is limited, and the largest of these studies has been found to be unreliable (*224*). However, findings of the OSCC case-control study were replicated in the MacMahon (*223*) case-cohort study, in particular findings there of very similar relative risks (RR) for leukemia, CNS cancer and other cancer mortality (although only for leukemia is the RR statistically significant). NCRP (*228*) also mentioned the decreased risk of childhood leukemia and other childhood cancers in twin cohorts despite the increased rate of obstetric radiography experienced by twins. However, even for the largest cohort of Swedish twins (*229*) there is limited statistical power to detect the predicted increased risk of exposure to X-rays (*224*) and Mole (*230*) has pointed out the similarity of RR of X-ray exposure for twins and singletons in the OSCC, which has also been found in twin case-control studies in Sweden (*229*) and Connecticut (*231*). NCRP (*228*) also pointed out the similarity of the RR estimates for almost all types of childhood cancers in the OSCC as being unusual. However, as above the RR are very similar between cancer types in the MacMahon (*223*) study and a similar pattern of RR estimates between cancer types was seen in the results of a meta-analysis of all childhood cancer case-control studies except the OSCC (*232*) so this finding is not confined to the OSCC.

Studies of computed tomography (CT)

Following concerns in the early 2000s about unnecessarily high radiation doses being delivered to children undergoing CT scans (*233*), and the rapid increase in use, several large-scale studies were launched. The UK-NCI CT cohort of ~180,000 patients with at least one CT examination under age 22 years found a dose-response relationship with leukemia and myelodysplastic syndrome (MDS) in relation to cumulative RBM dose (but not for leukemia excluding MDS), and for brain tumors in relation to brain dose (*234*). Careful evaluation of potential confounding by indication and reverse causation suggested that the brain tumor risks might be over-estimated, but there was minimal evidence of bias for leukemia (*235*). The multi-center EPI-CT study of ~950,000 children from 9 European countries, including an enlarged UK cohort, also reported a significant dose-response for brain cancers (*236*) and for hematological malignancies (*237*) based on refined dosimetry methods. There are significant excess risks for brain cancers (*236*), and for leukemia excluding CLL (*237*) (see Table 3). There were also significant dose-response relationships for non-Hodgkin lymphoma (NHL) and Hodgkin lymphoma (HL), both (as for leukemia) in relation to RBM dose (*237*). An Australian cohort of ~612,000 exposed children and 10.5 million unexposed children found significant risk for brain cancers (*238*). Mean brain doses in these studies were ~0.05 Gy (range 0 - 4.72) (*236, 238*). RBM doses were lower with a mean of ~0.015 Gy (range 0 - 1.68) (*237*). Results of the EPI-CT analyses suggest that among 10,000 children who undergo a (head) CT, about 1-2 additional hematological malignancies and 1 additional brain cancer are caused by the radiation exposure in the decade after the CT (*236, 237*). The dose-response relationships for brain cancers and leukemia are higher than, but statistically compatible with those from childhood exposure in the LSS; however the increase in ERR/Gy with increasing age at exposure for brain cancer in the EPI-CT study (*236*) (as in the earlier studies of Pearce *et al* (*234*) and Berrington *et al* (*235*)) is opposite to that seen in many other exposed populations (*8*). The increased risk of HL in EPI-CT with RBM dose was surprising as ionizing radiation exposure is not an established cause (*8*). Comparisons of findings for HL and NHL with previous studies are complicated by changing disease classification schemes. Further evaluation of potential confounding by indication is warranted for these outcomes in the study centers with data on underlying conditions. A simulation study closely modeled on the UK CT study suggested that reverse causation was unlikely to result in bias away from the null for brain cancer in relation to CT exposure (*239*). Other concerns have been raised by a number of researchers (*240-242*), some of them (e.g. in relation to reverse causation and confounding by indication) addressed above.

Other studies of diagnostic exposure

Breast cancer

The Massachusetts TB cohort included~~s~~ 13,500 patients who were exposed 1925-1954 and followed up for mortality until the end of 2002 (*219*, *243*). The Canadian Fluoroscopy Cohort Study (CFCS) included 93,000 TB patients (with similar numbers of males and females of all ages) exposed in the period 1930-1969 and followed up for mortality since 1950 and cancer incidence since 1969. Although each single exposure was low dose (0.01-0.1 Gy) (*244*) there were patients with cumulative doses to some organs >1 Gy because of the large number of examinations. Increased risks of breast cancer were reported in both the original Massachusetts (*51*, *219*, *245*) and Canadian (*246*) fluoroscopy cohort studies (see Table 3), and the absolute risk (but not the relative risk) was compatible with the LSS (*244*). Radiation risks decreased with increasing age at exposure and there were indications of risk attenuation after 40 years since first exposure (*246*).

A US cohort of 3,000 women with scoliosis who received multiple spine X-rays also found an increased risk of breast cancer~~ (*217*)~~, following a mean cumulative breast dose of ~0.13 Gy (range 0-1.11) (*221*) (see Table 3).

Lung cancer

In contrast to the breast cancer findings, there was no evidence of an increased risk of lung cancer mortality in either the Massachusetts or CFCS fluoroscopy cohorts (*220, 247, 248*). Various factors have been evaluated to try and understand this including biases from the underlying disease (TB), misclassification of causes of death and confounding by smoking. As these potential biases may~~do~~ not fully explain the differences with the breast cancer risks or the LSS an alternative explanation is that fractionation has a differential effect on the breast compared to lung tissue. Interestingly there is also no excess lung cancer mortality risk in the scoliosis cohort, but numbers of deaths are very small and lung doses somewhat lower than to the breast, ~0.04 Gy (range 0 - 0.68) (*222*) (see Table 3).

Other cancers

Significant excess thyroid cancer risk was observed in pooled analysis of two population-based French case-control studies, with thyroid cancers derived from population registries and history of medical diagnostic procedures reconstructed via telephone-administered questionnaire (*249*) (see Table 3). A positive but non-significant risk of thyroid cancer in relation to diagnostic radiation exposure was also seen in the US Radiologic Technologist cohort (USRT), based on questionnaire-assessed thyroid cancer diagnosis and medical diagnostic exposure (*250*) (see Table 3).

There was no significant excess risk of brain/CNS cancer at ages 10-24 in relation to diagnostic medical exposures in a large multi-national case-control study (*251*) (see Table 3). Brain cancer diagnosis and details of medical diagnostic exposures were questionnaire derived (*251*).

Non-Cancer Risk

Recent analysis of the pooled Massachusetts and CFCS TB fluoroscopy cohorts indicated significant trends with dose for all CVD, ~~ischemic heart disease (~~IHD~~)~~ and hypertensive disease for those exposed under 0.5 Gy, with significant or borderline significant trends for these endpoints for those exposed under 0.3 Gy (*252*). The use of this cutoff was not entirely arbitary, as there is biological data suggesting a difference in response above and below 0.5 Gy (*253*). Unlike a previous analaysis of the CFCS data (*254*) there was no indication of a dose rate or fractionation effect (*252*). The fractionation metric used in the CFCS data is slightly different from that employed in the pooled analysis, and the significance of the effect in the CFCS data disappeared if a lag period other than 10 years was employed (*254*).

MEDICAL THERAPEUTIC EXPOSURES

At the turn of the 20th century, the announcement of the discovery of X-rays was very quickly followed by the understanding of their potential application in medical settings as treatment for both malignant and non-malignant conditions (*255*, *256*). The use of RT expanded dramatically throughout the 20th century, with substantial improvement in patient outcomes resulting from rapid advances in clinical practice, including the shift from orthovoltage to megavoltage X-ray therapy and the introduction of LINACs, use of fractionation, the introduction of particle therapy, and more advanced approaches to brachytherapy. Nearly immediately after the introduction of X-ray therapy, however, various adverse health effects were also identified, and a number of strategies were employed to try to minimize such effects (e.g., crude shielding approaches). Despite this early recognition of the adverse health effects of RT, the first large-scale studies of these adverse effects were not undertaken until the mid-195~~6~~0s.

The various study designs utilized in the earliest studies of the adverse effects of RT—from relatively small single- or multi-institution cohorts with detailed patient and treatment data to large-scale population-based cancer registry data with very limited patient and treatment data, and nested case-control studies that attempted to leverage the strengths of both approaches—provided a robust framework for adverse effects studies that has flourished in the last half century and yielded numerous findings that have directly impacted clinical practice, and informed our understanding of the risks from high-dose fractionated, partial body radiation exposure. This section provides a history of key epidemiological studies of both cancer and non-cancer risks associated with therapeutic medical exposures.

Cancer Risk

Some of the earliest epidemiological studies of cancer risks following RT focused on patients who were treated for non-malignant conditions, most notably ankylosing spondylitis (*257-260*), tinea capitis in New York ~~(*261, 262*)~~ (*261-263*) and Israel (*264-267*), thymus gland enlargement (*268, 269*), peptic ulcer disease (*270-272*), benign head and neck conditions (*273*), and benign gynecological diseases (*274-278*). Although use of RT for these types of benign conditions has largely disappeared (in part due to reporting of the increased subsequent cancer risks), RT is still used in the treatment of some patients with benign meningioma (*279*), vestibular schwannoma (*280*), some types of hemangioma (*281*) and various other non-malignant conditions (*282-286*). Also, a number of the earlier populations treated with RT for benign disease continue to be followed, and have yielded interesting contrasts to the groups followed for cancer ~~(*256, 262, 266-268, 277, 278*)~~ (*259*, *272*, *276-278*, *287-289*) (see Table 4).

The Late Effects Study Group (LESG) was formed in the late 1970s to investigate the subsequent occurrence of malignancies associated with childhood cancer treatment. Combining detailed patient data from multiple institutions enabled the assessment of both RT- and chemotherapy-related risks, often with detailed dose data. The efforts of this group led to some of the first systematic reports of cancer risks associated with RT ~~(*282, 283*)~~ (*290-292*). The LESG analyses also highlighted the importance of considering other factors such as chemotherapy and genetic susceptibility (*293*), which was supported by reports of second cancer risks following RT for retinoblastoma (*294*, *295*).

During a similar timeframe, the first large-scale cancer registry-based studies of second cancer risks after RT were conducted, for example, the study of 180,040 women from 15 cancer registries in 8 countries (*296*), later expanded to a series of case-control studies nested within this cohort (*297*-*299*) (see Table 4). These efforts demonstrated the critical role that cancer registries can play in surveillance of risks for developing subsequent malignancies in cancer survivors because of their large sample size, systematic ascertainment of cancer diagnoses and mortality, and long-term follow-up, which is particularly important since radiation-related malignancy risks often do not appear until at least five years following exposure and may persist for decades. A comprehensive monograph of second cancer risks using US population-based cancer registry data was published in 2006 (*300*), and similar analyses of specific second cancers and/or specific patient populations using registry data from around the world are published regularly. While these studies provide valuable surveillance for second cancer risks, the lack of detailed treatment data limit their contribution for better understanding of radiation dose-response relationships and potential modifying factors, and thus limit their utility for modifying clinical practice. However, case-control studies within these cancer registry population have provided valuable dose response information and important findings on interactions with co-factors such as smoking (*301*).

Because children, adolescents, and young adults treated for cancer potentially have many years of life in which to experience adverse effects of RT, and because of potential concern that young individuals may be particularly susceptible to radiation-related damage, researchers investigating cancer risks associated with therapeutic medical exposures have dedicated substantial efforts to focus on these patient populations. Particularly notable efforts that have informed cancer risks include a number of large-scale cohorts of patients with HL, testicular cancer, and childhood cancers, many of which were initiated in the 1980s and 1990s and continue their follow-up today (*302-308*). Other susceptible populations, such as patients who are immunosuppressed as part of the clinical approach to hematopoietic stem cell transplantation, also have substantially increased risk of developing second cancers following total body irradiation ~~(*304-306*)~~ (*309-311*).

Over time, the importance of more detailed, organ-specific exposure assessment was recognized, and radiation dose-response relationships for specific cancer types were quantified. This methodological advance was highly reliant on parallel advances in dosimetry for RT, which is reviewed in a separate section. In brief, while registry-based studies typically have relied on an indicator variable for receipt of RT, subsequent studies used prescribed dose to the tumor as a surrogate for dose to the organ at risk for a subsequent malignancy (e.g., ~~(*307*)~~ (*312*)). More detailed nested case-control studies with detailed patient and treatment data have collected RT records and subsequently used treatment doses and field configurations to estimate the dose to the location of the subsequent malignancy for cases and a corresponding location for matched controls (e.g., (*313*)). While this approach greatly strengthened the etiological evidence, it cannot be used for the prediction of absolute risk. Currently available risk prediction models attempt to identify cancer survivors at high risk of subsequent malignancies based on RT (yes vs no) (e.g., (*314*)) or on prescribed dose (*315*). Nevertheless, the models are useful to recommend screening for survivors or treatment alternatives for new patients. This illustrates that the quality of the RT record is a substantial contributor to the uncertainty in radiation dose estimates, particularly for patients with long follow-up and therefore treatment in the distant past for whom only paper records with field drawings have been available (*55*). The collection of RT treatment planning simulation films for subsets of patients often reduced uncertainties, while current efforts to directly collect Digital Imaging and Communication (DICOM) data have substantial promise to reduce uncertainty, despite challenges in image and file standardization and storage. Uncertainty in dose estimates also can arise from uncertainty in tumor location and patient anatomy.

Despite these uncertainties, radiation dose-response modeling generally has demonstrated linear dose-response relationships through the full therapeutic dose range for all tumor types except for thyroid cancer, for which there is a downturn in risk at approximately 20 Gy, as described in several comprehensive reviews (*316-319*). Notably, the relative magnitudes of radiation-related cancer risks (per unit dose) after therapeutic exposures tend to be lower than those observed in groups such as the LSS and other groups exposed at much lower levels of dose (see Tables 1, 3, 15, 17). Several studies have evaluated whether second cancer risks may vary by the volume of tissue irradiated (*320, 321*), but future research on this topic and other clinical parameters such as hypo- and hyper-fractionation is needed. Overall, findings from studies of cancer risks associated with RT have altered clinical practice, such as the reduced use of RT, reduced field sizes, and/or reduced doses for many patient populations. They have also provided some of the first clear evidence of radiation-related cancer risks for organs such as the pancreas, and rectum.

Non-Cancer Risk

Cardiovascular disease (CVD)

Studies of groups treated for cancer in the late 1950s and early 1960s were the first to identify possible CVD risks associated with high dose RT (*322*, *323*), long before any excess risk was identified in the LSS. These early findings, and those in patients treated for HL (*324*) were instrumental in moves to limit heart dose for treatment of HL.

There have been two pooled analyses of CVD. The first of these is a pooling of patients treated for HL in 13 countries included in 9 randomized trials (*325*). Dose reconstruction was systematically applied across all trials and was independent of outcome. The second of these is a systematic review, combined with a pooled analysis of breast cancer clinical trials (*326*), but this is much less informative as a study of radiation dose response, since each woman was assigned the mean heart dose from the particular trial that she was in. This makes it in effect a species of ecological study, the potentials for bias in which are well known (*327, 328*). Both studies are unusual among modern studies of CVD in that there is little or no adjustment for major lifestyle and medical risk factors;~~:~~ nevertheless, the risk estimates are within the range seen elsewhere (see Table 5).

Childhood cancer survivor cohorts

The various analyses of the Childhood Cancer Survivor Study (CCSS), a largely US-based cohort of persons treated for cancer in childhood (*329-332*) generally do not exhibit significant increasing trend with dose, although many show significant excess risk, generally above 15 Gy (see Table 5). Strengths of the CCSS studies include the large size, efforts to validate self-report with medical records and adjustment for lifestyle/environmental factors in some of the studies (*329-332*), but limitations of the CCSS CVD studies include the lack of reporting of age at diagnosis of the CVD event for an appreciable fraction (11% of the cohort) (*329-331*), incomplete validation of self-reported outcomes, and lack of complete individualization of dose estimates (*55*). The French/French-UK studies (*333-337*) document significant excess mortality and incidence risks of IHD and cerebrovascular disease (CeVD) in childhood cancer survivors. Strengths of some of the French/French-UK studies included the source of diagnosis (e.g., national mortality registries (in France and UK) although for some of the studies endpoint information was via patient contact and medical record validation (*335*-*337*) and fully individualized dose estimates (*56*, *338*). The St Jude Lifetime cohort had the most complete adjustment for lifestyle/environmental/medical risk factors (*339*).

Hodgkin lymphoma (HL) cohorts

The three Dutch case-control studies (*340*-*342*) assessed incidence from various types of CVD in a group of survivors of HL, and in each case documented excess risk (see Table 5). Incidence was assessed via a postal questionnaire completed by the patients' general practitioner and/or cardiologist. There were some indications of upward curvature in the dose-response for some endpoints (e.g., valvular heart disease (*340*), heart failure (*342*)).

Adult cancer survivor cohorts

The Nordic case-control study of Darby *et al* (*343*) assessed IHD incidence in a group of women treated for breast cancer, as did similar studies in the Netherlands, Denmark, Germany and Sweden (*344*-*350*). A major strength of the Nordic study is that national incidence registries in Sweden and Denmark were used to assess incidence of IHD. Dosimetry reconstruction in all these studies was based on individual RT charts. Another strength of many of these studies is the rich covariate lifestyle and medical information, in particular the standard risk factors for CVD that are available and used for the analysis (see Table 5). However, the Swedish and German studies lacked any lifestyle/medical risk factor data (*349*, *350*) (see Table 5).

There were a number of small studies of CVD after RT for various other types of cancer (*351*-*373*) most of which demonstrated significant increases in various types of CVD with increasing dose.

Cohorts exposed for treatment of non-malignant disease

The US study of patients treated for peptic ulcer, who were given mostly a single treatment course of X-rays to the stomach documented significant excess mortality risks for all CVD and IHD, and indications of excess risk for CeVD (*374*). There were no significant (p>0.2) differences between ERRs by endpoint (IHD, CeVD, other CVD), and few indications of curvature in dose response (*374*). Using thyroid dose (a surrogate for carotid artery dose) for CeVD and heart dose for other CVD endpoints resulted in significant heterogeneity of risk (p=0.011) between endpoints, which was not the case when heart dose was used throughout (p=0.28) (*374*). A study of Israel tinea capitis patients found large and significant excess risks of IHD and modest (but still significant) elevated risks of CeVD and carotid stenosis (a subset of CeVD) (*375*). A much larger risk for carotid stenosis was obtained using (the more physiologically relevant) thyroid dose rather than breast dose (*375*). A cohort of persons receiving X-rays in infancy in Rochester for treatment of an enlarged thymus did not show excess incidence of CVD (*376*). There were borderline significant indications of curvature in the dose response (p=0.11), which appeared to increase and then turn over at higher levels of dose (*376*).

Non-cancer effects on the eye

Ocular diseases observed following therapeutic exposure include cataracts, neovascular glaucoma, retinopathy, papillopathy, maculopathy and optic neuropathy (*377*). These diseases, save cataracts, are induced by relatively high dose. There are many case reports and clinical studies that have relatively short follow up, but some studies provide risk estimates, e.g., following brachytherapy or external RT for childhood cancer (*378*), ^{131}I treatment for thyroid cancer (*379*), ocular tumors (e.g., uveal melanoma) (*380, 381*), CNS irradiation for leukemia (*382*), and total body irradiation preceding bone marrow or hematopoietic stem cell transplantation (*383-386*). However, very few studies evaluate radiation doses to the eye or eye lens; of the few that do (*378, 387-389*) there are only two studies yielding trend risk estimates (both significant), both studies of cataract (*378*, *388*) (see Table 5).

Effects in offspring of cancer survivors

There have been a number of studies of reproductive outcome in childhood cancer survivors. Although offspring of women treated for cancer in childhood and receiving uterine doses >5 Gy were more likely to be small for gestational age, there was no change in proportions of stillbirths or miscarriages in relation to either father's or mother's radiation treatment, nor was there variation in the proportion of offspring with simple malformation, cytogenetic defects or single-gene defects (*390*). There was no variation in rate of congenital abnormalities in offspring of male or female childhood cancer survivors with dose (to ovaries or testes) (*391*).

CHORNOBYL ACCIDENT

The explosion at reactor 4 of the Chornobyl nuclear power plant (NPP) in Ukraine on 26th April 1986 resulted in the most serious of any accidental radioactive releases, with releases of ~1.2-1.8 x 10^{18} Bq of short-lived ^{131}I and ~1.4 x 10^{17} Bq of much longer lived ^{134}Cs and ^{137}Cs (*392*). Ukraine and Belarus were the most highly contaminated areas, but other parts of the former USSR were also contaminated, and to a much lesser extent many parts of Western Europe (*392*, *393*).

Cancer Risk

Leukemia and other hemopoietic malignancies

Exposure in childhood

Studies comparing incidence of leukemia in children before and after the Chornobyl accident in countries outside the former Soviet Union that were closer to and far away from the accident failed to show any increase due to estimated radiation exposure (*394-397*). A collaborative international case-control study of childhood leukemia in Ukraine, Belarus and Russia included all persons exposed either *in utero* or under age 6 in the three republics and diagnosed in the period 26 April 1986-31 December 2000 (*398*). The central estimates of risk were large, and largely driven by the large and significant risks in Ukraine (but the CI for the risk estimates for the three countries overlapped) (see Table 6), although not inconsistent with those of other groups exposed in childhood (see Table 1, 3, 15, 17). Of the 421 cases, 311 ~~of the 421 cases~~ were ALL, with 86 AML and 24 acute unclassified leukemias (*398*). However, the authors note "the large and statistically significant dose-response might be accounted for, at least in part, by an overestimate of risk in Ukraine. Therefore, we conclude this study provides no convincing evidence of an increased risk of childhood leukaemia as a result of exposure to Chernobyl radiation, since it is unclear whether the results are due to a true radiation-related excess, a sampling-derived bias in Ukraine, or some combination thereof" (*398*). Significantly increased radiation risks of ALL among all participants and all leukemia among males whose estimated radiation exposure to the bone marrow was higher than 10 mSv were reported in a separate analysis of Ukrainian data alone which included a slightly different number of cases (*399*). Although uncertainties in dose were estimated in one of these studies (*398*), it is not clear if these were used in the analysis. A later case-control study of acute leukemia among children 0-5 years of age at the time of the accident in the most contaminated areas of Ukraine found a significant dose-response, but with a slope that was substantially lower than that for Ukraine reported earlier by the international collaboration (*400*).

There have been a number of ecological analyses of various types of cancer (e.g., (*395*, *401*, *402*)). As these are much less informative than studies with individual exposures, we shall not discuss them further.

Exposure in adulthood

A case-control study of cleanup workers from Belarus, Russia and the Baltic states yielded borderline significant ERR for incident NHL and hematological malignancies excluding multiple myeloma; risks were also adjusted for dose error, but this did not much change the central estimate, although CI were somewhat expanded (see Table 6) (*403*). A case-control study in Ukraine (with dose error adjusted using regression calibration) suggested that there were significant ERR for leukemia excluding CLL and also for CLL (*404*) (see Table 6). In neither study was there significant curvature in dose response, for any endpoint (*403*, *404*). A study of CLL cases in Ukraine cleanup workers reported that survival of CLL cases (adjusted for dose) was significantly shorter for those exposed at young age (*405*), also that tumor telomere length in radiation exposed CLL cases was significantly longer than for non-radiation-exposed CLL (*406*). It should be noted that neither NHL nor CLL are thought to be strongly radiogenic (*8*, *226*). It is also not clear what significance should be attached to telomere length changes, since both lengthening and shortening of telomere lengths have been seen following radiation exposure (*407*, *408*).

Thyroid cancer

In utero exposure

There was a significant increase in large (>10 mm) benign thyroid nodules, and a large but non-significant excess of thyroid cancer cases, but based on only 8 cases (see Table 6) (*409*). There does not appear to be any excess of small (<10 mm) benign thyroid nodules ~~(*398*)~~ (see Table 6). There was significant downward curvature for all types of nodules, all benign nodules and small benign nodules (*409*). Risk was not adjusted for dose error ~~(*398*)~~.

Exposure in childhood

Two large cohort studies in Ukraine and Belarus with 25,000 participants exposed to the Chornobyl fallout before the age 18 years were initiated ten years after the accident (*410*). In Ukraine, significant increasing trends for prevalent (*411*) and incident thyroid cancer (*412*), with borderline significant indications (p=0.101-0.112) of downward curvature in the dose response have been observed (*413*). In Belarus, there is a significant dose response for thyroid cancer prevalence, with borderline significant (p=0.057-0.078) downward curvature in the prevalence odds ratio (OR) dose response (*414*). Interestingly, very little difference is made by various types of adjustment for dose error in either dataset (*413, 414*).

Histopathological and molecular characteristics of thyroid cancer

Several studies of post-Chornobyl papillary thyroid cancer (PTC) after childhood exposure to ^{131}I have reported a high frequency of solid variant PTC, *RET-PTC* rearrangements, and/or aggressive tumor behavior associated with radiation dose (*415-418*). The most comprehensive study of PTC to date analyzed genomic, transcriptomic, and epigenomic profile of 359 cases from Ukraine with individual estimates of ^{131}I dose received ≤18 years (mean=0.25 Gy) (*419*). In multivariate analyses adjusted for age and sex, investigators found a linear dose-dependent enrichment of fusion drivers (including *RET* and other genes from the mitogen-activated protein kinase pathway) and increases in small deletions and simple structural variants that were clonal and bore hallmarks of non-homologous end-joining repair. Radiation-related genomic alterations were more pronounced among individuals younger at exposure. These findings indicate that ionizing radiation-induced DNA double-strand breaks represent an early event in thyroid carcinogenesis after ^{131}I exposure and provide a mechanistic support to epidemiological observations (*419*).

Cleanup workers' studies

There is a large and highly significant dose response for thyroid cancer incidence in relation to radiation doses from cleanup work and residential exposures in a case-control study within the Belarus, Russian and Baltic states cleanup worker (liquidator) cohort (*420*) (see Table 6). Adjustment for dose error made little difference to the trend, although CI were markedly wider

(*420*). Although without adjustment for dose error the excess odds ratio (EOR) /Gy in the Ukraine cleanup workers is much lower than for the Belarus/Russia/Baltic study (*421*), there is a remarkable increase (by about 50%) in risk when Monte Carlo maximum likelihood (MCML) methods are used to adjust for dose error, and for follicular tumors the trend becomes borderline significant (*p*=0.066) (*422*). Although thyroid cancer radiation risk after adult exposure is rather lower than in childhood, there is nevertheless accumulating evidence that it may be non-zero (*423*).

Breast cancer

Several studies reported increased breast cancer incidence in contaminated areas of Ukraine, Belarus and Russia after the Chornobyl accident (*424-426*); as all are ecological studies, bias is an important concern~~, primarily in relation to estimated district-average whole-body doses from external exposure and ingestion of long-lived radionuclides~~. To date, only one study has been conducted which evaluated the risk of female breast cancer in relation to individually estimated doses from the Chornobyl accident (*427*). This case-control study in Bryansk Oblast, Russia during 2008-2013 reported non-significantly increased excess risk (*427*) (see Table 6). The point estimate was substantially larger than those recently observed in the LSS (*31*) and in other exposed groups (*428*). There was much higher radiation-related risk for women exposed before age 13 years and those who were younger at the time of diagnosis (*427*). Risk was not adjusted for dose error (*427*).

Recently, several studies compared breast cancer rates among pregnant or lactating women with the general population rates (*425, 429, 430*). Generally, the standardized incidence ratios (SIR) were not significantly increased for women pregnant at the time of the accident but were elevated for women lactating at the time of accident. The SIRs were highest in women who were exposed at a younger age and during the earliest period subsequent to the accident (*430*). However, none of these studies had individual dose estimates, so the results should be interpreted cautiously and the findings need to be followed up with studies employing individual dose estimates.

Non-Cancer Risk

Benign thyroid disease

Prevalence of follicular adenoma, a benign thyroid neoplasm, was significantly associated with ^{131}I dose in the Ukraine (*431, 432*) and Belarus (*433*) pediatrically-exposed cohorts and EOR/Gy decreased with increasing age at exposure (*432, 433*). The ^{131}I risk of non-neoplastic thyroid nodules as a group was also significantly elevated in Belarus (*434*). Above 5 Gy there was evidence of turnover in dose response, with some dependence of EOR/Gy on nodule size and age at exposure (*434*). A qualitatively similar pattern of ^{131}I risk by size of non-neoplastic nodules, with risk much higher for large nodules than for small nodules, was found in the Ukraine cohort exposed *in utero* (*409*). A thyroid screening study of individuals exposed to ^{131}I at age ≤10 years in the Russian Federation found little evidence of dose response for solid thyroid nodules, cysts or goiter (*435*).

Of functional thyroid diseases, ~~weak statistically~~ significant associations with ^{131}I dose were~~as~~ observed for prevalence of hypothyroidism (thyroid-stimulating hormone (TSH)>4 mIU/L) in both childhood cohorts in Ukraine and Belarus, with ~~some evidence of~~ significant upward curvature in dose response in Belarus (*436, 437*). In both cohorts, the ^{131}I risk of hypothyroidism was higher among autoantibodies to thyroid peroxidase (ATPO) negative than ATPO positive individuals. In Belarus, it also decreased with increasing age at exposure, presence of diffuse goiter, and urban residence (*437*). There was no evidence of dose response for ATPO-positive hypothyroidism, autoimmune thyroiditis, and hyperthyroidism in either cohort (*436-439*). An association with ^{131}I dose for ATPO positivity was found in Ukraine (*438*), but the results in Belarus were null (*437*).

Cataract

Cataract was studied in a cohort of 8,607 clean-up workers in Ukraine 12-14 years after the accident; they were drawn from several groups of workers active on-site during 1986-1987 (*440*, *441*). For this cohort, γ doses ascertained from the official “recorded” doses were corrected and β particle doses added, and dose uncertainty was assessed (although not used in the analysis) (*441*). PSC or cortical cataracts were present in 25% of the subjects. A significant radiation dose response was found for stage 1 cataracts (considered as cataract onset) and for PSC (see Table 6). There was little~~weak~~ evidence of ~~upward~~ curvature in the dose response; although there was some evidence for threshold in dose, given the ~~there was otherwise little evidence~~absence of dose response curvature, and as discussed in the LSS section, the evidence of threshold is therefore maybe~~likely~~ artefactual (*208*).

Cardiovascular disease

There are significant excess CVD risks (and risks of various CVD subtypes) in the Russian cleanup workers (*442-447*) (see Table 6). A remarkable feature of the Russian cohort is the relatively high rate of CVD incidence, including for example 23,264 cases of CeVD in a cohort of 53,772 people, (*444*), contrasting with 15,025 deaths in a cohort of 91,013 (*447*); in interpreting these one should bear in mind the substantially elevated CVD mortality rates in the Russian population relative to those in other developed countries (*448*). There remain concerns about many design aspects of the Russian study, which also lacks any information about major lifestyle and medical CVD risk factors (*449*). Nevertheless, the ERR/Gy are not substantially greater than those seen in some other groups (see Table 1, Table 3, Table 5). There are some indications of excess risk in some populations of Ukraine cleanup workers (*450*), although not in all (*451*) (see Table 6).

Transgenerational effects

To investigate germline *de novo* mutations (DNMs) of parental radiation exposure, a parent-offspring trio study analyzed 130 children born in 1987-2002 to parents employed as cleanup workers or exposed to occupational and environmental ionizing radiation after the accident (*110*, *452*)~~ (*447, 448*)~~. Although dose uncertainties were estimated, no use was made of them in the analysis (*110*, *452*)~~ (*447, 448*)~~. Whole-genome sequencing of 130 children and their parents did not reveal paternal or maternal pre-conceptional dose-related increases in the rates, distributions, or types of DNMs, nor in leukocyte relative telomere length, although there were significant modifying effects of age (*453*) (see Table 6). Over this exposure range (paternal preconception dose 0-4.08 Gy, maternal preconception dose 0-0.55 Gy), evidence is lacking for a substantial effect on germline DNMs in humans, suggesting minimal impact from transgenerational genetic effects (*453*). The genetic doubling dose (=1/ ERR/Gy) implied by this study (*453*) (see Table 6) greatly exceeds, and is statistically incompatible with, the value of 1 Gy that is often assumed, largely based on 7-locus mouse data (*454*); indeed the entries given in Table 6 imply a lower 95% CI of paternal and maternal gonadal doubling dose of 1/ 0.0221/Gy ~ 45.2 Gy and 1/ 0.0910/Gy ~ 11.0 Gy respectively.

Psychological effects

Neuropsychological and psychological impairments associated with radiation exposure from Chornobyl have been reported for those exposed as children, in particular poor self-rated health as well as clinical and subclinical depression, anxiety, and post-traumatic stress disorder (*455*). The excess morbidity rate of psychiatric disorders among cleanup workers in the first year after a disaster was reported at 20% (*455*), and the rates of depression and post-traumatic stress disorder remained elevated decades later; elevated rates of suicide in a small Estonian cohort of cleanup workers (without dose estimates) are a possible marker of this (*456*). Many of the lingering effects were due to continuing worries about the adverse health effects of radiation exposures and to paucity of mental health care in affected regions (*455*). Future research is needed to clarify the dose-dependent incidence and prevalence of mental disorders for individual mental health effects.

OCCUPATIONAL STUDIES

Workers in NPP, nuclear reprocessing plants, nuclear weapons production plants, nuclear shipyard workers and various other groups that are exposed to radiation occupationally, for example medical radiation workers, aircrew and astronauts, and uranium miners, are predominantly exposed to radiation at low dose rates (<5 mGy/hour) (*457*), although sometimes to considerable cumulative dose, over 1 Gy. As such these groups are important in providing information on risks at low dose rate exposures. At least for cancer, the radiobiological understanding suggests that the slope of the dose response for such low dose rate exposure should coincide with that theoretically expected from low-dose exposure (*458*). We consider the various types of radiation workers in turn.

Nuclear Power Plant (NPP) and Nuclear Reprocessing Plant Workers

We consider first a large study of NPP and reprocessing workers, the International Nuclear Workers Study (INWORKS). We also describe a number of other, generally smaller (but in some cases also statistically powerful) NPP worker studies, including the Mayak workers and separate studies to be included in the Million Person Study (MPS).

INWORKS

INWORKS is a collaborative study of health effects observed in a pooled study of French, UK, and US radiation workers coordinated by the International Agency for Research on Cancer (IARC) (*87*, *459-466*). INWORKS builds upon IARC's previous investigations, which included the 3-Country Study (*467*, *468*) completed in the mid-1990s (using the Canadian, UK and US workers) and the 15-Country Study completed in the mid-2000s (*469-473*); although the INWORKS cohort is somewhat smaller than the 15-Country Study (309,932 vs 407,391), it has more person years of follow-up (10.72 vs 5.19 million). ~~Beginning with the most informative cohorts from those studies.~~

INWORKS comprises French, UK, and US workers who were monitored for external radiation and employed for at least one year at an included nuclear facility. However, whereas the UK and French components of INWORKS are essentially national studies, with many different types of radiation workers (in reactors, reprocessing plants, dockyards etc.), the US component includes only five sites (Hanford, Savannah River, Oak Ridge National Laboratory, Idaho National Laboratory, Portsmouth Naval Shipyard), but these also include a diverse variety of types of worker (including shipyard workers), in some cases with asbestos exposure, and it is the second largest group of workers (after the UK) in INWORKS. Several recent country-specific analyses of subsets of the INWORKS cohort have been published separately (*474-479*). Participating facilities/companies in INWORKS were selected based on records availability, quality, ~~and~~ completeness,~~;~~ ~~similarities in facility operations;~~ and shared exposure characteristics. In general, workers in INWORKS were predominantly exposed to low-level penetrating γ radiation from external sources; internal doses from intakes of radionuclides and neutron doses were not computed and some other occupational radiation exposures were not completely accounted for; 13% were flagged for possible neutron exposure and 16% were flagged for incorporated radionuclides or internal monitoring (*466*). The most recent analyses include 309,932 workers and 103,553 deaths (28,089 from solid cancers) observed between 1944–2016 (10.72 million person-years) (*466*). Recorded doses have been adjusted to estimate organ/tissue absorbed dose, as well as personal dose equivalent [*H*p(10)], accounting for differences in exposure scenarios, dosimetry, and recording practices over the study period (*87*). The average absorbed dose to the colon was 0.018 Gy. The cohort is predominantly male (87%) (*466*).

Cancer risk

The radiation dose-solid cancer mortality association was reasonably described by a linear model (see Table 7) using a 10-year lag, although some downward curvature was apparent. There was little evidence of significant heterogeneity by country. Excluding deaths from lung cancer did not appreciably change the risk estimate, providing some evidence against strong confounding by smoking, with the dose-response for all solid cancers excluding lung cancer showing little evidence of downward curvature. Restricting workers to those hired in 1958 or later (ERR/Gy=1.22; 90% CI: 0.74, 1.72) and 1965 or later (ERR/Gy=1.44; 90% CI: 0.65, 2.32) markedly increased estimates, which contrasts notably with the estimate for those hired before 1958 (ERR/Gy=0.20; 90% CI: -0.07, 0.49). The reasons for differences in risk by hire date are not readily elucidated in the current study but may be due in part, to limitations in dosimetry, especially in the early years of the nuclear industry. However, this may also illustrate the dangers of subset analysis, although 1958 and 1965 were selected *a priori* as years in which improvements in dosimetry occurred at the facilities~~with no precisely defined prior hypothesis being assessed~~. This pattern of risks by hire date was seen even more strongly in the US worker component of INWORKS (*466, 479, 480*). A difference in estimates was also observed for whether workers were flagged (ERR/Gy=0.21; 90% CI: -0.11, 0.56) or not flagged (ERR/Gy=0.82; 90% CI: 0.46, 1.22) for intakes of radionuclides, a pattern of risks also found in the UK component of INWORKS (*476*). Sensitivity analysis in which the workers (13% of the total) that were flagged for possible neutron exposure were excluded suggested no change in trend ERR/Gy (0.53 vs 0.53) (*466*). A concerted effort to better understand these differences in mortality patterns between earlier- and later-employed workers is needed.

Previous INWORKS studies have examined mortality from site-specific solid cancers and lymphohematopoietic cancers (*459, 464*). For solid cancers, ~~maximum likelihood estimates of the~~ linear ERR/Gy (lagged 10 years) were ~~positive for mortality from oral, esophagus, stomach, colon, rectum, pancreas, peritoneum, larynx, lung, pleura, bone and connective tissue, skin, ovary, testis, and thyroid cancer. Of these associations,~~ statistically significant for cancers of the rectum, peritoneum, larynx, skin, and testis ~~were statistically significant~~. In interpreting these results it must be pointed out that 24 cancer sites were evaluated (*464*), so it is possible that some of these sites (e.g. rectum, testis) which are not generally thought to be strongly radiogenic (*8, 481*), may have arisen by chance. For lymphohematopoietic cancers, there was strong evidence of a dose-response association for leukemia, excluding CLL, but not for myeloma or lymphomas (see Table 7). There was no evidence of curvature in the dose-response. ~~Chronic myeloid leukemia (~~CML~~)~~ was the main contributor to all leukemia risk and there was no evidence of an association between radiation and CLL.

Non-cancer risk

Patterns of non-malignant disease mortality (46,029 deaths) were examined in the cohort followed through 2005, with an average equivalent dose of 0.025 Sv (*482*). The study found a positive association between radiation dose and all non-malignant causes of death that was best described by a linear model (see Table 7). This association appeared driven by excess mortality from CVD. There was significant heterogeneity in circulatory disease risk by employer/facility (p = 0.01). There was no evidence of effect modification of CVD risk by age, employment duration, SES (derived from job titles), or time since exposure. Within CVD, positive dose-response associations were evident for mortality from CeVD and IHD (see Table 7). An important limitation of INWORKS and most occupational studies is the absence of information on important risk factors for circulatory diseases, such as smoking, diabetes, obesity, hypertension, dyslipidemia, diet and exercise.

Mayak workers

The Mayak nuclear plant is sited in Ozyorsk in the Southern Urals of Russia and is where the former USSR initiated nuclear operations on atomic bomb production in 1948. Five reactors were built to produce plutonium, with reprocessing to produce weapons grade material occurring onsite. Nuclear waste from the plant was initially discharged to the Techa River and in consequence many groups living downstream along the Techa River received substantial exposures (>0.5 Gy) (*105*, *483*). Most recent analyses are based on Mayak workers first employed in the period 1948-1982, with follow-up for mortality and (for those remaining within Ozyorsk) for morbidity to 2018 (*484-489*).

Although the Mayak cohort is of only moderate size (with just greater than 22,000 workers), it has a number of valuable features. The Mayak worker data are unusual in that the cohort received substantial internal (^{239}Pu) in addition to external γ (and neutron) doses, and ~~often~~ the effects of these on various health endpoints are significant and independent. Although not unique in that respect, for example there are some workers at Sellafield with substantial ^{239}Pu dose (*490*), the internal doses in the Mayak cohort are at a much higher level than in other workforces. For comparability with other groups, we present here risks in relation to external γ dose. Unlike most worker datasets there is rich lifestyle data, adjusted for in many analyses (*484-489*).

Cancer risk

There is significant excess incidence of AML in relation to external RBM dose, but for no other type of hematolymphoid malignancy (*491*) (see Table 8). AML risk is highest 2-5 years after exposure, decreasing substantially thereafter (*491*). There is little evidence of risk associated with ^{239}Pu for any hematolymphoid malignancy endpoint, and smoking adjustment makes little difference (*491*). In relation to external dose t~~T~~here is significant excess mortality and incidence risk of lung cancer~~ associated with external dose~~ (*492*), but not of bone or liver cancer (*493*). A significant excess mortality risk of solid cancers excluding lung, liver and bone in relation to external dose has been found (*494*), in particular for cancer of the esophagus, and a borderline non-significant excess risk of incidence of solid cancers excluding lung, liver and bone cancers (*495*) (see Table 8). In terms of the dose from intakes of plutonium, highly significant excess risks of lung cancer mortality and incidence have been found (*492*), and significant excess risks of mortality from liver and bone cancers (*493*).

Non-cancer risk

Analyses in relation to external doses show significant excess risks of certain~~all main~~ major subtypes of CVD incidence (*484-489*) (but not in general of mortality for these subtypes), and all CVD mortality (*496*) (see Table 8). For many endpoints there were independent incidence risks in relation to internal α particle dose to the liver (*484-486, 488*). There is significant excess risk of Parkinson’s disease incidence (*497*), but little ~~only weak indications~~evidence (only in subset analysis) of excess incidence of chronic bronchitis (*498*) (see Table 8). There are significant excess risks of all three main types of cataract, PSC, cortical and nuclear (*499*), but no excess risk of cataract surgery (*500*) (see Table 8). There is also borderline significant excess risk of normal-tension glaucoma, based on a small number (92) of cases, but no significant risk of any other type of glaucoma (*501*) (see Table 8). The Mayak CVD data, and in particular the differences between the mortality and incidence data, has been subject of a number of illuminating reviews (*449*, *502*, *503*).

Million Person Study (MPS)

The MPS proposes to examine the relationship between low-dose radiation exposure and mortality in 34~~29~~ individual cohorts of US workers~~ (*501*)~~ (*504*, *505*). To date, health effects have been investigated in over a third of these cohorts, including studies of NPP workers (*248*, *506-508*), medical workers (*248*, *509*), industrial radiographers (IR) (*248*, *507*, *508*), US atomic veterans (*248*, *507*, *510*, *511*), and nuclear weapons research and production workers (*248*, *507*, *512-517*). Three reports provide pooled information across several MPS cohorts to estimate excess risks from radiation (*248*, *507*, *508*), which we discuss below in the section on pooled studies. Like many other older groups of nuclear workers, such as INWORKS (*466*) – ~~—~~although in contrast to the Mayak workers (*484-489*), nested case-control studies within some other worker cohorts (*518*, *519*), and more recently assembled groups of medical workers (*520-522*) – there is no information on major lifestyle and medical risk factors, in particular cigarette smoking, although via linkage with MEDICARE/MEDICAID data it is possible that such data could be obtained for at least the newer part of the cohort (*523*).

Cancer risk

An ~~National Council on Radiation Protection and Measurements (~~NCRP~~)~~ report presented pooled information on NPP workers, ~~industrial radiographers~~IR and medical workers, comprising 367,722 persons, and with additional analysis including the Los Alamos workers (*512*), yielding no significant excess lung cancer risk (see Table 9) (*524*). A pooled analysis of NPP workers and IR~~industrial radiographers~~, comprising 253,632 workers, provided little evidence of excess mesothelioma risk associated with radiation (*508*) (see Table 9). As reported in a recent summary paper (*523*), five~~Only one~~ of the eight component studies describe~~d~~ an increased leukemia trend risk~~ and this was of borderline statistical significance~~, namely NPP (*506*), IR (*10*), medical radiation (*509*), Mound (*10*) and Rocketdyne (*10*), but three of these have yet to be published separately, appearing only in the summary publication and an earlier NCRP report (*10*); none are statistically significant~~. In several others there are negative central estimates of trend for leukemia (*501, 503, 507*)~~ (see Table 9).

Non-cancer risk

As summarized in a recent review, there is no excess risk of IHD in any of the MPS studies, and for 6 out of 7 cohorts the central estimates of ERR are negative (*525*), although a recently updated analysis of one of these 7 (the Mallinckrodt workers) has yielded a significant trend for IHD (*517*). There is a significant trend of elevated Parkinson's disease mortality in a meta-analysis of IR~~industrial radiographers~~, NPP workers, US atomic veterans, and nuclear weapons workers, comprising 517,608 persons (*507*) (see Table 9).

Uranium Workers and Miners

Uranium and other hard-rock miners

Agricola (*526*) documented high rates of lung disease among metal miners in the Schneeburg and Joachimsthal areas, on either side of the Erz mountains. Harting and Hesse (*527*) were the first to identify that the "miner's disease" was a malignancy, later shown to be primary lung cancer. Later case series showed 150 deaths in a workforce of ~650 men; histopathological review of subsequent case series established that the malignancy prevalent among miners in the Erz Mountains was primary lung cancer (*528, 529*). In the first decades of the 20th century radon was found in mines in both districts and was suspected as a cause of the lung cancer, a hypothesis confirmed in epidemiological studies of radon-exposed underground miners that were started in the 1950s and later. There are now more than 20 studies of lung cancer in radon-exposed miners, all of them male (*93, 530, 531*). Some of these had quantitative data on exposure that were analyzed by Lubin *et al* (*532*) and by the US Biological Effects of Ionizing Radiations (BEIR) IV (*533*) and BEIR VI (*95*) committees to develop risk models.

Risks have been estimated in terms of exposure to radon progeny expressed as Working Level Months (WLM), the product of time exposed in terms of 170-hour months and concentration expressed as Working Levels (WL) where 1 WL is defined as that concentration of short-lived radon decay products in equilibrium with activity 3700 Bq m^{-3} (100 pCi/L).

Cancer risk

Lung cancer

The BEIR VI committee (*95*) assessed lung cancer risk in 11 miner cohorts, of which 8 were uranium miners. The pooled data included nearly 1.2 million person-years of follow-up, with 2674 lung cancer deaths among workers with prior radon exposure, and 113 lung cancer deaths among workers without prior radon exposure (*95*). The large number of deaths permitted detailed examination of many factors that may modify the risk of radon-induced lung cancer. The ERR/WLM decreased with increasing time since exposure and attained age, and with increasing average radon concentration (the exposure–age–concentration model) or with decreasing duration of exposure (the exposure–age–duration model) (*95*). There was no variation in the ERR/WLM with age at first exposure (*95*). More recently, the Pooled Uranium Miner Analysis (PUMA) brought together the data from extended follow-up of five of the eight uranium miner cohorts included in BEIR VI (*95*) and added additional cohorts from Canada and Germany (*534*). PUMA recorded 7754 lung cancer deaths with 4.3 million person-years of follow-up (*535*). There were similar patterns of temporal modification as for BEIR VI (*95*), with highly significant reductions in risk with increased attained age, time since exposure and higher exposure rate (*536*). In the full cohort the aggregate ERR/WLM was not significantly different if analysis was restricted to miners with cumulative exposure of <100 WLM or if restricted to those hired before 1960 (*536*); however, after exclusion of early miners (hired before 1960, when exposures were higher and associated with much larger uncertainties), the estimated ERR/WLM was approximately twice that for the full cohort (*537*) (see Table 10). Overall, findings from the BEIR VI and PUMA models are comparable and complementary, but PUMA includes twice as many uranium miners and about three times as many lung cancer deaths. ~~The availability of the PUMA data sets will facilitate updating of the long-used BEIR VI risk models.~~

Smoking is the strongest risk factor for lung cancer, but unfortunately, most studies of miners did not take account of smoking habits. Nevertheless, available results indicate that the relationship between lung cancer mortality and radon exposure is not substantially confounded by ~~generally persists when~~ smoking ~~habits are taken into account~~, with only marginal changes in the risk of radon-associated lung cancer upon adjustment for smoking. Most analyses are consistent with a sub-multiplicative interaction between radon exposure and smoking status (*95*, *530*). Further analyses are needed to improve the characterization of the joint effect of radon and smoking.

Other cancers

A pooled analysis of cancers other than lung in the 11 miner cohorts used by BEIR VI (*95*) suggested increased risks of leukemia, and cancers of the stomach and liver, but these did not correlate with cumulative exposure (WLM) and so the authors concluded that they were unlikely to be caused by radon exposure (*538*). There was a borderline significant trend with radon exposure for pancreatic cancer based on a small number of deaths (see Table 10) (*538*). Since then, analysis of the German miners suggested non-significant excess risk of cancers of extra-thoracic airways (most of them cancers of the larynx n=94, but including cancers of the pharynx, n=74, tongue and mouth, n=55) (*539*), all smoking-related cancers (*540*). These do not materially add to the evidence for radon effects on any cancer except the lung (*530*).

Non-cancer risk

Analysis of French (*518*) and German uranium miners (*541*, *542*) suggest no significant radon-related excess risk for CVD, or other non-malignant disease (see Table 10). There are indications of gamma-related CeVD risk among French (*518*, *543*) uranium miners, but for no other CVD endpoint there nor in German (*544*) miners.~~The PUMA study should be informative on this matter.~~

Uranium processing workers

Uranium processing workers constitute only a small proportion of workers of the nuclear fuel industry and typically include workers involved in milling; refining and conversion; enrichment; and reconversion and fuel fabrication. Of the more than 500,000 workers employed worldwide in the nuclear fuel cycle in the last 40-50 years, only 10-15% were involved in uranium processing (*545*, *546*). Only a few studies conducted dose-response analyses of uranium processing workers with individual radiation doses (*516*, *517*, *547-562*), and an even smaller subset used individually estimated doses from uranium or other radionuclides (see Table 11) (*517*, *548*, *551*, *554*, *556*, *559-562*).~~ (*508, 509, 537, 538, 540, 543, 545, 549-551*).~~ A recent United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) report on biological effects of uranium summarized the evidence as indicating “a weak association of lung cancer risk with uranium exposure … but the currently available results are not consistent enough to demonstrate a causal association”,~~a weak association with lung cancer risk~~ and unclear evidence for risks of leukemia, other lymphohematopoietic malignancies, digestive system cancers, kidney and other urological cancers with uranium exposure (*563*). These conclusions were echoed by a recent ICRP report

(*564*). Since the publication of these two reports, several new studies have been published (*517, 556, 560, 562*). While the conclusions with regards to cancer outcomes have not changed, the new studies provided mostly null~~some~~ evidence of a possible CVD effect from exposures to uranium (see Table 11) (*517, 560, 562*). Only one of these new studies (*560*) (the only one to yield a significant risk), and none of the older studies, had any information on the major lifestyle and medical/environmental risk factors for CVD, so the evidence must be regarded as somewhat limited.

Only one pooled analysis of uranium processing workers has been conducted to date (*565*) and an international Pooled Analysis of Uranium Workers (iPAUW) from 9 cohorts from five countries is underway (*565*). The lack of pooled studies is due to the complicated radiation exposure profiles of workers in this industry. Uranium processing workers are typically exposed to γ-rays and long-lived radionuclides from uranium ore dust, but less to radioactive elements such as radium and radon which decay by emitting high-linear energy transfer (LET) α-radiation radon decay products, typical for uranium underground miners. However, in some early uranium plants pitchblende was processed, which had a high radium content and high radon level exposures (*566*). This required specialized techniques to determine dosimetry.

Medical Radiation Workers

Landmark studies of radiologists in the United Kingdom (*567*, *568*) and the United States (*569, 570*) that followed up workers first exposed during 1897-1920 and 1920-1939, respectively, and retrospective cohort studies of USRT (*571*), US radiologists (*572*), Japanese (*573*), Chinese (*574*), Danish (*575*) and Korean medical radiation workers (*576*) reported increased risks, of leukemia most consistently, generally among those first employed before 1950 (or before 1970 in China) when occupational radiation exposures were high (*577, 578*). A weakness of most of these studies is that there were no individual dose estimates, limiting their usefulness for quantitative risk assessment. Nevertheless, for some groups, for example the USRT and the Chinese and Korean medical workers cohort, individual dose estimates were generated, as we discuss below.

Cancer risk

Most of the cohorts of medical radiation worker cohorts ~~(*563-565, 567-571, 574-577*)~~ (*568-576, 579-581*) restricted radiation-associated risks reported to standardized mortality (SMR) or incidence (SIR) ratios. These studies suggested higher rates of cancer-specific mortality, particularly amongst early medical radiation workers compared to reference populations. Since estimates of excess risk per dose were not calculated, these studies will not be considered further here. Estimates of elevated risk from the three main studies that examined cancer risks per unit of radiation exposure are summarized in Table 12. The USRT cohort reported borderline significant ERR/Gy with radiation exposure for breast cancer mortality, strongest (and statistically significant) for workers born before 1930 but no increased ERR/Gy for breast cancer incidence for workers at any time point (*582*). No other malignancies demonstrated a significant dose-response (*583-587*). Korean diagnostic medical radiation workers showed no significant radiation dose-response for leukemia, all solid cancers or other individual cancer outcomes (*588*). Chinese medical radiation workers had a significantly increased ERR for all solid cancers, but dose-response findings were not reported for individual solid cancer or hematopoietic malignancy outcomes (*589*). The liver and lung were the most common outcomes (*589*). For these types of solid tumors, the authors pointed out the possible if not likely confounding by hepatitis, alcohol intake, and smoking consumption; however, such potentially confounding factors were not considered (*589*).

Non-cancer risk

In the USRT significant excess risks per dose were observed for self-reported cataract incidence (remaining statistically significant when analysis was restricted to <100 mGy) but not for cataract surgery (*522*) (see Table 12), in a technologist cohort numbering 67,246 (for cataract incidence) or 67,709 (for cataract surgery). Dose-response was not significantly increased for glaucoma or macular degeneration in the USRT (*590*). The cohort of 11,500 Korean diagnostic medical radiation workers overall showed no evidence of excess morbidity or mortality from CVD nor did 53,860 Korean medical workers enrolled in the National Dosimetry Registry, both after relatively short follow-up (*520, 591*).

Ongoing work and future directions

Although badge records during 1980-2015 for the entirety of 58,434 USRT have shown a steady decline from an annual median dose of 0.6 mSv in 1980 to minimal levels (*e.g.*, below the limit of detection) in 2015, annual median doses were substantially higher and did not decline for the subset of technologists performing nuclear medicine procedures particularly those performing positron emission tomography (PET) and cardiac procedures (*592*), and there are indications of particularly high eye lens doses for medical staff believed to have performed or assisted with fluoroscopically guided procedures. More detailed dosimetry studies are in progress in the USRT and the Korean medical radiation workers and will be followed by cohort studies applying improved dosimetry to ascertain cancer and non-cancer risks per unit dose for medical radiation workers overall and for those performing or assisting with nuclear medicine and with fluoroscopically guided procedures.

Other Radiation Workers

As well as the groups of studies considered above and the Chornobyl cleanup workers (considered in the section dealing with the Chornobyl accident), there are relevant studies of other workers not included in these groups that are employed in several occupational sectors, such as commercial nuclear power, aviation and space exploration. The most informative studies pool information on similar workers and directly estimate cause-specific risks at a given radiation dose, which is vital to understanding low-dose effects for malignant and non-malignant disease. Cancer mortality is the endpoint most often examined, although information on cancer incidence and non-malignant outcomes is also available. The predominant exposure assessed is low-LET penetrating γ radiation. In general, risk estimation in these studies was hampered by restrictions in cohort size, follow-up, and dose distributions. Potential exceptions are pooled national and international studies that, through larger numbers and longer follow-up, are better positioned to elucidate radiation risks if there is uniformity in the methods of assessing radiation exposures;~~.~~ if analysis takes account (as it easily can) of differences in the background rates of the pooled studies, confounding can be controlled by statistical means. More important is that uniform methods be used for example in disease coding (but differences in efficiencies of ascertainment can be adjusted for statistically). Selected findings from some of these studies are discussed and shown in ~~the~~ Table 13 to illustrate the range of information available.

Cancer risk

Several studies have pooled information on radiation workers employed in Australia, Canada, Germany, Japan, Korea and the US, among others (*593-600*). The largest of these involves analysis of mortality in Japanese nuclear workers (*597*). There was a positive but non-significant trend with dose for all cancers excluding leukemia, but a negative trend for leukemia (*597*) (see Table 13). Although a strong association between radiation and alcohol-related cancers (upper digestive tract and liver) was found, a subsequent study of a smaller group of these workers that adjusted for self-reported lifestyle factors did not find evidence of confounding by alcohol (*599*). The study reported a marked decrease in mortality risk from all cancers excluding leukemia after adjusting for smoking (*599*). A subsequent examination of several self-reported risk factors further demonstrated the potential effects of smoking in these workers (*601*).

There are several studies examining cancer in commercial aircrew members exposed to cosmic radiation (*602-613*), the cumulative doses to whom, particularly those working repeatedly at high altitudes, can be considerable (e.g. >50 mSv) ~~(*603*)~~ (*607, 614-616*). Most studies have conducted comparisons with an external referent, resulting in observed cancers well below expected numbers, indicating strong healthy worker effects. Nevertheless, a recent meta-analysis combining these estimates have suggested increased breast cancer in female flight attendants compared with the general population (*611*); however, a separate meta-analysis of aircrew found no elevation in breast cancer risk associated with cumulative dose (*617*). There is also some evidence suggesting increased risk of malignant melanoma among aircrews, although ultraviolet radiation (UVR) exposure may well be a confounder. For example, there was modest excess mortality from melanoma (SMR = 1.57; 95% CI: 1.06, 2.25) in aircrews compared to the general population in a study pooling information from 10 countries (*609*). Other aircrew studies have reported increased melanoma risk in external comparisons with relatively few observed cases (*607, 608, 616*). In contrast, there is little evidence of positive dose-response patterns for any cancer in aircrew studies reporting estimates from internal comparisons (*606, 608, 612, 613*).

US atmospheric nuclear test veterans are included in the MPS ~~(*497*)~~ (*510*), and~~but~~ other such military groups have been studied, in the UK (*618, 619*), Australia (*620, 621*) and New Zealand (*622*). The US series is the largest, with *n*=114,270 persons, but doses have only been ascertained for about 1.7% of these (*510*). The UK study is the second largest, with *n*=21,357 test participants and a matched set of *n*=22,312 controls, with dose records available for about 23% of the test participants (*618*). ~~and~~ S~~s~~uccessive analyses have yielded consistent evidence of excess of leukemia associated with nuclear test involvement (*618*, *619*, *623-625*). However, the excess is not dose-related and remains unexplained.

Non-cancer risk

There was little evidence of increased risk of non-malignant diseases in studies of nuclear workers, commercial aircrews or astronauts (*595, 598, 599, 606, 609, 616, 626*).

~~NON-CHORNOBYL~~ ENVIRONMENTAL EXPOSURES EXCLUDING CHORNOBYL

This section is largely concerned with the effects of exposures to natural radiation but also covers environmental exposures to man-made radiation, excluding those from Chornobyl. The most radiologically significant of these exposures is to ^{222}Rn, a chemically inert gas that arises from the decay of ^{238}U, which is present throughout the earth's crust. People can be exposed to radon in dwellings and other buildings, mainly via seepage from the subsoil beneath buildings. If radon is inhaled, its short-lived progeny – including ^{218}Po and ^{214}Po – tend to deposit on the bronchial epithelium and hence expose sensitive cells to α radiation. Worldwide, exposure to radon and its decay products is responsible for nearly one half of the total effective dose from all sources of natural radiation (*627*).

As noted in previous sections, it took until the 20th century to identify radon as the most likely cause of the "miner's disease" (later known to be primary lung cancer) first described in cobalt (but also silver and bismuth) Schneeburg miners in the sixteenth century (*628*). Modern interest in natural radiation was stimulated by UNSCEAR in the 1950s (*629*) to collect data on these exposures. The availability of regional exposure measurement data on radon and terrestrial γ rays, with or without cosmic rays, opened the way to studies to quantify associations between disease, particularly cancers, and radiation exposure. Radon and γ rays are quite different kinds of radiation, the former, high LET, and involving short-lived decay products, delivering very inhomogeneous doses across the body; the latter, low LET, and with much less variation in absorbed dose. Some of the early studies were ecological, speculative and underpowered (*95, 630*), whereas later better designed studies, including measurements in indoor dwellings, offered the prospect of providing direct evidence of the risks of low doses delivered at low dose rates.

Cancer Risk

Residential radon

Concentrations of radon in homes can vary considerably, depending on local conditions. As documented by UNSCEAR (*627*), some early investigations of the health impact of residential radon exposure used an ecological study design to compare geographical area-specific lung cancer rates and average radon levels. However, these ecologic studies were prone to bias, particularly of their inability to take full account of potential confounding by smoking (*327*). Furthermore, radon concentrations may differ notably between homes within the same area. Consequently, most epidemiological studies of residential radon and lung cancer have used a case-control design, to collect individual-specific information on radon concentrations in homes occupied over much of the previous 15 years or more, and on smoking habits. Several systematic reviews/meta-analyses (e.g., (*93*, *631-633*)) have been conducted based on published findings from these studies. However, these systematic reviews/meta-analyses have been limited by variations between publications in the way that radon exposure has been categorized, and at least for those which include smokers (*93*, *632*, *633*),~~ and~~ in how adjustment was made for the impact of smoking. Stronger evidence comes from pooled analyses that brought together individual data in order to investigate the consistency of different studies and estimate more precisely the association between lung cancer and radon. The largest combined analyses were conducted in Europe (*96, 634*) and in North America (*97*, *635*); smaller combined analyses have been carried out in China (*636*) and, more recently, in Spain (*637*). A recent NCRP commentary (*524*) provides an informative summary of these studies of residential radon.

The results of these studies are summarized in Table 14, and are seen to yield comparable risk estimates, similar also to those in recent meta-analyses (*93*, *631-633*). In both the European and the North American combined analyses, the data were consistent with a linear dose-response relationship with no threshold. Furthermore, there was no evidence that the ERR varied by sex or smoking status, nor – in the European analysis – by attained age; in contrast, there was slight evidence in the North American analysis that the ERR decreased with increasing attained age (p=0.09). Both the European combined analysis and more recent meta-analyses that included studies from Europe reported significant associations between radon and lung cancer for both never-smokers and ever-smokers (*631*) and suggested that – amongst subtypes of lung cancer - the association with radon was particularly strong for small cell cancer (*632*). In terms of lung cancer overall, the results from case-control studies of residential radon exposures and from cohorts of recent uranium miners show reasonable coherence (*93*, *530*). So for example UNSCEAR (*627*) estimated a combined ERR/100 WLM = 0.59 (95% CI 0.35, 1.0) based on all occupational studies; a higher combined ERR/100 WLM estimate = 1.53 (95% CI 1.11, 1.94) was obtained when restricting the analysis to more recent work periods and lower exposures. Using a conversion between radon concentration and cumulative radon progeny exposure so that 100 Bq m^{-3} = 13.2 WLM (*628*), UNSCEAR (*627*) estimated a combined residential ERR/100 WLM estimate = 1.21 (95% CI 0.38, 2.35), which is close to the above occupational estimate of ERR/100 WLM =1.53 (95% CI 1.11, 1.94) at low exposure. It should be pointed that “the risk of lung cancer from exposure to radon is not expected to be the same for residents and miners because of the different conditions under which they are exposed” (*93*).

Quantification of the lung cancer risk linked to residential radon can be influenced by errors in measuring radon in homes, of both classical and Berkson type (1). In the European combined analysis, both the ERR per 100 Bq m^{-3} and the width of the associated confidence interval doubled, to 0.16 (95% CI 0.05, 0.31), after adjustment for both classical and Berkson measurement errors (*96*, *634*). Today, research on lung cancer and radon continues, including study of the molecular determinants of cancer, especially the role of somatic genetic drivers (*638*).

Compared with lung cancer, there have been fewer epidemiological studies of residential radon and other cancers (*639*) and dosimetric arguments suggest that doses to other tissues and therefore any other effects would be smaller (*640*). Many of these studies have followed an ecological design or using modeled estimates of individuals' exposure to radon. Findings from these studies have been variable, possibly reflecting differences in study design, and overall the literature does not support strong associations between radon and non-lung cancers (*639*), but further research on this topic is warranted (*638*), particularly focused on miner studies given the likely lack of statistical power at residential levels of exposure.

Childhood cancer and natural radiation

Many epidemiological studies of naturally occurring radiation have focused on childhood cancer because of children's greater sensitivity, particularly for leukemia, and low background rates of disease, also because measurements of radiation exposure (as relating to age at diagnosis) are more likely to correlate with those in the relevant exposure period, in early life. The UK Childhood Cancer Study (UKCCS) (*641*, *642*) was both one of the largest, and also of case-~~/~~control design. Even so, it was of borderline power and limited by selection bias, which occurs because parents of children with leukemia who belonged to all social classes agreed to participate in the study whereas parents of healthy children who belonged to higher social classes (better educated, higher income and more interested in research) tended to preferentially participate (*641*). The problem of low statistical power affects almost all studies of childhood cancer in relation to radon exposure (*643*), even those of substantial size such as those in UK (*641*), Denmark (*644*) and US (*645*); as can happen some (e.g. (*644*)) yield significant excess risk, suggesting the possibility of upward bias (*646*).

A number of register-based studies have been conducted (*644, 647-654*); note that that of Spycher *et al* (*655*) is updated and subsumed within Mazzei-Abba *et al* (*654*). These register-based studies involved no contact with the study subjects and thus avoided the danger of selection bias. Importantly, they could more easily be of adequate power. However, it is not possible to make measurements of the radiation exposure of participants and doses must be estimated using models. Register-based studies of natural background radiation have been reviewed (*656*) and there have also been more general reviews of studies of radon and leukemia (*657-659*). The results of these record-based studies for leukemia and for CNS tumors are summarized in Table 15 (*644, 647-654*). Several studies offer general support for very small increases in risks of these childhood cancers associated with exposure to terrestrial γ/cosmic rays or possibly to radon and are consistent with the existence of a dose-risk relationship even at low doses, although further work is desirable, with larger cohorts and improved dosimetry.

Areas of high natural background radiation (HNBR)

Levels of natural background radiation vary from place to place and some geographic regions have dose rates several times the global average (*91*). Since large populations could be exposed to these high dose rates, a number of epidemiological studies were set up to try to detect and quantify any~~the~~ effects.

These studies were stimulated by the high radiation levels in the geographic region, in contrast to the register-based studies in the previous section which were stimulated by the existence of large and comprehensive registers of disease. The two best developed of these HNBR studies are set in Karunagappally, Kerala, India (*660, 661*) and in Yangjiang, ~~Guandong~~Guangdong Province, China (*662*). These two studies observed no increased risk of solid cancer with cumulative dose. Other ecologic studies have been conducted in Guarapari, Brazil, and in Ramsar, Iran. These studies have been reviewed by Hendry *et al* (*663*), Boice *et al* (*664*), NCRP (*10*) and UNSCEAR (*92*). Apart from questions of power, studies of HNBR have difficulties in finding suitable control areas, similar to the HNBR areas in everything except radiation dose. They also have various other problems (*92*), including those of lack of information and assessment of potential confounders and of dose estimation.

Other environmental exposures

Fukushima Daiichi nuclear accident

The Great East Japan earthquake and tsunami on March 11, 2011 resulted in breakdown of the reactor cooling systems in 3/6 reactors at the Fukushima Daiichi NPP, and over the ensuing few days meltdown of the cores of these reactors released 100-500 x 10^{15} Bq ^{131}I and 6-20 x 10^{15} Bq ^{137}Cs (*100*). This was the most serious nuclear accident apart from Chornobyl, although releases were a factor ~5-10 lower. Nevertheless, because of stringent measures to evacuate the population from affected parts of Fukushima prefecture (at least ~150,000 persons were evacuated (*100*)) and to restrict consumption of potentially contaminated food (*665*), the population exposure has been relatively much less serious than at Chornobyl. Nevertheless there are substantial non-radiological impacts of the disaster, with a large increase in mortality among the displaced elderly population (*666*) and increased frequency of mental and metabolic disorders in impacted populations (*667*).

An ultrasound thyroid screening study of Fukushima prefecture residents aged under 18 documented an increase in the prevalence of thyroid cancer, which the authors of the study attributed to the accident (*668*); but the results and conclusions of the study remain controversial, in that, for example, the increase is not confined to the contaminated areas of the prefecture (*669*, *670*). Today, this increase appears to be essentially attributable to the screening, with no relationship with radiation exposure (*671-673*).

Taiwan steel reinforcing bar study

A small study in Taiwan of persons exposed to steel reinforcing bars that had been accidentally contaminated with ^{60}Co yielded significant excess risk of leukemia excluding CLL, female breast cancer, all solid cancer and all cancer (*674*) (see Table 16). Some of the doses in this study are substantial, with mean dose 0.0477 Gy (range <0.001-2.363 Gy) (*674*), but despite this the study is likely of very low power (*675*).

Studies associated with releases from nuclear reprocessing or weapons plants and nuclear weapons testing

Environmental radiation associated with residential proximity to nuclear weapons plants and above ground nuclear testing has stimulated particular public interest and concern. Particularly in the early days, nuclear wastes were discharged from the plants into the atmospheric and marine/riverine~~residentially proximate~~ environment~~ and waters~~. Early nuclear weapons tests were frequently conducted above ground with large consequent releases into the atmosphere. Many epidemiological studies have evaluated cancer and to a lesser extent other serious health outcomes associated with the radiation exposures and releases.

Techa River cohort

The Mayak nuclear plant in the Southern Urals associated with plutonium production for the former-USSR nuclear bombs, deposited large quantities of nuclear waste in the Techa R~~r~~iver primarily during ~~from the late~~ 195~~4~~0-1956 (*92*)~~s onwards~~, and all communities living downstream alongside and near the Techa River received substantial exposures to a mixture of external γ and internal exposures from ^{90}Sr and ^{137}Cs (mean bone marrow dose 0.29 Gy, range 0-9 Gy) (*105*, *676*). A cohort of persons born before 1950 and who lived in a community alongside the Techa River in the period 1950-1960 has been assembled, and a number of sets of individual organ doses estimated, the most recent being Techa River Dosimetry System (TRDS) 2009. There is a significant excess risk of solid cancer mortality (*676*) and leukemia incidence excluding CLL, as well as CML (*105*) in this cohort (see Table 16). There is no significant non-linearity either for solid cancer mortality (*676*) or for leukemia (*105*).

Hanford study

Large quantities of ^{131}I were intentionally released to the atmosphere between 1944-1957 from the Hanford plant in Washington State during the production of plutonium for military purposes. A retrospective (historical) cohort study was set up to determine if thyroid disease is increased among those~~children~~ exposed to these releases at a young age (*677*). The cohort included a sample of all births from 1940 through 1946 to mothers with usual residence in seven counties in eastern Washington State. Participants were examined for signs of thyroid disease and their thyroid doses were estimated from residence and dietary histories obtained by interview. Thyroid dose spanned a considerable range (mean 0.174 Gy, range 0-2.823 Gy). There was no evidence of a relationship between Hanford radiation dose and the cumulative incidence of any of the thyroid-related outcomes (*677*) (see Table 16), although the power to detect an increased risk of thyroid cancer was low. ~~A meta-analysis of thyroid cancer incidence or mortality in the vicinity of NNPs in various countries did not report an elevated risk (*664*).~~

Sellafield and other studies of cancer clusters around nuclear installations

The cluster of childhood leukemia cases in Seascale, a village near the Sellafield nuclear reprocessing plant in the UK has been much investigated, together with a number of investigations of the apparent excess incidence around both Sellafield and other nuclear plants in the UK in relation to possible radiation exposures from the plants (*678-682*). Environmental exposure to radiation from discharges has been found to be much too low to explain these clusters (*683*). Studies have also been conducted ~~and~~ ~~also~~ in other countries (*684-686*), and the cluster of childhood leukemia cases around the Krummel NPP is particularly notable, but detailed investigations have not implicated discharges from the plant (*687*). Studies of areas where nuclear plants were planned but never built have also been carried out (*688*). A case-control study in West Cumbria, which includes Seascale, suggested that paternal preconceptional radiation exposure at Sellafield might explain the cluster of cases (*689*), but this association has not been generally confirmed in a number of other studies of this and other nuclear workforces (*690-692*). Population mixing in Seascale has also been suggested as an explanation (*693*), inspired in part by various investigations of Kinlen about unusual urban/rural population mixing in remote locations, based on a plausible hypothesis about rare response (leukaemia) to some infective agent (*694-696*). Several reviews have been performed on this question; no elevated risk of childhood leukemia near nuclear installations is observed globally, but the explanation for the observed clusters remain unclear (*697, 698*). Of note in this respect is the remarkable cluster of childhood leukemia in Fallon, Nevada, which is not near any nuclear installation and remains unexplained (*699*).

Atmospheric nuclear weapons tests and civilian populations exposed

Numerous studies have been conducted of the exposed populations associated with the various atmospheric nuclear bomb tests, for example in the Marshall Islands including the Castle Bravo test, the largest of the US thermonuclear tests~~ (*683, 684*)~~ (*700-702*), but without linked radiation dose estimates for the exposed populations these do not yield quantitative radiation risks. Nevertheless, a number of assessments of the doses from these activities have been conducted with links to health outcome data.

Various atmospheric nuclear tests were carried out at the NTS. There have been two related investigations into possible associations between radioiodine releases and thyroid disease (*703*, *704*). A cohort of persons ~~in grades 6-12 (~~aged~~s~~ ~12-18 years~~)~~ in southwestern Utah, southeastern Nevada, and southeastern Arizona in 1965-1966 were assembled and subsequently examined for various types of malignant and non-malignant thyroid ~~cancers and other thyroid~~ disease~~s~~. Individual radiation doses to the thyroid were estimated by combining consumption data with radionuclide deposition rates. Doses ranged up to 4.6 Gy and averaged 0.17 Gy in Utah. Elevated risks of thyroid neoplasms and ~~various other types of thyroid disease~~thyroid nodules were reported (*704*) (see Table 16). Leukemia in relation to external exposure has also been studied in a case-control study of persons exposed via the NTS, and borderline significant~~weak~~ indications of excess risk observed, particularly for ALL (*p*=0.068) and acute leukemia excluding CLL (*p*=0.084), despite the fact that doses were very low (maximum RBM dose 0.026 Gy) (*705*).

The weapons tests conducted at the Semipalatinsk nuclear test site in Kazakhstan from 1949 onwards resulted in considerable exposure of the local population, with doses spanning 0.07-4.14 Sv (*706*). Populations born before 1961 in 10 highly exposed settlements were followed for mortality for the period 1960-1999, along with those in 6 control settlements a few hundred km away (*706*). The dosimetry is somewhat crude, taking account only of the 8 largest tests, and also taking account of individual's lifestyle, shielding, time of year, and whether evacuated during the 1953 test; internal as well as external dose was calculated (*706*). Because of doubts as to the comparability of the control groups, results presented using only the highly exposed settlements are to be preferred, and demonstrate significant excess risk for all solid cancer, and cancers of the stomach and lung (see Table 16). There is a small *in utero* group included, exclusion of which did not materially affect risk. Unusually, increasing age at exposure resulted in increased relative risk (exposed vs not) (*706*). A prevalence study of malignant and non-malignant thyroid disease among persons exposed under the age of 21, an update of an earlier analysis of almost exactly the same dataset with improved stochastic dosimetry (*707*), suggested excess risk of thyroid nodules among males (but not females), although not of thyroid cancer (*146*) (see Table 16).

The series of 41 weapons tests conducted between 1966-1974 in French Polynesia were less extensive than the above series. However, they have the advantage that high quality dosimetry was conducted on ~~at least~~ groups of participants, backed by a cancer registry. ~~Given that t~~The mean thyroid doses are low (mean 0.0047 Gy, range 0-0.036) (*708*) and there ~~it is unsurprising that the~~ is no excess risk~~s~~ of differentiated thyroid carcinoma ~~are non-significantly elevated~~ (*708*) (see Table 16).

Non-Cancer Risks

Non-cancer effects of residential radon on the nervous system (e.g., Parkinson's disease, Alzheimer's disease, multiple sclerosis, motor neuron disease) have been studied, but there is no peer-reviewed literature documenting a significant excess radiation risk (*709*).

In the Semipalatinsk cohort, there was no significant radiation mortality risk of all CVD, heart disease and stroke from exposure to radioactive fallout, nor of hypertension or stroke prevalence (*710-712*) (see Table 16). There was no significant mortality from all non-cancer diseases in the residents of the HNBR area in Yangjiang, China (*662*). However, a significant association between intima media thickening of carotid artery (a marker for the early stage of CVD development) and background radiation exposure has been reported in female residents of the HNBR area in Kerala, India (*713*). In residents of the HNBR area in China, there was a significantly increased risk for PSC and cortical lens opacities~~cataracts~~, but not of nuclear opacities~~cataracts~~ (*714*) (see Table 16).

CVD mortality has been assessed in the Techa River cohort followed during 1950-2003 (*483*). There are large but non-significant excess risks of CVD and IHD mortality when using 5-year lagged dose, although significance is attained at conventional levels for both endpoints when (arguably implausible) lags of 15 or 20 years are employed (*483*) (see Table 16).

POOLED STUDIES

Pooled analysis of individual health records is a way of boosting statistical power, thereby enabling more precise estimates of risk, which for rare endpoints such as leukemia is of considerable concern. Pooled analysis, which uses individual health records, including dose, follow-up and outcome ~~and interview~~ data combined from different studies, is distinct from meta-analyses, in which a systematic review of the literature is combined with a statistical weighting of the published results, and which has obvious limitations, for example in treatment of confounding variables and taking account of differences in background rates and calendar years of coverage. There have been a number of recent meta-analyses for cancer (*715-717*) and non-cancer (*449*, *718*, *719*), which we shall not discuss further. In this section we briefly deal with pooled analyses considering more than one of the types of radiation-exposed population discussed above. Occupational pooling studies such as INWORKS (*466*, *482*), PUMA (*535*) or iPAUW (*565*) and medical diagnostic studies such as EPI-CT (*236*, *237*) or fluoroscopy studies (*252*) are discussed above in the relevant sections. Limitations of many pooled analyses include the lack of consideration of the type of radiation exposure (e.g., acute vs fractionated vs protracted), potentially important confounders, indications for treatment in populations undergoing diagnostic or therapeutic radiation procedures, and other possibly relevant but unrecorded factors that differ between the sub-studies that make up the pooling.

Cancer Risk

Leukemia and other hematolymphoid malignancies

Analysis of an earlier version of the LSS incidence data, UK ankylosing spondylitis mortality data and the International Radiation Study of Cervical Cancer Patients (IRSCCP) case-control study, assessed a total of 283,139 persons (*185*). There were significant excess risks of AML, CML, ALL and all leukemia, in each case the optimal ERR model being quadratic-exponential in dose, with adjustment for time since exposure (for ALL, CML) or attained age (AML) (*185*) (see Table 17).

A large international consortium assessed hematolymphoid malignancies in ten eligible datasets, representing all available groups exposed to radiation in childhood and adolescence (at 6/2014), but excluding those treated for malignant disease, with a total of 310,905 persons (*720*). Over the full dose range there were significant linear ERR/Gy for AML, CML, and ALL, with upward curvature in the dose-response for ALL and AML, although at lower doses (<0.5 Gy) curvature for ALL was downwards (*720*) (see Table 17). There was no significant overall inter-cohort heterogeneity in ERR/Gy for these three endpoints (*720*). In the analysis restricted to <0.1 Gy there were significant trends with dose for AML, AML+MDS, and ALL, but no clear dose-response for CML (*721*). There were no indications of inter-cohort heterogeneity or departures from linearity in the <0.1 Gy range (*721*). For AML+MDS and for ALL, the dose responses remained significant for doses <0.05 Gy, indeed for ALL this was so for doses <0.02 Gy (*721*).

Additional analysis of lymphoma and multiple myeloma in 9 of these 10 datasets (among 143,136 persons) using RBM dose did not exhibit significant trends for any endpoint (*722*).

However, in 6 cohorts with estimates of lymphatic tissue dose, ~~borderline~~ significant increased trends with dose (*p*=0.02~~-0.07~~) were observed for ~~NHL, CLL and~~ NHL+CLL (*722*) (see Table 17).

A pooled analysis of children born to Mayak workers or exposed from living near the contaminated Techa River suggested excess leukemia incidence and excess all hematolymphoid malignancy incidence after *in utero* exposure; no associations were observed in mortality analysis, which is presumably a less reliable endpoint, and numbers of deaths were substantially fewer (*723*) (see Table 17).

Thyroid cancer

Analysis of 12 radiation exposed cohorts (most of the larger cohorts then available), an update of a previous analysis of 7 cohorts (*724*) documented a significant excess risk of thyroid cancer, with significantly downwardly curving dose response, ERR tending to decrease at doses >20 Gy (*725*) (see Table 17). Four of these 12 studies were childhood cancer survivors, seven cohorts were treated for benign disease, and the LSS was also included (*725*). Doses for therapy for the benign diseases were over 5 Gy. Analysis restricted to <0.2 Gy or <0.1 Gy found significant dose response over both ranges (see Table 17), with no significant non-linearity (*726*).

Breast cancer

The combined analysis of the LSS incidence and Massachusetts TB fluoroscopy mortality data suggested that the ERR was significantly higher in the LSS by a factor 2.11 (95% CI 1.05, 4.95), although the excess absolute risks (EAR) in the two cohorts were statistically compatible (*244*). There was more extreme heterogeneity, both for ERR and EAR, in an 8-cohort pooled analysis, which included these two cohorts (*428*). The analysis did not resolve this issue, but clearly risks were very different between the LSS, the Swedish benign breast disease study and the two Swedish hemangioma studies (*428*). The results support the linearity of the radiation dose response for breast cancer, highlight the importance of age and age at exposure on the risks, and suggest a similarity in risks for acute and fractionated high dose rate exposures with much smaller effects from low-dose-rate protracted exposures (*428*).

Non-Cancer Risk

Pooled analysis of CVD outcomes in the Massachusetts and CFCS fluoroscopy studies are discussed above.

THE FUTURE

New Statistical and Other Methodology to Improve Dose Estimation, Address Issues of Confounding and Reduce Bias

Interpretation of epidemiological studies of radiation exposures routinely face concerns about bias related to measured and unmeasured confounding, measurement error (broadly, including uncertainty in estimated radiation doses and measured confounders, and misclassification in outcomes), and incorrect model specification (*8-10*). Some recent statistical innovations in machine learning (ML) models, which can flexibly describe non-linear processes and take account of high order interactions while avoiding overfitting, have shown promise in reducing problems of model misspecification, and in some contexts overcoming challenges with control for measured confounders. By design, many ML models sacrifice a modest increase in bias against reduction in variance (*727*). They are of particular value in very large datasets and in settings where the number of explanatory variables may approach or exceed the number of records (*727*). These include the random forest (RF) algorithm (*728*), the stochastic gradient boosting machine (SGBM) model (*729, 730*), and neural networks (NN) (*731*). RF models (*728*) have proved particularly popular, because of their flexibility, ease of use and statistical performance, and availability in many software packages (*732-736*). RF models with modifications to tree-expansion rules (*737, 738*) and SGBM models have been applied to a large (~10,200) set of indoor γ measurements (*647*) to illustrate a prediction model that can be used to impute γ doses to locations lacking measurement, and the cross-validated predictive performance of the generalized RF model was superior to that of SGBM (*739*). Further work done on these data suggest that these models outperform most standard geospatial models. NN have been much used to segment image data (*740-742*), a necessary first step in RT treatment planning as well as retrospective determination of organ dose, and there have already been many applications of ML methods to prospectively and retrospectively assess patient dose (*743*).

Approaches to address unmeasured confounders include random assignment to exposure (in trial settings), 'natural' experiments, instrumental variables (*134, 744*), and use of negative controls (*745, 746*); future work may make greater use of such approaches to address concerns about residual confounding (*747-749*). In particular, statistical methods designed to support causal inference under clearly defined identification conditions have been developed to address measured and unmeasured confounding. These methods have been applied in epidemiological studies of air pollution (*750*), but, to date, have not been applied in radiation epidemiology studies. There are a number of sources of uncertainty in epidemiological studies, including dose uncertainty, incomplete disease ascertainment or inaccurate diagnoses, insufficient adjustments for age and sex and environmental factors such as smoking, and model uncertainties (*11*). These are discussed below.

Errors in classification of endpoints have the potential to bias dose response, particularly if a radiogenic endpoint is likely to be misdiagnosed as one that is not radiogenic. There are statistical methods of dealing with such errors, although they require that there be data that would enable misclassification probabilities to be estimated. This has been done in the LSS, using autopsy data to guide estimation of misclassification probabilities of cancer as non-cancer mortality; when this was done the magnitude of the non-cancer dose response was reduced by about 20%, but remained statistically significant (*751*). A comprehensive assessment of 26 low dose cancer epidemiology studies judged that the likelihood of bias due to misclassification or due to loss of follow-up, where this could be estimated, was small (*752*).

Despite the relatively high quality of radiation dose information in many epidemiological studies of radiation exposed populations (when compared to studies of chemical carcinogens, for example), measurement error remains an important concern in interpretation of studies. Approaches to address uncertainties in measures of radiation exposure have been recently reviewed (*753*) and many studies have implemented these methods ~~(*137, 179, 183, 184, 404, 405, 413, 675, 737-742*)~~ (*139*, *183*, *187*, *188*, *413*, *414*, *422*, *754-761*). Often the effect of adjustment for dose error is quite modest ~~However, as Gilbert *et al*~~ (*675*) ~~summarize often the effect of adjustment for dose error is quite modest~~. ~~Although studies are beginning to yield direct estimates of radiation risk at low dose (<0.1 Gy) low-LET radiation (*647, 648, 653, 658*) (see Table 17), f~~For most cancer endpoints radiation risk estimates have been derived for the low dose range via interpolation between the cancer risks observed among groups exposed at moderate and high levels of dose and the risk observed in an unexposed (or very low exposed) reference group. Crucial to the resolution of uncertainty in this interpolation are the modeling of the dose-response relationship and the importance of both systematic and random dosimetric errors for analyses of the dose response, both of which can result in bias~~. It is well recognized that the relationship between a cancer outcome and a mismeasured dose variable may differ from the relationship with the true dose value, in some cases resulting in biased estimates of dose response curvature~~ (*134*). Dose measurement errors can arise in a number of different ways. In RT, for example, a machine may be used for delivering radiation doses to a patient, and these true values are randomly distributed around the measured dial setting on the RT machine, implying that the dial setting and error are independent, resulting in so-called Berkson error (*134*). Alternatively, the measured dose can be distributed at random around the true dose, in such a way that the true dose and error will often be independent, resulting in so-called classical error (*134*), as for example the determination of individual survivor location i~~. I~~n the LSS~~atomic bomb survivors, radiation nominal doses are generally thought to be lognormally distributed around the true doses, implying a classical error model~~ (*762*). However, it is likely that there is also a Berkson error term, for example arising from use of average shielding transmission factors; methods have been developed for dealing with this (*763*).

~~Correcting for dose error, or better taking account of the uncertainty introduced by dose error requires external information about the measurement error structure, for example from a validation substudy (which is almost never available in radiation studies), or from consideration of the error structure based on external biological and physical samples (*15*).~~ One method that has been frequently used to correct for the effects of classical error is regression calibration (RC) (*134*). However, RC is known to yield biased estimates of trend when the magnitude of errors is large, or there is substantial curvature in the dose response (*134, 764, 765*). When errors are larger methods that take account of the full error distribution such as MCML (*413, 414, 422*) or the so-called 2DMC with Bayesian Model Averaging (2DMC+BMA) method (*766*) or the Frequentist Model Averaging method (FMA) (*767*) are likely to perform better. A new type of extended regression calibration (ERC) model has been recently developed and tested (against MCML, RC, ~~and~~ 2DMC+BMA and FMA) using synthetic datasets in which there was varying degrees of ~~substantial~~ upward curvature in the true dose response, and varying (and sometimes substantial) amounts of classical and Berkson error (*768, 769*). The statistical performance of ERC was generally superior to that of MCML, RC, 2DMC+BMA or FMA, for various magnitudes of Berkson or classical errors (*768*, *769*). ~~Other methods have been developed for dealing with measurement error, in cases of shared pure Berkson error (*699*) which have been applied in a few radiation cohorts (*700, 701*), or pure classical error, via the so-called simulation extrapolation (SIMEX) algorithm (*702*), which have also been applied in a few cases (*689*, *703*). Methods based on instrumental variables have also been described (*103*).~~

Although there is much to be said for detailed consideration and correction ~~techniques such as correcting~~ for confounders and for the effects of dose errors, the most fundamental way to get the precision needed to evaluate response at low doses is large cohort size. Given the limited opportunities to form new, large cohorts, pooled or meta-analyses provide an alternative. As noted above, pooling studies have been much used to get more accurate assessments, particularly of low dose risk, also more accurate estimates of interactions and effect modifications (*428*, *715*, *716*, *721*, *726*). Such studies are likely to be increasingly important. However, one of the issues in pooling and also meta-analysis is the selection of studies going into the evaluations. A large uncertain study may dominate over a smaller and higher quality investigation. Selective removal of each study in turn can be useful in at least highlighting sources of heterogeneity.

Studies that combine biological information with epidemiological data may also be important, such as those recently used for thyroid (*770*) and lung cancer (*771*). However, the tumor models used at least for parts of both studies, based on the so-called two mutation model (*772*) are very likely drastic simplifications of the underlying biology. It is likely that the true cancer models have many more than two-rate limiting stages and multiple pathways (*773*), possibly incorporating genomic instability (*774-776*).

New Populations and Data Sources

Future epidemiologic and dosimetry research has great potential for making novel discoveries by (a) leveraging new populations and data sources based on evolving radiation exposures, (b) expanded use of electronic records and corresponding advances in data linkages, (c) advances in genomic technologies, and (d) increasing emphasis on data pooling, particularly important for studies at low dose. Key considerations when taking advantage of these new populations and data sources is consideration of fundamental methodologic issues, in particular statistical power and avoidance of bias. Discovery will be facilitated by promoting data sharing (*777*) and transparency in data sources and analysis (*778*) in radiation research should be facilitated.

Evolving radiation exposures of particular interest include both diagnostic and therapeutic medical radiation exposures as well as other little studied environmental and occupational exposures. From the recent EPI-CT studies of children and young adults described above reporting excess risks of brain tumor and hematological malignancies (*236, 237*) questions remain about the notable variation in risk among countries participating in the study, and, despite state-of the-art dosimetry, incomplete ascertainment of CT examinations; there is a need for ongoing follow-up. To evaluate radiation-associated health effects in the millions of persons internationally who have undergone fluoroscopically-guided and nuclear medicine diagnostic and therapeutic procedures (*779, 780*), future epidemiologic studies will need to expand beyond the recently reported single populations (*287, 288, 781*, *782*) or meta-analysis (*783*) efforts, for example similar to~~via~~ the Harmonic project (*784*). Emphasis should be on assessing a wider spectrum of malignant and non-malignant outcomes. Continuing follow-up of the Japanese atomic bomb survivors will undoubtedly provide valuable new information about the pattern of radiation dose-response for all solid and type-specific cancers and for certain non-cancer outcomes. Future studies of populations exposed from the Chornobyl accident will pool data from follow-up studies of persons exposed *in-utero* at the time of the accident (e.g. via a study in Ukraine (*409*) to be combined with a similar (but as yet unpublished) study in Belarus), and will examine the genomic profile of follicular thyroid carcinomas and adenomas arising in radiation-exposed residents. For the nascent studies in South Korea, the US and France to investigate cancer and non-cancer disease outcomes among workers performing or assisting with fluoroscopically guided procedures, consideration should be given to use similar protocols to facilitate pooling of the results. Monitoring of technological advances in diagnostic and therapeutic procedures will provide impetus for initiating new epidemiologic investigations with high-quality dosimetry in exposed patients and workers for public health and radiation protection purposes.

Given the public health priority to study the rapidly increasing numbers of cancer survivors, electronic databases can facilitate epidemiologic studies beginning with identification of cancer and mortality outcomes of survivors through linkage of survivor cohorts with nationwide cancer and mortality registries. The forthcoming US Virtual Pooled Registry will soon enable this type of linkage in the US (*785*, *786*) ~~(*768*)~~. Future dosimetry efforts to support studies of cancer survivors include development of protocols for collection of DICOM data, harmonization of data across countries, and creation of approaches for accurately determining tumor location (*787*, *788*) and patient anatomy for cohort studies of cancer survivors. To address concerns about possible health effects in the large number of patients worldwide being exposed to higher-dose proton beam RT, among whom many studies have already assessed local control and early toxicity of these and more conventional types of RT (*789-791*), new studies are underway in US and Canada to assess cancer risks in pediatrically proton-beam-treated groups (https://www.pediatricradiationregistry.org/). Carbon beam RT, already being used in over 12~~0~~

centers worldwide~~ (*775*)~~ (*792*, *793*) (but none of them in USA), is likely to be increasingly important. Strategies are needed for high-throughput scanning of medical records to extract information needed for estimation of organ-specific radiation dose, and to collect detailed information about any concomitant chemotherapy as well as important demographic, lifestyle, medical history (e.g., conditions and non-chemotherapy drugs) information for statistical adjustment since these data are not widely available in a standardized electronic form. The availability of substantial biobanks of genotype and phenotype data that exist in many countries are a considerable resource, that is already being used to assess risks of a number of types of disease and endpoints, and with increasing follow-up these will become increasingly powerful, in particular for studying radiation effects. The UK Biobank for example, a database of over 500,000 persons aged 40-69 at recruitment, represents an approximately 5% sample of the 9.2 million invited in the relevant age range, and has been followed for nearly 15 years, and plans for expansion include cancer treatment information (*794*). Even the largest of these internationally only include a relatively small proportion of the national population, but this may change. The Early Detection of Disease Research Platform study planned in the UK, with a planned recruitment of 5 million adults and prospectively ascertained lifestyle and medical data (*795*) is an example of the sort of dataset of a size that may facilitate assessment of radiation risk and its relation to other lifestyle and medical risk factors~~address some of these questions~~. Although it will be ~~somewhat~~ smaller (when recruitment is complete) than these UK datasets, the US Connect cohort (https://dceg.cancer.gov/research/who-we-study/cohorts/connect~~)~~) will have particularly rich phenotype data, and also spanning a much larger range of latitudes, so better able to investigate effects of UVR. For certain radiation-exposed cohorts, in particular the Mayak workers and the LSS there are substantial longitudinal biorepositories.

An important clinical and public health goal is to identify individuals with greater sensitivity to radiation as early in life as possible, in order to tailor their diagnostic and therapeutic procedures to avoid ionizing radiation to the extent possible. To this end, a roadmap is needed to determine the strategies from radiation biomarker discovery to implementation in patients (*796*). Since it is believed that the genetic contribution to radiation susceptibility is likely to follow a polygenic model, agnostic approaches using multi-dimensional genomic, transcriptomic, epigenomic and proteomic investigations in large populations exposed to moderate-to-high radiation levels and ideally with individual high-quality exposure assessment and complete follow-up (*797*). Validation of biomarkers associated with radiosensitivity is critical. Somatic g~~G~~enomic, transcriptomic, and epigenomic studies, similar to the investigation by Morton *et al* (*419*) are needed to identify the mechanisms of carcinogenesis of radiation-associated neoplasms occurring in excess in patients treated with radiotherapy and in those in other populations (e.g., thyroid adenomas and breast cancer in lactating women) in residents living near Chornobyl (*409*, *430*).

Another key priority for radiation-associated adverse health outcomes of public health importance are assessment of risks at low doses and dose rates as reviewed by the National Academies of Science, Engineering and Medicine (NASEM) (*798*). Low doses are of concern for cancer, CVD (*449*), cataract (*377*), possibly also in relation to neurocognitive effects (*718*, *719*) and adverse effects on the immune system (*799*). Unlike studies at high dose, there are substantial issues of statistical power and bias that must be considered in planning a study and thus maximizing power particularly for rare outcomes (*e.g.* for leukemia (*721*) and thyroid cancer (*726*)), implying maximization of size. However, as discussed above there are difficulties in use of pooling studies. Reduction of bias implies that information on the likely relevant confounders should be available. Maximization of statistical power also is best achieved if the population under study is at higher risk and the disease outcome is known/suspected to be moderately- to strongly-linked with increased radiation-associated risk, thus ideally restricting attention to sensitive groups. One example is those exposed early in life when there may be fewer potential confounders, although confounders may become present, and require adjustment for, in adulthood. Given the possibility of residual confounding the size of the radiation effect in comparison with those associated with potentially confounding factors must be borne in mind. Studies of persons exposed in adulthood, where the size of the radiation effect is generally relatively small compared with exposures in earlier life, combined with the presence of many lifestyle factors with substantial risks may mean that some bias may be unavoidable in studies of adulthood exposure to moderate and low dose (*675*). A major review led by investigators from the US National Cancer Institute of 26 low dose studies (with mean dose <0.1 Gy) published since the BEIR VII report (*800*) assessed the likelihood of bias due to dose uncertainty, confounding, selection bias and outcome misclassification. In most of the 26 studies it was judged that the likelihood of bias in ERR/Gy away from the null associated with these issues was slight (*675*, *717*, *752*, *801-803*), suggesting that the likelihood of a spurious positive result arising from most of these studies was small.

DISCUSSION

We have documented the wide variety of epidemiological studies of ionizing radiation exposure focusing primarily on those that provide information on dose-response and related quantitative measures ~~of human populations~~. There is reasonable consistency in the risks per unit dose that have been seen both for cancer and some non-cancer endpoints in most of the major studies, with the possible exception of groups receiving RT for cancer and non-malignant disease, where relative risks for cancer tend to be lower than in groups exposed at lower levels of dose (*316-318*) (see Tables 1, 3, 4, 15, 17). The elevated underlying cancer rates in some of these groups, and the highly selected nature of the populations, in particular for development of the first primary cancer, is a likely explanation. It is frequently observed that radiogenic ERR~~relative risks~~ in groups at high underlying cancer risk are lower than in groups at lower risk (*244*, *804*); however, radiation-associated EAR are frequently higher in the groups with elevated underlying risk. For some types of cancer (e.g., thyroid cancer) cell sterilization effects from RT could account for part of the discrepancy (*725*, *805*). There continues to be controversy about the size or even the existence of cancer and other outcomes risk at doses below about 0.1 Gy whole body dose equivalent (*806*-*808*), but some large and pooled studies provide evidence of increased risks both for cancer (*236*, *237*, *466*, *721*, *726*) and for cataract (*522*).

There have been many surveys of the radiation epidemiology evidence, in particular by the ICRP (*4*, *809*, *810*), UNSCEAR (*8*, *92*, *93*, *392*) and the US BEIR committee (*95*, *800*). Reviews by various other national and international bodies are conducted occasionally, in particular focusing on risks of low dose exposure (*10*, *675*, *717*, *801*, *802*).

Radiation dosimetry for epidemiological studies has advanced considerably in recent years, with very detailed and accurate computerized models of the human body for calculating dose to many organs and tissues from external exposure to penetrating radiations (X- and γ-rays, neutrons), and concomitant development of detailed models for internal exposure to radiations from radioactive materials taken into the human body by inhalation, ingestion, or other routes of exposure ~~(12, 16, 135)~~ (*12*, *16*, *88*, *137*). In addition to being useful going forward, this allows more accurate retrospective estimation of doses in cohorts with risks previously reported in relation to earlier dosimetry. Stable chromosome aberrations have been used to validate the dosimetry in the Sellafield workers (*811*) and in the USRT (*757*); dicentrics, an unstable type of chromosome aberration, have been used to validate the dosimetry in a mixed Chornobyl-exposed group (*111*).

Epidemiological knowledge is increasing at levels of dose below 0.1 Gy and for doses received at low dose-rates. Further studies would be warranted to estimate risks at lower dose: e.g., around 0.01 Gy as recently recommended by NASEM (*798*), although such studies are challenging to conduct and interpret. There continue to be efforts to assemble larger and larger cohorts to obtain increased precision of estimates at low doses, such as by pooled studies. The possibilities of bias, resulting from confounding and other factors substantially increases as the dose level is reduced, and made much more likely following exposure in adulthood (*675*).

Continued mechanistic developments and their integration with epidemiology are needed, e.g., with the adverse outcome pathway approach to determine parameters for biologically-based dose response models (*812*).

Assessment of uncertainties in radiation dose is an important ~~crucial~~ aspect of developing risk estimates and their uncertainties. New statistical methods for taking account of dose error have been the subject of much recent work (*764*, *765*, *768*, *813*), and some of these methods have already been applied (*183*, *422*, *760*, *761*). A forthcoming NCRP report will address statistical methods to account for dose uncertainty (*814*).

It is clear from 125 years of observation on the health consequences of exposure to ionizing radiation that much has been learnt~~ed~~, with substantial impact on radiological~~ation~~ protection for patients, general population and workers. There have been substantial clinical and public health benefits, in addition to radiological~~ation~~ protection, of radiation epidemiology studies. With the launch of new large studies, with more pooling studies undertaken, it will be possible to provide more stable estimates of risks in subgroups. New studies are needed whose goal should be to enroll radiation-exposed underserved and minority populations with exposures to medical, environmental and occupational sources of radiation ~~and, ideally some of these subgroups will~~

~~include underserved and minority populations~~. Further investigations are needed of late effects in patients undergoing repeated (e.g., fluoroscopically guided diagnostic or therapeutic interventions) and high-dose (nuclear medicine therapeutic procedures). With the expansion of higher-dose diagnostic (PET/CT) and newer therapeutic modalities (proton and carbon radiotherapy) there is an urgent need to establish large cohorts to follow up on late effects. As susceptible population subgroups are identified in current and future studies, more tailored screening protocols and radiation safety recommendations can be implemented to reduce or prevent future radiation-related risks of these subgroups. Radiation epidemiologists are needed for emergency response were a nuclear accident (whether associated with a nuclear site or detonation) to occur. In the short term they would be needed to provide guidance on triage of large populations by level of exposure (e.g., separating the "worried well" from those needing medical care), including devising recommendations on administration of possible countermeasures (*815*). In the longer term they would be needed to set up rosters of people living in the exposed areas, and working with dosimetrists establish registers of the relevant measures of dose, and linking the exposed roster with population registers (which may need to be established) to enable long-term follow-up; all of these are necessary preconditions of any long term assessment of radiation effects in the exposed population (*816*). Further analysis is needed as well as continuing follow-up of existing nuclear (INWORKS and MPS) and medical radiation workers (USRT, Korean and Chinese) as well as pooling of uranium miners. In addition, medical workers performing fluoroscopically guided and nuclear medicine procedures require high-quality dosimetry and longitudinal epidemiologic investigation. Greater understanding of signaling mechanisms such as methylation and senescence will provide insight into a number of radiation-associated chronic diseases, and will require longitudinally organized registers of biosamples.

ACKNOWLEDGMENTS

The work of MPL, CL, MSL and LMM was supported by the Intramural Research Program of the National Institutes of Health, National Cancer Institute, Division of Cancer Epidemiology and Genetics. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention. The authors are grateful for the very detailed and helpful comments of the two referees.

Table 1. Results from the most current epidemiological studies of cancer and non-cancer disease in Japanese atomic bomb survivors

Author, year, reference	Study years	Endpoint	ERR/Gy or EOR/Gy (95% CI)	Cases/deaths	Comments (in general appropriate organ dose used unless otherwise indicated)
Cancer incidence (all using relevant DS02R1 organ dose unless otherwise stated)					
Hsu *et al* (2013) (*175*)	1950-2001	Leukemia other than CLL or ATL	4.7 (3.3, 6.5)	416	Using DS02 bone marrow dose
		NHL male	0.46 (-0.08, 1.29)	501	Using DS02 bone marrow dose
		NHL female	0.02 (<-0.44, 0.64)		
		HL	0.20 (-1.03, 2.63)	42	
		Multiple myeloma	0.38 (-0.23, 1.36)	181	
Furukawa *et al* (2013) (*39*)	1958-2005	Thyroid cancer age at exposure <20	1.36 (0.59, 2.7)	191	Sex averaged, adjusted for age 60, exposure age 10, using DS02 dose.
		Thyroid cancer age at exposure >20	0.27 (<0, 1.07)	180	Sex averaged using DS02 dose.
Little and McElvenny (2017) (*176*)	1958-1998	Male breast cancer	27.68 (1.81, 90.16)	7	Using DS02 dose, adjusted for attained age and age at exposure.
Grant *et al* (2017) (*23*)	1958-2009	All solid cancers	0.50 (0.42, 0.59)[a]	22,538	Sex-averaged.
Cahoon *et al* (2017) (*32*)	1958-2009	Lung	0.83 (0.58, 1.09)[a]	2446	Sex-averaged, adjusted for the non-smoking group.
Brenner *et al* (2018) (*31*)	1958-2009	Female breast	1.12 (0.73, 1.59)[a]	1470	

Sadakane *et al* (2019) (*33*)	1958-2009	Liver	0.53 (0.23, 0.89)[a]	2016	Sex-averaged.
Utada *et al* (2019) (*36*)	1958-2009	Uterine corpus	0.73 (0.03, 1.87)	224	
		Uterine cervix	0.00 (-0.22, 0.31)	982	
Sakata *et al* (2019) (*177*)	1958-2009	Oral/pharyngeal	0.24 (-0.08, 0.72)	344	
		Salivary gland	2.54 (0.69, 6.1)	50	
		Esophagus	0.32 (-0.008, 0.80)	486	
		Stomach	0.36 (0.22, 0.50)	5661	
Sugiyama *et al* (2020) (*34*)	1958-2009	Colon	0.63 (0.34, 0.98)[a]	1914~~765~~	Sex-averaged.
		Rectum	0.025 (-0.087, 0.14)[a]	1046	
Brenner *et al* (2020) (*38*)	1958-2009	Central nervous system	1.40 (0.61, 2.57)	285	
Utada *et al* (2021) (*35*)	1958-2009	Ovary	0.30 (-0.22, 1.11)	288	
Grant *et al* (2021) (*178*)	1958-2009	Urinary tract	1.4 (0.82, 2.1)	493	Sex-averaged
Mabuchi *et al* (2021) (*37*)	1958-2009	Prostate	0.65 (0.30, 1.08)	851	
Preston *et al* (2008) (*180*)	1958-1999	Solid cancer after exposure *in utero*	1.3 (0.2, 2.8)	94	DS02 maternal uterine dose
		Solid cancer after exposure in childhood (age <6)	2.0 (1.4, 2.8)	649	DS02 colon dose
		Cancer mortality (all using relevant DS02 organ dose unless otherwise stated)			

Ozasa *et al* (2012) (*28*)	1950-2003	All solid	0.47 (0.38, 0.56)	10,929	Using colon dose.
		Esophagus	0.51 (0.11, 1.06)	339	Using stomach dose.
		Stomach	0.28 (0.14, 0.42)	3125	
		Colon	0.54 (0.23, 0.93)	621	
		Rectum	0.17 (-0.17, 0.64)	427	Using bladder dose.
		Liver	0.36 (0.18, 0.58)	1519	
		Gallbladder	0.45 (0.10, 0.90)	419	Using liver dose.
		Pancreas	0.08 (-0.18, 0.44)	513	
		Other digestive	1.29 (0.14, 3.25)	84	Using colon dose.
		Lung	0.63 (0.42, 0.88)	1558	
		Female breast	1.60 (0.99, 2.37)	324	
		Uterus	0.22 (-0.09, 0.64)	547	
		Ovary	0.79 (0.07, 1.86)	157	
		Prostate	0.33 (NA, 1.25)	130	Using bladder dose
		Bladder	1.12 (0.33, 2.26)	183	
		Kidney parenchyma	0.52 (-0.15, 1.75)	80	Using colon dose.
		Renal pelvis and ureter	2.62 (0.47, 7.25)	33	Using colon dose.
		Other solid	0.47 (0.24, 0.76)	864	Using colon dose.
		Malignant lymphoma	0.16 (-0.13, 0.59)	284	
		Multiple myeloma	0.54 (-0.04, 1.58)	93	

		Other neoplasms	0.65 (0.26, 1.14)	518	
		Leukemia	3.1 (1.8, 4.3)	318	Sex-averaged, using ERR at 1 Gy from fit of linear-quadratic model
Little and McElvenny (2017) (*176*)	1950-2003	Male breast cancer	9.48 (0.38, 154.90)	6	Adjusted for attained age and age at exposure.
Sugiyama *et al* (2021) (*157*)	1950-2012	Male solid cancer after exposure *in utero*	-0.18 (<-0.77, 0.95)	80	Using maternal uterine dose
		Female solid cancer after exposure *in utero*	2.24 (0.44, 5.58)	57	
Non-cancer mortality (all using relevant DS02 organ dose unless otherwise indicated)					
Ozasa *et al* (2012) (*28*)	1950-2003	Cardiovascular diseases	0.11 (0.05, 0.17)	19,054	Using colon dose.
		Blood diseases	1.70 (0.96, 2.70)	238	Using bone marrow dose.
		Respiratory diseases	0.21 (0.10, 0.33)	5119	Using colon dose.
		Digestive diseases	0.11 (-0.01, 0.24)	3394	Using colon dose.
		Genitourinary diseases	0.14 (-0.06, 0.38)	1309	Using colon dose.
		Infectious diseases	-0.02 (-0.15, 0.13)	1962	Using colon dose.
		Other diseases	0.01 (-0.1, 0.12)	4487	Using colon dose.
		External causes	-0.11 (-0.21, 0.02)	2432	Using colon dose.
Cardiovascular disease (CVD) mortality (all using DS02)					
Shimizu *et al* (2010) (*203*)	1950-2003	Heart disease	0.18 (0.11, 0.25)[b]	14,018	Using colon dose.
		CeVD	0.12 (0.05, 0.19)[b]	12,139	

Takahashi *et al* (2017) (*29*)	1950-2008	All CVD apart from heart disease, stroke	0.58 (0.45, 0.72)[b]	5846	Using colon dose.
		All CVD	0.15 (0.10, 0.20)[b]	25,113	
		All heart disease	0.14 (0.06, 0.22)	9303	
		IHD	0.03 (-0.08, 0.15)	3556	
		Valvular heart disease	0.45 (0.13, 0.85)	744	
		Heart failure	0.21 (0.07, 0.37)	3334	
		Hypertensive organ damage	0.36 (0.10, 0.68)	1122	
Cardiovascular disease morbidity					
Yamada *et al* (2004) (*204*)	1958-1998	IHD	0.05 (-0.05 to 0.16)	1546	Using DS86 stomach dose, adjusted for smoking and drinking.
		Stroke	0.07 (-0.08, 0.24)	729	
Cataract					
Nakashima *et al* (2006) (*206*)	2000-2002	Cortical	0.30 (0.10, 0.53)	618	Uses DS86
		Posterior subcapsular	0.44 (0.19, 0.73)	214	
		Nuclear opacity	0.07 (-0.11, 0.30)	415	
		Nuclear color	0.01 (-0.17, 0.24)	358	
Neriishi *et al* (2012) (*207*)	1986-2005	Surgical removal	0.32 (0.17, 0.52)	1028	Uses DS02
Retinal degeneration					
	2000-2002	Diabetic retinopathy	0.71 (0.26, 0.97)	20	

Minamoto *et al* (2004) (*209*)		Retinal arteriosclerosis (excluding diabetic retinopathy)	0.49 (0.15, 0.94)	69	Uses DS86 eye dose (or mothers DS86 uterus dose for those in gestation)
		Retinal degeneration (excluding diabetic retinopathy and arteriosclerosis)	0.42 (0.00, 1.02)	41	
		Retinal atrophy (excluding diabetic retinopathy and arteriosclerosis)	0.49 (0.04, 1.14)	22	
		Glaucoma			
Kiuchi *et al* (2013) (*210*)	2006-2008	Primary open angle normal tension glaucoma (IOP ≤21 mmHg)	0.31 (0.11, 0.54)	226	Uses DS02 eye dose
		Primary open angle high tension glaucoma (IOP >21 mmHg)	-0.21 (-0.48, 0.21)	36	
		Primary angle-closure glaucoma	-0.46 (-0.71, 0.02)	25	
		Macular degeneration			
Itakura *et al* (2015) (*211*)	2006-2008	Early age-related macular degeneration	-0.07 (-0.25, 0.15)	191	Uses DS02 eye dose
		Late age-related macular degeneration	-0.21 (-0.79, 1.94)	6	
		Any age-related macular degeneration	-0.08 (-0.25, 0.14)	197	
		Miscellaneous other non-cancer incidence endpoints			
Wong *et al* (1993) (*214*)	1958-1986	Dementia	0.11 (-0.18, 0.64)	84	Using DS86 dose.

Yamada *et al* (2004) (*204*)	1958-1998	Thyroid disease	0.33 (0.19, 0.49)	964	Using DS86 dose.
		Chronic liver disease+cirrhosis	0.15 (0.06, 0.25)	1774	
		Uterine myoma	0.46 (0.27, 0.67)	922	
Sera *et al* (2013) (*212*)	2004-2007	Moderate chronic kidney disease	0.15 (-0.11, 0.48)	149	Using DS02 dose
		Severe chronic kidney disease	2.19 (0.63, 5.25)	13	
		Moderate+severe chronic kidney disease	0.29 (0.01, 0.63)	162	

Notes: ATL: adult T-cell leukemia; CeVD: cerebrovascular disease; CI: confidence intervals; CLL: chronic lymphocytic leukemia; CVD, cardiovascular disease; DS02: Dosimetry System 2002; DS86: Dosimetry System 1986; EOR: excess odds ratio; ERR: excess relative risk; HL: Hodgkin lymphoma; IHD: ischemic heart disease; IOP, intraocular pressure; NA: not available; NHL: non-Hodgkin lymphoma.

[a] adjusted (via centering) for age at exposure (30 y) and attained age (70 y).

[b] analysis using underlying or contributing cause of death.

Table 2. Sex-specific cancer and non-cancer excess relative risks (and 95% confidence intervals) from the LSS study.

Site	LSS mortality						LSS incidence					
		Females			Males			Females			Males	
	Author, year, reference	Years	n	ERR/Gy (95%CI)[a]	n	ERR/Gy (95%CI)[a]	Reference	Years	n	ERR/Gy (95%CI)[a]	n	ERR/Gy (95%CI)[a]
Cancer												
All solid cancer	Brenner *et al* (2022) (*181*)	1958-2009	7895	0.60 (0.46, 0.74)	7,524	0.28 (0.18, 0.40)	Brenner *et al* (2022)[b] (*181*)	1958-2009	12,065	0.64 (0.52, 0.77)	10,473	0.28 (0.19, 0.38)
Lung	Ozasa *et al* (2012)[b] (*28*)	1950-2003	657	1.1 (0.68, 1.6)	901	0.40 (0.17, 0.67)	Cahoon *et al* (2017)[b] (*32*)	1958-2009	1001	1.32 (0.90, 1.82)	1445	0.34 (0.14, 0.58)
Breast	Ozasa *et al* (2012) (*28*)	1950-2003	324	1.5 (0.93, 2.3)	6	9.1 (0.52, 128)	Brenner *et al* (2018) (*31*)	1958-2009	1470	1.12 (0.73, 1.59)	10	5.7 (0.3, 30.8)
Malignant brain							Brenner *et al* (2020)[c] (*38*)	1958-2009	186	0.77 (0.05, 1.95)	99	2.46 (1.00, 4.89)
Esophagus	Ozasa *et al* (2012) (*28*)	1950-2003	79	1.1 (0.04, 3.0)	260	0.39 (–0.006, 0.97)	Sakata *et al* (2019) (*177*)	1958-2009	92	1.11 (–0.02, 3.13)	394	0.26 (0.02, 0.62)[d]
Stomach	Ozasa *et al* (2012) (*28*)	1950-2003	1436	0.51 (0.28, 0.78)	1689	0.13 (–0.02, 0.30)	Sakata *et al* (2019) (*177*)	1958-2009	2571	0.47 (0.28, 0.70)	3090	0.21 (0.10, 0.35)
Colon	Ozasa *et al* (2012) (*28*)	1950-2003	359	0.58 (0.16, 1.1)	262	0.50 (0.09, 1.09)	Sugiyama *et al* (2020) (*34*)	1958-2009	1132	0.50 (0.20, 0.90)	782	0.77 (0.36, 1.30)
Liver	Ozasa *et al* (2012) (*28*)	1950-2003	640	0.46 (0.15, 0.85)	879	0.30 (0.08, 0.58)	Sadakane *et al* (2019) (*33*)	1958-2009	850	0.63 (0.24, 1.14)	1166	0.44 (0.17, 0.81)
Kidney	Ozasa *et al* (2012) (*28*)	1950-2003	38	1.5 (0.01, 4.9)	42	0.11 ([e], 1.4)	Grant *et al* (2021)[b] (*178*)	1958-2009	100	-2.1 ([e], [e])	118	0.62 (-0.20, 2.1)
Bladder	Ozasa *et al* (2012) (*28*)	1950-2003	83	1.5 (0.21, 3.8)	100	0.88 (0.02, 2.3)	Grant *et al* (2021)[f] (*178*)	1958-2009	215	2.2 (1.2, 3.5)	411	0.64 (0.18, 1.2)
Thyroid	Ozasa *et al* (2012) (*28*)			-		-	Preston *et al* (2007) (*174*)	1958-1998	381	0.65 (0.27, 1.25)[g]	90	0.49 (0.15, 1.15)[g]
Leukemia	Ozasa *et al* (2012) (*28*)	1950-2003	155	3.9 (2.5, 6.1)	163	4.6 (3.0, 6.9)	Hsu *et al* (2013)[h] (*175*)	1950-2001	n=312; sex-averaged estimate ERR/Gy=1.74[i]			
Malignant lymphoma	Ozasa *et al* (2012) (*28*)	1950-2003	159	–0.18 (–0.21, 0.24)	125	0.70 (0.08, 1.7)	Hsu *et al* (2013)[j, k] (*175*)	1950-2001		0.02 (<–0.44, 0.64)		0.46 (–0.08, 1.29)
Multiple myeloma	Ozasa *et al* (2012) (*28*)	1950-2003	59	0.86 (0.02, 2.5)	34	0.11 (–0.28, 1.6)	Hsu *et al* (2013) (*175*)	1950-2001	n=136; sex-averaged estimate ERR/Gy=0.38 (–0.23, 1.36)			
Non-cancer												
Circulatory diseases	Ozasa *et al* (2012) (*28*)	1950-2003	11,447	0.14 (0.06, 0.23)	7607	0.07 (–0.001, 0.16)						
Heart disease overall	Takahashi *et al* (2017) (*29*)	1950-2008	5799	0.21 (0.10, 0.33)	3504	0.06 (–0.05, 0.18)						

Ischemic heart disease	Takahashi *et al* (2017) (*29*)	1950-2008	2112	–0.01 (–0.15, 0.17)	1444	0.07 (–0.09, 0.26)	Yamada *et al* (2004)[l] (*204*)	1958-1998	52	0.30	65	0.22
Valvular heart disease	Takahashi *et al* (2017) (*29*)	1950-2008	513	0.64 (0.22, 1.19)	231	0.06 ([e], 0.68)						

[a] ERR/~~-~~Gy from the linear term unless otherwise stated;
[b] *p*-value heterogeneity by sex <0.05;
[c] tumors of the central nervous system (CNS), 65/67 gliomas, 6/107 meningiomas and 0/49 schwannomas were malignant;
[d] quadratic term;
[e] could not be estimated;
[f] estimates for urinary tract cancer of which 80% were due to bladder cancer;
[g] 90% CI;
[h] all leukemias other than chronic lymphocytic leukemia or adult T-cell leukemia;
[i] sex-averaged estimate ERR/Gy=1.74, with a linear term 0.79 (0.03, 1.93) and a quadratic term 0.95 (0.34, 1.80) for the ERR at age 70, after exposure at age 30;
[j] estimate for NHL which accounts for 90% of malignant lymphoma in Japan;
[k] combined number of NHL cases for males and females is 402;
[l] estimates for myocardial infarction.
Abbreviations: CI, confidence interval; ERR/Gy, excess relative risk per gray; LSS: Life Span Study.

Table 3. Results of analyses of cancer and non-cancer risk in diagnostic medically exposed populations

Author, year, reference	Study description	Endpoint (incidence unless otherwise stated)	ERR/Gy or EOR/Gy (95% CI)	Cases/deaths	Comments (using the appropriate organ dose, unless otherwise indicated)
		Cancer risk			
Hauptmann *et al* (2023) (*236*)	EPI-CT brain cancer pediatric CT pooling study	All brain cancer	12.7 (5.1, 26.9)	165	5-year lagged brain dose
		Glioma	11.1 (3.6, 25.9)	121	
		All brain cancer excluding glioma	21.3 (2.5, 136)	44	
Bosch de Basea *et al* (2023) (*237*)	EPI-CT hemopoietic malignancies pediatric CT pooling study	All hematological malignancies	19.6 (11.0, 31.2)	790	2-year lagged bone marrow dose.
		Lymphoid malignancies	20.1 (10.2, 34.2)	578	
		Myeloid malignancies	20.2 (4.7, 47.7)	203	
		Leukemia excluding CLL	16.6 (4.3, 37.4)	271	
Smoll *et al* (2023) (*238*)	Australian pediatric CT cohort study	Brain	8.0 (5.4~~7~~, 10.6)	4472	2~~5~~-year lagged brain dose
Little & Boice (1999) (*244*)	Massachusetts TB fluoroscopy study	Breast	0.58 (0.19, 1.15)	229	Adjusted for attained age = 50
Boice *et al* (2022) (*248*)	Canadian TB fluoroscopy data	Lung mortality	0.02 (-0.03, 0.08)	912	Males: 10 year lagged lung dose
			-0.07 (-0.15, 0.02)	266	Females: 10 year lagged lung dose

Ronckers *et al* (2008) (*221*)	US Scoliosis cohort	Breast	2.87~~9~~ (-0.06~~1~~, 8.66)	78	5-year lagged breast dose
Ronckers *et al* (2010) (*222*)	US Scoliosis cohort	Breast mortality Lung mortality	4.0 (1.0, 9.4) -1.4 (-7.1, 3.1)	112 17	10-year lagged breast/lung dose
Pasqual *et al* (2020) (*251*)	MOBI-KIDS multinational case-control study	Brain/CNS	0 (0, 10)	844	Persons receiving diagnostic medical irradiation in early life, attained age 10-24
Zidane *et al* (2021) (*249*)	Two case-control studies of differentiated thyroid cancer	Thyroid	17 (0.6, 35)	1071	No lagged thyroid dose
Little *et al* (2018) (*250*)	Medical diagnostic exposure in US radiologic technologists	Thyroid	2.29 (-0.91, 7.01)	414	5-year lagged thyroid dose
Bithell & Stiller (1988) (*227*)	Oxford Survey of Childhood Cancers case-control study, *in utero* obstetric exposure	Cancer mortality	20.8 (0.27, 61.8) 28.8 (17.1, 43.6)	8513	2nd trimester exposure 3rd trimester exposure
Non-cancer risk					
Cardiovascular disease					

Tran *et al* (2017) (*252*)	Massachusetts and Canadian TB fluoroscopy mortality	All CVD ICD9 390-459	-0.024 (-0.042, -0.005)	12,983	Using 5-year lagged lung dose
		All CVD ICD9 390-459: <0.5 Gy	0.246 (0.036, 0.469)	10,209	
		IHD ICD9 410-414	-0.037 (-0.060, -0.013)	8158	
		IHD ICD9 410-414: < 0.5 Gy	0.268 (0.003, 0.552)	6410	
		CeVD ICD9 430-438	-0.014 (-0.067, 0.044)	1953	
		CeVD ICD9 430-438: < 0.5 Gy	0.441 (-0.119, 1.090)	1561	
		Hypertensive heart disease ICD9 401-405	-0.035 (-0.152, 0.153)	323	
		Hypertensive heart disease ICD9 401-405: < 0.5 Gy	1.121 (-0.351, 3.228)	244	
		Heart disease apart from hypertensive and IHD ICD9 390-400, 406-410	-0.010 (-0.064, 0.043)	1679	
		Heart disease apart from hypertensive and IHD ICD9 390-400, 406-410: < 0.5 Gy	-0.226 (-0.679, 0.307)	1309	
		All CVD apart from heart and cerebrovascular ICD9 439-459	0.055 (-0.028, 0.164)	870	
		All CVD apart from heart and cerebrovascular ICD9 439-459: < 0.5 Gy	0.507 (-0.322, 1.541)	685	

Notes: CeVD: cerebrovascular disease; CI: confidence intervals; CLL: chronic lymphocytic leukemia; CNS: central nervous system; CT: computed tomography; CVD: cardiovascular disease; EOR: excess odds ratio; ERR: excess relative risk; ICD: International Classification of Diseases; IHD: ischemic heart disease; TB: tuberculosis.

[a] 90% CI.

Table 4. Risks of cancer after radiotherapy for malignant and non-malignant disease

Study	Author, year, reference	Organ used	Endpoint (mortality unless otherwise indicated, mean heart dose unless otherwise indicated)	Excess relative risk Gy^{-1} (95% CI)	Deaths/ cases	Comments
Studies of radiotherapy for cancer						
International Radiation Study of Cervical Cancer Patients	Boice *et al* (1988) (*297*)	Stomach	Stomach	0.69 (0.01, 2.25)^{a}	348	Case-control study
		Colon	Colon	0.00 (-0.01, 0.02)^{a}	409	
		Rectum	Rectum	0.02 (0.00, 0.04)^{a}	488	
		Pancreas	Pancreas	0.00 (-0.28, 0.62)^{a}	221	
		Ovary	Ovary	0.01 (-0.02, 0.14)^{a}	309~~184~~	
		Vagina	Vagina	0.03 (0.00, 0.08)^{a}	105	
		Bladder	Bladder	0.07 (0.02, 0.17)^{a}	273	
		Kidney	Kidney	0.71 (0.03, 2.24)^{a}	14~~6~~8	
		Thyroid	Thyroid	12.30 (-1.00, 76.0)^{a}	43	
International Radiation Study of Cervical Cancer Patients	Boice *et al* (1987) (*298*)	Bone marrow	AL+CML	0.031 (-0.057, 0.119)^{b}	143	Case-control study
Lung cancer after breast cancer	Inskip *et al* (1994) (*817*)	Lung	Lung	0.20 (-0.62, 1.03)	61	Case-control study b~~B~~ased on dose to affected lung
Lung cancer after Hodgkin~~'s~~ lymphoma	Gilbert *et al* (2003) (*787*)	Lung	Lung	0.15 (0.06, 0.39)	227	Case-control study
International Radiation Study of Cervical Cancer Patients	Boice *et al* (1989) (*299*)	Breast	Female breast	0.27 (-1.54, 3.85)	140~~561~~	Case-control study, c~~C~~omputed from RR (irradiated vs not) for ~~for~~ women without ovaries, using mean dose of 0.26 Gy
~~Childhood Cancer Survivors Study~~Patients treated for Hodgkin~~'s~~ lymphoma	Travis *et al* (2003) (*788*)	Breast	Female breast	0.049 (0.004, 0.34)	35	Case-control study, w~~W~~omen receiving >5 Gy to ovaries or alkylating agent chemotherapy
				0.15 (0.04, 0.73)	59	Case-control study, w~~W~~omen receiving chest radiotherapy only
French-British childhood cancer	Guibout *et al*	Breast	Female breast	0.13 (<0, 0.75)	16	

cohort	(2005) (*818*)					
USA-UK study of children with RB	Little *et al* (2014) (*804*)	Breast	Female breast – among heritable RB	-2.29 (-5.53, 0.43)	29~~1~~	Via log-linear logistic model, fitted using exact methods, adjusted for blindness
			Female breast – among non-heritable RB	6.72 (0.57, +∞)	18~~5~~	
Dutch Hodgkin lymphoma cohort	Roberti *et al* (2022) (*321*)	Breast	Female breast	0.19 (0.05, 1.06)	173	Case-control study, in relation to mean breast dose
Pooled stomach cancer after Hodgkin lymphoma, testicular cancer, cervical cancer	Gilbert *et al* (2017) (*313*)	Stomach	Stomach	0.091 (0.036, 0.20)	327	Case-control study
French-British childhood cancer study	Little *et al* (1998) (*819*)	Brain region	Brain tumor total	0.19 (0.03, 0.85)	22	Case-control study nested within cohort, based on dose to tumor location (10 specified regions within the brain)
			Benign brain tumor	>1000 (0.25, >1000)	10	
			Malignant brain tumor	0.07 (<0, 0.62)	12	
Childhood Cancer Survivors Study	Neglia *et al* (2006) (*820*)	Brain	Glioma	0.33 (0.07, 1.71)	40	Case-control study nested within cohort, based on dose to tumor location
			Meningioma	1.06 (0.21, 8.15)	66	
British Childhood Cancer Survivors Study	Taylor *et al* (2010) (*821*)	Brain	Glioma/PNET	0.079 (0.021, 0.229)	81	Case-control study nested within cohort, based on dose to tumor location, adjusted for intrathecal methotrexate
			Meningioma	5.1 (0.7, 107.7)	134	
Patients treated for uterine cancer	Curtis *et al* (1994) (*822*)	Bone marrow	Non-CLL leukemia	0.10 (<0, 0.23)	151	Case-control study
Pooled childhood cancer survivors (BrCCSS, SFOP, Euro2K), LESG	Allodji *et al* (2020) (*823*)	Bone marrow	Leukemia	1.55~~6~~ (0.14, 14.3)	15~~47~~	Case control study, EOR for children without chemotherapy
				0.02 (-0.01, 0.09)	132	Case control study, EOR for children with chemotherapy
Studies of radiotherapy for non-malignant disease						
Cancer after X-ray for peptic ulcer	Little *et al* (2013) (*272*)	Bone marrow	Leukemia excluding CLL	1.087 (-0.018, 4.925)	14	A lag of 2 years is used for leukemia, 5 years for all other cancers.
		Stomach	Stomach	0.042 (-0.002, 0.119)	60~~7~~	
		Pancreas	Pancreas	0.055 (-0.002, 0.157)	56~~8~~	
		Lung	Lung	0.559 (0.221, 1.021)	193~~8~~	
		Stomach	All other cancer	0.006 (-0.008, 0.024)	366~~77~~	
Cancer after X-ray treatment for ankylosing spondylitis	Weiss *et al* (1994) (*259*)	Lung	Lung	0.05 (0.002, 0.09)	563	
		Lung	Neoplasms apart	0.11 (0.04, 0.18)	1586	

			from leukemia			
		Lung	Neoplasms apart from lung cancer and leukemia	0.10 (0.02, 0.18)	1023	
Cancer after radium treatment for uterine bleeding	Inskip *et al* (1990) (*276*)	Uterus	Uterus	0.006 (-0.01, 0.05)[a]	75	
		Bladder	Bladder	0.20 (0.08, 0.35)[a]	19	
		Rectum	Rectum	0.03 (-0.14, 0.19)[a]	15	
		Colon	Colon	0.51 (-0.08, 5.61)[a]	73	
		Stomach	Stomach	0.27 (-4.25, 4.80)[a]	23	
Leukemia after pelvic radiotherapy for benign disease	Inskip *et al* (1993) (*277*)	Bone marrow	AL+CML	3.7 (-1.0, 15)[a]	29	Dose from radium only
				0.5 (-0.6, 3.3)[a]	7	Dose from X-rays only
				2.1 (0.5, 8.3)[a]	42	Dose from radium + X-rays
Metropathia haemorrhagica cohort	Darby *et al* (1994) (*278*)	Ovary	Ovary	0.02 (-0.08, 0.12)	18	
		Uterus	Uterus (including cervix)	0.09 (-0.02, 0.19)	25	
		Bladder	Bladder	0.40 (0.15, 0.66)	20	
		Rectum	Rectum	0.04 (-0.09, 0.16)	14	
		Colon	Colon	0.13 (0.01, 0.26)	47	
		Bone marrow	Leukemia excluding CLL	0.74 (-0.11, 1.59)	12	
Cancer mortality in patients with hyperthyroidism treated with ^{131}I	Kitahara *et al* (2019) (*287*)	Mucosa	Oral cavity	-0.1 (<-0.1, 3.0)	31	
		Esophagus	Esophagus	0.1 (<0, 8.7)	38	
		Stomach	Stomach	0.3 (<-0.2, 2.8)	97	
		Colon	Colon	1.9 (<-2.0, 11.7)	258	
		Rectum	Rectum	5.4 (<-2.5, 55.3)	49	
		Liver	Liver	-0.1 (<-0.1, 1.2)	34	
		Pancreas	Pancreas	1.3 (<-0.3, 5.6)	132	
		Lung	Lung or bronchus	0.2 (<-0.1, 0.7)	437	
		Bladder	Bladder	-0.4 (<-0.4, 11.5)	54	
		Kidney	Kidney	3.2 (<-0.3, 83.4)	48	
		Brain	Brain/CNS	0.7 (<-0.7, 19.8)	39	
		Thyroid	Thyroid	2.0 (<0, 51.0)	15	
		Breast	Breast	1.2 (0.0, 3.2)	291	
		Uterus	Uterus	5.4 (-0.2, 24.2)	63	
		Ovary	Ovary	3.2 (<-1.0, 14.6)	104	
		Prostate	Prostate	0.4 (<-1.4, 14.2)	52	
		Stomach	All other solid cancers	0.2 (<-0.2, 1.6)	242	
		Marrow	Leukemia excluding CLL	-0.3 (<-0.4, 2.6)	59	
		Marrow	Non-Hodgkin lymphoma	0.7 (<-0.4, 5.4)	70	

		Marrow	Multiple myeloma	6.9 (<-0.3, >50.0)	30
Breast cancer among persons treated with ^{131}I for thyroid cancer	Tran *et al* (2022) (*288*)	Breast	Breast	0.5 (0.0, 1.4)	335

Notes AL: acute leukemia; CLL: chronic lymphocytic leukemia; CML: chronic myeloid leukemia; CNS: central nervous system; ERR: excess relative risk; PNET: primitive neuroectodermal tumor; RB: retinoblastoma; SE~~D~~: standard ~~deviation~~error.

[a] 90% CI

[b] derived by ERR ± 1.96 x SE~~D~~

Table 5. Risks of non-cancer disease in studies of radiotherapy for malignant and non-malignant disease. Entries for CVD are reproduced from systematic review of Little *et al* (*449*), excluding any study with fewer than 100 cases or deaths.

Study	**Author, year, reference**	**Organ used**	**Variables (other than age, sex, year) available to assess possible confounding**	**Endpoint (mortality unless otherwise indicated, using mean heart dose unless otherwise indicated)**	**Excess relative risk Gy^{-1} (95% CI)**	**Deaths/ cases**	**Comments**
Cardiovascular disease							
Pooled studies of radiotherapy for cancer							
EORTC 9-cohort Hodgkin lymphoma study	Maraldo *et al* (2015) (*325*)	Heart	Anthracyclines, vinca alkaloids. country	All cardiovascular event incidence	0.015 (0.006, 0.024)	1238	
				Major cardiovascular event incidence	0.019 (0.009, 0.028)	639	
Pooled analysis of clinical trial data published during 2010-2015	Taylor *et al* (2017) (*326*)	Heart or lung	NA	Cardiac disease	0.041 (0.024, 0.062)	1253	Pooled analysis, using mean dose per trial
Other studies of radiotherapy for cancer							
Childhood Cancer Survivor Study	Mueller *et al* (2013) (*329*)	Brain	Smoking, diabetes, hypertension, use of oral contraceptives, NF1 history, racial/ethnic group	Cerebrovascular disease incidence, using maximum (4-segment) brain dose	0.097 (-0.052, 0.246)[a]	292	
Childhood Cancer Survivor Study	Mulrooney *et al* (2020) and Shrestha *et al* (2021) (*331, 332*)	Heart	Smoking, BMI, diabetes, hypertension, dyslipidemia, racial/ethnic group, education, chemotherapy	All cardiac disease incidence CTCAE v4.03 ≥3	0.063 (-0.067, 0.193)[b]	658	
				Heart failure incidence CTCAE v4.03 ≥3	0.022 (-0.093, 0.138)[b]	272	
				Coronary artery disease incidence CTCAE v4.03 ≥3	0.066 (-0.020, 0.152)[b]	190	
				Valvular disease incidence CTCAE v4.03 ≥3	0.064 (-0.178, 0.306)[b]	40	
				Pericardial disease incidence CTCAE v4.03 ≥3	-0.005 (-0.082, 0.072)[b]	22	
				Arrhythmia incidence CTCAE v4.03 ≥3	0.005 (-0.049, 0.058)[b]	72	
St Jude Lifetime childhood cancer cohort	Mulrooney *et al* (2016) (*339*)	Heart	Smoking, BMI, diabetes, hypertension, alcohol consumption, dyslipidemia, physical activity+fitness, anthracyclines	Cardiomyopathy incidence	0.032 (-0.077, 0.141)[c]	118	
French (Institut Gustave Roussy) childhood cancer cardiac study	Haddy *et al* (2016) (*335*)	Heart	Smoking, BMI, anthracyclines, alkylating agents, vinca alkaloids,	Cardiac disease (ICD9 391, 393-397, 410-413, 420, 423-424, 426–428; ICD10 I05–I09, I20–I25, I30–I32, I44–I50) incidence: without anthracyclines	0.49 (0.26, 1.3)	106	

			epipodophyllotoxins, antimetabolites	Cardiac disease incidence: with anthracyclines	0.07 (0.03, 0.13)	128
French Childhood Cancer Study case-control study	Mansouri *et al* (2019) (*337*)	Heart	Smoking, BMI, physical activity, anthracyclines, alkylating agents, vinca alkaloids	Heart failure incidence (CTCAE v4.03 grade ≥1) with concomitant anthracyclines	0.09 (0.02, 0.22)	239 cases, 1042 controls
				Heart failure incidence (CTCAE v4.03 grade ≥1) without concomitant anthracyclines	0.44 (0.18, 1.12)	
Netherlands Hodgkin lymphoma coronary heart disease case-control study	van Nimwegen *et al* (2016) (*341*)	Heart EQD2	Smoking, BMI, diabetes, hypertension, hypercholesterolemia, physical activity, alkylating agents, procarbazine, vincristine, anthracyclines, splenectomy	Coronary heart disease incidence (myocardial infarction, angina pectoris requiring intervention) CTCAE v4.0 grades ≥2	0.074 (0.033, 0.148)	325 cases, 1204 controls
Nordic breast cancer case–control study	Darby *et al* (2013) (*343*)	Heart	Smoking, BMI, diabetes, hypertension, analgesic medication, thyroid medication, surgery, HRT, chemotherapy, ovarian ablation, history of IHD or COPD	IHD incidence (ICD10 I20-I25)	0.074 (0.029, 0.145)	963 cases, 1205 controls
Sweden breast cancer study	Killander *et al* (2020) (*350*)	Heart	Endocrine treatment, chemotherapy (tamoxifen, cyclophosphamide, methotrexate, 5-fluorouracil),	Cardiac disease (ICD10 I05-I07, I11, I13, I20-I22, I25, I33-I38, I40, I42, I44-I51)	-0.073 (-0.352, 0.326)	137
				Cardiac disease incidence (ICD10 I05-I07, I11, I13, I20-I22, I25, I33-I38, I40, I42, I44-I51)	-0.061 (-0.252, 0.179)	≥347
Netherlands-NKI-Rotterdam breast cancer case-control study	Jacobse *et al* (2019) (*344*)	Heart	Smoking, BMI, hypertension, diabetes, surgery, chemotherapy, endocrine therapy, prior CVD	Myocardial infarction incidence	0.064 (0.013, 0.160)	183 cases, 183 controls
Netherlands-NKI-Rotterdam breast cancer case-control study	Boekel *et al* (2020) (*346*)	Heart	Smoking, BMI, diabetes, hypertension, hypercholesterolemia,	Heart failure (CTCAE v3.0, v4.0 grade ≥2) incidence – no treatment with anthracyclines	0.00 (-0.03, 0.08)	102 cases, 306 controls
				Heart failure (CTCAE v3.0, v4.0 grade	0.08 (-0.03, 0.43)	

			menopausal status, chemotherapy, endocrine therapy, surgery	≥2) incidence – treatment with anthracyclines			
				Heart failure (CTCAE v3.0, v4.0 grade ≥2) incidence	0.01 (-0.02, 0.10)		
Case-control study nested within ESCaRa breast cancer cohort study	Baaken *et al* (2022) (*349*)	Heart	BMI, chemotherapy, endocrine therapy, previous CVD	Incidence of myocardial infarction, angina pectoris, congestive heart failure, dysrhythmia, valvular heart disease, or mortality from cardiac infarction (ICD10 I21-I23), chronic IHD (ICD10 I25.0-I25.9), acute IHD (ICD10 I21.0-I24.9), congestive heart failure (ICD10 I50.0-I50.9), angina pectoris (ICD10 I20.0-I20.9), cardiac arrest (ICD10 I46), dysrhythmia/conduction disorder (ICD10 I44.0-I49.9), vitium cordis (ICD10 I34.0-I37.9)	-0.01 (-0.06, 0.05)	494 cases, 988 controls	
Studies of radiotherapy for non-malignant disease							
Peptic ulcer study	Little *et al* (2012) (*374*)	Heart	Smoking, alcohol consumption, marital status	IHD (ICD9 410-414)	0.102 (0.039, 0.174)	1003	
		Thyroid		CeVD (ICD9 430-438)	0.422 (-1.455, 3.039)	226	
		Heart		All other CVD ICD9 390-409, 415-429, 439-459	0.050 (-0.053, 0.194)	240	
		Heart		All CVD (ICD9 390-459)	0.082 (0.031, 0.140)	1469	
Israeli tinea capitis prevalence study	Sadetzki *et al* (2021) (*375*)	Breast	Smoking, BMI, diabetes, hypertension, SES	IHD incident prevalence	7 (1, 14)^{d}	1261	
		Brain		CeVD incident prevalence	0.20 (0.12, 0.29)^{d}	1089	
		Salivary		Carotid artery stenosis incident prevalence	0.33 (0.04, 0.71)^{d}	321	
Rochester thymus enlargement study	Adams *et al* (2018) (*376*)	Heart	Smoking, dyslipidemia, diabetes, hypertension, family history of myocardial infarction	Coronary heart disease incidence (ICD10 I21-I25, I46)	-0.03 (-0.07, 0.10)	350	
				Myocardial infarction incidence (ICD10 I21-I24)	-0.06 (-0.16, 0.06)	213	
Cataract							
Childhood Cancer Survivor Study	Chodick *et al* (2016) (*388*)	Eye lens	Chemotherapy, alcohol intake, cigarette smoking, history of diabetes, use of corticosteroids	Self-reported cataract incidence	0.92 (0.65, 1.20)	2~~4~~83	No medical validation, using maximal dose to left or right eye lens, followed >5 years after first cancer diagnosis
French-UK Euro2K childhood	Allodji *et al*	Dose to the	All types of cancer	Self reported cataract incidence	0.99 (0.06, 1.91)	47~~52~~	Medical

cancer study	(2016) (*378*)	eye	treatment, alcohol use, smoking, calendar year	validation available on 47/52 cases, using maximal dose to left or right eye

Notes: BMI: body mass index; CeVD: cerebrovascular disease; CI: confidence intervals; COPD: chronic obstructive pulmonary disease; CTCAE v: Common Terminology Criteria for Adverse Events version; CVD: cardiovascular disease; EORTC: European Organisation for Research and Treatment of Cancer; HRT: hormone replacement therapy; ICD: International Classification of Diseases; NA: not available; NF1: neurofibromatosis 1; SES, socioeconomic status.

[a] estimate derived via~~by~~ fitting by (inverse variance) weighted least squares to excess hazard ratio, and assuming mean maximum brain doses of 15.25, 40 and 60 Gy for the 1.5-29, 30-49 and 50+ Gy maximum brain dose groups given by model I of Table 3 of Mueller *et al* (*329*): see Supplements S1 and S2. The mean dose is obtained by weighting these mean doses by the case count in Table 1.

[b] estimate derived via~~by~~ fitting a linear model by (inverse-variance) weighted least squares, applied to the aggregate data provided in Table 3 of Mulrooney *et al* (*331*) and in Table 2 of Shrestha *et al* (*332*). For the data of Mulrooney *et al* (*331*) (all endpoints except all cardiac disease) average cardiac doses of 0, 7.5, 25, and 45 Gy were assumed for the respective groups with the following specified ranges of cardiac doses: 0, 1-15, 15.1-34.99 Gy, ≥35 Gy. For the data of Shrestha *et al* (*332*) average cardiac doses of 0, 5, 15, 25 and 35 Gy were assumed for the respective groups with the following specified ranges of cardiac doses: 0, 0.1-9.9, 10-19.9, 20-29.9 Gy, ≥30 Gy, and the central estimates of ERR/Gy given in Figure 5 were used to correct the central estimates of trend.

[c] estimate derived via~~by~~ fitting a linear model by (inverse-variance) weighted least squares, applied to the aggregate data provided in Table 5 of Mulrooney *et al* (*339*). Average cardiac doses of 0, 7.5 and 25 Gy were assumed for the respective groups with the following specified ranges of cardiac doses: 0, 1-15, ≥15 Gy.

[d] prevalence excess odds ratio per Gy.

Table 6. Risks of cancer and non-cancer disease in Chornobyl-exposed populations

Author, year, reference	Study description (component study populations)	Endpoint	ERR/Gy or EOR/Gy (95% CI)	Cases/deaths	Comments (using the appropriate organ dose, unless otherwise indicated)
Cancer risk					
Leukemia after exposure *in utero* or age<6					
Davis *et al* (2006) (*398*)	Belarus	All leukemia	4.09 (NA, 37.7)	114	Case-control study.
	Russia		-4.94 (NA)	39	
	Ukraine		78.8 (22.1, 213)	26~~5~~8	
	All countries		32.4 (8.78, 84.0)	421	
Leukemia in cleanup workers					
Kesminiene *et al* (2008) (*403*)	Belarus, Russia, Baltic states	All hematological malignancies	6.0 (-0.2, 23.5)[a]	70~~117~~	Case-control study.
		All hematological malignancies excluding MM	6.9 (0.0, 27.1)[a]	65~~109~~	
		Leukemia excluding CLL	5.0 (-3.8, 57)[a]	19~~37~~	
		CLL	4.7 (NA, 76.1)[a]	21	
		NHL	28.1 (0.9, 243)[a]	20~~34~~	
Zablotska *et al* (2013) (*404*)	Ukraine	CLL	2.58 (0.02~~3~~, 8.43)[b]	65[b] ~~79~~	Case-control study.
		Leukemia excluding CLL	2.21 (0.05, 7.61)[b]	52[b] ~~8~~	
		All leukemia	2~~1~~.~~26~~38 (0.49~~03~~, ~~3~~5.~~5~~87)[b]	11~~3~~7[b]	
Thyroid cancer *in utero*					
Hatch *et al* (2019) (*409*)	Ukraine	Thyroid cancer	3.91 (-1.49, 65.66)	8	
		Large (>10 mm) benign thyroid nodule	4.19 (0.68, 11.62)	43	
		Small (<10 mm) benign thyroid nodule	0.34 (-0.67, 2.24)	178	
Thyroid cancer after exposure in childhood					
Brenner *et al* (2011) (*412*)	Ukraine	Thyroid cancer incidence	1.91 (0.43, 6.34)	65	
Little *et al* (2014) (*413*)	Ukraine	Thyroid cancer prevalence unadjusted for dose error	5.38 (1.86, 21.01)	45	Based on 4th screening cycle

		Thyroid cancer prevalence adjusted for dose error via MCML	4.78 (1.64, 19.69)		
Tronko *et al* (2017) (*432*)	Ukraine	Thyroid cancer	1.36 (0.39, 4.15)	47	Based on 5th screening cycle (2012-2015).
		Follicular adenoma	2.03 (0.55, 6.69)	33	
Little *et al* (2015) (*414*)	Belarus	Thyroid cancer prevalence unadjusted for dose error	1.51 (0.53, 3.86)	87	
		Thyroid cancer prevalence adjusted for dose error via MCML	1.48 (0.53, 3.87)		
Thyroid cancer in cleanup workers					
Kesminiene *et al* (2012) (*420*)	Belarus, Russia, Baltic states	Thyroid cancer	3.8 (1.0, 10.9)	127	Dose error adjusted for via MCML. Case-control study.
Gudzenko *et al* (2022) (*421*)	Ukraine	Thyroid cancer	0.40 (-0.05, 1.48)	149	Dose error unadjusted for. Case-control study.
Little *et al* (2022) (*422*)	Ukraine	Thyroid cancer	0.437 (-0.042, 1.577)	149	Dose error adjusted for via RC. Case-control study.
			0.517 (-0.039, 2.035)		Dose error adjusted for via MCML. Case-control study.
		Follicular morphology tumors	3.224 (-0.082, 30.615)	24	Dose error adjusted for via RC. Case-control study.
			4.708 (-0.075, 85.143)	24	Dose error adjusted for via MCML. Case-control study.
Breast cancer among non-cleanup worker populations					
Rivkind *et al* (2020) (*427*)	Russia	All breast cancers among women age <55	57 (-0, 1550)	468	Case-control study, adjusted for menopausal status, breast cancer in 1st degree relatives, nulliparity, age at 1st live birth, education, employment in metallurgy or mining

Non-cancer risk					
Cataract in cleanup workers					
Worgul *et al* (2007) (*441*)	Ukraine	Stage 1 cataract	0.49 (0.08, 1.06)	1870~~[b]~~[c] / 381~~[c]~~[d]	Slit-lamp biomicroscopy using Merriam-Focht scoring.
		Stage 1-5 cataract	0.70 (0.22, 1.38)	1944~~[b]~~[c] / 387~~[c]~~[d]	
		Stage 1 non-nuclear cataract	0.52 (0.10, 1.12)	1693~~[b]~~[c] / 268~~[c]~~[d]	
		Stage 1-5 non-nuclear cataract	0.65 (0.18, 1.30)	1757~~[b]~~[c] / 274~~[c]~~[d]	
		Stage 1 posterior subcapsular cataract	0.42 (0.01, 1.00)	1464~~[b]~~[c] / 252~~[c]~~[d]	
Cardiovascular disease in cleanup workers					
Ivanov *et al* (2006, 2007) (*442, 443*)	Russia	Hypertension (ICD10 I10-I15)	0.26 (-0.04, 0.56)	15,484	Cardiovascular disease incidence
		Essential hypertension (ICD10 I10)	0.36 (0.005, 0.71)	11,910	
		Hypertensive heart disease (ICD10 I11)	0.04 (-0.36, 0.44)	7680	
		IHD (ICD10 I20-I25)	0.41 (0.05, 0.78)	10,942	
		Acute myocardial infarction (ICD10 I21)	0.19 (-0.99, 1.37)	948	
		Other acute IHD (ICD10 I24)	0.82 (-0.62, 2.26)	849	
		AP (ICD10 I20)	0.26 (-0.19, 0.71)	6613	
		Chronic IHD (ICD10 I25)	0.20 (-0.23, 0.63)	7021	
		Other heart disease (ICD10 I30-I52)	-0.26 (-0.81, 0.28)	3572	
		CeVD disease (ICD10 I60-I69)	0.45 (0.11, 0.80)	12,832	
		Diseases of arteries, arterioles and capillaries (ICD10 I70-I79)	0.47 (-0.15, 1.09)	3934	
		Diseases of veins, lymphatic vessels and lymph nodes (ICD10 I80-I89)	-0.26 (-0.70, 0.18)	5572	
		All CVD (ICD10 I00-I99)	0.18 (-0.03, 0.39)	32,189	
Kashcheev *et al* (2016) (*444*)	Russia	CeVD (ICD10 I60-I69) after no diabetes	0.35 (0.18, 0.53)	23,264	Cardiovascular disease incidence
		CeVD (ICD10 I60-I69) after diabetes	1.29 (0.63, 1.94)		
		CeVD (ICD10 I60-I69) after no atherosclerosis	0.43 (0.25, 0.62)		

		CeVD (ICD10 I60-I69) after atherosclerosis	0.50 (0.09, 0.90)		
		CeVD (ICD10 I60-I69) after no hypertensive disease	0.38 (0.08, 0.68)		
		CeVD (ICD10 I60-I69) after hypertensive disease	0.48 (0.27, 0.68)		
		CeVD (ICD10 I60-I69) after no IHD	0.41 (0.14, 0.68)		
		CeVD (ICD10 I60-I69) after IHD	0.47 (0.25, 0.69)		
		CeVD (ICD10 I60-I69) after no concomitant disease	0.38 (0.13, 0.64)		
		All CeVD (ICD10 I60-I69)	0.45 (0.28, 0.62)		
Kashcheev *et al* (2017) (*445*)	Russia	IHD (ICD10 I20-I25)	0.42 (0.25, 0.60)	22,220	Cardiovascular disease incidence
		CVD (ICD10 I00-I99)	0.47 (0.31, 0.63)	27,456	
Chekin *et al* (2022) (*447*)	Russia	CVD (ICD10 I00-I99)	0.349 (0.146, 0.564)	15,025	Cardiovascular disease mortality
Shafransky *et al* (2020) (*446*)	Russia	IHD (ICD10 I20-I25)	0.46 (-0.007, 1.04)	643	Including doses from their work at 10 other nuclear power plants
Tatarenko (2018) (*451*)	Ukraine	Myocardial infarction	1.450 (-4.311, 7.700)[~~d~~e]	251	Cardiovascular disease prevalence, adjusted for diabetes, hypercholesterolemia, serum creatinine
Krasnikova *et al* (2013) (*450*)	Ukraine	Chronic CeVD (ICD10 I67, I69)	0.52 (0.35, 0.77)	NA	Cardiovascular disease incidence, adjusted for smoking, diabetes, hypertension, hypercholesterolemia, alcohol abuse, salt intake, thyroid disease, physical and emotional strain
		Cerebral atherosclerosis (ICD10 I67.2)	1.13 (1.06, 1.20)	NA	
Transgenerational effects					
	Ukraine	Paternal *de novo* mutations	-0.00594 (-0.0340, 0.0221)	NA	

Yeager *et al* (2021) (*453*)			Maternal *de novo* mutations	-0.176 (-0.443, 0.0910)	NA	Poisson log-linear relative risk model
			Paternal relative telomere length	0.00203 (-0.0238[~~e~~f], 0.0279[~~e~~f])	NA	Relative telomere length assessed using a log-linear model
			Maternal relative telomere length	-0.275 (-0.518[~~e~~f], -0.032[~~e~~f])	NA	

Notes: AP: angina pectoris; CeVD: cerebrovascular disease; CI: confidence intervals; CLL: chronic lymphocytic leukemia; CVD: cardiovascular disease; EOR, excess odds ratio; ERR, excess relative risk; ICD: International Classification of Diseases; IHD: ischemic heart disease; MCML: Monte Carlo maximum likelihood; MM: multiple myeloma; NA, not available; NHL: non-Hodgkin lymphoma; RC: regression calibration; SE: standard error.

[a] 90% CI

[b] excluding cases with in-person interviews <2 years from start of chemotherapy

[c~~b~~] prevalence in both eyes

[d~~c~~] incidence in both eyes

[e~~d~~] estimate derived via~~by~~ dividing ln[odds ratio] (for >50 mSv vs <50 mSv) from Tatarenko *et al* (*451*) by difference in mean doses for the >50 mSv and <50 mSv groups (91, 31 mSv), and similarly for the CI.

[f~~e~~] CI derived from ERR and SE via ERR ± 1.96 x SE

Table 7. Cancer and non-cancer risks in INWORKS study

Author, year, reference	**Follow-up**	**Adjustments used**	**Outcome**	**ERR/Gy (90% CI)**	**Number of deaths**	**Comments**
			Cancer mortality			
Richardson *et al* (2023) (*466*)	1944–2016	age, sex, birthyear, SES~~socioeconomic status~~, country, duration of employment or radiation work, neutron monitoring status	all solid cancers	0.52 (0.27, 0.77)	28,089	linear model, 10-year lag; evidence of downward curvature.
			all solid cancers: restricted to workers hired 1958+	1.22 (0.74, 1.72	14,868	
			all solid cancers: restricted to workers hired 1965+	1.44 (0.65, 2.32)	8119	
			all solid cancers: restricted to workers hired <1958	0.20 (–0.07, 0.49)	13,221	
Richardson *et al* (2018) (*464*)	1944–2005	age, sex, birthyear, SES~~socioeconomic status~~, country, duration of employment or radiation work, neutron monitoring status	rectum (ICD9 154)	1.87 (0.04, 4.52)	539	21 solid cancer sites assessed; linear model, 10-year lag; ~~were estimated using a~~ maximum-likelihood ~~method~~ estimates shown
			peritoneum (ICD9 158-159)	4.21 (0.42, 11.07)	145	
			larynx (ICD9 161)	6.44 (1.36, 15.28)	185	
			lung (ICD9 162)	0.51 (0.00, 1.09)	5802	
			skin (ICD9 172-173)	2.53 (0.15, 6.01)	369	
			testis (ICD9 186)	32.55 (4.48, 105.7)	48	
Leuraud *et al* (2015) (*459*)	1944–2005	age, sex, calendar period, country	leukemia, excluding CLL	2.96 (1.17, 5.21)	531	linear model, 2-year lag for leukemias, 10-year lag for myeloma and lymphomas;
			CML	10.45 (4.48, 19.65)	100	
			AML	1.29 (–0.82, 4.28)	254	

Author, year, reference	**Follow-up**	**Adjustments used**	**Outcome**	**ERR/Gy (90% CI)**	**Number of deaths**	**Comments**
			ALL	5.80 (NE, 31.57)	30	linear model, 10-year lag;
			CLL	–1.06 (NE, 1.81)	138	
			multiple myeloma	0.84 (–0.96, 3.33)	293	
			non-Hodgkin lymphoma	0.47 (–0.76, 2.03)	710	
			Hodgkin lymphoma	2.94 (NE, 11.49)	104	
			Noncancer mortality			
Gillies *et al* (2017) (*482*)	1944–2005	age, sex, birthyear, SES~~socioeconomic status~~, employer/facility, duration of employment	all non-malignant disease	0.19 (0.07, 0.30)	46,029	All non-malignant deaths and 12 disease groupings assessed; linear model, 10-year lag
			circulatory disease	0.22 (0.08, 0.37)	27,848	
			cerebrovascular disease	0.50 (0.12, 0.94)	4,444	
			ischemic heart disease	0.18 (0.004, 0.36)	17,463	
			respiratory disease	0.13 (−0.17, 0.47)	5,291	
			digestive disease	0.11 (−0.36, 0.69)	2,180	

Notes: ALL: acute lymphocytic leukemia; AML: acute myeloid leukemia; CI: confidence intervals; CLL: chronic lymphocytic leukemia; CML: chronic myeloid leukemia; ERR: excess relative risk; ICD: International Classification of Diseases; NE: not estimable; SES: socioeconomic status.

Table 8. Cancer and non-cancer risk in Mayak workers

Author, year, reference	Adjustments used	Endpoint	ERR/Gy or EOR/Gy (95% CI)	Cases/deaths	Comments (using the appropriate organ dose, unless otherwise indicated)
Cancer risk					
Kuznetsova *et al* (2016) (*491*)	Smoking	AML	13.23 (4.25, 49.45)[a]	24	Cancer incidence, using external bone marrow dose. Additional adjustment of the baseline model for smoking did not improve the model significantly.
		CML	1.39 (-0.22, 7.32)[a]	13	
		CLL	-0.02 (NA, NA)[a]	21	
		Leukemia other than AML, CML, CLL	0.79 (-0.03, 3.76)[a]	19~~21~~	
		NHL	0.09 (-1.52, 1.45)[a]	31	
		HL	-0.02 (NA, NA)[a]	24	
		MM	2.39 (-1.28, 35.47)[a]	11	
Sokolnikov *et al* (2008) (*493*)	Smoking	Lung	0.19 (0.05, 0.39)	681	Cancer mortality, using external dose
		Liver	0.21 (<0, 1.0)	75	
		Bone	0.35 (<0, 4.4)	30	
Sokolnikov *et al* (2017) (*494*)	Smoking	Solid cancer other than lung, liver, bone	0.12 (0.03, 0.21)	1825	Cancer mortality, using external γ dose adjusted for ^{239}Pu
Non-cancer risk					
Cardiovascular and other non-ocular disease					
Azizova *et al* (2023) (*489*)	Smoking, alcohol consumption, internal α particle liver dose	CRHD incidence (ICD9 390-398)	0.27 (-0.14, 1.04)	559	Using liver external γ dose, lagged by 10 years
		IHD incidence (ICD9 410-414)	0.19 (0.12, 0.26)	7722	
		AMI incidence (ICD9 410)	-0.01 (NA, 0.09)	2185	
		AP incidence (ICD9 413)	0.20 (0.11, 0.30)	3976	
		HF incidence (ICD9 428)	0.27 (0.18, 0.38)	4939	
		CACD incidence (ICD9 426-427)	0.23 (0.14, 0.34)	3689	
Azizova *et al* (2015) (*485*)	Smoking, BMI, hypertension alcohol consumption	IHD mortality (ICD9 410-414) < 4 Gy	0.07 (<0, 0.16)	2848	Using external γ dose, lagged by 5 years.

Azizova *et al* (2022) (*488*)	Smoking, alcohol consumption	CeVD incidence (ICD9 43~~1~~0-438~~14~~)	0.39 (0.31, 0.48)	9448~~2078~~	Using liver external γ dose, lagged by 10 years
		CeVD incidence (ICD9 43~~1~~0-438~~14~~) < 3 Gy	0.36 (0.28, 0.45)	9395~~2025~~	
Azizova *et al* (2022) (*824*)	Smoking, alcohol consumption, internal α dose, migration status	All cardiovascular disease mortality (ICD9 390-459)	0.02 (-0.04, 0.09)	3828	Using liver absorbed γ dose, lagged by 10 years.
		IHD mortality (ICD9 410-414)	0.07 (-0.02, 0.18)	2267	
		CeVD mortality (ICD9 430-438)	-0.02 (-0.12, 0.11)	1168	
Azizova *et al* (2014) (*484*)	Smoking, BMI, hypertension, alcohol consumption	CeVD mortality (ICD9 430-438)	0.05 (-0.04, 0.16)	1575~~8~~	Using external γ dose, lagged by 5 years.
Azizova *et al* (2015) (*496*)	Smoking, BMI, hypertension, alcohol consumption	All cardiovascular disease mortality (ICD9 390-459) < 4 Gy	0.08 (0.02, 0.14)	<4699 (~4673)~~5010~~	Using external γ dose, lagged by 5 years.
Azizova *et al* (2016) (*486*)	Smoking, BMI, hypertension, alcohol consumption	Lower extremity arterial disease incidence (ICD9 440.2)	0.30 (0.13, 0.53)	942~~3~~	Using external γ dose, lagged by 5 years.
Azizova *et al* (2019) (*487*)	Smoking, BMI, alcohol consumption	Hypertension incidence (ICD9 401-404)	0.15 (0.09, 0.21)	8230~~425~~	Using external γ dose, lagged by 5 years.
Azizova *et al* (2017) (*498*)	Smoking, pre-employment occupational hazards	Chronic bronchitis incidence, males	0.10 (-0.03, 0.27)	1706~~274~~	Unlagged γ dose to the lung
		Chronic bronchitis incidence, females	0.13 (NA, 0.67)	429~~367~~	
Azizova *et al* (2020) (*497*)		Parkinson's disease incidence	1.03 (0.60, 1.64)	300	Using external γ dose, lagged by 10 years.
Ocular disease					
Azizova *et al* (2018) (*499*)		Posterior subcapsular cataract	0.90 (0.67, 1.19~~20~~)	1239	Using external γ dose, lagged by 5 years.
		Cortical cataract	0.62 (0.50, 0.75)	3132	

		Nuclear cataract	0.47 (0.35, 0.60)	2033	
Azizova *et al* (2019) (*500*)		Cataract surgery	0.09 (-0.02, 0.22)	697~~701~~	Using external γ dose, lagged by 5 years, with stratification by birth cohort and neutron dose.
Azizova *et al* (2022) (*501*)		Normal tension glaucoma	0.53 (0.01, 1.68)	92	Using external γ dose, lagged by 5 years.
		High tension glaucoma	-0.01 (-0.16, 0.21)	447	
		Total primary open angle glaucoma	0.07 (-0.08, 0.29)	539	
		Total primary angle closure glaucoma	0.04 (-0.51, 1.53)	32	

[a] 90% CI

Notes: AMI: acute myocardial infarction; AML: acute myeloid leukemia; AP: angina pectoris; BMI: body mass index; CACD: cardiac arrhythmia and conduction disorder; CeVD: cerebrovascular disease; CI: confidence intervals; CLL: chronic lymphocytic leukemia; CML: chronic myeloid leukemia; CRHD: chronic rheumatic heart disease; EOR, excess odds ratio; ERR, excess relative risk; HF: heart failure; HL: Hodgkin lymphoma; IHD: ischemic heart disease; ICD: International Classification of Diseases; MM: multiple myeloma; NA, not available; NHL: non-Hodgkin lymphoma.

Table 9. Results of pooled studies of cancer and non-cancer mortality in Million Person Study

Author, year, reference	Cohorts used	Endpoint	ERR/Gy (95% CI)	Deaths	Comments
		Cancer mortality			
Boice *et al* (2022) (*506*)	US nuclear power plant (NPP) workers (1957–2011)	All solid cancer	0.1 (–0.3, 0.5)	8445	Underlying and contributing cause; linear model, adjusted for age, year of birth, sex, and SES; 10-year lag
NCRP (2022) (*524*)	~~Nuclear power plant (~~NPP~~)~~ workers, industrial radiographers, medical radiation workers	Lung: male	0.155 (-0.33, 0.64)	6009	CI are derived from given SE~~D~~ and central estimate of ERR via ERR ± 1.96 SE~~D~~
		Lung: female	-0.51 (-2.67, 1.65)	475	
		Lung: total	0.137 (-0.34, 0.61)	6484	
Mumma *et al* (2022) (*508*)	NPP workers, industrial radiographers (including those working at shipyards and other than at NPP) (1969-2011)	Mesothelioma	0.9 (-0.5, 2.6)	421	ERR/Gy derived from hazard ratio at 100 mGy, adjusted for sex, birthyear, asbestos exposure, SES, first year and duration of monitoring, 10-year lag
Boice *et al* (2022) (*506*)	US ~~nuclear power plant (~~NPP~~)~~ workers (1957–2011)	Leukemia excluding CLL	1.5 (–0.01, 3.1)[a]	311	Underlying and contributing cause; linear model, adjusted for age, ~~year of~~ birthyear, sex, and ~~socioeconomic status~~education; 2-year lag
Boice *et al* (2023) (*509*)	US medical workers (1965-2016)	Leukemia excluding CLL	1.0 (-3.4, 5.4)	139	Underlying and contributing cause; linear model, adjusted for age, year of birth, sex, and socioeconomic status; 2-year lag
Boice *et al* (2022) (*510*)	US male military participants at eight aboveground nuclear weapons test series (1945–2010)	Leukemia excluding CLL	–3.7 (–10.8, 3.3)	710	Underlying and contributing cause; linear model, adjusted for age, year of birth, test area and military pay grade; 2-year lag

Boice *et al* (2022) (*512*)	US workers employed at the Los Alamos National Laboratory (1943–2017)	Leukemia excluding CLL	–4.3 (–11.1, 2.4)	160	Underlying and contributing cause; linear model, adjusted for age, year of birth, sex, and education; 2-year lag
Golden *et al* (2022) (*516*)	US White male workers employed at the Mallinckrodt uranium processing plant (1942–2012)	Leukemia excluding CLL	–1.4 (–6.0, 3.3)	18	Underlying and contributing cause; linear model, adjusted for age, year of birth, and pay type; 2-year lag
Non-cancer mortality					
Dauer *et al* (2024~~3~~) (*507*)	NPP workers, industrial radiographers, medical radiation workers, Los Alamos National Laboratory workers, Rocky Flats workers, atomic test veterans	Parkinson's disease~~s~~	0.17 (0.05, 0.29)	1573	Summary estimate from a random effects inverse variance-weighted meta-analysis of six MPS cohorts.

Notes: CI: confidence intervals; CLL: chronic lymphocytic leukemia; ERR: excess relative risk; NPP: nuclear power plant; SD: standard deviations; SES: socioeconomic status.

[a] 90% CI

Table 10. Risk estimates for cancer and non-cancer mortality from studies of radon daughter exposure of underground miners

Author, year, reference	Study	Endpoint	Observed deaths	Excess relative risk /100 WLM (95% CI)	Comments
Cancer risk					
Kelly-Reif *et al* (2023) (*536*)	PUMA seven cohort pooled uranium miners	Lung	7754	4.68 (2.88, 6.96)[a]	Full cohort
			3266~~NR~~	4.35 (1.67, 8.80)[a]	<100 WLM cumulative exposure
			6537	4.49 (2.49, 6.85)[a]	Pre-1960 hires
Richardson *et al* (2022) (*537*)	PUMA seven cohort pooled uranium miners – miners hired after 1960	Lung	1217	8.38 (3.30, 18.99)[b]	Hired from 1960
			1000	7.97 (2.43, 16.25)	Hired from 1960 and ≤~~<~~ 50 WLM cumulative exposure
Darby *et al* (1995) (*538*)	11-cohort pooled miners	Pancreas	91	0.07 (0.01, 0.12)	
Xuan *et al* (1993), Lubin *et al* (1995) (*532*, *825*)	Chinese tin miners	Lung	936	0.16 (0.1, 0.2)	Derived from UNSCEAR (*8*)
Hodgson *et al* (1990) (*826*)	Cornish tin miners	Lung	82	0.045	Derived from UNSCEAR (*8*)
Villeneuve *et al* (2007) (*827*)	Newfoundland fluorspar miners	Lung	206	0.47 (0.28, 0.65)	
Jonsson *et al* (2010) (*828*)	Swedish iron miners	Lung	122	2.2 (0.72, 3.68)[c]	
Kreuzer *et al* (2014) (*539*)	German uranium miners	Extrathoracic airways	234	0.035 (-0.009, 0.080)	
Non-cancer risk					

Drubay *et al* (2015) (*518*)	French uranium miner case-control study	Cardiovascular disease	442	0.43 (-0.29, 1.87)	Unadjusted for circulatory disease risk factors
				0.15 (-0.52, 1.78)	Adjusted for obesity, hypertension, resting heart rate, smoking, diabetes, hypercholesterolemia, hypertriglyceridemia, hyperuricemia, CKD, high GGT
Kreuzer *et al* (2010) (*541*)	German uranium miners	Cardiovascular disease	7395	0.001 (*p*>0.5)	
Kreuzer *et al* (2013) (*542*)	German uranium miners	All non-malignant respiratory disease without silicosis or other pneumoconiosis	1361	0.005 (*p*=0.41)	
		Chronic obstructive pulmonary disease	715	0.007 (*p*=0.41)	
Villeneuve *et al* (2023) (*829*)	Newfoundland fluorspar miners	CVD	480	0.002 (-0.020, 0.023)	5-year lagged exposure
		IHD	285~~90~~	0.005 (-0.031, 0.022)	
		AMI	170~~5~~	0.026 (-0.018, 0.070)	
		CeVD	60	-0.35 (-0.76, 0.00)	

Notes: AMI: acute myocardial infarction; CeVD: cerebrovascular disease; CI: confidence intervals; CKD: chronic kidney disease; CVD: cardiovascular disease; GGT: gamma glutamyl transpeptidase; IHD: ischemic heart disease; NR: not reported; PUMA: Pooled Uranium Miner Analysis; WLM: Working Level Month.

[a] among miners who were less than 55 years of age and were exposed in the prior 5 to <15y at annual exposure rates of <0.5 Working Levels

[b] among miners who were less than 55 years of age and were exposed at ≥35 years of age and at annual exposure rates of <0.5 Working Levels

[c] 95% CI for the given ERR/WLM are derived by scaling from the ERR / kBq y/m^3 reported as 0.046 (95% CI 0.015, 0.077) by Johnson *et al* (*828*)

Table 11. Analyses of cancer and non-cancer risk in uranium processing workers. Studies reporting fewer than 100 cases or deaths are not shown.

Author, year, reference	Study description (component study populations)	Endpoint	ERR/Gy or EOR/Gy (95% CI)	Deaths	Comments (using the appropriate organ dose, unless otherwise indicated)
Cancer Risk					
All cancer					
Kreuzer *et al* (2015) (*554*)	~~German Wismut~~ 4~~,~~054 male uranium millers (1946–2008) from the German Wismut cohort who had never worked as uranium miners and were exposed ~~in relation~~ to external radiation, radon, ~~and~~ LLR~~ exposure~~, and silica.	All cancer mortality	ERR per 100 kBqh/m^3 =−0.43 (−1.31, 0.44)~~,~~	457	Estimate for LLR a~~A~~djusted for radon exposure, no smoking information available. Exposure estimated via a ~~job exposure matrix~~ JEM for each radiation type, with no confirmation of LLR doses estimated by JEM by urinalyses.
Bouet *et al* (2019) (*561*)	4541 workers in five plants involved in the French nuclear fuel cycle (1958-2006) and followed up 1968-2013	All cancer mortality	8.0 (-3.6, 26.5)	180	Adjusted for sex, age, year of birth, socioeconomic status
Lung cancer					
Zablotska *et al* (2018) (*559*)	German Wismut 4431 uranium workers (1946-2008) and Port Hope 3000 uranium workers (1932-1980, and followed to 1999), of both sexes	Lung cancer mortality	0.43 (<-0.46, 2.13)	262	Estimate for external gamma adjusted for radon, calendar time, age at risk, cohort, duration of employment.
Kreuzer *et al* (2015) (*554*)	~~German Wismut~~ 4~~,~~054 male uranium millers (1946–2008) from the German Wismut cohort who had never worked as uranium miners and were exposed to	Lung cancer mortality	ERR per 100 kBqh/m^3 =−0.61 (−1.42, 0.1~~.~~9)	159	Estimate for LLR n~~N~~ot adjusted for radon, no smoking information available. Exposure estimated via a job exposure matrix JEM for each radiation type, with no confirmation of LLR doses estimated by JEM by urinalyses.

	external radiation, radon, ~~and~~ LLR ~~exposure~~, and silica.				
Silver *et al* (2013) (*551*)	-5211~~6,409~~ White male ~~uranium~~ workers (1951-2004) at the US Fernald Feed uranium processing facility ~~(USA) (1951-2004)~~ exposed to external radiation, radon, and LLR	Lung cancer mortality	22 (−9.3, 7~~6~~0)	269	U~~sed u~~rine uranium concentration data were used to estimate exposure to internally deposited uranium compounds. Analyses took into account radon and external radiation. No smoking data,
Richardson and Wing (2006) (*548*)	3~~,~~864 White male workers (1947-1990) at the US Oak Ridge~~,~~ ~~USA~~ Y-12 nuclear materials fabrication plant	Lung cancer mortality	–0.77 (–2.53~~0~~, ~~10~~0.99)[a]	111	Internal radiation doses were based on *in vivo* monitoring and urinalysis results and imputed for unmonitored employment-years. Risk estimate adjusted for external radiation. No smoking data,
Yiin *et al* (2017) (*556*)	29,303 male and female workers (1948-2011) at three US gaseous diffusion plants for uranium enrichment	Lung cancer mortality	--750 (-2~~,~~310, 1~~,~~120)	1~~,~~172	Internal radiation doses were based on urinalysis results and imputed for unmonitored employment-years. Minimal impact of ~~Risk estimate~~ adjustment~~ed~~ for external radiation and work-related medical X-Rays. No smoking data,
Milder *et al* (2024~~3~~) (*517*)	2,514 White male workers (1942-2019) at the US Mallinckrodt uranium processing facility	Lung cancer mortality	−1 (<−1.6, 0.8)	162	Internal radiation doses were based on urinalysis results. Analyses were based on organ doses which included LLR, radon and external radiation from γ- and X-rays. No smoking data.
Digestive tract cancers					
Kidney cancer					
Yiin *et al* (2017) (*556*)	29,303 male and female workers (1948-2011) at three US gaseous diffusion plants for uranium enrichment	Kidney cancer mortality	140 (-160, 660)	110	Internal radiation doses were based on urinalysis results and imputed for unmonitored employment-years. Minimal to moderate impact of ~~Risk estimate~~ adjustment~~ed~~ for external radiation and work-related medical X-Rays. No smoking data,
Leukemia and lympho-hematopoietic malignancies					
Non-Cancer Risk					
Non-malignant respiratory diseases					

Richardson and Wing (2006) (*548*)	3864 White male workers (1947-1990) at the US Oak Ridge Y-12 nuclear materials fabrication plant	Mortality from non-malignant respiratory diseases	–0.85 (–3.73, 2.03)	50	Internal radiation doses were based on *in vivo* monitoring and urinalysis results and imputed for unmonitored employment-years. Risk estimate adjusted for external radiation. No smoking data.
Silver *et al* (2013) (*551*)	5211 White~~ 6,409~~ male~~ and female~~ workers (1951-2004) at the US Fernald Feed uranium processing facility exposed to external radiation, radon, and LLR	Mortality from ~~non-~~chronic obstructive pulmonary~~malignant respiratory~~ disease~~s~~	−62 (−65~~70~~, 0.62)	102	U~~sed u~~rine uranium concentration data were used to estimate exposure to internally deposited uranium compounds. Analyses took into account radon and external radiation. No smoking data,
Yiin *et al* (2017) (*556*)	29,303 male and female workers (1948-2011) at three US gaseous diffusion plants for uranium enrichment	Mortality from non-malignant diseases of the respiratory system~~diseases~~	80 (-330, 1~~,~~880)	1194~~309~~	Internal radiation doses were based on urinalysis results and imputed for unmonitored employment-years. No impact of ~~Risk estimate ~~adjustment~~ed~~ for external radiation and work-related medical X-Rays. No smoking data.~~,~~
Milder *et al* (2024~~3~~) (*517*)	2~~,~~514 White male workers (1942-2019) at the US Mallinckrodt uranium processing facility	Mortality from non-malignant respiratory diseases	0. 1 (<−1.3, 2.5)	139	Internal radiation doses were based on urinalysis results. Analyses were based on organ doses which included LLR, radon and external radiation from γ- and x-rays. No smoking data.
Cardiovascular diseases					
Kreuzer *et al* (2015) (*554*)	~~German Wismut~~ 4~~,~~054 male uranium millers (1946–2008) from the German Wismut cohort who had never worked as uranium miners and were exposed to external radiation, radon, LLR, and silica	Ischemic heart disease mortality	ERR per 100 kBqh/m^3 =–0.09 (–0.84, 0.65)	341	~~Exposure e~~Estimate for LLR, adjusted for radon exposure, no smoking information available.~~d~~ Exposure estimated via a ~~job exposure matrix~~ JEM for each radiation type, with no confirmation of LLR estimated by JEM by urinalyses.
		C~~c~~erebrovascular disease mortality	ERR per 100 kBqh/m^3 = –0.17 (–1.14, 0.80)	171	
-Zhivin *et al* (2018) (*560*)	Nested case-control study of CVD among 2,897 male and female workers (1968-2006) of the	Mortality from circulatory system diseases	200 (4, 500)	102	Used urine and fecal uranium concentration data were used to estimate exposure to internally deposited uranium compounds. Cases and controls matched on attained age, sex, birth cohort and socioprofessional status.
		Ischemic heart disease mortality	200 (-10, 1000)	44~~1~~	

	French AREVA NC Pierrelatte plant	Cerebrovascular disease mortality	700 (100, 3000)	31	Analyses adjusted for smoking, BMI, BP, total cholesterol, glycemia, external γ-ray radiation dose.
-Anderson *et al* (2021) (*562*)	-29,283 male and female workers (1948-2011) at three US gaseous diffusion plants for uranium enrichment	Ischemic heart disease mortality	19 (−77, 260)	3488	Internal radiation doses were based on urinalysis results and imputed for unmonitored employment-years. No smoking data.
		Cerebrovascular disease mortality	−130 (−420, 440)	746	
Milder *et al* (2024~~3~~) (*517*)	2~~,~~514 White male workers (1942-2019) at the US Mallinckrodt uranium processing facility	All CVD	1.4 (0.2, 2.9)	716	Internal radiation doses were based on urinalysis results. Analyses were based on organ doses which included LLR, radon and external radiation from γ- and X~~x~~-rays. No smoking data.
		Ischemic heart disease mortality	1.3 (0.00, 3.1)	563	

Notes: CI, confidence interval; CVD, cardiovascular diseases; EOR, excess odds ratio; ERR, excess relative risk; JEM: job exposure matrix; kBqh/m^3, kiloBecquerel x hour per cubic meter; LLR, long-lived radionuclides from uranium ore dust; SE, standard error.

[a] computed via mean ±1.96 SE

Table 12. Cancer and non-cancer risks in medical radiation workers in the United States, South Korea, and China

Author, year, reference	**Follow-up years**	**Adjustments**	**Outcomes**	**Number of cases or deaths**	**ERR / Gy (95% CI)**	**Comments**
			Cancer risks			
			US Radiologic Technologists			
Preston *et al* (2016) (*582*)	1983-2008	Attained age, birth cohort, number of live births, menopause status, family history of breast cancer, baseline BMI, hormone replacement therapy, alcohol consumption	Breast cancer incidence	1922	0.7 (-0.05, 1.9)	Linear dose-response for technologists born before 1930 and 1st worked before 1950
			Breast cancer mortality	586	3.1 (1.1, 6.7)	The exposures of early workers were the main determinants of risk
Linet *et al* (2020) (*587*)	1983-2012	Attained age, sex, birth year	Acute myeloid leukemia mortality	85	0.002 (<-0.2, 2.4)	No evidence of dose-response for technologists born in early decades, 1st worked before 1950 or worked with higher-dose procedures
			Leukemia excluding CLL mortality	155	0.5 (<-0.9, 2.4)	Leukemia excluding CLL: no evidence of dose-response for technologists born in early

Author, year, reference	**Follow-up years**	**Adjustments**	**Outcomes**	**Number of cases or deaths**	**ERR / Gy (95% CI)**	**Comments**
						decades, 1st worked before 1950 or worked with higher-dose procedures. Lymphoid neoplasms: n~~N~~o significant dose-response for CLL, NHL, MM
Kitahara *et al* (2018) (*586*)	1983-2013	Attained age, sex, year of birth, BMI, pack-years smoked	Thyroid cancer incidence	476	-0.5 (<-1.0, 3.4)	No significant dose-response for those born in early decades, 1st worked before 1950 or worked with higher-dose procedures
Lee *et al* (2015) (*584*)	1983-2005	Calendar period, sex, education, income, smoking, alcohol consumption, BMI, hours of exercise/week, eye color, skin complexion, blistering sunburn, skin reactions,	Basal cell carcinoma incidence	3615	-0.01 (-0.43, 0.52)	

Author, year, reference	**Follow-up years**	**Adjustments**	**Outcomes**	**Number of cases or deaths**	**ERR / Gy (95% CI)**	**Comments**
		cumulative UVR, dental X-rays				
		Calendar period and sex			0.03 (-0.39, 0.56)	
Kitahara *et al* (2017) (*585*)	1983-2012	Attained age, sex	Brain/CNS mortality	193	1.0 (<-3, 15)	No significant dose response for those born in early decades, 1st worked before 1950 or worked with high-dose procedures
Velazquez-Kronen *et al* (2020) (*583*)	1983-2012	Attained age, sex, year of birth, pack-years smoked, years since quit smoking	Lung mortality	1090	-0.2 (<0, ~~0.~~1.3)	Interaction between radiation and smoking appeared sub-multiplicative
South Korea diagnostic medical radiation workers						
Lee *et al* (2021) (*588*)	1996-2017	Attained age, sex, birth year, employment duration	All solid cancer incidence	3220	1.5 (-2.0, 5.1)	Using 5-year lagged colon dose for solid cancers, 2-year lagged RBM dose for hematopoietic cancers
			Breast cancer incidence	326	-3.8 (-6.8, -0.8)	
			Leukemia incidence	58	-5.4 (-35.4, 24.5)	
			NHL incidence	61	-4.1 (-28.8, 20.7)	
			Thyroid cancer incidence	986	-3.1(-12.4, 6.2)	
			Brain/CNS cancer incidence	43	-2.9 (-31.4, 25.5)	
			Non-melanoma skin cancer incidence	38	-3.8 (-21.7, 14.1)	
			Lung cancer incidence	159	11.5 (-7.1, 30.2)	
China diagnostic medical radiation workers						

Author, year, reference	**Follow-up years**	**Adjustments**	**Outcomes**	**Number of cases or deaths**	**ERR / Gy (95% CI)**	**Comments**
Sun *et al* (2016) (*589*)	1950-1995	Attained age, sex, birth year~~Sex averaged~~	All solid cancer incidence	795 in exposed cohort	0.87 (0.48, 1.45)	Using 5-year lagged colon dose
					0.30 (0.17, 0.51)	Using 5-year lagged badge dose
Non-cancer risks						
US Radiologic Technologists						
Little *et al* (2018) (*522*)	1994-2012	Diabetes, BMI, smoking, race, sex, birth year, cumulative UVB exposure	Cataract incidence	12,336	0.69 (0.27, 1.16	Using 5-year lagged eye lens dose
			Cataract incidence < 100 mGy	9264	1.16 (0.11, 2.31)	
			Cataract surgery	5509	0.34 (-0.19, 0.97)	
Little *et al* (2018) (*590*)	1994-2012 or 2003-2012	Stratification by sex, race, birth year and adjustment for diabetes, BMI, smoking	Glaucoma incidence	1631	-0.57 (-1.46, 0.60)	Using 5-year lagged eye lens dose
			Macular degeneration incidence	1331	0.32 (-0.32, 1.27)	
South Korea diagnostic medical radiation workers						
Cha *et al* (2020) (*520*)	2006-2016	Attained age, sex, birth year	All CVD morbidity (ICD10 I00-I99)	2270	1.4 (-5.7, 9.9)	Using 10-year lagged heart dose
			Hypertension morbidity (ICD10 I10-I15)	955	-1.8 (-10.6, 9.7)	Using 10-year lagged heart dose
			IHD morbidity (ICD10 I20-I25)	190	12.2 (-7.1, 47.3)	Using 10-year lagged heart dose
			CeVD morbidity (ICD10 I60-I69)	109	31.0 (-7.5, 115.9)	Using 10-year lagged heart dose
			Others (ICD10 I70-I99)	755	-0.6 (-15.7, 21.7)	Heart dose
South Korea male diagnostic medical radiation workers						

Author, year, reference	**Follow-up years**	**Adjustments**	**Outcomes**	**Number of cases or deaths**	**ERR / Gy (95% CI)**	**Comments**
Bang *et al* (2023) (*591*)	1996-2019	Attained age, birth year, duration of employment, smoking, alcohol, duration of sleep, shift work	All CVD mortality	320	8.1 (-1.1, 17.4)	Using 10-year lagged heart dose
			IHD mortality	124	11.6 (-6.7, 29.9)	Using 10-year lagged heart dose
			CeVD mortality	98	2.7 (-4.1, 9.6)	Using 10-year lagged thyroid dose

Notes: BMI: body mass index; CeVD: cerebrovascular disease; CI: confidence intervals; CLL: chronic lymphocytic leukemia; CNS: central nervous system; CVD: cardiovascular disease; ERR: excess relative risk; ICD: International Classification of Diseases; IHD: ischemic heart disease; MM, multiple myeloma; NHL: non-Hodgkin lymphoma; UVB: ultraviolet B; UVR: ultraviolet radiation.

Table 13. Cancer and non-cancer risk in groups other than INWORKS, Mayak PA, MPS, uranium miners and workers, medical radiation workers exposed to radiation

Author, year, reference	Follow-up	Adjustments used	Outcome (mortality unless otherwise indicated)	ERR/Gy (95% CI)[a]	Number of deaths or cases	Comments
			Cancer risk			
Ahn *et al* (2008) (*594*)	1992–2004	age, calendar period, employment sector	all cancer	7.2 (–5, 21)[b]	256	Korean radiation workers exposed 1984–2004, both sexes (86.9% male); linear model, 1-year lag for leukemia, 5-year lag for all other cancers
			lung cancer	1.2 (–5, 52)[b]	38	
			all leukemias	16.8 (–34, 149)[b]	9	
			I~~i~~ncidence: all cancers	2.6 (–4, 10)[b]	564	
			I~~i~~ncidence: lung cancer	–2.5 (–6, 38)[b]	46	
			I~~i~~ncidence: all leukemias	15.8 (–31, 108)[b]	14	
Akiba and Mizuno (2012) (*597*)	1991–2002	age, calendar period, area of residence	all cancers excluding leukemia	1.26 (–0.27, 3.00)	2,636	Japanese male nuclear workers exposed 1957–2002; linear model, 2-year lag for leukemia, 10-year lag for others
			lung cancer	–0.73 (–3.32, 2.79)~~[b]~~	560	
			all leukemias	–1.93 (–6.12, 8.57)~~[b]~~	80	
Dreger *et al* (2020) (*613*)	1960–2014	age, calendar period, employment status	solid cancer among male cockpit crew	RR at 10 mSv: 0.93 (0.83, 1.04)	195	German aircrew first employed 1960–1997, both sexes (63.7% female); loglinear model; 10-year lag
			solid cancer among female cabin crew	RR at 10 mSv: 1.04 (0.94, 1.14)	213	
			solid cancer among male cabin crew	RR at 10 mSv: 1.04 (0.93, 1.16)	72	
			melanoma among male cockpit crew	RR at 10 mSv: 1.29 (0.78, 2.40)	10	
Friedman-Jimenez *et al* (2022) (*830*)	1969–1995	Age, time since hire, time onboard,	solid cancers	5.2 (–3, 18)	492	US male submariners serving between 1969–1982; linear
			lung cancer	4.5 (–10, 19)	159	

Author, year, reference	Follow-up	Adjustments used	Outcome (mortality unless otherwise indicated)	ERR/Gy (95% CI) [a]	Number of deaths or cases	Comments
		attendance at nuclear power school	leukemia excluding CLL	0.3 (–29, 30)	46	model; 2-year lag for leukemia, 10-year lag for others
Hammer *et al* (2012) (*606*)	1960–2004	age, calendar period, employment status	all cancer	RR at 10 mSv: 1.05 (0.91, 1.20)	127	German male airline pilots employed 1960–1997; loglinear model; 10-year lag
			lung cancer	RR at 10 mSv: 1.00 (0.69, 1.46)	17	

Author, year, reference	Follow-up	Adjustments used	Outcome (mortality unless otherwise indicated)	ERR/Gy (95% CI) [a]	Number of deaths or cases	Comments
Jeong *et al* (2010) (*596*)	1992–2005	age, birthyear, monitoring status, smoking	I~~i~~ncidence: all cancers	1.69 (–2.07, 8.21)	99	Korean male NPP workers employed 1978–2005; linear model; 10-year lag
			I~~i~~ncidence: lung cancer	–0.58 (NE, 19.59)	10	
Kudo *et al* (2018) (*599*)	1999–2010	age, calendar period, birthyear, area of residence, smoking	all cancers excluding leukemia	0.29 (–0.81, 1.57)[b]	1,326	Japanese male nuclear workers; linear model; 2-year lag for leukemia, 10-year lag for others
			lung cancer	0.94 (–1.24, 3.90)[b]	319	
			leukemia excluding CLL	–2.00 (–5.68, 1.68)[b]	44	
Pukkala *et al* (2012) (*607*)	1953–2005	age, calendar period, parity (breast cancer only)	Incidence: leukemia excluding CLL	OR at 10 mSv: 1.66 (0.77, 3.55)	9	Multinational (Finland, Iceland and Sweden) nested case-control study of female airline crew; loglinear model; 10-year lag
			Incidence: breast cancer	OR at 10 mSv: 0.98 (0.80, 1.20)	152	
Tao *et al* (2023) (*831*)	1957–2011	age, sex, race, age at first exposure, calendar period, SES, solvent exposure	leukemia excluding CLL	1.78 (–0.85, 4.40)	446	US nuclear shipyard workers, exposed between 1945–2011; linear model; 2-year lag
			AML	3.08 (–1.17, 7.32)	208	
			ALL	–0.46 (–3.44, 2.52)	19	
			CML	3.56 (–5.16, 12.27)	57	
			CLL	–0.46 (–3.13, 2.21)	99	
			multiple myeloma	0.04 (–2.69~~70~~, 2.77~~8~~)	263	
			non-Hodgkin lymphoma	2.27 (–0.28, 4.81)	511	
			Non-cancer risk			
Hammer *et al* (2012) (*606*)	1960–2004	age, calendar period, employment status	cerebrovascular disease	RR at 10 mSv: 0.65 (0.44, 0.96)	24	German male airline pilots employed 1960–1997; loglinear model; 10-year lag
			cardiovascular disease	RR at 10 mSv: 0.78 (0.65, 0.94)	93	

Author, year, reference	Follow-up	Adjustments used	Outcome (mortality unless otherwise indicated)	ERR/Gy (95% CI) [a]	Number of deaths or cases	Comments
Kudo *et al* (2018) (*599*)	1999–2010	age, calendar period, birthyear, area of residence, smoking	smoking-related non-cancer disease [c]	0.79 (–0.84, 2.80) [b]	624	Japanese male nuclear workers; linear model; 10-year lag
			nonsmoking-related noncancer disease [c]	–0.24 (–2.04, 2.25) [b]	380	

Notes: ALL: acute lymphocytic leukemia; AML: acute myeloid leukemia; CI: confidence intervals; CLL:~~;~~ chronic lymphocytic leukemia; CML: chronic myeloid leukemia; ERR: excess relative risk; RR: relative risk; NE: not estimable; NPP: nuclear power plant; OR: odds ratio; RR: relative risk; SES: socioeconomic status; US: United States.

[a] Unless otherwise indicated.

[b] 90% confidence interval.

[c] Smoking-related diseases included ischemic heart disease, cerebrovascular disease, abdominal aortic aneurysm, pneumonia, chronic obstructive pulmonary disease, and digestive ulcer. Nonsmoking diseases included circulatory diseases, respiratory diseases and digestive diseases other than those listed as smoking-related.

Table 14. Results of combined analyses of residential radon and lung cancer

Author, year, reference	**Study description (component study populations)**	**ERR/Bq m^{-3} or EOR/ Bq m^{-3} for lung cancer (95% CI)**	**Cases / controls**	**Comments**
Darby *et al* (2005, 2006) (*96, 634*)	Based on data from 12 case-control studies and one cohort study in Europe (in Austria, Czech Republic, Finland, France, Germany, Italy, Spain, Sweden & UK).	0.08 (0.03, 0.16)	7148 / 14,208	Risk estimate is unadjusted for radon measurement errors.
Krewski *et al* (2005, 2006) (*97, 635*)	Based on data from seven case-control studies in North America (in Connecticut, Iowa, Missouri, New Jersey, Utah/South Idaho and Winnipeg).	0.11 (0.00, 0.28)	3662 / 4966	Risk estimate is based on subjects with α-track radon measurements within the previous 5-30 years. Estimate is unadjusted for radon measurement errors.
Lorenzo-González *et al* (2020) (*637*)	Based on data from three case-control studies in Northwest Spain.	Not reported. OR for >200 Bq m^{-3} relative to <50 Bq m^{-3} was 2.06 (1.61, 2.64)	1842 / 1862	Data from one of the studies in this pooling were also included in the European combined analysis. No adjustment was made for radon measurement errors.
Lubin *et al* (2004) (*636*)	Based on data from two case-control studies in China (in Gansu and Shenyang)	0.13 (0.01, 0.36)	1050 / 1996	Risk estimate is unadjusted for radon measurement errors.

Notes: CI: confidence intervals; EOR: excess odds ratio; ERR: excess relative risk; OR: odds ratio.

Table 15. Nationwide Register-based Studies of Natural Background Radiation and childhood leukemia and CNS Tumors

		Leukemias			**CNS Tumors**		
Author, year, reference	**Country**	**Cases**	**ERR, Radon (95% CI)**	**ERR, γ (95% CI)**	**Cases**	**ERR, Radon (95% CI)**	**ERR, γ (95% CI)**
Raaschou-Nielsen *et al* (2008) (*644*)	***Denmark***	1153	0.34 (-0.03, 0.85)[a]		922	-0.08 (-0.31, 0.22)[a]	
Nikkilä *et al* (2016) (*649*)	***Finland***	1093		-0.03~~1~~ (-0.11~~03~~, 0.06~~5~~)[e]			
Nikkilä *et al* (2020) (*653*)	***Finland***	1093	-0.06 (-0.36, 0.37)[a]				
Demoury *et al* (2017) (*650*)	***France***	2763	0.00 (-0.03, 0.02)	0.00 (-0.01, 0.01)			
Berlivet *et al* (2020) (*651*)	***France***				5471	0.02 (-0.04, 0.07)[b]	0.03 (-0.02, 0.09)[e]
Spix *et al* (2017) (*652*)	***Germany***	13,374		0.04 (-0.09, 0.20)[d]	9048		0.35 (0.17, 0.57)[d]
Kendall *et al* (2013) (*647*)	***Great Britain***	9058	0.03 (-0.04, 0.11)	0.12 (0.03, 0.22)	6585	0.15 (-0.12, 0.50)	0.02 (-0.04, 0.09)[c]
Hauri *et al* (2013) (*648*)	***Switzerland***	283	-0.10 (-0.32, 0.19)[b]		258	0.19 (-0.09-0.57)[b]	
Mazzei-Abba *et al* (2021) (*654*)	***Switzerland***	951		0.06 (0.01, 0.10)[c]	701		0.06 (0.01, 0.11) [c]

Notes: CI: confidence intervals; CNS: central nervous system; ERR: excess relative risk.

Data are excess relative risk (or excess odds ratio) per mSv cumulative equivalent dose to the red bone marrow unless otherwise stated

[a] per 10^3 Bq m^{-3} years

[b] per 10^2 Bq m^{-3}

[c] per mSv cumulative effective dose (whole body)

[d] Comparing 1.5 vs 0.5 mSv/a for acute lymphoid leukemia and for all CNS tumors

[e] per 50 nSv

Table 16. Cancer and non-cancer risk in other environmentally exposed groups

Author, year, reference	Study description (component study populations)	Endpoint	ERR/Gy or EOR/Gy (95% CI)	Cases/ deaths	Comments (using the appropriate organ dose, unless otherwise indicated)
Cancer risk					
Jayalekshmi *et al* (2021) (*661*)	Kerala incidence follow-up 1990-2017	Cancers excluding leukemia	-0.05 (-0.33, 0.29)	6804	Using 10-year lagged colon dose, adjusted for smoking, tobacco chewing, alcohol consumption
Schonfeld *et al* (2013) (*676*)	Techa River mortality follow-up 1950-2007	All solid cancer	0.61 (0.04, 1.27)	2303	Using 5-year lagged stomach dose
Krestinina *et al* (2013) (*105*)	Techa River incidence follow-up 1953-2007	Chronic lymphocytic leukemia (CLL)	0.1 (<0, 1.2)	27	Using 2-year lagged RBM dose
		Leukemia other than CLL	2.2 (0.8, 5.4)	72	
		Chronic myeloid leukemia	3.1 (0.5, 18)	25	
		Acute/subacute leukemia	1.8 (0.4, 5.9)	41	
Hsieh *et al* (2017) (*674*)	Taiwan ^{60}Co rebar incidence, exposed 1982 - early 1990s and followed 1982-2012	Leukemia excluding CLL	1.5 (0.3, 2.4)[a]	11	Using 2-year lagged dose
		Female breast cancer	1.2 (0.4, 1.7)[a]	40	Using 5-year lagged dose
		All solid cancer	0.4 (0.1, 0.8)[a]	274	Using 5-year lagged dose
		All cancer	0.5 (0.0, 0.8)[a]	282	Using 2-year lagged dose for leukemia, 5-year lagged dose for solid cancer
Davis *et al* (2004) (*677*)	Hanford thyroid study	All thyroid neoplasia (19 thyroid cancer, 14 benign adenoma)	~0.7~~1~~ (NS)	33	

Lyon *et al* (2006) (*704*)	Nevada test site thyroid disease study following exposure in childhood	Thyroid nodules	4.65 (1.1~~7~~, 12~~9~~.3)	49	
		Non-neoplastic nodules	1.82 (0.0, 8.3)	32	
		Thyroid neoplasms	13.02 (2.7, 68.7)	20	
		Benign thyroid neoplasms	*p*-trend = 0.000117	13	
		Thyroid cancer	0.8 (0.0, 14.9)	8	
		Thyroiditis	4.9 (2.0, 10.0)	123	
		Thyroiditis with hypothyroidism	2.89 (0.0, 11.7)	35	
		Any thyroid disease	2.37 (0.9, 4.6)	220	
Bauer *et al* (2005) (*706*)	Semipalatinsk residents exposed via USSR atmospheric nuclear tests and control regions	All solid cancer	1.77 (1.35, 2.27)	889	Unlagged external γ ray dose
		Esophageal cancer	2.37 (1.47, 3.63)	317	
		Stomach cancer	1.68 (0.83, 2.99)	150	
		Liver cancer	0.45 (-0.18, 1.71)	60	
		Lung cancer	2.60 (1.38, 4,63)	130	
		Female breast cancer	1.28 (0.27, 3.28)	61	
	Semipalatinsk residents exposed via USSR atmospheric nuclear tests only	All solid cancer	0.81 (0.46, 1.33)	532	
		Esophageal cancer	0.18 (-0.09, 0.66)	NA	
		Stomach cancer	0.95 (0.17, 3.49)	NA	
		Liver cancer	-0.08 (-0.41, 1.00)	NA	
		Lung cancer	1.76 (0.48, 8.~~,~~83)	NA	
		Female breast cancer	1.09 (-0.05, 15.8)	NA	
		Male thyroid nodule	4.83 (2.48, 9.33)	177	

Land *et al* (2015) (*146*)	Semipalatinsk residents exposed under age 21 via USSR atmospheric bomb tests	Female thyroid nodule	0.07 (-0.08, 0.29)	571	Using likelihood-based methods, with mean dose
		Male thyroid nodule	9.99 (2.33, 19.07)	177	Using Bayesian model averaging
		Female thyroid nodule	0.35 (0.00, 1.00)	571	
de Vathaire *et al* (2023) (*708*)	Residents of French Polynesia exposed to French nuclear tests	Differentiated thyroid cancer	40 (-90, 170)	395 cases, 555 controls	Case-control study, in relation to thyroid dose received before age 15
		Differentiated thyroid cancer excluding unifocal noninvasive microcarcinoma	110 (-150, 360)	258 cases, 359 controls	
Non-cancer risk					
Cardiovascular disease					
Krestinina *et al* (2013) (*483*)	Techa River mortality follow-up 1950-2003	Cardiovascular disease	18 (-13, 52)	7595	Using 5-year lagged muscle dose
			24 (-8, 59)		Using 10-year lagged muscle dose
			36 (2, 75)		Using 15-year lagged muscle dose
			46 (9, 88)		Using 20-year lagged muscle dose
		Ischemic heart disease	26 (-22, 81)	3194~~1933~~	Using 5-year lagged muscle dose
			40 (-11, 99)		Using 10-year lagged muscle dose
			56 (1, 119)		Using 15-year lagged muscle dose
			77 (17, 147)		Using 20-year lagged muscle dose
Grosche *et al* (2011) (*710*)	Semipalatinsk nuclear test study	Heart disease (ICD9 410-429): all settlements	3.22 (2.33,~~ to~~ 4.10)	1721	

		Heart disease (ICD9 410-429): exposed settlements	0.06 (-0.39,~~ to~~ 0.52)	878	Using 10-year lagged external dose, adjusted for ethnic group, settlement status
		Stroke (ICD9 430-438): all settlements	2.96 (1.77,~~ to~~ 4.14)	839	
		Stroke (ICD9 430-438): exposed settlements	-0.06 (-0.65,~~ to~~ 0.54)	453	
		Cardiovascular disease (ICD9 390-459): all settlements	3.15 (2.48,~~ to~~ 3.81)	2856	
		Cardiovascular disease (ICD9 390-459): exposed settlements	0.02 (-0.32,~~ to~~ 0.37)	1498	
Markabayeva *et al* (2018) (*711*)	Semipalatinsk nuclear test hypertension study	Essential hypertension prevalence (ICD10 I10)	3.528 (-3.188,~~ to~~ 10.245)[c]	655	Using effective dose, adjusted for smoking, BMI, total cholesterol, alcohol consumption
Semenova *et al* (2022) (*712*)	Semipalatinsk nuclear test stroke study	Ischemic stroke prevalence	15.70 (2.11,~~ to~~ 29.30)[c]	6830	Using effective dose, adjusted for diabetes, obesity, hypertension, atrial fibrillation, chronic heart failure, recurrent stroke, urban-rural status, income
		Haemorrhagic stroke prevalence	17.44 (-11.50,~~ to~~ 46.38)[c]	1281	
Cataract					
Su *et al* (2021) (*714*)	Chinese high natural background radiation area	Posterior subcapsular cataract	7.3 (0.5, 18.5)	23	Lens opacity determined using slit lamp and graded using LOCS III system.
		Cortical cataract	2.6 (0.0, 6.0)	101	
		Nuclear cataract	-1.9 (-3.6, 0.1)	245	

Notes: BMI: body mass index; EOR: excess odds ratio; ERR: excess relative risk; ICD: International Classification of Diseases; LOCS: Lens Opacity Classification System; NS: not significant; RBM: red bone marrow.

[a] 90% CI

[b] estimate derived via~~by~~ fitting a linear model by (inverse-variance) weighted least squares, applied to the adjusted odds ratio (OR) provided in Table 2 of Markabayeva *et al* (*711*). Median cardiac doses of 0.009, 0.041, 0.070, and 0.326 Sv were assumed for the respective groups with the following specified ranges of effective doses: <20, 20-59, 60-185, >185 mSv, as given by Markabayeva *et al* (*711*).

[c] estimate derived via~~by~~ fitting a linear model by (inverse-variance) weighted least squares, applied to the adjusted hazard ratio (HR) provided in Table 5 of Semenova *et al* (*712*). Mean doses of 0.01, 0.04, 0.123, and 0.3 Sv were assumed for the respective groups with the following specified ranges of effective doses: <20, 20-59, 60-185, >186 mSv, as given by Semenova *et al* (*712*).

Table 17. Results of pooled analyses of cancer and non-cancer risk

Author, year, reference	Study description (component study populations)	Endpoint	ERR/Gy or EOR/Gy (95% CI)	Cases/deaths	Comments (using the appropriate organ dose, unless otherwise indicated)
		Cancer risk			
		Leukemia			
Little *et al* (1999) (*185*)	Three cohort analysis (LSS, IRSCCP, ankylosing spondylitis)	AML	4.00 (NA)	204	Quadratic-exponential dose response, adjusted for time since exposure (ALL, CML) or attained age (AML), ERR evaluated at 1 Gy, 25 y after exposure, attained age 50 y, using ABM dose
		CML	2.75 (NA)	100	
		ALL	1.33 (NA)	52	
Little *et al* (2023) (*720*)	10 cohort analysis, childhood exposed, excluding those treated for malignant disease, full range of estimated exposures	AML+MDS	1.43~~0~~ (0.59~~86~~, 2.72~~5~~)	158	Using ABM dose
		AML	1.48~~75~~ (0.59~~1~~, 2.85~~47~~)	140	
		CML	1.77~~69~~ (0.384, 4.504)	61	
		ALL	6.654 (2.79~~2~~, 14.83)	71	
Little *et al* (2018) (*721*)	10 cohort analysis, childhood exposed, excluding those treated for malignant disease, < 0.1 Gy	AML+MDS	20.9 (4.1, 49.2)	87	Using ABM dose
		AML	15.6 (0.9, 40.6)	79	
		CML	-6.4 (<-10, 13.6)	36	
		ALL	46.6 (3.5, 187.1)	40	
		Lymphoma and myeloma			
Little *et al* (2021) (*722*)	9 cohort analysis, childhood exposed, excluding those	NHL	0.068 (0.253, 0.421)	422	Using ABM dose
		CLL	0.320 (-0.678, 1.712)	66	
		NHL+CLL	0.099 (-0.149, 0.433)	488	

	treated for malignant disease	HL	-0.113 (-0.669, 0.709)	107	
		MM	0.149 (-0.513, 1.063)	122	
Little *et al* (2021) (*722*)	6 cohorts from 9 cohort analysis with information on lymphatic tissue dose, childhood exposed, excluding those treated for malignant disease	NHL	0.631 (-0.045, 1.704)	342	Using lymphatic tissue dose
		CLL	4.511 (-0.031, 20.020)	34	
		NHL+CLL	0.790 (0.083, 1.882)	376	
		HL	0.492 (-2.426, 5.855)	71	
		MM	0.281 (-1.130, 2.489)	96	
Schüz *et al* (2017) (*723*)	Mayak worker and Techa River *in utero* exposure	All hematolymphoid malignancy mortality	1.6 (-0.9, 11.9)	36	
	Mayak worker and Techa River postnatal exposure		0.8 (-0.5, 7.2)	36	
	Mayak worker and Techa River *in utero* exposure	Leukemia mortality	-0.9 (NA, 13.3)	23	
	Mayak worker and Techa River postnatal exposure		2.2 (-0.3, 13.2)	23	
	Mayak worker and Techa River *in utero* exposure	All hematolymphoid malignancy incidence	7.7 (0.2, 25.6)	58	
	Mayak worker and Techa River postnatal exposure		2.1 (-0.5, 11.0)	58	
	Mayak worker and Techa River *in utero* exposure	Leukemia incidence	4.0 (0.7, 24.1)	28	

	Mayak worker and Techa River postnatal exposure		1.7 (-0.5, 12.4)	28	
	Mayak worker and Techa River *in utero* exposure	Lymphoma incidence	9.0 (-0.9, 56.6)	28	
	Mayak worker and Techa River postnatal exposure		3.7 (-0.5, 36.1)	28	
Thyroid cancer					
Veiga *et al* (2016) (*725*)	12 cohorts	Thyroid cancer	6.5 (5.1, 8.5)	1070	ERR at 1 Gy, without an exposure indicator for the Israeli tinea study
Lubin *et al* (2017) (*726*)	9 cohorts with cumulative dose < 0.2 Gy		11.1 (6.6, 19.7)	252	
	9 cohorts with cumulative dose < 0.1 Gy		9.6 (3.7, 17.0)	184	
		Breast cancer			
Little and Boice (1999) (*244*)	Massachusetts TB fluoroscopy and LSS incidence	Breast cancer	1.25 (0.89, 1.69)	758	Breast cancer adjusted to attained age 50
Preston *et al* (2002) (*428*)	8 cohort analysis		0.97 (0.8, 1.3)	1502	Simple pooled ERR model adjusted for attained age, adjusted for attained age 50

Notes: ABM: active bone marrow; ALL: acute lymphocytic leukemia; AML: acute myeloid leukemia; CI: confidence interval; CLL: chronic lymphocytic leukemia; CML: chronic myeloid leukemia; EOR: excess odds ratio; ERR: excess relative risk; HL: Hodgkin lymphoma; IRSCCP: International Radiation Study of Cervical Cancer Patients; LSS: Life Span Study; MDS: myelodysplastic syndromes; MM: multiple myeloma; NA: not available; NHL: non-Hodgkin lymphoma; TB: tuberculosis.

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