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Article

ARTICLE

Outcome Assessment in Epidemiological Studies of Low-Dose Radiation Exposure and Cancer Risks: Sources, Level of Ascertainment, and Misclassification

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Abstract

Background: Outcome assessment problems and errors that could lead to biased risk estimates in low-dose radiation epidemiological studies of cancer risks have not been systematically evaluated. **Methods:** Incidence or mortality risks for all cancers or all solid cancers combined and for leukemia were examined in 26 studies published in 2006–2017 involving low-dose (mean dose $\leq$100 mGy) radiation from environmental, medical, or occupational sources. We evaluated the impact of loss to follow-up, under- or overascertainment, outcome misclassification, and changing classifications occurring similarly or differentially across radiation dose levels. **Results:** Loss to follow-up was not reported in 62% of studies, but when reported it was generally small. Only one study critically evaluated the completeness of the sources of vital status. Underascertainment of cancers ("false negatives") was a potential shortcoming for cohorts that could not be linked with high-quality population-based registries, particularly during early years of exposure in five studies, in two lacking complete residential history, and in one with substantial emigration. False positives may have occurred as a result of cancer ascertainment from self- or next-of-kin report in three studies or from enhanced medical surveillance of exposed patients that could lead to detection bias (eg, reporting precancer lesions as physician-diagnosed cancer) in one study. Most pediatric but few adult leukemia studies used expert hematopathology review or current classifications. Only a few studies recoded solid cancers to the latest International Classification of Diseases or International Classification of Diseases for Oncology codes. These outcome assessment shortcomings were generally nondifferential in relation to radiation exposure level except possibly in four studies. **Conclusion:** The majority of studies lacked information to enable comprehensive evaluation of all major sources of outcome assessment errors, although reported data suggested that the outcome assessment limitations generally had little effect on risk or biased estimates towards the null except possibly in four studies.

The internal validity of observational cohort studies requires complete and accurate outcome assessment for both exposed and comparison persons. High-quality outcome assessment is critical for accurate cancer risk estimation in relation to low-dose radiation dose-response for both cohort and case-control studies. Comprehensive reviews of epidemiological studies of cancer and other health effects associated with low-dose radiation, including some of the 26 studies evaluated in this article (1–29), have identified several sources of uncertainty (30) and potential bias (31), but the reviews and textbooks (32) provide less description of methodological problems due to inaccurate outcome assessment and potential biases associated with these problems for risk estimates than those related to exposure assessment or confounding.

Major sources of error in outcome assessment that could result in potentially biased cancer risk estimates in epidemiological studies of low-dose radiation exposure include differential (between exposed and comparison populations or across

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radiation dose categories) loss to follow-up, under- or overascertainment of outcomes, misclassification, and application of changes in classification over time. The most common designs for epidemiological studies of ionizing radiation are retrospective record linkage-based cohort (or nested case-control) studies or mixtures of retrospective and prospective cohort follow-up (26–28,33). These study designs enable long-term follow-up of large populations but may have limitations for outcome assessment.

In this review, the major sources of methodological problems and errors and potential biases associated with such errors in outcome assessment of total cancer (all-cancer sites combined), total solid cancers, leukemia, and a few site-specific solid cancers in relation to low-dose radiation exposures (≤100 mGy) are systematically appraised for 26 epidemiological studies. The selected studies were published subsequent to the Biological Effects of Ionizing Radiation VII report (30) during the period 2006–2017.

Methods

Study Populations

The study eligibility requirements, exclusion criteria, features, and findings are provided in the Rationale and Overview article included in this monograph (34). In brief, eligible cohort or case-control epidemiological studies were those of human populations exposed to low-dose (mean dose ≤100 mGy), predominantly low Linear Energy Transfer radiation with individualized cumulative radiation dose estimates and dose-response analyses reporting cancer risks and associated confidence intervals per unit dose or at a given exposure level. A total of 26 eligible studies included eight populations with environmental, four with medical, and 14 with occupational radiation exposures characterized by mean estimated exposures ranging from 0.1 mSv (2) to 82 mGy (20) (see table 1 in Berrington de González et al in this monograph (34)).

Exposure Assessment

For persons with medical and occupational radiation exposure, doses were estimated for individuals. In most of the studies of background radiation exposure, doses of individuals were modelled with the same dose generally assigned to those persons considered to be similar in geographic location. Analyses estimated risk per unit dose or risk at a specified dose. The dosimetry methods for the 26 studies are described by Daniels et al. in this monograph (35).

Outcome Assessment: Sources of Error and Likely Impact on Risk Estimates

As described in the overview article in this monograph (34), this review focuses on the results for all solid cancers and for leukemia separately rather than site-specific solid cancer analyses, which may lack power, may be more prone to misclassification, and may be difficult to interpret due to multiple testing issues. Most of the studies included in this review involved whole-body uniform radiation exposure, although a few assessed more localized exposures. For studies of nonuniform exposures, however, the results are generally for specific cancer sites that were highly exposed and/or highly radiosensitive, for example, brain tumors after pediatric computed tomography scans and breast cancer after medical or occupational exposures. Table 1 and the text immediately below summarizes the major sources of methodological problems and errors in outcome assessment that could lead to potential biases associated with these problems.

Loss to Follow-Up

Complete follow-up to ensure identification of all cancer outcomes in exposed and comparison populations is critical to ensure accurate cancer risk estimates in exposure response analyses (36–38). The accuracy of risk estimates in nested case-control studies could also be affected by loss to follow-up in the target cohort (36). Follow-up in cohort studies ideally continues until the event (which may include one or multiple outcomes of specific interest), the date individuals are censored when they can no longer be followed, or the end of the follow-up period. At the end of the study, persons may be alive and diagnosed with the outcome(s) of interest, alive and free of the outcome(s) being assessed, deceased with known or unknown causes or dates of death, or lost to follow-up at some time before the end of the study period. Loss to follow-up can occur under two different scenarios. In the first instance, persons can move from the geographic area (a city, state, region, or country) where the investigator has been able to link the person with a population register or otherwise contact the person to ascertain the outcome(s) of interest to a geographic area where such linkage or follow-up is no longer possible and the date of the inability to follow-up the person is known. In this circumstance, analyses generally censor the person at the date when the person's status was last known. In the second instance, persons move from the geographic area where follow-up can be undertaken to another area where follow-up is not feasible, but the investigator does not know when the persons moved. In this second scenario, the "date of censoring" is unknown, and the time point at which accurate follow-up ceases is also unknown.

A key consideration affecting the level and interpretation of loss to follow-up is whether investigators have carried out "active" or "passive" individual follow-up. Active individual follow-up is defined as direct contact with persons and/or linkage of the person with different types of alternative registries or other sources that provide credible information about vital status to the end of the study or diagnosis of incident cancer or death. Passive individual follow-up is characterized by linkage or indirect follow-up such that the vital status of the person is "assumed alive" or "assumed deceased," but rigorous confirmatory documentation may be lacking or is unclear. Active individual follow-up, if highly successful, can lead to improved ascertainment, whereas linkage with vital status, cancer, and death registries may be less complete if substantial fractions of the population are missing from registries or the persons are missing key information for linkage.

Under- or Overascertainment

Under- or overascertainment of cancer outcomes is another potential source of error. Loss to follow-up may result in underascertainment. Underascertainment may occur in the absence of active individual follow-up if not comprehensive or successful. Underascertainment may also occur if cohort members have incomplete identifiers that may result in problems with linkage, if the registers are incomplete and missing a substantial fraction of population members, if there is substantial emigration, or if registers are not established until after the exposure period of a

Table 1. Major sources of error in outcome assessment in radiation epidemiological studies

Source of error	Description	Potential effect on dose response		Strategies to reduce error in risk assessment of outcomes
		Nondifferential	Differential	
Loss to follow-up	Usually due to relocation and loss of contact, discontinued participation, or other reasons Date of loss to follow-up can be known or unknown	Should not result in bias if same data sources, methods, and level of effort used to trace and/or link in both exposure groups but may result in loss of statistical power	Bias may occur if loss substantial and associated with both exposure and outcome (eg, used different data sources for tracing or linkage, different methods or levels of effort in exposed compared with unexposed)	Use standardized methods and all available sources to target 100% follow-up. If active tracing of all patients not feasible (best approach), investigators should aim for linkage with high-quality vital status registries and data sources. Investigators should characterize level of completeness of vital status databases. High-quality nationwide mortality registries may be better for outcome assessment when nationwide high-quality cancer registries unavailable.
Under- or over ascertainment of outcomes	Underascertainment: cancer outcomes not identified or misclassified as another type of cancer or a noncancer disease Overascertainment: may occur if benign entity or lesion that rarely becomes malignant is designated as cancer. Clinical assessment and screening in absence of symptoms may result in overascertainment. Broad categories (eg, "all cancers") may be less susceptible to over- or underascertainment	Should not result in bias if same data sources, methods, and classification system used	Bias may occur with use of different (by exposure status) sources of outcome data or methods for identifying cancer outcomes (eg, self-administered interviews, population-based cancer registry linkage, clinical assessment, cancer screening) or classification systems	Use of rigorous standardized methods, same data sources, and most recent classification systems (including reclassification where applicable or possible) should result in complete and accurate identification of all cancers. Cohort linkage with high-quality population-based cancer registries may still result in underascertainment for certain outcomes generally identified and treated in physicians' practices or diagnosed solely by imaging. Use of multiple sources of data will likely yield high ascertainment. Screen-detected cancer outcomes should be excluded if identified in exposed groups only.
Misclassification, changes in classification over time, or indeterminate classification	Misclassification: nonmalignant condition classified as malignancy or vice versa; specific type of cancer classified as another type; or within neoplasm misclassification of a neoplasm that includes benign and malignant variants Changes in cancer classification over time: increased specificity of histologic or molecular subtypes; new ICD codes; reclassification from benign to malignant or vice versa; or one category to another Neoplasms of indeterminate classification	Could lead to under- or overestimation if substantial differences in outcome(s) misclassified between exposed vs unexposed populations	May result in biased cancer risk estimates. If efforts are made to reclassify cancer outcomes according to new criteria, bias could occur with usage of different sources of data, different approaches, or different levels of effort in exposed vs unexposed populations.	Undertake expert pathology review Comprehensive reclassification may not be feasible if tumor tissue, pathology, or medical records are not available; a modification of most recent classification may be the only possibility. Conduct sensitivity analyses using older classification schemes to compare findings of current study with those from earlier studies.

study population commences. Overascertainment may occur if persons inaccurately self-report cancer outcomes that are incorrect or if screening or regular medical surveillance is undertaken such that preclinically cancerous lesions are identified. If the same level of under- or overascertainment occurs in exposed and unexposed individuals included in a study (or a low-exposure referent group), then risk estimates are unlikely to be biased, but if differential by radiation exposure level then there is the potential for biased risk estimates. The impact of outcome assessment errors on cancer risk estimates depends on the type of risk measure (eg, relative vs absolute excess risk). In this monograph, we focused on reviewing the relative risks and thus evaluated the biases relevant to relative risks. The data sources and methods used to identify and validate cancer outcomes are important determinants of the likelihood of under- or overascertainment.

Misclassification and Changes in Classification Systems.
Misclassification of outcomes in cohort or case-control studies may be another source of inaccurate risk estimation if the misclassification differs by radiation exposure level (39,40). Incorrect outcome information may be derived from inaccurate diagnoses provided by self-reports or listed in death certificates, medical records, physician reports, cancer registries, or other sources. Misclassification errors may occur if a nonmalignant condition is incorrectly reported as a malignancy, a malignancy is wrongly reported as a nonmalignant condition, or a specific type of malignancy is reported as another type of malignancy. Disorders that include benign and malignant variants (eg, meningioma, ovarian tumors) may be misclassified. Misclassification can also occur if a preclinical or in situ lesion identified in screening tests, self-reports, or medical records is incorrectly designated as a frank malignancy because such lesions may not transform into frank malignancies or may regress. Changes in cancer classification over time may lead to misclassification if there is increased specificity of histological or molecular subtypes; new International Classification of Diseases (ICD) codes added (eg, mesothelioma); reclassification from benign to malignant (eg, myelodysplastic syndromes [MDS], certain myeloproliferative disorders) or malignant to benign (eg, pilocytic astrocytoma); reclassification to another category of neoplasm (eg, chronic lymphocytic leukemia [CLL] changed from "leukemia" to "lymphoma"); and indeterminate with designation as borderline malignant (eg, certain ovarian tumors, meningioma). Cancer screening may be more likely to be undertaken in radiation-exposed than in unexposed populations or in populations with higher radiation exposure levels. Risk estimation may be biased upward or downward if the level of outcome ascertainment or misclassification differs between the radiation-exposed and comparison populations or across radiation exposure categories (32). A detailed description of qualitative and quantitative effects of nondifferential or differential misclassification by exposure level can be found in Greenland et al. (32). Statistical methods to assess the effect of misclassification on cancer and noncancer mortality risk estimates and to determine whether an observed noncancer mortality radiation dose response could be attributed to misclassification of cancer as noncancer outcomes on death certificates are described by Sposto et al. (41).

Secular Changes in Classification and Revisions in Classification Systems
Changes in classification of cancers over time and revisions in cancer classification during the course of long-term follow-up of radiation-exposed populations may affect the completeness of outcome ascertainment but are unlikely to result in bias unless occurring differentially in exposed and unexposed study individuals. Examples of such changes include the World Health Organization 2000 (42) reclassification of MDS and myeloproliferative disorders from "benign" conditions to malignancies, and of lymphoma subtypes (43–45); lack of ICD/International Classification of Diseases for Oncology codes for certain cancers (eg, mesothelioma before ICD-10); or cancers for which there is long-standing controversy about whether they should be considered "benign" or "malignant" (eg, pilocytic astrocytoma and borderline ovarian tumors) (46). Ideally, cohort and case-control studies in which internal comparisons are emphasized should employ the most recent internationally recognized classification scheme for outcomes and should reclassify outcomes using earlier classifications. However, reclassification should be conducted with great care (ideally with assistance from expert pathologists), because inadvertent errors may result.

Combining Heterogeneous Disorders for Analysis to Increase Statistical Power
Grouping of heterogeneous disorders (eg, "all solid tumors combined," "gastrointestinal cancers not otherwise specified," "total leukemia") for analysis may be problematic. Although such grouping is often done to increase statistical power (47), radiation risks may be diluted if disease entities with known differences in radiogenic sensitivity are grouped and considered as a single "homogeneous" entity. Differences in methods of ascertainment by radiation exposure level (eg, screening of radiation-exposed individuals using ultrasound or radiologic imaging procedures vs identification based on physical symptoms in the comparison group, or more detailed expert review of histopathologic or molecular characteristics of tumors in exposed vs use of death certificates only in the comparison group) could further exacerbate dissimilarity with respect to homogeneity between exposed study individuals and the comparison group.

Outcome Evaluation Methods

The 26 studies were reviewed for information relevant to cancer outcome assessment (see Table 2). The criteria evaluated included study design; specific outcomes evaluated; numbers of study cases and study controls or numbers of outcomes and cohort size; source and method of cancer ascertainment; internationally recognized quality rating of the national or regional vital status, cancer, and mortality registries by the International Agency for Research on Cancer (IARC) (48); and exposure and follow-up periods.

In Table 3 the methods used for follow-up (active individual follow-up vs linkage with registries and other databases), loss to follow-up, the likelihood of major sources of error in cancer outcome assessment, and other classification issues were described. The potential for bias was determined based on the evaluation of the major sources of error listed in Table 1 and described for each study in Table 3. We concluded that the potential for bias was clear (with the designation of "yes") and that there was no potential for bias (with the designation of "no") or that we could not rule out that there was a potential for bias (with the designation of "possible"), but these designations were somewhat subjective. The designation of "possible" was usually due to an absence of sufficient detail about the methods employed to reach a conclusion about the potential for bias.

Results

Study Design and Major Category of Outcome

As shown in Table 2, 21 of the 26 studies employed a cohort design and generally followed-up persons for incident cancers, deaths from cancer and other causes of death, or study end, although a few ended the cohort follow-up at a predetermined age (3,5,10,17) or at the time of emigration (5,6).

Cancer incidence was the outcome for all studies of medical radiation exposure and all but one study of environmental radiation exposure (Table 2). Six cancer incidence studies focused primarily on pediatric radiation exposures and pediatric cancer outcomes (1,4,5,7,10,11) (although follow-up of study individuals in the UK computed tomography study extended

Table 2. Populations and study design, outcomes and ascertainment methods, IARC classification of registry quality, exposure and follow-up periods in 26 low-dose radiation epidemiological studies

Study name and reference	Design, censoring, matching	Specific outcome evaluated	Numbers of cases and numbers of controls; outcomes and cohort size,	Cancer ascertainment method	IARC classification; mortality: 1–6; incidence: A-G*	Exposure period	Follow-up period
Environmental							
Chernobyl-exposed children (1)	Case-control; matched regional clinic controls	Childhood leukemia incidence (<6 y ATA)	421 acute leukemia cases vs 842 controls	Hospital records, population-based cancer registries	A: Belarus (after 1997) and Ukraine; NA: Russian Federation	1986–2000	1986–2000
TMI residents (2)	Cohort study; TMI population registry enrolled 93% residents living within 5 miles; study end or cancer diagnosis	Incidence of all and selected malignancies, including leukemia	1651 total incident malignancies, 56 incident leukemias in 22 069 TMI cohort members	TMI population registry matched annually with PA cancer registry	A: PA state cancer registry designated gold-level standard	1979	1982–1995
Chinese background (3)	Cohort study in high background and low background regions; in 1979, village household registry established to ascertain mortality	Mortality for all cancers, excluding leukemia and for leukemia	956 total cancer deaths (of 6005 total deaths), 15 leukemias in 736 942 p-y follow-up	Household surveys, medical records of deceased, village doctors, family and next of kin	4: Incomplete vital registration	1905–1998	1979–1998
GB background (4)	Case-control; matched controls from same birth registry	Childhood cancer incidence	27 447 total incident cancers (9058 leukemias) vs 36 793 controls with all cancers (11 912 leukemias)	National cancer registry	A: High-quality national	1991–1996	1980—2006
Swiss children background (5)	Cohort study from persons in 1990 and 2000 censuses; death, study end, age 16 y, emigration	Childhood cancer incidence	1782 cancers, 530 leukemias among 2 093 660 children	National cancer registry	B: High-quality regional	1974–2008	1990–2008
Techa River residents (6)	Cohort study of residents near Techa River or in Chelyabinsk City during some or all of 1956–2007; death, study end, emigration	Solid cancer incidence	1933 solid cancers among 12 759 cohort members	Medical records from oncology dispensaries, regional oncology clinics, health centers, and death certificates; death certificate-only diagnoses were 19% (range 4–56%) by subtype	2: Medium-quality vital registration	1951–2007	1956–2007
Finnish background (7)	Nested case-control study; matched population register controls	Childhood leukemia incidence	1039 cases vs 3279 controls	National cancer registry	A: High-quality national	1990–2011	1990–2011
Taiwanese residents (8)	Cohort study; cancer diagnosis, death, study end	Cancer incidence	111 cancers excluding leukemia (6 leukemias identified in 6242 persons with residential radiation exposure history who were followed-up)	National cancer registry	A: Currently; population cancer registry established in 1979 with notable improvement in quality over time	1982–1992	1983–2012

(continued)

Table 2. (continued)

Study name and reference	Design, censoring, matching	Specific outcome evaluated	Numbers of cases and numbers of controls; outcomes and cohort size,	Cancer ascertainment method	IARC classification; mortality: 1–6; incidence: A-G*	Exposure period	Follow-up period
Medical							
Cardiovascular imaging patients (9)	Cohort study: constructed from hospital discharge summary Quebec province-wide database	Cancer incidence; groupings by general anatomic sites but not type-specific	12 020 incident cancers in 82 861 patients (77% underwent $\geq$ 1 cardiac imaging or therapeutic procedure)	Hospital admission and outpatient visits; review of diagnostic codes	Not applicable because hospital and outpatient clinic records were source of outcomes	1996–2006	1996–2006
French pediatric CT (10)	Cohort study: children who had first CT scan $\leq$10 y old identified from 23 radiology departments nationwide; cancer diagnosis, death, study end	Cancer incidence in children focusing on CNS, leukemia, lymphoma	27 CNS, 25 leukemia, 21 lymphomas among 67 274 in cohort	National registry of childhood cancers	A: High-quality national; 2 = medium quality for vital status	2000–2010	2000–2011
UK pediatric CT (11)	Cohort study: children with first CT scan $\leq$22 y old identified from electronic radiology information systems at 81 hospitals throughout GB within National Health Service; cancer diagnosis, death, study end	Cancer incidence in children focusing on leukemia, MDS, CNS	65 leukemias, 9 MDS, 135 CNS among 178 604 in cohort	National cancer registry, national mortality data, pathology reports from cancer registries and hospitals	A: High-quality national	1980–2002	1980–2008
PIRATES (low dose) (12)	Pooled data from 9 cohort studies of those undergoing irradiation in childhood: incident thyroid cancer, death, loss to follow-up	Thyroid cancer incidence	252 cases in 2 588 559 p-y of follow-up in irradiated (184 cases in 2 114 683 p-y of follow-up for $<$0.1 mSv), 142 cases in 1 865 957 p-y of follow-up in nonirradiated cases	National cancer registries for 5 Nordic countries, hospital based for other 4 studies	Variable: national, regional, some not available	1926–2000	1935–2009
Occupational							
Korean radiation workers (13)	Cohort study: assembled from central registry for radiation workers (legally mandated medical surveillance for radiation workers)	Cancer incidence (total and 6 specific types) and mortality	935 deaths (256 total cancers, 9 leukemias) and 564 total incident cancers (14 leukemias) in 79 679 radiation workers vs 206 deaths (53 cancers) and 254 incident cancers in 190 816 auto manufacturing workers	Deaths: Korean National Statistical Office registry (>95% registration); incident cancers: national health insurance claim data (>99% complete)	1: High-quality complete vital registration Not applicable for incidence because insurance claim data were used instead of national cancer registry	1984–2004	I: 2000–2005 M: 1992–2004
Belarus, Russia, and Baltic CL (14)	Nested case-control study within 66 000 Belarus, 65 000 Russian, and 15 000 liquidators from	Hematologic neoplasm incidence	117 incident hematologic neoplasms (69 leukemias, 34 non-Hodgkin lymphoma and 14 others);	National cancer registries in Belarus and Baltic countries, National Medical	A: Belarus and Baltic countries; not applicable in Russia	1986–1987	1986–2006

(continued)

Table 2. (continued)

Study name and reference	Design, censoring, matching	Specific outcome evaluated	Numbers of cases and numbers of controls; outcomes and cohort size,	Cancer ascertainment method	IARC classification; mortality: 1–6; incidence: A-G*	Exposure period	Follow-up period
	Baltic countries; each case matched on age to 4 controls from liquidator population		analyses restricted to 70 cases (40 leukemias, 20 NHL, and 10 others) with reliable work information; outcomes reviewed by expert international pathologists' panel	Dosimetry Registry in Russia, and Registry of Hematologic Disorders in Belarus			
UK NRRW NW (15)	Cohort study: population identified from UKNRRW; cancer diagnosis, death, and end of follow-up	Total cancer incidence and total, excluding leukemia, and most specific neoplasms; mortality from all causes and most specific neoplasms	26 731 deaths (8107 cancers, 216 leukemias) in 3 301 400 p-y of follow-up; 11 113 incident cancers, 267 leukemias	National cancer registry	1: High-quality complete vital status A: High-quality national cancer registration	1946–2001	mortality:1965–2001;incidence:1971-2001
Korean male NP NW (16)	Cohort study: assembled from nuclear workers at 20 plants who were issued dosimeters during 1978–2005; comparison group worked at same facilities but not issued a dosimeter; cohort members invited to participate in survey and clinical evaluation during 1992–2005	Total cancer incidence and total excluding leukemia, leukemia and 4 other types of neoplasms	96 cancers excluding leukemia (3 leukemias) identified in 8429 radiation workers and 101 cancers excluding leukemia (3 leukemias) in 7807 unmonitored workers	Korean Central Cancer Registry	A: High-quality national cancer registry	1978–2005	1992–2005
Rocketdyne NW (17)	Cohort study: identified from work history cards, electronic files, and radiation monitoring files from Radiation and Health and Safety Department; compared with workers at same facilities not monitored for radiation; death, age 95 y, loss to follow-up or end of study	Mortality from all causes, all cancers, leukemia, and most specific cancer types	2354 deaths (672 total cancers, 33 leukemias) among 5743 radiation workers with 194 731 p-y of follow-up compared with 14 854 deaths (4163 cancers) among 41 169 unmonitored workers with 1 392 648 p-y of follow-up	Linkage of cohort with NDI, California Death statistical Master File, SSA death master file, other SSA files and commercial information service providers	1: High-quality national vital status information	1948–1999	1948–2008
Japanese male NW (18)	Cohort study: nuclear workers identified from radiation worker registry; death, study end, date last known alive	Mortality from all causes, total cancers excluding leukemia, leukemia and some other selected cancer types	2703 total cancers (2636 total cancers excluding leukemia, 80 leukemias) in 200 583 male workers with 1 373 000 p-y of follow-up	Deaths identified from residence registration cards (vital status) and linked with vital statistics death	3: Low-quality complete vital status registration	1957–2002	1991–2002

(continued)

Table 2. (continued)

Study name and reference	Design, censoring, matching	Specific outcome evaluated	Numbers of cases and numbers of controls; outcomes and cohort size,	Cancer ascertainment method	IARC classification; mortality: 1–6; incidence: A-G*	Exposure period	Follow-up period
				records (cause of death)			
Canadian NW (19)	Cohort study; nuclear workers identified from National Dose Registry of all radiation-exposed workers	Mortality from all solid cancers and all excluding leukemia, leukemia	437 solid cancers and 21 leukemias in 45 656 nuclear workers	Deaths identified from historic summary tax file and Canadian Mortality Data Base	1: High-quality national vital status information	1956–1994	1956–1994
Ukrainian CL (20)	Nested case-control study: identified from 110 645 Ukrainian liquidators in Chernobyl State Registry of Ukraine; controls matched 5:1 (on place of residence, alive at corresponding case diagnosis, and year of birth using incidence density sampling	Incidence of leukemia and other hematologic neoplasms	162 leukemias	Potential leukemia cases in worker cohort identified from all health care institutions in study area during 1986–2000; cases diagnosed 2001–2006 identified from linkage of worker cohort with Ukrainian Cancer Registry	A: High-quality national level since 1997	1986–1987	1986–2006
German NP NW (21)	Cohort study: identified from comprehensive accident insurance and prevention list; death, study end, last available information date	Mortality from all cancers, total cancers excluding leukemia, solid cancers and cancer groupings related to exposure	126 total cancer deaths; 7 deaths from leukemia	Causes of death from federal and state vital statistics offices	2: Medium-quality vital registration	1966–2008	1991–2008
US NW (22)	Pooled cohort: assembled from 5 previously studied cohorts (employed >30 d, ever monitored, hired between facility start-up or when work history records first available); death, study end for those alive ≥1979 or last employment date when last known alive <1979	Mortality from all causes, all cancers excluding leukemia, leukemia, several specified cancers, and cancer groupings related to exposures	10 389 (9979 excluding leukemia and 410 leukemias) in 119 196 workers with 2 664 782 p-y of follow-up	Mortality and cause-of-death from previous studies used and extended through 2005 with linkage to SSA Death Master File and national tax records to confirm vital status; cause of death from NDI	1: High-quality vital registration	1944–2005	1944–2005
INWORKS NW (23, 24)	Pooled cohort: assembled from updated cohorts of nuclear workers from France, UK, and US; date of death, study end, loss to follow-up	Mortality from all cancer, all cancer other than leukemia, and all solid cancer; mortality from leukemia excluding CLL	19 748 all cancers (19 064 cancers other than leukemia, 17 957 solid cancers) among 308 297 workers with 8.2 million p-y of	Linkage with national and regional death registries, employer records, and SSA and NDI	1: UK and USA; 2: France	1944–2005	1944–2005

(continued)

Table 2. (continued)

Study name and reference	Design, censoring, matching	Specific outcome evaluated	Numbers of cases and numbers of controls; outcomes and cohort size,	Cancer ascertainment method	IARC classification; mortality: 1–6; incidence: A-G*	Exposure period	Follow-up period
			follow-up; 531 leukemias excluding CLL				
US atomic veterans (25)	Cohort study: assembled from Nuclear Test Review Program Information System; included military members from previous follow-up study; date of death, study end, loss to follow-up	Mortality from all causes of death, all cancers, leukemia and some other specific cancers	236 total cancers (19 leukemias) among 12 219 participants with 264 664 p-y of follow-up	Linkage of cohort with SSA Death Master ile and NDI; other sources included Internal Revenue Service, Department of Veterans Affairs Beneficiary Identification Record Location System	1: High-quality vital registration	1945–1963	1957–2010
USRT (26–28)	Cohort study: assembled from American Registry of Radiologic Technologists	Incidence and mortality of breast cancer, incidence of basal cell skin carcinoma, and mortality of brain cancer	1922 incident breast cancers among 66 915 female techs; 586 breast cancer deaths among 83 538 female techs; 3615 incident basal cell carcinomas of the skin among 65 719 Caucasian techs; 193 brain cancer deaths among 110 297 technologists	Self-report in 4 surveys with validation by medical records; linkage of cohort with SSA Death Master File and NDI	Breast cancer and basal cell carcinoma of the skin incidence: not applicable because based on self-report 1: High-quality vital registration	1916–1997	1983–2008
French NW (29)	Cohort study: pooled from 2 nuclear worker cohorts assembled in 1990s that were previously followed-up; death, study end, loss to follow up	Mortality from all causes, all solid cancers, leukemia and many other specific cancers	2356 solid cancers and 57 leukemias excluding CLL among 59 004 workers with 1 469 949 p-y follow-up	National death registry and self-report	2: Medium-quality vital status registration	1950–2004	1968–2004

*International Agency for Research on Cancer quality of estimates for mortality and incidence data by country. Mortality: 1 = high-quality vital registration; 2 = medium-quality vital registration; 3 = low-quality vital registration; 4 = incomplete vital registration; 5 = other sources; 6 = no data. Incidence: A = high-quality national or high-quality regional data (coverage >50%); B = high-quality regional (coverage >10%); C = high-quality regional data (coverage <10%); D = national data (population-based cancer registries); E = regional data (population-based cancer registries); F = frequency data (hospital based or pathology based); G = no data. GLOBOCAN 2012 Classification (http://globocan.iarc.fr/Pages/DataSource_and_methods.aspx.

ATA = at the time of the accident; CL = Chernobyl Liquidator; CLL = chronic lymphocytic leukemia; CNS = central nervous system; CT = computed tomography; GB = Great Britain; I = incidence; IARC = International Agency for Research on Cancer; INWORKS = International Nuclear Workers Study; M = mortality; MDS = myelodysplastic syndromes; NDI = National Death Index; NP = nuclear power; NW = nuclear worker; PIRATES = Pooled International Radiation and Thyroid Cancer Epidemiology Studies; p-y = person-years; RBM = red bone marrow; RT = radiologic technologist; SSA = Social Security Administration; TMI = Three Mile Island; UKNRRW = United Kingdom National Registry for Radiation Workers; US = United States of America; USRT = United States Radiologic Technologists.

Table 3. Follow-up methods and results of loss to follow-up, ascertainment type and completeness, classification issues, and potential for bias in 26 low-dose radiation epidemiological studies

Study name (reference)	Method of follow-up: active vs linkage	Loss to follow-up*	Likelihood of A. Differential ascertainment B. Incomplete ascertainment C. False negative outcomes D. False positive outcomes	Other classification issues	Comment	Potential for bias (Y/N possible)
Environmental						
Chernobyl-exposed children (1)	NA*	NA	A. NA B. Unlikely C. Unlikely D. Unlikely	Expert hematologists reviewed each case	Authors state: high degree of completeness of case ascertainment but no further details; Ukraine component had higher percent of controls than cases from less contaminated regions	No
TMI residents (2)	Linkage	1.6% lost to follow-up; annual follow-up via post office address change	A. No B. Unlikely C. Unlikely D. Unlikely	TMI population registry matched annually with PA state cancer registry from 1982 onward	Population-based cancer registry not established until 3 y after accident: possible incomplete ascertainment of leukemia	No
Chinese background (3)	Active	Villages visited annually to assess cancer mortality; 1.6% lost to follow-up in higher background radiation and 2.8% in lower background radiation regions, both mostly due to emigration	A. Possible; older mean attained age in lower background than in higher background radiation regions; tuberculosis mortality lower in higher background than in lower background radiation regions; slightly lower cancer mortality rate in higher background than in lower background radiation regions B. Likely ↓ C. Likely D. Unlikely	Basis of diagnosis of variable quality	No national mortality registers. Some diagnoses from hospital records, but others from interviews of village doctors, family, or next of kin; thus, ascertainment of cancer incidence and mortality, particularly for leukemia, likely incomplete, potentially greater in the lower background radiation region.	Possible for both solid cancers and leukemia. Uncertain direction of bias because false negatives could be substantial in both higher and lower background radiation regions.
GB background (4)	Linkage	NA	A. No; birth register controls linked to National Registry of Childhood Tumors B. Unlikely C. Unlikely D. Unlikely	Specialized pediatric cancer registry used; cases classified using ICCC		No
Swiss children background (5)	Linkage	NK*†; 1.7% excluded due to uncertain residence	A. No B. Possible ↓ C. Possible D. Possible	<4% Potential false positives; >400 cancers not linked that are potentially false negatives; ≤7% linkages resulted in false matches	Authors state: no evidence that false negatives differed from linked cases in radiation exposure	No

(continued)

Table 3. (continued)

Study name (reference)	Method of follow-up: active vs linkage	Loss to follow-up*	Likelihood of A. Differential ascertainment B. Incomplete ascertainment C. False negative outcomes D. False positive outcomes	Other classification issues	Comment	Potential for bias (Y/N possible)
Techa River residents (6)	Active: case ascertainment from oncology clinics, medical records, and death certificates (latter percent declined over time)	NK[†]; outcome available on 73% of cohort; 21% periodically lived outside study region; 5.7% nonmigrants lost to follow-up	A. No B. Possible ↓ C. Likely D. Possible	20% incident cancers were death certificate diagnoses	Authors state: no indication that migration confounds results, although other studies suggest that healthier persons more likely to emigrate	No
Finnish background (7)	Linkage	NA; very small numbers of exclusions (0.0036% prohibited use of data; residence data incomplete for 3.3-4.4%)	A. No; population register provided information about residences for 94% cases, 95% controls B. Unlikely C. Unlikely D. Unlikely			No
Taiwanese residents (8)	Linkage	NK[§]; residential history based on interview; loss to follow-up not stated	A. No B. Possible ↓ C. Possible D. Unlikely	Improving quality of cancer registry over time; ICD-O first edition used	Incomplete and missing occupancy data	No
Medical Cardiovascular imaging patients (9)	Linkage	NK[‖]; loss to follow-up not reported	A. Possible; those undergoing diagnostic or therapeutic procedures with imaging more likely to have cancer outcomes detected B. Likely ↑ C. Possible D. Likely	No estimates provided for total cancers, total solid cancers, or leukemia. Nonstandard anatomic site groupings used to report outcomes.		Possible. Increased risk of solid cancer may have been observed in those exposed due to increased imaging
French pediatric CT (10)	Linkage	NK[¶]; loss to follow-up not reported	A. No B. Unlikely C. Unlikely D. Unlikely			No
UK pediatric CT (11)	Linkage and medical record review	Unlikely to bias results	A. No; detailed clinical review undertaken following initial report. No indication of differential by exposure status (ever CT vs never CT), but availability of detailed additional clinical information was lower for noncancer cases (40% available) than cancer cases (90% available). B. Unlikely C. Likely (brain tumors only) D. Unlikely		15.7% of potentially eligible patients identified in Radiology Information Systems database were excluded because could not be traced using National Health Services Central Register, but unlikely to differ by exposure status	No

(continued)

Table 3. (continued)

Study name (reference)	Method of follow-up: active vs linkage	Loss to follow-up*	Likelihood of A. Differential ascertainment B. Incomplete ascertainment C. False negative outcomes D. False positive outcomes	Other classification issues	Comment	Potential for bias (Y/N possible)
PIRATES (low dose) (12)	Pooled analysis: outcomes for 4 cohort outcomes identified via linkage; 4 cohorts through active follow-up; 1 cohort (a-bomb) via linkage from 1958 onward	NK**; loss to follow-up not reported	A. No B. Possible ↓ C. Possible D. Possible	No major changes in classification of total thyroid cancer over lengthy follow-up period; histologic confirmation required for cases		No
Occupational						
Korean radiation workers (13)	Linkage	NK††; loss to follow-up not reported	A. Possible; medical surveillance required for radiation workers but not for general population or worker comparison group (motor vehicle manufacturing) B. Possible ↑ C. Unlikely D. Possible	Use of a modification of ICD-10 that is closer to ICD-9 for hematopoietic neoplasms	Follow-up (mortality: 1992–2004; incidence: 2000–2005) began several years after dose monitoring was initiated	Possible. Increased solid cancer and leukemia risks due to required medical surveillance of those exposed, whereas not required in unexposed
Belarus, Russia, and Baltic CL (14)	Linkage	NA	A. NA; authors state: underascertainment likely but little reason that any underascertainment would be related to dose level B. Likely ↓; authors noted this limitation, particularly for Russia component C. Unlikely D. Unlikely	Expert hematopathologists reviewed each case		No
UKNRRW NW (15)	Linkage	Unlikely to bias results	A. No B. Unlikely C. Unlikely D. Unlikely		Refusal rate for participation approximately 1%	No
Korean male NP NW (16)	Linkage	NK‡‡; loss to follow-up not reported	A. No; unmonitored workers were those who worked in same nuclear power facilities as radiation-monitored workers B. Unlikely C. Unlikely D. Unlikely	None; ICD10 used	Follow-up (1992–2005) began 14 y after dose monitoring initiated	No

(continued)

Table 3. (continued)

Study name (reference)	Method of follow-up: active vs linkage	Loss to follow-up*	Likelihood of A. Differential ascertainment B. Incomplete ascertainment C. False negative outcomes D. False positive outcomes	Other classification issues	Comment	Potential for bias (Y/N possible)
Rocketdyne NW (17)	Linkage	Unlikely to bias results; 0.6% loss to follow-up	A. No B. Unlikely C. Possible D. Unlikely	ICD9		No
Japanese male NW (18)	Linkage	NK[§§]; 27.4% loss to follow-up for period before prospective follow-up (1986–1991) but 0.3% subsequently (1991–1997)	A. Yes; retrospective follow-up included higher proportion of young, newly employed workers than did prospective follow-up; early loss to follow-up likely related to higher dose B. Likely; excess risks for certain gastrointestinal cancers likely explained by selection bias characterizing retrospective follow-up and confounding by lifestyle factors C. Possible D. Unlikely	ICD9	Loss to follow-up was higher in early years when doses were higher	Possible. Incomplete assessment of risks of solid cancers and leukemia due to loss to follow-up of early workers
Canadian NW (19)	Linkage	97.6% vital status ascertainment	A. No B. Unlikely C. Unlikely D. Unlikely	ICD9 used to recode underlying cause of death from original ICD code in use at time of death	Cause known for 99.9% of deaths; a subset of workers (AECL) had problematic dosimetry and were therefore excluded.	No
Ukrainian CL (20)	Medical facility follow-up before 2001, linkage after	NA	A. No; case ascertainment procedures changed: cases identified from local health-care facilities before 2001 and subsequently through linkage with Ukrainian Cancer Registry B. Possible ↓; nationwide coverage by Ukrainian Cancer Registry not complete until 1997 C. Unlikely D. Unlikely	Expert hematopathologists reviewed each case	Reflects high level of medical surveillance: unexpected similar radiation-related risks for CLL and non-CLL leukemias. Unexpectedly high proportion of CLL cases in study (58%) compared with 40–44% in general populations of European descent in other countries	No

(continued)

Table 3. (continued)

Study name (reference)	Method of follow-up: active vs linkage	Loss to follow-up*	Likelihood of A. Differential ascertainment B. Incomplete ascertainment C. False negative outcomes D. False positive outcomes	Other classification issues	Comment	Potential for bias (Y/N possible)
German NP NW (21)	Follow-up through linkage of last known residence with vital status	NK[‖‖]; low loss to follow-up (0.7%)	A. No B. Possible ↓ C. Possible; 4% of death certificates requested not obtained D. Unlikely	ICD9 and ICD10	Follow-up (1991–2008) began 25 y after dose monitoring initiated	No
US NW (22)	Linkage	1.1% lost to follow-up	A. No; cause of death unavailable for 1.1% of decedents B. Unlikely C. Possible D. Unlikely	Used mortality/cause of death ascertained in earlier follow-up. Confirmed vital status with SSA Death Master File, cause of death from the NDI, and newly identified deaths coded to the latest ICD revision.		No
INWORKS NW (23, 24)	Linkage	Loss to follow-up not described for pooled cohorts	A. No B. Unlikely C. Possible D. Unlikely	See French nuclear workers below. Ascertained vital status through linkage of participating French, UK, and US cohorts with employer and SSA records. Identified cause of death through linkage with national and regional cancer registries.	Certain outcomes (smoking- and asbestos-related cancers) may have reflected confounding of radiation-related dose response by these exposures	No

(continued)

Table 3. (continued)

Study name (reference)	Method of follow-up: active vs linkage	Loss to follow-up*	Likelihood of A. Differential ascertainment B. Incomplete ascertainment C. False negative outcomes D. False positive outcomes	Other classification issues	Comment	Potential for bias (Y/N possible)
US atomic veterans (25)	Linkage	Vital status determined for 95.3%	A. No; cause of death unavailable for 3% of decedents B. Unlikely C. Possible D. Unlikely		Follow-up (1957–2010) began 12 y after first exposure; deaths occurring pre 1957 not identified. Findings for certain malignant and nonmalignant outcomes and lack of healthy worker effect observed among participants in 1 test (designated SMOKY) but not others.	No
USRT (26–28)	Linkage to national mortality register; questionnaire-based ascertainment of incidence	NK¶¶; <0.2% loss to follow-up	A. No; internal analysis used exclusively for dose-response risk assessment; no evidence of differential ascertainment by level of radiation exposure B. Breast, skin incidence likely↓ because source of ascertainment is questionnaire-based self-report. Brain tumor mortality: possible ↓ C. Breast, skin incidence: possible Brain tumor mortality: possible D. Breast, skin incidence: possible Brain tumor mortality: possible	• Some misclassification of breast and skin cancer is likely due to ascertainment from questionnaire self-report despite efforts to confirm these outcomes with medical records. Self-report compared with medical record diagnoses have shown only a small percent misclassified. • Use of death certificates as only source for primary brain tumors likely has resulted in some misclassification, but no validation has been performed.		No

(continued)

Table 3. (continued)

Study name (reference)	Method of follow-up: active vs linkage	Loss to follow-up*	Likelihood of A. Differential ascertainment B. Incomplete ascertainment C. False negative outcomes D. False positive outcomes	Other classification issues	Comment	Potential for bias (Y/N possible)
French NW (29)	Linkage	NK***; 0.2% of workers lost to follow-up	A. No; cause of death unavailable for 2.3% of decedents B. Possible ↓; cause of death information not available before 1968 C. Possible D. Unlikely	Causes of death were coded to ICD revision in effect at time of death.	French National Death Registry established1968; prior deaths not identified. Potential confounding by socioeconomic status. Many contractor workers not included because of poor follow-up, incomplete company records, problematic identifying information, and incomplete dosimetry reconstruction.	No

Notes: In the fourth column (differential/incomplete ascertainment and false negatives or positives), definitions of the terms used include: likely = evidence there was a problem; unlikely = evidence there was no problem; possible = could not rule out a problem; downward arrows = evidence of notable reduced ascertainment; upward arrows = evidence of notably increased ascertainment of clinically nonapparent or precancer neoplasms. The basis of these qualitative assessments is described in the sixth column (comments). In the seventh column (potential for bias), definitions of the terms used include: yes = potential for bias is evident; no = potential for bias is not evident; possible = could not rule out the potential for bias. Estimates of differential or incomplete ascertainment, false negative, or false positive outcomes are qualitative and somewhat subjective. Quantification of these elements is not possible for almost all of the studies due to absence of critical information about methods.

*AECL = Atomic Energy of Canada Limited; CL = Chernobyl liquidators; CLL = chronic lymphocytic leukemia; GB = Great Britain; ICCC = International Childhood Cancer Classification; ICD = International Classification of Diseases; ICD-O = International Classification of Diseases for Oncology; INWORKS = International Nuclear Workers Study; NK = not known; NP = nuclear power; NW = nuclear workers; TMI = Three Mile Island; UK = United Kingdom; UKNRRW = United Kingdom National Registry for Radiation Workers; US = United States; USRT = US Radiologic Technologists.

†NK: Swiss children background cohort identified and residence determined from 1990 and 2000 national censuses and linked with the Swiss Childhood Cancer Registry (the latter estimated >90% complete). Unclear residential history between censuses because active follow-up was not undertaken, but the Swiss National Cancer Registry includes all residences from diagnosis back to birth and is therefore potentially more complete.

‡NK: Techa River residents study had loss to follow-up of 15% in 2007 publication that declined to 5.7% in the current publication; results from studies of migrants suggest that migration wqas more likely by healthier persons, although the authors explicitly indicated it was unlikely that migration acts as a confounding factor.

§NK: Taiwan residents' cohort was established in 1992, interviewed in 1995–2000 to reconstruct residential history from 1983 onward; incomplete and missing occupancy data resulted in exclusion of 1020 cohort members from 7262 registered as living in the building.

‖NK: Quebec (Canada) patients newly diagnosed with myocardial infarction (77% undergoing diagnostic or therapeutic procedures involving radiation exposure) were not actively followed-up for cancer and deaths; linkage for outcomes was limited to Quebec insurance databases for which no information was provided about level of completeness; no information about loss to follow-up or emigration.

¶NK: French pediatric CT population followed-up using vital status register designated medium quality; loss to follow-up not stated.

**NK: PIRATES, likely highly complete identification of thyroid cancer incidence from four cohorts linked with high-quality nationwide population-based and cancer registries and the a-bomb survivors from 1958 onward when high-quality cancer registries were available; likely underascertainment for four cohorts with other methods of follow-up and before 1958 for the a-bomb survivors.

††NK: Korean radiation workers were defined as all workers under medical surveillance because of ionizing radaition exposures as required by law, but there was little information about the source and completeness of this cohort. Follow-up began at the date of first exposure surveillance (as early as January 1984 or later) or January 1992, whichever was later. Hence, outcomes that ocurred before 1992 were not considered.

‡‡NK: Korean nuclear power industry workers radiation workers were defined as those who were issued with a dosimeter at nuclear power facilities until 2005. Follow-up for cancer incidence was undertaken for male nuclear power industry workers who were compared with unmonitored workers from the same facilities during the period 1992–2005. Outcomes that occurred before 1992 were not considered.

§§NK: Japanese nuclear workers were characterized by 27.4% loss to follow-up during 1986–1991 due to incorrect address information provided by nuclear facility or lack of availability of residential addresses, which were only maintained for 5 years; only 0.3% loss to follow-up during 1991–2002 because follow-up was initiated in 1991 and residential addresses were fully available during the 1991–2002 follow-up.

‖‖NK: German nuclear workers were followed-up by search of the regional population registry based on the last known address to determine vital status. No information about loss to follow-up or inability to identify workers in the regional population registries. Dose monitoring was initiated 25 years before follow-up was launched. Deaths occurring before 1991 were not identified.

¶¶NK: For the USRT, annual individual dose estimates were reconstructed for the period 1926–1997, although follow-up did not commence until completion of a baseline questionnaire (eg, 1983–1989 or 1994–1998, depending on which "baseline" questionnaire patients completed). The historical dose reconstruction required incorporation of questionnaire (work history, work procedures, radiation protection) information because badge doses were missing for a substantial fraction of technologists, particularly for the period before 1977.

***NK: In the French nuclear workers, dose monitoring was initiated 18 years before follow-up was possible because a national death register was only available from 1968 onward. Deaths before 1968 were not systematically identified, but an earlier analysis revealed that the standardized mortality ratio for the period 1946–2004 was similar to that for the period 1968–2004 (49).

into adulthood) (11), one on pediatric radiation and thyroid cancer at any age (12), a few on single adult cancer outcomes including two on leukemia (14,20), one each on breast (26) and skin cancers (27), and one on poorly defined cancer incidence outcomes not specified by recognized cancer categories (9). In contrast, seven (17–19,21,23,25,29) of the 14 occupational radiation studies assessed only mortality risks. Cancer incidence is a preferred outcome particularly for cancers with long survival and/or indolent clinical course, but the absence of national population-based cancer registries may preclude the feasibility of assessing incidence rather than mortality.

Cancer Incidence Studies

Population-based cancer registries were the primary source of cancer incidence ascertainment in 13 of 17 populations; 12 (1,4,5,7,8,10–12,14–16,20) were linked with national and one (2) with regional cancer registries. The remaining four identified cancer outcomes from national health insurance data (13), hospital discharge and outpatient clinic information (9), self-administered questionnaires (26,27), or multiple sources (6); two (6,26,27) of the four studies were carried out in geographic regions lacking national cancer registries. IARC rated cancer registries as high quality in all but two studies (5,12) based on coverage greater than 50%, although the high-quality designation for some registries to which the cohorts were linked (8,14) applied only to the latter part of follow-up.

Among the 17 cancer incidence studies, 13 reported leukemia incidence (1,2,4,5,7,8,10,11,13–16,20). The six pediatric leukemia studies included expert pathology review (1) and use of the International Childhood Cancer Classification (4,5) or the current International Classification of Diseases for Oncology (7,10,11), whereas five (2,8,13,15,16) of the seven studies reporting leukemia incidence in adults used older classifications and only two used expert pathology review (14,20).

Exposure periods for the 26 populations spanned from 1926 through 2011. However, follow-up periods were generally within the period of 1974 to 2011 or earlier for all but four studies (6,12,15,26–28). Follow-up for cancer incidence generally began later than for mortality because population-based cancer registries were established more recently than mortality registries [e.g., in the UK radiation worker study (15), mortality and cancer incidence ascertainment began in 1955 and 1971, respectively] (50). Follow-up was 20 years or less for all but five (6,8,11,12,15) of the 12 cancer incidence cohort studies.

Cancer Mortality Studies

Eleven of 12 cancer mortality studies [except for the China background study (3)] linked the study populations with national death registries. The cancer mortality registries were mostly characterized as high quality by IARC except for two designated as medium (21,29) and one low quality (18). Although active individual follow-up was employed in the Chinese background study (3), the absence of population-based cancer incidence and mortality registries, variable cancer outcome ascertainment sources, and lack of histopathologic confirmation likely led to incomplete vital status registration. In addition, the lack of blinding of members of the Chinese data collection team to natural background radiation exposure status may have led to differential cancer ascertainment in the geographic region with higher background radiation vs that in the region with lower background radiation.

Eleven of the 12 cancer mortality studies reported leukemia risks (3,13,15,17–19,21,22,24,25,29). Death certificates may lack altogether or provide incompletely specified leukemia subtype, particularly in earlier decades. None of the leukemia mortality studies used newer classifications for myeloid or lymphoid neoplasms, although most reported risks for leukemia excluding CLL and a few reported CLL risks separately (data not shown). For cancer outcomes, the emphasis of the current analysis was on total cancer or all solid cancers, and thus there should be little misclassification resulting from lack of information about type of solid cancer and level of specification of specific solid cancers. Estimates of radiation dose response for total cancer would include leukemia, but the rarity of leukemias compared with total solid cancer would result in relatively little effect of inclusion vs exclusion of leukemias. Clinico-pathologic characteristics of leukemias differ notably from nonhematopoietic solid cancers, so misclassification of these two major cancer groupings is highly unlikely.

Exposure periods for the cancer mortality studies ranged from 1916 to 2008. A majority included persons first exposed as early as the 1940s (15,22–29) and 1950s (16,18,19). Follow-up periods were 36 years or more for six cohorts and 11–25 years for the others.

Follow-Up, Ascertainment, and Classification Issues and Potential for Bias

Follow-Up Issues

Only two cancer incidence studies (6,12) and two cancer mortality studies (3,22) carried out active follow-up of individual persons. Information about loss to follow-up was not reported in the majority (N = 16) of the 26 studies (Table 3). For those incidence studies that did report loss to follow-up, most reported loss to follow-up of less than 5%. Exceptions included the 21% emigration in Techa River residents (6) and 38% loss-to-follow-up among the Taiwanese residents, many of whom were students who only resided a few years in the contaminated buildings (8). Most cancer mortality studies reported loss to follow-up of less than 5% (3,17,19,21,22,25–28); however, loss to follow-up was reported to be “low” but not specified in the French nuclear workers (29), and the Japanese nuclear worker study reported loss to follow-up of 27.4% (18). In the Chinese background study (3), the methods for follow-up of mortality changed part-way through the study.

Close to one-half of the studies including incidence (5,6,8–10,12,13,16,26,27) and mortality outcomes (13,18,21,26,28,29) had methodological features that potentially precluded accurate quantification of loss to follow-up (see Table 3). Loss to follow-up will be greater if the approach used is “passive individual follow-up” rather than active individual follow-up as described above. Loss to follow-up was likely to be greater in studies when exposure periods were evaluated before registers were established to enable systematic follow-up of incidence (13) and mortality outcomes (13,16,18,21,23,24,26,28). Validity would only be affected if follow-up completeness was related to dose; control for calendar year period would be helpful in this situation. Incomplete information about residential history (5,8) may also have affected completeness of follow-up.

Ascertainment Issues

Incomplete ascertainment of cancer was likely in three cancer incidence studies (9,14,26) and two cancer mortality studies (3,18) and was possible in several other cancer incidence

(5,6,8,12,13,20) and cancer mortality studies (13,21,28) (Table 3). Four studies appeared to be characterized by differential ascertainment associated with radiation level (3,9,13,18).

Classification Issues

False negatives (ie, underdiagnosis) were likely in two studies with cancer incidence (6,11) and two with cancer mortality outcomes (3,13) and possible in other cancer incidence (5,8,9,12,26) and cancer mortality studies (17,18,21–26,28,29) (Table 3). The occurrence of false negatives does not result in bias if this shortcoming is not related to radiation exposure status by radiation dose levels. False positives (ie, overdiagnosis) were likely in one cancer incidence study (9) and possible in other cancer incidence (5,6,12,26) and cancer mortality (28) studies. False positives in cancer mortality studies could occur if metastases to a site (eg, brain, liver, or other) are reported as the primary site. False positives could result in bias if occurring differentially according to radiation exposure status, but false positives are less likely to be a problem in mortality studies of "all cancer" as an outcome compared with studies focusing on specific cancer outcomes. Only the three case-control studies of the Chernobyl residents and liquidators' populations (1,14,20) included expert hematopathologists' review. Several long-term studies reclassified solid cancers using the latest ICD classification (19,22,23,26). Two studies had potential variability in the accuracy of diagnoses, mostly due to different sources of cancer outcome data (3,6), and one study reported risks for anatomic site groupings not routinely used (9).

Potential for Bias

Four studies were judged to be possibly biased in cancer outcome assessment (3,9,13,18). Three of the studies were also possibly biased in outcome assessment due to the potential for differential levels in medical surveillance in the radiation-exposed vs the comparison populations in these studies (3,9,13) (Table 3). In the China background study, differential levels of surveillance used in the geographic regions with higher vs lower background radiation along with lack of population-based mortality registers may have resulted in overestimation of the excess relative risk for leukemia (3). Use of diagnostic or therapeutic imaging procedures along with cancer outcome reporting by nonstandard anatomic site groupings in the cardiovascular imaging study would have been more likely to result in differential ascertainment and/or misclassification in the exposed population but not the comparison population (9). For the study of Korean radiation workers, medical surveillance was required for radiation workers but not for the comparison group of motor vehicle manufacturing workers (13). Akiba and Mizuno refer to the article describing the earlier follow-up of the Japanese nuclear workers for details about the methods (51). As noted by Iwasaki et al. (51), at the start of cohort follow-up of the Japanese nuclear workers, more precise information on residential address (the primary method of follow-up) could be obtained for workers who were alive and currently working compared with those who were deceased. The investigators stated that "since currently employed workers were included more frequently in the higher-dose group than the lower-dose group, differential follow-up rates were introduced in the 'retrospective' (1986–1990) component of the study" (51). Although difficult to estimate, the net effect is likely to be attenuation of the excess relative risk per unit radiation dose through early loss to follow-up during periods with higher radiation exposures. The investigators indicated that the prospective component of the follow-up was less affected by this selection bias; the more recent report of the extended follow-up excluded the retrospective (1986–1990) component, restricting follow-up to 1991 and later (18).

Discussion

The systematic evaluation of cancer outcomes in 26 studies of low-dose or low-dose rate external radiation revealed that the majority of studies lacked information to enable comprehensive evaluation of major sources of cancer outcome assessment. For most of the studies, the outcome information was generally ascertained from high-quality, population-based cancer registries (76%) or mortality registries (67%). Follow-up rates were not described in the majority (62%) of the 26 studies, and only one of the studies using registry linkage provided a critical assessment of the quality, completeness, or accuracy of the vital status, cancer, or mortality registries used (22). Underascertainment of outcomes (false negatives) was likely if populations could not be linked with high-quality national registries that were lacking altogether, for example, in the United States (52,53), or not established during early exposure years (13).

Linkage may not have been feasible in studies lacking detailed individual residential history (5,8) or those with substantial emigration (6), thus affecting tracing (eg, obtaining detailed personal identifier information to enable registry linkage and locating and contacting a person to verify that personal identifier information is correct and, for some studies, to request participation in a questionnaire survey). Incomplete ascertainment of myeloid neoplasms, such as MDS and myeloproliferative disorders, due to misclassification or changing classification was likely in early years as discussed below. False positives may have occurred as a result of cancer ascertainment from self- or next-of-kin report (3,26,27), through misclassification of benign entities as malignant, or inclusion of screen-identified cancer precursors or borderline neoplastic disorders in studies with enhanced medical surveillance (9). All pediatric leukemia studies had expert hematopathology review or used the most recent International Classification of Diseases for Oncology or International Childhood Cancer Classifications (54), whereas the adult studies of leukemia incidence and mortality often used older classifications. Some, but not all, long-term studies recoded solid cancers to the latest ICD classification in use. These outcome ascertainment shortcomings were mostly nondifferential by radiation exposure level and either had little effect or reduced risk estimates towards the null. We concluded that the Chinese high background radiation-exposed residents (particularly for leukemia mortality ascertainment) (3), cardiovascular imaging patients (9), Korean radiation workers (13), and Japanese nuclear workers (18) may have had cancer ascertainment that was possibly differential by radiation exposure level.

Linkage of a large US cohort with high-quality, population-based cancer registries found close to 90% of medical record-verified cancers to have been identified in the registries (55). Comparison of questionnaire-derived self-report with registry report revealed 21–39% underreporting (56–59), particularly noting this problem for myeloid neoplasms (60) that may have led to underascertainment of myeloid leukemias and the related MDS. The reported international variation in underreporting as summarized by Navarro et al. (61) and particularly poor

reporting of primary liver and uterine cervical cancer (62) should not have had a major impact on the studies evaluating nonleukemia cancers in the current review because the primary outcomes focused on total cancers or total solid cancers. Death certificates may be inaccurate and incomplete for some causes of death based on comparisons with autopsy studies (63), but comparison of breast cancer on death certificates with hospital discharge records revealed only a modest level of misclassification and no statistically significant differences between screen-detected and nonscreen-detected cases (64). All-cancer sites combined (or those representing broad site groupings) have been found to have relatively high sensitivity and specificity on death certificates (63,65,66).

For the minority of studies reporting loss to follow-up, the fraction of persons "lost" was generally less than 5%. If this percent is an accurate estimate, such a relatively small loss should have little impact on true radiation-related risk estimates, whereas a loss to follow-up of 20% or greater could lead to bias in risk estimates based on simulation studies because persons lost to follow-up are generally not missing at random (67). Even if persons appear to be missing completely at random, investigators have found that as loss to follow-up increases, the precision of the risk estimate decreases (68). Nevertheless, even if reported loss to follow-up is very small, all incident cancers in the cohort may not be identified in the absence of active individual follow-up and/or linkage with highly complete vital status and population-based registries.

Because loss to follow-up is generally not random, those who are lost often have notably different profiles than those who are followed up (67). In addition to the healthy worker or person effect, comparison of "exposed" workers or "patients" with the general population may be problematic because the "exposed" population undergoes tracing (eg, follow-up of individual persons to identify vital status, diagnosis and date of diagnosis of incident cancers, and cause of death and date of death for deceased cases) whereas the general population does not (69). In addition to some persons missing from registries, emigration may also contribute to loss to follow-up, but this issue has been evaluated in relatively few studies (70–72). Although some studies have reported similarities between emigrants and nonemigrants in serious health outcomes, others have reported that emigrants may have higher levels of skills (70) and better health than those who remain behind (73) but that emigrants who are very ill may return to their country of origin to be with family close to death (73,74).

False negatives are largely due to loss to follow-up and other forms of incomplete ascertainment as described above but may result from changes in classification. Substantial changes were made in the landmark 2001 World Health Organization classification of hematopoietic and lymphoproliferative neoplasms that included reclassification of MDS (previously known as "refractory anemia") and myeloproliferative neoplasms as malignancies (75). These myeloid neoplasms were formerly and even recently frequently diagnosed as benign hematological disorders and often worked up in physicians' offices or misdiagnosed and not reported to population-based registries (60). Myelodysplastic syndromes and other nonleukemia myeloid neoplasms may transform to acute myeloid leukemia (AML); certain systemic chemotherapy agents, benzene, and ionizing radiation may cause both AML and MDS (76). Therefore, epidemiological studies have increasingly combined MDS with AML to evaluate these associations (77,78). Ascertainment of MDS and myeloproliferative neoplasms is a potential problem for both incidence and mortality studies but is a greater problem for the latter due to poor specificity of these entities on death certificates.

Radiation epidemiology mortality studies that rely on death certificates have struggled with the approach for handling indeterminate or incompletely specified leukemias, particularly in long-term studies due to major changes in leukemia classification during the past 50 years. Because leukemia latency is short and occupational radiation doses were higher in the middle decades of the 20th century than subsequently, it is possible that poor leukemia subtype classification in the early years of follow-up may cause bias in subtype-specific risk estimates. For example, the US pooled nuclear worker study (22), which followed a large cohort of workers for up to 60 years, found that the excess relative risk per Sievert for non-CLL leukemia (eg, used in the present systematic appraisal) increased by 50–80% when excluding leukemias of indeterminate subtype, all of which occurred in years covered by ICD 6th and 7th revision classifications (79). Although the risk per unit dose was higher following the exclusions, the small percent and numbers of cases excluded (22 of 206 total non-CLL leukemia cases) limited firm conclusions about potential bias.

False positives are a possibility if screening radiation-exposed persons, but not the comparison unexposed persons or other referent population, resulted in higher levels of reporting of "in situ" neoplasms or precursors that are classified as malignancies but might not otherwise be identified in an unscreened population and may undergo involution or might never come to clinical attention. Other screen-detected entities might be misclassified as malignancies (eg, certain types of colon adenomas or borderline ovarian tumors). If the category "all leukemias" is used, particularly before 2001, and there is no exclusion for CLL, there could be false positives because CLL has been classified as a form of non-Hodgkin lymphoma since 2001.

Strengths of this evaluation included the comprehensive nature of the outcome assessment focusing on reported and unreported aspects of loss to follow-up, under- and overascertainment, misclassification, and changing classification. Comprehensive reviews of the radiation epidemiology literature for adults (30,80–84) and children (85) have not previously evaluated critically the key elements of outcome assessment as described in this article.

Limitations derive primarily from lack of detailed description of methods in the reports for the 26 studies about the potential for missing vital status, absence of information about the methods used and the results of loss to follow-up for the majority of studies, incomplete cancer or mortality registry data for an unknown fraction of population members in linkage studies, unknown levels of outcome misclassification, or, for several cohorts, a description of specific methods for outcome ascertainment for exposure periods before establishment of registries. Lack of active follow-up in all but four studies and the resulting underascertainment of cancer outcomes affects statistical power. If the level of active follow-up is differential between radiation-exposed and comparison populations, such a difference in level of effort could limit several aspects of outcome assessment. The classification of cancer and mortality registries according to quality criteria by IARC was primarily driven by more recent performance; the IARC classification did not include a comprehensive historical evaluation since the start of the registries. It is therefore possible that the quality measure assigned may not reflect earlier quality levels. Substantial reporting of large and heterogeneous categories (all-cancer sites combined, all solid cancers, all leukemias) in most of the studies focusing on multiple outcomes, which were likely

related to the radiation protection emphasis and to limited statistical power, provided little consideration of morphologic subtypes and virtually no consideration of molecularly characterized tumor subtypes, which may differ in radiation-related risks. In the absence of detailed information about key elements needed to comprehensively and quantitatively evaluate all major sources of potential outcome assessment errors, the characterization of the potential likelihood of differential or incomplete ascertainment or false negative or false positive outcomes and the potential for bias is necessarily qualitative and somewhat subjective in nature. From the data presented and missing information as described above, it was not possible to quantify the impact of some of the key shortcomings.

Validation methods and statistical approaches might in some cases be used to reduce the effect of the outcome assessment limitations and errors described above. Comparison of diagnoses from registries and other electronic databases with persons' medical records could provide information that would allow for correction of errors in outcome classification. In addition, completeness of accurate outcome ascertainment can be improved by including medical record-confirmed cases that are listed by nonspecific and secondary codes in registries or electronic databases that are the source of case ascertainment (86). For problems with incomplete follow-up, adjustment of person-years by censoring could be useful (87). In studies with the follow-up curtailed due to emigration, one should censor follow-up at the time of emigration if the date is known (6); if unknown, it may be possible to estimate period, sex, and exposure status–dependent person-year adjustment factors to use in the analysis (41). If there are variables that are related to both exposure levels and completeness of case ascertainment, then one might consider adjusting the baseline risk for these variables (88). Following implementation of substantial improvements in outcome assessment in ongoing and future epidemiological studies, it would be important to use quantitative bias analysis to provide more definitive estimates of the direction, magnitude, and uncertainty arising from systematic errors (89).

In conclusion, the evaluation of outcome assessment in 26 studies of low-dose or low dose–rate radiation exposure and cancer risks has identified several methodological issues. Despite the shortcomings in outcome assessment, only four studies (3,9,13,18) may have had the potential for bias, but evidence is not conclusive. The findings from this evaluation point to the need to implement more rigorous active follow-up of exposed and comparison persons to clearly establish vital status such as used in the cohort study of US nuclear workers (22). Cohort studies also need to report not only loss to follow-up but also the details of the completeness and accuracy of the population-based cancer and mortality registries used for linkage and determination of outcome status. In addition, efforts should be undertaken to implement expert pathology review, particularly for hematopoietic and lymphoproliferative neoplasms; this may not be possible for mortality studies with follow-up beginning decades ago. Ongoing follow-up is also needed to assess radiation-related cancer risks at older ages in many radiation-exposed populations, such as nuclear workers and medical radiation workers, particularly those performing newer diagnostic and therapeutic procedures using imaging technologies. Use of multiple sources of validation and state-of-the-art statistical approaches that may help to overcome outcome assessment problems and errors, as described above, is also encouraged.

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Notes

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References

1. Davis S, Day RW, Kopecky KJ, et al.; International Consortium for Research on the Health Effects of Radiation Writing Committee, Study Team. Childhood leukaemia in Belarus, Russia, and Ukraine following the Chernobyl power station accident: results from an international collaborative population-based case-control study. *Int J Epidemiol*. 2006;35(2):386–396.
2. Han YY, Youk AO, Sasser H, et al. Cancer incidence among residents of the Three Mile Island accident area: 1982-1995. *Environ Res*. 2011;111(8):1230–1235.
3. Tao Z, Akiba S, Zha Y, et al. Cancer and non-cancer mortality among inhabitants in the high background radiation area of Yangjiang, China (1979-1998). *Health Phys*. 2012;102(2):173–181.
4. Kendall GM, Little MP, Wakeford R, et al. A record-based case-control study of natural background radiation and the incidence of childhood leukaemia and other cancers in Great Britain during 1980-2006. *Leukemia*. 2013;27(1):3–9.
5. Spycher BD, Lupatsch JE, Zwahlen M, et al. for the Swiss Pediatric Oncology Group. Background ionizing radiation and the risk of childhood cancer: a census-based nationwide cohort study. *Environ Health Perspect*. 2015;123(6):622–628.
6. Davis FG, Yu KL, Preston D, et al. Solid cancer incidence in the Techa River incidence cohort: 1956-2007. *Radiat Res*. 2015;184(1):56–65.
7. Nikkila A, Erme S, Arvela H, et al. Background radiation and childhood leukemia: a nationwide register-based case-control study. *Int J Cancer*. 2016;139(9):1975–1982.
8. Hsieh WH, Lin IF, Ho JC, et al. 30 years follow-up and increased risks of breast cancer and leukaemia after long-term low-dose-rate radiation exposure. *Br J Cancer*. 2017;117(12):1883–1887.
9. Eisenberg MJ, Afilalo J, Lawler PR, et al. Cancer risk related to low-dose ionizing radiation from cardiac imaging in patients after acute myocardial infarction. *CMAJ*. 2011;183(4):430–436.
10. Journy N, Rehel JL, Ducou Le Pointe H, et al. Are the studies on cancer risk from CT scans biased by indication? Elements of answer from a large-scale cohort study in France. *Br J Cancer*. 2015;112(1):185–193.
11. Berrington de Gonzalez A, Salotti JA, McHugh K, et al. Relationship between paediatric CT scans and subsequent risk of leukaemia and brain tumours:

assessment of the impact of underlying conditions. *Br J Cancer*. 2016;114(4):388–394.
12. Lubin JH, Adams MJ, Shore R, et al. Thyroid cancer following childhood low-dose radiation exposure: a pooled analysis of nine cohorts. *J Clin Endocrinol Metab*. 2017;102(7):2575–2583.
13. Ahn YS, Park RM, Koh DH. Cancer admission and mortality in workers exposed to ionizing radiation in Korea. *J Occup Environ Med*. 2008;50(7):791–803.
14. Kesminiene A, Evrard AS, Ivanov VK, et al. Risk of hematological malignancies among Chernobyl liquidators. *Radiat Res*. 2008;170(6):721–735.
15. Muirhead CR, O'Hagan JA, Haylock RG, et al. Mortality and cancer incidence following occupational radiation exposure: third analysis of the National Registry for Radiation Workers. *Br J Cancer*. 2009;100(1):206–212.
16. Jeong M, Jin YW, Yang KH, et al. Radiation exposure and cancer incidence in a cohort of nuclear power industry workers in the Republic of Korea, 1992-2005. *Radiat Environ Biophys*. 2010;49(1):47–55.
17. Boice JD Jr, Cohen SS, Mumma MT, et al. Updated mortality analysis of radiation workers at Rocketdyne (Atomics International), 1948–2008. *Radiat Res*. 2011;176(2):244–258.
18. Akiba S, Mizuno S. The third analysis of cancer mortality among Japanese nuclear workers, 1991-2002: estimation of excess relative risk per radiation dose. *J Radiol Prot*. 2012;32(1):73–83.
19. Zablotska LB, Lane RS, Thompson PA. A reanalysis of cancer mortality in Canadian nuclear workers (1956-1994) based on revised exposure and cohort data. *Br J Cancer*. 2014;110(1):214–223.
20. Zablotska LB, Bazyka D, Lubin JH, et al. Radiation and the risk of chronic lymphocytic and other leukemias among Chornobyl cleanup workers. *Environ Health Perspect*. 2013;121(1):59–65.
21. Merzenich H, Hammer GP, Troltzsch K, et al. Mortality risk in a historical cohort of nuclear power plant workers in Germany: results from a second follow-up. *Radiat Environ Biophys*. 2014;53(2):405–416.
22. Schubauer-Berigan MK, Daniels RD, Bertke SJ, et al. Cancer mortality through 2005 among a pooled cohort of U.S. nuclear workers exposed to external ionizing radiation. *Radiat Res*. 2015;183(6):620–631.
23. Richardson DB, Cardis E, Daniels RD, et al. Risk of cancer from occupational exposure to ionising radiation: retrospective cohort study of workers in France, the United Kingdom, and the United States (INWORKS). *BMJ*. 2015;351:h5359.
24. Leuraud K, Richardson DB, Cardis E, et al. Ionising radiation and risk of death from leukaemia and lymphoma in radiation-monitored workers (INWORKS): an international cohort study. *Lancet Haematol*. 2015;2(7):e276–81.
25. Caldwell GG, Zack MM, Mumma MT, et al. Mortality among military participants at the 1957 PLUMBBOB nuclear weapons test series and from leukemia among participants at the SMOKY test. *J Radiol Prot*. 2016;36(3):474–489.
26. Preston DL, Kitahara CM, Freedman DM, et al. Breast cancer risk and protracted low-to-moderate dose occupational radiation exposure in the US Radiologic Technologists Cohort, 1983–2008. *Br J Cancer*. 2016;115(9):1105–1112.
27. Lee T, Sigurdson AJ, Preston DL, et al. Occupational ionising radiation and risk of basal cell carcinoma in US radiologic technologists (1983-2005). *Occup Environ Med*. 2015;72(12):862–869.
28. Kitahara CM, Linet MS, Balter S, et al. Occupational radiation exposure and deaths from malignant intracranial neoplasms of the brain and CNS in U.S. Radiologic Technologists, 1983–2012. *AJR Am J Roentgenol*. 2017;208(6):1278–1284.
29. Leuraud K, Fournier L, Samson E, et al. Mortality in the French cohort of nuclear workers. *Radioprotection*. 2017;52(3):199–210.
30. National Research Council (NRC). Health risks from exposure to low levels of ionizing radiation. In: *Biological Effects of Ionizing Radiation (BEIR) VII. Phase 2*. Washington, DC: National Research Council; 2006:265–266, 278, 284–286.
31. National Council on Radiation Protection and Measurements. *NCRP Commentary 27. Implications of Recent Epidemiologic Studies for the Linear-Nonthreshold Model and Radiation Protection*. Bethesda, MD: National Council on Radiation Protection and Measurements; 2018.
32. Greenland S, Lash TL. Bias analysis. In: Rothman KJ, Greenland S, Lash TL, eds. *Modern Epidemiology*. 3rd ed. Philadelphia: Wolters Kluwer/Lippincott Williams and Wilkins; 2008:358–359.
33. Sakata R, Grant EJ, Ozasa K. Long-term follow-up of atomic bomb survivors. *Maturitas*. 2012;72(2):99–103.
34. Berrington de Gonzalez A, Daniels RD, Cardis E, et al. Epidemiological Studies of Low-Dose Ionizing Radiation and Cancer: Rationale and Framework for the Monograph and Overview of Eligible Studies. *JNCI Monographs*. 2020;2020(56):97–113.
35. Daniels RD, Kendall GM, Thierry-Chef I, et al. Strengths and Weaknesses of Dosimetry Used in Studies of Low-Dose Radiation Exposure and Cancer. *JNCI Monographs*. 2020;2020(56):114–132.
36. Greenland S. Response and follow-up bias in cohort studies. *Am J Epidemiol*. 1977;106(3):184–187.
37. von Allmen RS, Weiss S, Tevaearai HT, et al. Completeness of follow-up determines validity of study findings: results of a prospective repeated measures cohort study. *PLoS One*. 2015;10(10):e0140817.
38. Xue X, Agalliu I, Kim MY, et al. New methods for estimating follow-up rates in cohort studies. *BMC Med Res Methodol*. 2017;17(1):155.
39. Edwards JK, Cole SR, Chu H, et al. Accounting for outcome misclassification in estimates of the effect of occupational asbestos exposure on lung cancer death. *Am J Epidemiol*. 2014;179(5):641–647.
40. Gilbert R, Martin RM, Donovan J, et al. Misclassification of outcome in case-control studies: methods for sensitivity analysis. *Stat Methods Med Res*. 2016;25(5):2377–2393.
41. Sposto R, Preston DL, Shimizu Y, et al. The effect of diagnostic misclassification on non-cancer and cancer mortality dose response in A-bomb survivors. *Biometrics*. 1992;48(2):605–617.
42. World Health Organization (WHO). *International Classification of Diseases for Oncology*. 3rd ed. Geneva: World Health Organization; 2000.
43. Al-Hamadani M, Habermann TM, Cerhan JR, et al. Non-Hodgkin lymphoma subtype distribution, geodemographic patterns, and survival in the US: a longitudinal analysis of the National Cancer Data Base from 1998 to 2011. *Am J Hematol*. 2015;90(9):790–795.
44. Bowen JM, Perry AM, Laurini JA, et al. Lymphoma diagnosis at an academic centre: rate of revision and impact on patient care. *Br J Haematol*. 2014;166(2):202–208.
45. Glaser SL, Clarke CA, Keegan TH, et al. Time trends in rates of Hodgkin lymphoma histologic subtypes: true incidence changes or evolving diagnostic practice? *Cancer Epidemiol Biomarkers Prev*. 2015;24(10):1474–1488.
46. Hauptmann S, Friedrich K, Redline R, et al. Ovarian borderline tumors in the 2014 WHO classification: evolving concepts and diagnostic criteria. *Virchows Arch*. 2017;470(2):125–142.
47. Gilbert ES, Little MP, Preston DL, et al. Issues in Interpreting Epidemiologic Studies of Populations Exposed to Low-Dose, High-Energy Photon Radiation. *JNCI Monographs*. 2020;2020(56):176–187.
48. Ferlay J, Soerjomataram I, Ervik M, et al. GLOBOCAN 2012: estimated cancer incidence, mortality and prevalence worldwide in 2012. V1.0. IARC CancerBase No. 11. http://globocan.iarc.fr/pages/datasource_and_methods. Accessed October 26, 2019.
49. Metz-Flamant C, Laurent O, Samson E, et al. Mortality associated with chronic external radiation exposure in the French combined cohort of nuclear workers. *Occup Environ Med*. 2013;70(9):630–638.
50. Muirhead CR, Hagan JA, Haylock RGE, et al. *HPA-RPD-062 - Third analysis of the National Registry for Radiation Workers: Occupational Exposure to Ionising Radiation in Relation to Mortality and Caner Incidence*. Didcot, Oxfordshire, UK: Health Protection Agency, Centre for Radition, Chemical, and Environmental Hazards, Radiation Protection Division; 2009:14–15.
51. Iwasaki T, Murata M, Ohshima S, et al. Second analysis of mortality of nuclear industry workers in Japan, 1986-1997. *Radiat Res*. 2003;159(2):228–238.
52. Bender TJ, Beall C, Cheng H, et al. Methodologic issues in follow-up studies of cancer incidence among occupational groups in the United States. *Ann Epidemiol*. 2006;16(3):170–179.
53. Ruder AM, Hein MJ, Hopf NB, et al. Cancer incidence among capacitor manufacturing workers exposed to polychlorinated biphenyls. *Am J Ind Med*. 2017;60(2):198–207.
54. Steliarova-Foucher E, Stiller C, Lacour B, et al. *International Classification of Childhood Cancer*. 3rd ed. *Cancer*. 2005;103(7):1457–1467.
55. Michaud A, Midthune D, Hermansen S, et al. Comparison of cancer registry case ascertainment with SEER estimates and self-reporting in a subset of the NIH-AARP Diet and Health Study. *J Regist Manag*. 2005;32(2):70–75.
56. Bergmann MM, Calle EE, Mervis CA, et al. Validity of self-reported cancers in a prospective cohort study in comparison with data from state cancer registries. *Am J Epidemiol*. 1998;147(6):556–562.
57. Desai MM, Bruce ML, Desai RA, et al. Validity of self-reported cancer history: a comparison of health interview data and cancer registry records. *Am J Epidemiol*. 2001;153(3):299–306.
58. Parikh-Patel A, Allen M, Wright WE, et al. Validation of self-reported cancers in the California Teachers Study. *Am J Epidemiol*. 2003;157(6):539–545.
59. Freedman DM, Sigurdson AJ, Doody MM, et al. Comparison between cancers identified by state cancer registry, self-report, and death certificate in a prospective cohort study of US radiologic technologists. *Int J Epidemiol*. 2006;35(2):495–497.
60. Jacobs EJ, Briggs PJ, Deka A, et al. Follow-up of a large prospective cohort in the United States using linkage with multiple state cancer registries. *Am J Epidemiol*. 2017;186(7):876–884.
61. Navarro C, Chirlaque MD, Tormo MJ, et al. Validity of self reported diagnoses of cancer in a major Spanish prospective cohort study. *J Epidemiol Community Health*. 2006;60(7):593–599.
62. Cho S, Shin A, Song D, et al. Validity of self-reported cancer history in the health examinees (HEXA) study: a comparison of self-report and cancer registry records. *Cancer Epidemiol*. 2017;50(Pt A):16–21.
63. Mieno MN, Tanaka N, Arai T, et al. Accuracy of death certificates and assessment of factors for misclassification of underlying cause of death. *J Epidemiol*. 2016;26(4):191–198.
64. Goldoni CA, Bonora K, Ciatto S, et al. The IMPACT Working Group. Misclassification of breast cancer as cause of death in a service screening area. *Cancer Causes Control*. 2009;20(5):533–538.
65. Fink AK, German RR, Heron M, et al. Impact of using multiple causes of death codes to compute site-specific, death certificate-based cancer mortality statistics in the United States. *Cancer Epidemiol*. 2012;36(1):22–28.

66. Percy C, Stanek E, 3rd, Gloeckler L. Accuracy of cancer death certificates and its effect on cancer mortality statistics. *Am J Public Health*. 1981;71(3):242–250.
67. Kristman V, Manno M, Cote P. Loss to follow-up in cohort studies: how much is too much? *Eur J Epidemiol*. 2003;19(8):751–760.
68. Twisk J, de Vente W. Attrition in longitudinal studies. How to deal with missing data. *J Clin Epidemiol*. 2002;55(4):329–337.
69. Johnson ES. Bias on withdrawing lost subjects from the analysis at the time of loss, in cohort mortality studies, and in follow-up methods. *J Occup Med*. 1990;32(3):250–254.
70. Wadsworth ME, Mann SL, Rodgers B, et al. Loss and representativeness in a 43 year follow up of a national birth cohort. *J Epidemiol Community Health*. 1992;46(3):300–304.
71. Kristensen P, Bjerkedal T. Dealing with emigration in cohort studies: follow-up of mortality and cancer incidence among Norwegians born between 1967 and 1976. *Eur J Epidemiol*. 2010;25(3):155–161.
72. Gushulak BD, MacPherson DW. The basic principles of migration health: population mobility and gaps in disease prevalence. *Emerg Themes Epidemiol*. 2006;3(1):3.
73. Davey-Smith G, Chaturvedi N, Harding S, et al. Ethnic inequalities in health: a review of UK epidemiological evidence. *Critical Public Health*. 2000;10(4):375–408.
74. Abraido-Lanza AF, Dohrenwend BP, Ng-Mak DS, et al. The Latino mortality paradox: a test of the "salmon bias" and healthy migrant hypotheses. *Am J Public Health*. 1999;89(10):1543–1548.
75. Jaffe ES, Harris NL, Stein H, et al. World Health Organization classification of tumours. In: *Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissue*. Lyon, France: IARC Press; 2001:45–72.
76. Linet MS, Morton LM, Devesa SS, et al. Leukemias. In: Thun MJ, Linet MS, Cerhan JR, Haiman C, Schottenfeld D, eds. *Schottenfeld and Fraumeni Cancer Epidemiology and Prevention*. 4th ed. New York, NY: Oxford University Press; 2018:715–744.
77. Linet MS, Gilbert ES, Vermeulen R, et al. Benzene exposure response and risk of myeloid neoplasms in Chinese workers: a multicenter case-cohort study. *J Natl Cancer Inst*. 2019;111(5):465–474.
78. Morton LM, Dores GM, Schonfeld SJ, et al. Association of chemotherapy for solid tumors with development of therapy-related myelodysplastic syndrome or acute myeloid leukemia in the modern era. *JAMA Oncol*. 2018;10–1001.
79. Schubauer-Berigan MK, Daniels RD, Fleming DA, et al. Risk of chronic myeloid and acute leukemia mortality after exposure to ionizing radiation among workers at four U.S. nuclear weapons facilities and a nuclear naval shipyard. *Radiat Res*. 2007;167(2):222–232.
80. United Nations Scientific Committee on the Effects of Atomic Radiation. *Sources and Effects of Ionizing Radiation*. Vol I. New York: United Nations Scientific Committee on the Effects of Atomic Radiation; 2008. https://www.unscear.org/docs/publications/2008/UNSCEAR_2008_report_Vol1.pdf https://www.unscear.org/docs/publications/2008/UNSCEAR_2008_report_VolII.pdf.
81. United Nations Scientific Committee on the Effects of Atomic Radiation. *Sources and Effects of Ionizing Radiation*. Vol. I. New York: United Nations Scientific Committee on the Effects of Atomic Radiation; 2000. https://www.unsear.org/docs/publications/2000/UNSCEAR_2000_report.pdf.
82. United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). Effects and Risk of Ionizing Radiation. Report to the General Assembly with Scientific Annexes. Annex A: Attributing health effects to ionizing radiation exposure and inferring risks. New York, NY: United Nations Scientific Committee on the Effects of Ionizing Radiation; 2012. https://www.unscear.org/docs/publications/2012/UNSCEAR_2012_Report.pdf.
83. United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR). Effects and Risk of Ionizing Radiation. Report to the General Assembly with Scientific Annexes. Annex A: Principles and criteria for ensuring the quality of the committee's reviews of epidemiologic studies of radiation exposure. In. New York, NY: United Nations Scientific Committee on the Effects of Ionizing Radiation; 2017. https://www.unscear.org/docs/publications/2017/UNSCEAR_2017_Report.pdf.
84. Berrington de Gonzalez A, Bouville A, Rajaraman P, et al. Ionizing radiation. In: Thun MJ, Linet MS, Cerhan JR, Haiman C, Schottenfeld D, eds. *Schottenfeld and Fraumeni Cancer Epidemiology and Prevention*. 4th ed. New York, NY: Oxford University Press 2018:227–248.
85. United Nations Scientific Committee on the Effects of Atomic Radiation. Report to the General Assembly with Scientific Annexes, Annex B: Effects of radiation exposure of children. In: Sources, Effects, and Risks of Ionizing Radiation. In. New York, NY: United Nations Scientific Committee on the Effects of Atomic Radiation; 2013.
86. Pisa F, Castellsague J, Drigo D, et al. Accuracy of International Classification of Diseases, 9th Revision, Clinical Modification codes for upper gastrointestinal complications varied by position and age: a validation study in a cohort of nonsteroidal anti-inflammatory drugs users in Friuli Venezia Giulia, Italy. *Pharmacoepidemiol Drug Saf*. 2013;22(11):1195–1204.
87. Greenland S, Applications of stratified analysis methods. In: Rothman KJ, Greenland S, Lash TL, eds. *Modern Epidemiology*. 3rd ed. Philadelphia: Wolters Kluwer/Lippincott Williams and Wilkins 2008:289–293.
88. Sokolnikov M, Preston D, Gilbert E, et al. Radiation effects on mortality from solid cancers other than lung, liver, and bone cancer in the Mayak worker cohort: 1948-2008. *PLoS One*. 2015;10(2):e0117784.
89. Lash TL, Fox MP, MacLehose RF, et al. Good practices for quantitative bias analysis. *Int J Epidemiol*. 2014;43(6):1969–1985.