

A New Era of Low-Dose Radiation Epidemiology

Cari M. Kitahara¹ · Martha S. Linet² · Preetha Rajaraman³ · Estelle Ntowe⁴ · Amy Berrington de González⁵

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Abstract The last decade has introduced a new era of epidemiologic studies of low-dose radiation facilitated by electronic record linkage and pooling of cohorts that allow for more direct and powerful assessments of cancer and other stochastic effects at doses below 100 mGy. Such studies have provided additional evidence regarding the risks of cancer, particularly leukemia, associated with lower-dose radiation exposures from medical, environmental, and occupational radiation sources, and have questioned the previous findings with regard to possible thresholds for cardiovascular disease and cataracts. Integrated analysis of next generation genomic and epigenetic sequencing of germline and somatic tissues could soon propel our understanding further regarding disease risk thresholds, radiosensitivity of population subgroups and individuals, and the mechanisms of radiation carcinogenesis. These advances in low-dose radiation epidemiology are critical to our understanding of chronic disease risks from the burgeoning use of newer and emerging medical imaging tech-

nologies, and the continued potential threat of nuclear power plant accidents or other radiological emergencies.

Keywords Ionizing radiation · Neoplasms · Cardiovascular diseases · Cataract · Epidemiology

Introduction

The characterization of ionizing radiation as an important human carcinogen, which can cause cancer in the majority of organs, was a major achievement of epidemiological and experimental radiation studies in the twentieth century. Although most national and international committees that have reviewed the epidemiological and biological data conclude that the evidence *supports* the linear no-threshold model for radiation protection, the evidence does not directly *prove* it with full certainty [1–3]. The linear no-threshold model as-

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✉ Cari M. Kitahara
kitaharac@mail.nih.gov

Martha S. Linet
linetm@mail.nih.gov

Preetha Rajaraman
rajarama@mail.nih.gov

Estelle Ntowe
estelle.ntowe@nih.gov

Amy Berrington de González
berringtona@mail.nih.gov

¹ Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 9609 Medical Center Drive, Rm 7E566, Rockville, MD 20850, USA

² Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 9609 Medical Center Drive, Rm 7E458, Rockville, MD 20850, USA

³ Center for Global Health, National Cancer Institute, 9609 Medical Center Drive, Rockville, MD 20850, USA

⁴ Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 9609 Medical Center Drive, Rm 7E550, Rockville, MD 20850, USA

⁵ Radiation Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, 9609 Medical Center Drive, Rm 7E452, Rockville, MD 20850, USA

sumption is that there is no dose below which there is no cancer risk. The dose at which there is considered to be *direct* evidence of an increased risk of cancer has been very gradually lowered by extensive research to about 50–100 mGy [4]. In addition, there is emerging evidence that the threshold for other stochastic late effects may be lower than originally observed [5]. Many have questioned whether radiation epidemiology has reached its limits in characterizing risks at the lower dose range and assumed that further material advancements were unlikely. In the last decade, however, changing patterns of exposure and technological advances have supported a new era of large-scale radiation epidemiology studies of medically, environmentally, and occupationally exposed populations, and it is those studies and advances that we highlight in this review.

We focus our review on key epidemiologic studies (see Tables 1 and 2 for details) identified from PubMed and published since the most recent major national/international reports, such as BEIR VII phase 2 [1] and the UNSCEAR 2006 Report [2]. The studies highlighted in this review were selected based on the contributions that they have made to the following fundamental questions:

- Is the linear no-threshold assumption reasonable?
- Can low-doses of radiation cause stochastic effects other than tumors, including circulatory diseases and cataracts?
- What is the potential public health impact of the changing patterns of low-dose radiation exposure?
- How could next generation genomic and epigenetic sequencing of germline and somatic tissues produce a paradigm shift in the field?

From Environmental to Medical Radiation Exposure and Back Again

In the early 1980s, natural background radiation exposure, primarily from indoor radon, was estimated to be the predominant source of exposure to the US population, and the estimated per capita annual dose was 3.6 mSv. By 2006, the estimated per capita dose had nearly doubled to 6.2 mSv per year [6] (Fig. 1). The increase was entirely due to the revolution in medical imaging, particularly computed tomography (CT scans), which rose from 3 million to 70 million scans per year over those three decades in the USA. CT scans save lives and reduce unnecessary medical procedures, but the associated radiation exposure is an order of magnitude higher than a conventional X-ray. The greatest concerns were raised about overuse of CT scans in children, because of their greater radiosensitivity [1] and because exposure settings were not optimized for their smaller body size [7]. These concerns prompted the establishment of a series of retrospective cohort

epidemiological studies in Europe, Australia, Israel, and North America to directly assess the potential cancer risks [8, 9–11]. Other higher-dose evolving diagnostic procedures, such as nuclear medicine and interventional procedures, have also increased over the same period and now account for 26 and 14 % of the collective effective doses from medical sources in the US [5]. Unlike CT scans, these procedures also present increased occupational radiation exposure levels to the physicians and technologists who perform them [12, 13]. Concerns about the higher exposures and risks of cancer and other radiation-related disease risks to medical workers have resulted in the establishment of new retrospective cohort epidemiologic studies for groups, such as cardiologists and radiologic technologists, who perform these procedures [12, 14].

In 2011, the Fukushima nuclear accident in Japan returned the spotlight to environmental radiation exposure. This event not only prompted an immediate need to assess potential risks to the exposed Japanese population [15], but also served as an important reminder of the possible risks to populations surrounding every nuclear power plant. Epidemiological studies based on the Chernobyl accident have been reinvigorated as they can provide information used to estimate the long-term impact of internal radiation exposure from Fukushima and potential future accidents [16].

Exposure Assessment

Accurate estimation of organ or tissue doses from exposure to ionizing radiation and assessment of uncertainties in dose estimation are critical for quantifying radiation-associated health risks in epidemiologic studies. The key measure of dose in epidemiologic studies is absorbed dose, defined as the energy imparted within a given volume and averaged over the mass of an organ (e.g., “organ dose”) measured in Gray (Gy). Biologic effects caused by ionizing radiation derive primarily from damage to DNA and differ by radiation type (e.g., photons, electrons, protons, neutrons or alpha particles) and energy level. Equivalent or radiation-weighted dose incorporates the differences in biologic effects of these different types of radiation by multiplying the absorbed dose by a radiation weighting factor, which places these effects from exposure to different types of radiation on a common scale using a metric designated as Sievert (Sv).

Notable improvements in dose estimates for individuals in epidemiological studies have derived from more sophisticated understanding of the need to assess radiation type and energy level and exposure conditions (e.g., external vs internal, the geometry of exposure conditions, and anatomic site) and individual characteristics [17–19]. It is also important to capture temporal characteristics (e.g., age and time since first exposure), all sources of individual exposure, biologically relevant latency periods, and to incorporate sources of uncertainty for

Table 1 Summary of select publications on low-dose radiation and cancer published after 2006

First author, year	Design	Study population	Follow-up	Age at exposure	Exposure assessment	Doses	Effect estimate
Medical exposures							
Ronekers, 2008	Cohort	3,010 women with spinal curvature	Spinal curvature diagnosis (1912–65) through survey/interview (1992–93)	0–19 years	Medical record abstraction, doses estimated from radiographs	Mean cumulative dose to breast=12.1 cGy	Breast cancer incidence =ERR/Gy=2.86, 95 % CI -0.07, 8.62
Rajaraman, 2010	Case-control	2,690 childhood cancer cases; 4,858 controls from UK Childhood Cancer Study	n/a	In utero or early infancy (0–100 days)	Medical record abstraction, any vs no exposure to diagnostic X-rays	Not available	All cancer incidence=OR (in utero)=1.14, 95 % CI 0.90, 1.45; OR (infancy)=1.16, 95 % CI 0.83, 1.62 Leukemia incidence=OR (in utero)=1.36, 95 % CI 0.91, 2.02; OR (infancy)=1.39, 95 % CI 0.87, 2.23 Acute myeloid leukemia incidence=(in utero)=1.36, 95 % CI 0.91, 2.02; OR (infancy)=1.63, 95 % CI 0.42, 6.35
Pearce, 2012	Cohort	>175,000 patients in Great Britain who underwent a CT scan in childhood/adolescence	CT scan year (1985–2002) through 2008	0–21 years	Medical record abstraction, RBM, and brain doses estimated from CT scans	Not provided	Leukemia and myelodysplasia incidence=ERR/mGy=0.036, 95 % CI 0.005, 0.120 Brain tumor incidence=ERR/mGy=0.023, 95 % CI 0.010, 0.049
Mathews, 2013	Cohort	Individuals from Australian Medicare records, exposed ($n=680,000$) and unexposed (>10,000,000) to CT scans in childhood/adolescence	CT scan year (1985–2005) through 2007	0–19 years	Medical record abstraction, effective, RBM, and brain doses estimated from CT scans	Collective effective dose (1-year lag)=3900 Sv (4.5 mSv per scan)	Solid cancer incidence (other than brain cancer)=ERR/mGy=0.027, 95 % CI 0.017, 0.037 Leukemias and myelodysplasia incidence=ERR/mGy=0.039, 95 % CI 0.014, 0.070 Brain cancer incidence=ERR/mGy=0.021, 95 % CI 0.014, 0.029
Environmental exposures							
Krestinina, 2013	Cohort	28,223 residents of the Russian Southern Urals exposed to multiple radionuclides, primarily strontium, from production of nuclear weapons	1953–2007	Majority <20 years	TRDS-2009 dosimetry system; based on external and internal dose estimates	Mean cumulative RBM dose=0.42 Gy (range 0–9 Gy)	Leukemia=ERR/mGy=0.12, 95 % CI 0.04, 0.25 Leukemia (excluding CLL)=ERR/mGy=0.22, 95 % CI 0.08, 0.54 Leukemia subtypes also examined (data not shown)
Schonfeld, 2013	Cohort	29,730 residents of the Russian Southern Urals	1950–2007	Majority <20 years	TRDS-2009 dosimetry system; based on	Mean cumulative stomach dose 5 years	

Table 1 (continued)

First author, year	Design	Study population	Follow-up	Age at exposure	Exposure assessment	Doses	Effect estimate
Kendall, 2013	Case-control	exposed to multiple radionuclides, primarily strontium, from production of nuclear weapons 27,447 cancer and non-malignant brain tumor cases and 36,793 controls in Great Britain	n/a	At birth	external and internal dose estimates Exposure from cosmic rays and radon in the home was estimated for residences at birth using the County District mean gamma-ray dose-rates from cosmic rays and exposure to radon and a predictive map based on domestic measurements for radon	prior to end of follow-up=0.035 Gy (range 0–0.96 Gy) Mean cumulative RBM equivalent dose from birth to diagnosis (controls)=4.0 mSv (range=0–31 mSv), with radon contributing about 10 % of the dose, on average	Solid cancer mortality =ERR/Gy=0.61, 95 % CI 0.04, 1.27 Leukemia=ERR/mSv=0.12, 95 % CI 0.03, 0.22 Lymphoid leukemia =ERR/mSv=0.13, 95 % CI 0.02, 0.24
Occupational exposures Cardis, 2007	Collaborative cohort study	407,391 workers in 15 countries from 154 facilities who received exposure predominantly from higher-energy photon radiation (X-ray and gamma), worked in the facility for 1+ years, and monitored for external radiation exposure	Variable	Variable	Dosimetric history was reconstructed using recorded photon doses from individual facilities and/or national dose registries	Mean cumulative dose=19.4 mSv	All-cause mortality=ERR/Sv =0.42, 90 % CI 0.07, 0.79 Cancer mortality=ERR/Sv =0.97, 90 % CI 0.28, 1.77 Leukemia (excluding CLL) mortality=ERR/Sv=1.93, 90 % CI <0, 7.14 Lung cancer mortality =ERR/Sv= 1.86, 90 % CI 0.49, 3.63 Non-significant positive associations for multiple myeloma, liver, and pancreatic cancer mortality (31 malignant cancers examined in total)
Kesminiene, 2008	Nested case-control study	117 leukemia cases, 34 NHL cases, 14 other hematological malignancies and 481 matched controls nested in Belarus, Russian, and Baltic cohorts of Chernobyl liquidators	n/a	Adults	RADRUE used to assess individual dose from external radiation received during clean-up mission; combined work history data with field radioactivity measurements	Average reported doses were 170 mGy in 1986 and decreased from year to year	Leukemia=ERR/100 mGy =0.60, 90 % -0.02, 2.35 Leukemia (excluding CLL) =ERR/100 mGy=0.50, 90 % CI -0.38, 5.70 NHL=ERR/100 mGy =2.81, 90 % CI 0.09, 24.30
Muirhead, 2009	Cohort	174,541 nuclear workers in the National Registry for Radiation Workers (NRRW) in the UK	1955 (or date started working or date from which full dose data were available) through 2001	Adults	Surface exposure from personal dosimeters, mostly X- and γ-rays but also particles and neutrons	Mean cumulative dose=24.9 mSv	Cancer (excluding leukemia) incidence=ERR/Sv=0.27, 90 % CI 0.04, 0.51 Leukemia (excluding CLL) incidence=ERR/Sv=1.78, 90 % CI 0.17, 4.36

Table 1 (continued)

First author, year	Design	Study population	Follow-up	Age at exposure	Exposure assessment	Doses	Effect estimate
Zablotska, 2013	Nested case-control study	137 leukemia cases, 65 CLL cases and 863 controls in the Ukrainian cohort of Chernobyl liquidators	n/a	Adults	RADRUE used to assess individual dose from external radiation received during clean-up mission; combined work history data with field radioactivity measurements	Mean bone marrow dose=132.3 mGy (cases) and 81.8 mGy (controls)	Significant positive associations for rectal cancer, skin cancer, non-melanoma skin cancer, and multiple myeloma incidence (29 malignancies examined in total) Mortality also examined (results not shown) Leukemia=ERR/Gy=2.38, 95 % CI 0.49, 5.87 Leukemia (excluding CLL)=ERR/Gy=2.21, 95 % CI 0.05, 7.61 CLL=ERR/Gy=2.58, 95 % CI 0.02, 8.43

external [20–22] and internal [23] radiation exposures. Since epidemiologic studies are usually launched several years to decades after initial radiation exposure, radiation doses of exposed individuals must be reconstructed for the relevant time period(s) [24–28].

Methods for validation of estimated doses for external irradiation include assessment of chromosomal translocations in lymphocytes and electron paramagnetic resonance of tooth enamel or fingernails [29]. For internal radiation, direct bioassays measure radioactivity in the whole body or specific organs [18].

Limitations of exposure assessment and potential sources of uncertainty in epidemiologic studies of low-dose or low-dose-rate exposures [21–23, 30, 31] include lack of single and repeated measurements at the individual level, inaccurate or incomplete monitoring, and limited information about shielding, individual radiation protection, or behaviors and activities that could influence doses. Failure to identify the many sources of uncertainty, account for the various sources, and incorporate measures to account for shared or unshared sources, may seriously impact individual exposure estimates and disease risk estimates.

The Linear No Threshold Assumption and Cancer Risk

The Life Span Study (LSS) of survivors of the Japanese atomic bombs in 1945 has been foundational for radiation epidemiology because of the large population exposed at all ages to a single acute dose with long-term follow-up and well characterized doses that range from very low to very high. Its power to assess the cancer risk from very low-dose exposure is limited, however, and studies of this population cannot address the question of protracted radiation exposure which are the types of exposures that most of the general population are likely to receive. As reviewed below, recent studies that have directly evaluated cancer risks following relatively low-dose or low-dose-rate exposure to ionizing radiation have overcome some of the limitations of the LSS by compiling larger study populations of the most radiosensitive individuals, incorporating more accurate dose assessments, and assessing cancer types that are relatively uncommon in Japan. Risk of radiation-related outcomes in the LSS and other studies with detailed individual radiation dose information is often estimated by the excess relative risk (ERR), i.e., the proportion of relative risk (RR) due solely to radiation exposure ($ERR=RR-1$).

Medical Exposures

Recent studies of medical radiation exposures, particularly from diagnostic X-rays and CT scans occurring in utero and during childhood/adolescence, have vastly improved

Table 2 Summary of select publications on low-dose radiation and circulatory diseases or cataracts published after 2006

First author, year	Design	Study population	Follow-up	Age at exposure	Exposure assessment	Doses	Effect estimate
Vrijheid, 2007	Collaborative cohort study	275,312 workers in 15 countries from 154 facilities who received exposure predominantly from higher-energy photon radiation (X-ray and gamma), worked in the facility for 1+ years, and monitored for external radiation exposure	Variable	Variable	Dosimetric history was reconstructed using recorded photon doses from individual facilities and/or national dose registries	Mean cumulative dose=20.7 mSv	All non-cancer mortality=ERR/Sv=0.20, 95 % CI -0.26, 0.72 Circulatory disease mortality=ERR/Sv=0.09, 95 % CI -0.43, 0.70 Ischemic heart disease mortality=ERR/Sv=-0.01, 95 % CI -0.59, 0.69 Cerebrovascular disease mortality=ERR/Sv=0.88, 95 % CI -0.67, 3.16
Muirhead, 2009	Cohort	174,541 nuclear workers in the National Registry for Radiation Workers (NRRW) in the UK	1955 (or date started working or date from which full dose data were available) through 2001	Adults	Surface exposure from personal dosimeters, mostly X- and γ -rays but also particles and neutrons	Mean cumulative dose=24.9 mSv	Circulatory disease incidence=ERR/Sv=0.25, 90 % CI 0.03, 0.49

Table 2 (continued)

First author, year	Design	Study population	Follow-up	Age at exposure	Exposure assessment	Doses	Effect estimate
Cataracts Worgul, 2007	Prevalence analysis embedded in a cohort	8607 Chernobyl liquidators who underwent an ophthalmological examination approximately 12 and 14 years after exposure	n/a	Adults	Dosimetry varied by subgroup depending on available exposure information—badge doses, tasks and movements of early on-site liquidators, and group-dosimetry method, group-estimation method, and tooth enamel electron paramagnetic resonance	67 % of workers with lens doses of ≥ 100 mGy	Stage 1 cataract=OR at 1 Gy=1.49, 95 % CI 1.08, 2.06 Stage 2–5 cataract=OR at 1 Gy=1.57, 95 % CI 0.79, 3.11
Chodnick, 2008	Cohort	35,705 US radiologic technologists	1983–2004	Adults (24–44 years at baseline)	Based on lifetime work history, individual film badge readings, and dose estimates from the literature	Mean cumulative lens dose=28.1 mGy	ERR/Gy=1.98, 95 % CI –0.69, 4.65

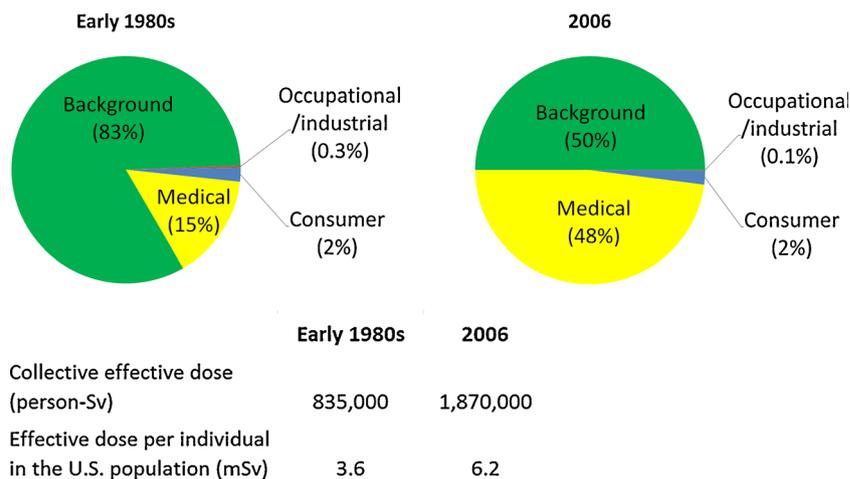
assessment of both exposure and disease by use of medical record abstraction and electronic record linkages. Pearce and colleagues estimated absorbed doses to the red bone marrow (RBM) and brain from CT scans occurring before age 22 years using data abstracted from the medical records of more than 175,000 patients, machine parameters imputed using data from UK-wide surveys (1989–2003), and a series of hybrid computational human phantoms and Monte Carlo radiation transport techniques [8•, 27]. A linear dose–response relationship was observed for increasing radiation dose to the RBM and brain and increased risk of leukemia ($n=74$ cases) and brain tumors ($n=135$ cases), respectively. Risks of both these cancers were approximately tripled for mean organ doses of 50–60 mGy compared with <5 mGy. A subsequent study of cancer risks after CT scan exposure before age 20 in Australia similarly linked medical record information on CT scans with subsequent cancer registrations [9]. This study found increased risks of several cancer types with increasing numbers of CT scans. It is difficult to compare these study findings directly with the LSS or the UK CT study until the ongoing organ-specific dose–response relationships are published. Additional work is ongoing in both these cohorts to evaluate the influence of underlying cancer-predisposing conditions and the indications for the CT scans. Within the next 5 years, there should be results from retrospective pediatric CT cohorts including approximately two million children [32].

In the US Scoliosis Cohort Study, fractionated exposure to radiation from diagnostic X-rays in childhood and adolescence, assessed using individual patient records, was associated with a non-statistically significant increased risk of breast cancer ($n=78$ cases, ERR/Gy=2.86, 95 % CI=0.07, 8.62) [33]. Data from the United Kingdom Childhood Cancer Study showed that any (versus no) exposure from diagnostic X-rays in utero was associated with a non-significant increased risk of childhood cancer ($n=2690$ cases, OR=1.14, 95 % CI 0.90, 1.45), driven largely by a non-significant positive association with leukemia, specifically acute myeloid leukemia (OR=1.36, 95 % CI 0.91, 2.02) [34]. No differences were observed by trimester of first exposure. In the US Radiologic Technologists Study, cohort dose reconstruction is in progress for the self-reported diagnostic medical procedures that will allow assessment of dose–response relationships for thyroid, breast, and other radiosensitive cancers in this unique setting (<http://www.radtechstudy.nci.nih.gov>).

Environmental Exposures

Large-scale record linkage has also resulted in significant improvements in the ability to assess the cancer risks from background radiation exposure. All previous studies of this question were ecological or under-powered [35–40]. In the UK childhood cancer case–control study in Great Britain, natural background exposure from cosmic rays and radon in the home was

Fig. 1 Effective doses to the United States population in the early 1980s and in 2016 by ionizing radiation exposure source [6] (reprinted with permission of the National Council on Radiation Protection and Measurements, <http://NCRPpublications.org>)



estimated for residences at birth using the County District mean gamma-ray dose-rates and a predictive map based on domestic measurements for radon for 27,447 childhood cancer cases and controls [41]. The authors found a significant dose–response for cumulative RBM dose from gamma radiation and childhood leukemia that was driven largely by the most common leukemia subgroup, lymphoid leukemia (mean cumulative equivalent REB dose in controls=4.0 mSv, range=0–31 mSv). These associations were in reasonable agreement with risk predictions based on BEIR VII and UNSCEAR models [1, 2]. No significant associations were observed for gamma-ray or radon exposure with risk of other childhood cancers. The key limitation of the study is that exposure was based on residence at birth, and information on potential confounders (e.g., exposure to ionizing radiation from other sources such as medical exams, predisposing genetic syndromes, and birth weight) was not available except for socioeconomic status based on post-code. More detailed exposure assessment and expansion of the study is in progress. A recent study in Switzerland with a similar design to the UK study found increased risks of total cancer, leukemia, lymphoma, and central nervous system tumors associated with terrestrial and cosmic radiation based on locations of residence [42] and no association between domestic radon exposure and childhood cancer [43].

The Techa River Cohort, comprised of individuals exposed to a wide range of radionuclides following the release of radioactive waste into the Techa River by the Mayak Radiochemical Plant between 1949 and 1956, is one of the few general population studies of protracted environmental radiation exposures with long-term follow-up for cancer. Exposure to strontium has been of particular interest in understanding risks of leukemia as it concentrates in the bone. Using an updated dosimetry system, increased risks consistent with linearity were observed for solid cancer mortality [44], all leukemias, leukemia excluding chronic lymphocytic leukemia (CLL), chronic myeloid leukemia (CML), and acute/subacute leukemias through 2007, but no evidence was found for an increased risk of CLL [45].

Occupational Exposures

Updated analyses based on data from the 15-Country Study of nuclear workers, which includes some data from all of the cohorts from the National Registry for Radiation Workers-3 (NRRW-3) and the 3-Country Study except Rocky Flats, focused particularly on risks of leukemia, leukemia excluding CLL, and cause-specific cancer mortality following chronic, low-dose occupational exposure to radiation [46]. Although limited information was available on potential confounding factors, particularly lifestyle-related exposures such as cigarette smoking, this source of bias would have had less influence on risk estimates of leukemia compared with solid cancers. This study, with a mean cumulative dose of 19.4 mSv, showed a non-significant linear association between radiation exposure and mortality from leukemia excluding CLL. A strong but borderline increased risk was observed for CML mortality (ERR/Sv=10.1, 90 % CI –0.86, 40.2), but no associations were observed for mortality from CLL, ALL, or AML. Significant elevated risks for all-cause mortality, all-cancer mortality, and lung cancer mortality were also observed. However, the excess risk for solid cancer was three times higher than that observed in LSS, and was largely driven by data from the earliest workers in the Atomic Energy of Canada Limited worker cohort [47, 48]; Zablotska et al. concluded that the findings for the earliest workers are more likely attributable to missing dose information than a true effect, and that excluding these individuals from the 15-Country Study would have substantially attenuated the risks observed for all cancer excluding leukemia [47]. Occupational radiation dose was significantly positively associated with cancer (excluding leukemia) and leukemia (excluding CLL) incidence and mortality in the NRRW-3 [49]. A large-scale pooling study of cancer mortality (INWORKS) is in progress, which includes the NRRW-3, French, and US cohorts, and results are expected later in 2015.

Updated analyses from cohorts of clean-up workers of the 1986 Chernobyl nuclear power plant accident in Ukraine [50]

and Belarus, Russia, and Baltic countries [51] have yielded new insights on risks of leukemia and leukemia subtypes resulting from low-dose protracted exposures (mainly gamma and beta particle radiation). A significant linear, dose–response association between protracted exposure (mean bone marrow dose=132.3 mGy for cases and 81.8 mGy for controls) and leukemia risk was observed in the Ukrainian cohort [50]. Risk of leukemia was similarly elevated but not statistically significant in the cohort of workers in Belarus, Russia, and Baltic countries [51]. Both risk estimates were consistent with those from LSS despite lower mean estimated cumulative doses in the Chernobyl clean-up workers compared with the atomic bomb survivors. Significant positive associations for CLL and non-CLL leukemia of a similar magnitude (ERR/Gy=2.58 [95 % CI 0.02, 8.43] and 2.21 [95 % CI 0.05, 7.61], respectively) were observed in the Ukrainian cohort. The Ukrainian Chernobyl clean-up worker cohort is one of the first to report a positive association between radiation exposure and risk of CLL besides the most recent report from LSS, which included just 12 cases [52]. However, CLL incidence is very low in Japan compared with western populations [52]. Moreover, other studies of protracted, low-dose radiation exposure, including the Techa River cohort [44] and 15-Country Study [46, 53], have thus far shown no associations with risk of CLL. As radiation dose estimation was retrospectively assessed and relied on data from in-person interviews, the results from clean-up worker studies may have been biased in the positive direction due to differential recall between cases and controls. Assessment of dose–uncertainty and recall is ongoing.

Individual and collaborative studies of uranium miners have provided consistent evidence linking greater exposure to radon and its decay products, including exposure at lower levels, with an increased risk of lung cancer [54–57]. Mean exposure levels from individual miner studies have ranged from about 20 to 800 working-level months (WLM; one WLM equals 170 h of exposure to air with an alpha dose rate from radon decay product of one WL) [57]. The positive dose–response relationship between radon and lung cancer has been confirmed in studies of residential radon exposure in the general population based on lower exposure doses (at a concentration of about one hundredth to one tenth that found in underground mines [54]), with very similar risks observed per unit radon concentration [55]. A pooled analysis of 13 European studies, with mean measured radon levels of 104 Bq/m³ among lung cancer cases and 97 Bq/m³ in controls, showed an excess risk of lung cancer of 8 % (95 % CI 3–16 %) per 100 Bq/m³ that increased to 16 % per 100 Bq/m³ (95 % CI 5–31 %) after correcting for random uncertainties in measuring radon concentrations [58]. UNSCEAR (2006) estimated that the ERR per 100 Bq/m³ in miners is 0.12 (95 % CI 0.04, 0.2), assuming an ERR per WLM of 0.59 (95 % CI 0.35, 1.0) [55]. Studies of uranium miners have additionally provided important evidence regarding age- and time-related

modifiers, including a decline in risk with increasing time since exposure and, to a lesser extent, attained age. Several miner studies have shown an inverse modifying effect of exposure rate, but this effect was not observed at lower levels of cumulative exposure [54, 59, 60]. Cigarette smoking is another potentially important effect modifier; however, smoking data have generally been limited in uranium miner studies. In 1999, the BEIR VI report presented results based on six miner studies having partial smoking information, which supported a sub-multiplicative interaction between smoking and radon on lung cancer [54]. A similar but non-significant sub-multiplicative interaction was observed in a recent collaborative analysis of three case–control studies in Europe in which smoking information was constructed based on self-administered questionnaires and occupational medical archives [60]. The ERR/WLM was 0.010 (95 % CI 0.002, 0.078) for never smokers and 0.005 (95 % CI 0.002, 0.13) for ever smokers (*P* interaction=0.42). This study also confirmed that the association between radon exposure and lung cancer death persisted after adjustment for smoking (ERR/WLM=0.008, 95 % CI 0.004, 0.014).

Can Low Dose Radiation Exposure Cause Circulatory Disease?

Until the 1990s, cancer was the only established stochastic effect after ionizing radiation exposure. Beginning in the late 1990s, evidence began to emerge that very high cardiac doses from radiotherapy were related to increased cardiovascular mortality [61], and doses above 0.5 Gy appeared to increase risk also in the LSS [62]. Whether doses less than 0.5 Gy influence risk of circulatory diseases has remained uncertain, in part due to lack of information regarding possible biological mechanisms. Both BEIR VII and UNSCEAR concluded that there were insufficient data regarding an association between lower-dose ionizing radiation and an increased risk of circulatory disease [1, 2]. Since those reviews, a number of occupational cohorts have reported possible increased risks of ischemic heart disease and stroke at lower doses, including studies of Mayak workers [63, 64], some data from the NRRW-3 study of nuclear industry workers [49], and a cohort of male employees at British Nuclear Fuels Public Limited Company (which contributed some data to NRRW-3) [65]. However, no association was observed for circulatory disease mortality in the 15-Country Study, which included data from multiple cohorts of occupationally exposed workers at nuclear facilities, including the NRRW [66]. A systematic review and meta-analysis of studies based on LSS data and occupational cohorts published between 1990 and 2010 on low-to-moderate whole-body ionizing radiation and circulatory disease risks found an elevated ERRs/Sv for four broad groups of circulatory diseases: ischemic heart disease (0.10, 95 % CI 0.05, 0.15), non-ischemic

heart disease (0.12, 95 % CI –0.01, 0.25), cerebrovascular disease (0.20, 95 % CI 0.14, 0.25), and circulatory diseases not including ischemic heart and cerebrovascular disease (0.10, 95 % CI 0.05, 0.14) [67•]. There was, however, significant heterogeneity observed between studies most likely due to varying quality of dose estimates and classification of endpoints. Although the excess relative risk is much lower for CVD than for cancer, the higher background rates mean that if the low-dose risk is confirmed in future studies, the absolute excess risks are similar to cancer risks [67•].

A major concern in studies of low-dose ionizing radiation exposure and circulatory disease risks is the potential for confounding by smoking and other lifestyle-related factors, particularly in the nuclear worker cohorts, which lack this information. Of the published studies to date, data on lifestyle risk factors for circulatory diseases were only collected in the LSS [68] and Mayak worker [63, 64] cohorts exposed generally to low-to-moderate doses of radiation. Associations observed for radiation exposure and ischemic heart disease and cerebrovascular disease in these cohorts did not differ materially after adjustment for these additional risk factors, including hypertension, body mass index, cigarette smoking, alcohol intake, and history of diabetes [63, 64, 68]. Furthermore, the NRRW-3 cohort, which did not collect information on potential confounders, showed significant excess risks for all circulatory diseases combined that were slightly stronger than, but nonetheless compatible with, findings from LSS [49•]. The US Radiologic Technologists cohort provides a unique opportunity to assess low-dose radiation and cardiovascular and stroke risk with adjustment for potential confounders from detailed questionnaire information. Results are expected in the next couple of years.

In the largest study to date of patients exposed to fractionated low-to-moderate radiation (mean cumulative lung dose = 0.79 Gy, range 0–11.60 Gy), Zablotska and colleagues found that exposure to multiple fluoroscopy examinations to monitor tuberculosis was associated with a significant increased risk of mortality from ischemic heart disease overall after adjusting for dose fractionation, as well as a significant inverse dose-fractionation association, with the highest doses observed for patients with the fewest fluoroscopic procedures per year [69•]. Ischemic heart disease risk declined with increasing time since first exposure and age at first exposure. These results, while informative for radiation-exposed patient populations, require replication.

Risks of Cataracts

Recent studies have challenged the previous conclusions [70, 71] that only high radiation exposure to the lens of the eye (>2 Gy for acute and >5 Gy for fractionated or protracted exposures) influences subsequent risks of cataracts. A large

prospective study of US radiologic technologists found a non-significantly positive ERR/Gy (1.98, 95 % CI –0.69, 4.65) for the association between occupational exposure to ionizing radiation and risk of cataracts [72]. Increased risks of borderline statistical significance were observed for workers in the highest (mean = 60 mGy) versus lowest (mean = 5 mGy) category of occupational dose to the lens (HR = 1.18, 95 % CI 0.99, 1.40). In addition, having personally received three or more diagnostic X-rays to the face and/or neck was associated with a 25 % increased risk of cataracts (HR = 1.25, 95 % CI 1.06, 1.47) after adjusting for occupational exposure doses and other covariates [72]. A study of Chernobyl liquidators, 94 % of whom were exposed to <400 mGy to the lens, found a suggestive dose–response association for stage 2–5 cataracts at doses over 200–400 mGy; early, precataractous changes were observed at lens doses under 400 mGy [73]. These findings are consistent with a study based on the LSS showing increased risks of cataracts at low-to-moderate doses and dose thresholds well below 1 Gy [74], and have important implications for radiation safety regulations. As a result, the International Commission on Radiologic Protection (ICRP) issued a statement in 2011 that decreased the threshold in absorbed dose to the lens of the eye to 0.5 Gy [5].

Next Generation Sequencing

The notion that some individuals show greater sensitivity to the effects of radiation than others has been long supported by increased sensitivity in individuals with certain rare hereditary disorders (e.g., ataxia telangiectasia and Nijmegen breakage syndrome) [75, 76]. However, these cancer susceptibility syndromes affect only a small proportion of the general population. It is believed that at least some part of the genetic contribution defining radiation susceptibility is likely to follow a polygenic model, which predicts elevated risk resulting from the inheritance of several low penetrance risk alleles (the “common-variant-common-disease” model) based on the fact that multiple genetic pathways (including DNA damage repair, radiation fibrogenesis, oxidative stress, and endothelial cell damage) have been implicated in radiosensitivity [77].

The BEIR VII section on biological effects of radiation focused on the cellular level, since epidemiological data addressing genetic susceptibility to radiation effects were scant at the time [1]. Since then, a number of population-based epidemiological studies have examined genetic susceptibility to radiation-related risk of cancer using the “candidate-SNP” approach, which assumes prior knowledge of one or more functional single nucleotide polymorphisms (SNPs). Suggestive interactions have been observed between DNA repair SNPs and ionizing radiation for glioma [78, 79], as well as between ionizing radiation and common variants in genes involved in DNA damage repair, apoptosis, and proliferation

in a series of nested case–control studies of breast cancer in US radiologic technologists [80–83] and a small hospital-based study of breast cancer [84]. However, none of these results have been convincingly replicated to date. A slightly different approach has been to examine breast cancer risk associated with diagnostic X-ray or mammogram exposure in groups of high-risk individuals (carriers of *BRCA1* and *BRCA2* mutations). Most [85–87], but not all [88], studies of chest x-rays have reported a slightly elevated risk of breast cancer in at least one subgroup of exposure. For mammograms, the association has generally been null [89–91]. Interpretation of these findings is difficult given that all of these studies are subject to one or more of the following biases: exposure based on self-report, the possibility of confounding by indication, lack of a consistent dose–response association, subgroup findings that could be due to chance, and overlap of study populations. The observation of statistically significant associations with exposure to X-rays but not mammograms points to the strong probability of recall bias for the first set of findings given that self-reported mammogram use is highly accurate [92].

While earlier genetic studies focused on a handful of candidate genes, it is now possible to comprehensively examine the approximately 25,000 coding genes and associated functional elements thanks to the advent of high-throughput technologies that can simultaneously analyze thousands of genetic markers at relatively low-cost, the mapping of linkage disequilibrium between common SNPs across the genome [93], and the definition of functional elements critical for regulation and genomic stability [94]. The genome-wide association study (GWAS) approach has successfully identified hundreds of risk loci in germline DNA for various cancers [95]. However, the assessment of gene–environment interaction for many known environmental carcinogens, including radiation, has remained elusive. Genome-wide association studies have been undertaken of adult contralateral breast cancer in the WECARE study [96] and subsequent malignancies in the Childhood Cancer Survivor Study [97] (both of which have detailed radiation doses from radiotherapy) but results are yet to be published.

The huge advances in DNA sequencing technology have also yielded path-breaking insights into our understanding of somatic mutations. The Cancer Genome Atlas (TCGA), launched in 2005, and the International Cancer Genome Consortium (ICGC), launched in 2008, have been the two main projects driving our comprehensive understanding of the genetics of cancer. These projects characterize not only the genome, but also various aspects of the transcriptome and epigenome, to give a fuller understanding of how genes contribute to tumorigenesis. To date, over 30 distinct human tumor types have been analyzed through large-scale genome sequencing and integrated multi-dimensional analyses, yielding insights into both individual cancer types and across

cancers, particularly with respect to the accurate molecular classification of tumors [98]. The bulk of these new discoveries focuses on the genome rather than associated environmental factors. However, a recent landmark paper examining 4,938,362 mutations from 7042 cancers identified strong mutational signatures in tumor tissue marking exposure to tobacco carcinogens and ultra-violet irradiation [99]. The tobacco signal was most evident in cancers of the lung, head and neck, and liver; and the ultra-violet irradiation signal was observed mainly in malignant melanoma and squamous carcinoma of the head and neck. Studies to look for a similar tumor tissue signature for ionizing radiation are currently being planned in populations environmentally exposed to low doses of ionizing radiation.

Certainly, the new era of low-dose radiation epidemiologic studies of cancer and other serious disease risks will continue to feature a search for common genetic markers that can identify individuals susceptible to radiation risk effects and “signatures” that can identify radiation exposure as a causal factor for a particular tumor. While these studies face several challenges (including the need for large sample sizes, high-quality exposure assessment for both radiation and potential confounding factors, and meaningful replication sets), the integrated characterization of germline and somatic alterations as genotyping and analysis methods evolve rapidly in the next few decades promises to yield exciting new avenues of research. If a radiation “signature” could be identified in individuals who received low dose exposure, this would be a paradigm shift in the linear no-threshold field.

Conclusions

The last decade has introduced a new era of low-dose radiation epidemiology. Record linkage studies have suggested for the first time that pediatric CT scans may increase cancer risk, and that natural background radiation may contribute to childhood leukemia. Large pooling projects of occupational cohorts have provided additional insights into the risks from protracted radiation exposure, and also raised questions about the risk of other stochastic effects after low-dose exposures including cardiovascular disease and cataracts. There are potential sources of bias in all of these populations, but the case for causality is strengthened by the evidence of a dose–response and consistency with the existing evidence at higher doses. In the next decade, integrated characterization of both germline and somatic alterations (including inherited mutations, somatic, and epigenetic changes) in populations with well-characterized exposure to ionizing radiation could propel our understanding further regarding thresholds, radiosensitivity of population subgroups and individuals, and the mechanisms of radiation carcinogenesis. These developments will be keenly followed as medical imaging technologies continue

to advance and spread, and nuclear power plant accidents and other radiological emergencies remain a threat for populations around the world.

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Compliance with Ethics Guidelines

Conflict of Interest The authors declare that they have no competing interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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