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Article

ARTICLE

Evaluation of Confounding and Selection Bias in Epidemiological Studies of Populations Exposed to Low-Dose, High-Energy Photon Radiation

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Abstract

Background: Low-dose, penetrating photon radiation exposure is ubiquitous, yet our understanding of cancer risk at low doses and dose rates derives mainly from high-dose studies. Although a large number of low-dose cancer studies have been recently published, concern exists about the potential for confounding to distort findings. The aim of this study was to describe and assess the likely impact of confounding and selection bias within the context of a systematic review. **Methods:** We summarized confounding control methods for 26 studies published from 2006 to 2017 by exposure setting (environmental, medical, or occupational) and identified confounders of potential concern. We used information from these and related studies to assess evidence for confounding and selection bias. For factors in which direct or indirect evidence of confounding was lacking for certain studies, we used a theoretical adjustment to determine whether uncontrolled confounding was likely to have affected the results. **Results:** For medical studies of childhood cancers, confounding by indication (CBI) was the main concern. Lifestyle-related factors were of primary concern for environmental and medical studies of adult cancers and for occupational studies. For occupational studies, other workplace exposures and healthy worker survivor bias were additionally of interest. For most of these factors, however, review of the direct and indirect evidence suggested that confounding was minimal. One study showed evidence of selection bias, and three occupational studies did not adjust for lifestyle or healthy worker survivor bias correlates. Theoretical adjustment for three factors (smoking and asbestos in occupational studies and CBI in childhood cancer studies) demonstrated that these were unlikely to explain positive study findings due to the rarity of exposure (eg, CBI) or the relatively weak association with the outcome (eg, smoking or asbestos and all cancers).
Conclusion: Confounding and selection bias are unlikely to explain the findings from most low-dose radiation epidemiology studies.

In experimental epidemiological study designs, comparability of exposed and unexposed participants is obtained through random assignment to exposure or treatment groups. Randomization leads (in expectation) to balance between exposure groups in other factors that affect risk of disease. However, except in rare circumstances (eg, where exposure confers an immediate clinical benefit), contemporary radiation epidemiological studies are not randomized experiments, because ionizing radiation exposure is recognized to be harmful.

Instead, epidemiologists typically rely on observational studies of disease occurrence among people who were exposed to ionizing radiation from medical, environmental, or occupational sources. Without the benefit of random assignment, exposure groups may differ with respect to factors other than

radiation. If these factors are also related to the disease of interest, then the observed effect of radiation on disease risk may be mixed with effects of these other disease risk factors. This is referred to as confounding. Inadequately accounting for confounding can lead to bias in an estimate of the association between radiation exposure and disease.

Bias also can occur if selection into the study (through design or in analysis) is affected by exposure and disease status: we refer to this as selection bias. For example, suppose environmental exposures vary by neighborhood affluence, people in more affluent neighborhoods agree to participate in an epidemiological study more often than people in less affluent neighborhoods, and healthy people are more likely to participate than sick people. In such a setting, a study of just those people who agree to participate may lead to a biased estimate of the underlying association between environmental exposure and disease.

Given the potential for bias in observational epidemiological studies, it is important to consider the key adjustment variables as well as those potential confounders that are omitted or not available, including the potential direction and magnitude of bias. In this article, we conducted a comprehensive review of these issues for the eligible studies considered in this monograph. We used a multi-step process where first we described the potential confounders for each study, then assessed the evidence that they could actually be confounders in this study setting, and, if so, the degree to which they may confound the association. Where available, we reviewed evidence for or against confounding (eg, the impact of adjusting for smoking status on the radiation-dose response estimate). We also reviewed evidence from related publications, for example nested case-control studies (within a cohort) that provided information on the relationship between radiation exposure and smoking. When no direct evidence was available, we used indirect methods to assess the potential for and magnitude of confounding, using a variant (1) of the Axelson-Steenland approach (2).

This article contributes to a larger review, coordinated by the National Cancer Institute, of potential biases in recent low-dose and low dose–rate epidemiology studies (3). In addition to this article, companion articles consider other sources of potential bias, such as dosimetry or outcome ascertainment errors (4,5), as well as the impact of interpretation approaches (6).

Methods

We conducted a systematic literature review of epidemiological studies on cancer risk published after the Biological Effects of Ionizing Radiation VII report in 2006 through December 31, 2017. Studies were eligible for inclusion if they were epidemiological studies of human populations exposed to low-dose (mean absorbed dose <100 mGy), predominantly low-linear energy transfer radiation. We required individualized dose estimates for the study participants and that the publications provided estimates of a cumulative radiation dose–response association and associated confidence intervals.

For each eligible study, two reviewers independently reviewed the variables that the authors accounted for in a study. We included design variables (eg, those controlled via restriction) and analytical variables (eg, those controlled via stratification or regression modeling). We also considered those variables that the authors analyzed but were found to have minimal impact on dose response estimates. Where information was available, we summarized the impact of adjustment for the confounder as an assessment of the magnitude of the bias.

Next, we described the major uncontrolled confounders of potential concern in the analysis of associations between radiation and solid cancers and leukemia. Two reviewers independently reviewed the factors that were either described by the authors or are of common concern for the exposure and population setting (eg, occupational, environmental, or medical) as unmeasured variables that were potential confounders of associations between radiation and solid cancers and leukemia in a study. For example, such factors of common concern are routinely adjusted for in studies of the exposed population [e.g., duration of employment in studies of nuclear workers as a means of partially controlling for the healthy worker survivor effect (7)] or have been identified as known human carcinogens by the International Agency for Research on Cancer and are likely to either occur frequently in the population (eg, asbestos exposure) or to be differentially distributed by radiation dose (eg, smoking). We also considered the potential for residual confounding, in which the adjustment method may have incompletely adjusted for the confounder (eg, socioeconomic status [SES] and birth cohort as a means of adjusting for smoking). We noted the potential for selection bias as a result of restriction or conditioning on variables affected by radiation exposure.

We then reviewed each paper and related studies to collect information on indirect assessment of evidence of confounding by those major uncontrolled (or under-controlled) confounders identified (eg, evaluating radiation dose response for mesothelioma as a way of indirectly assessing whether asbestos exposure was related to dose or analyzing smoking-related and nonsmoking related cancers separately). In addition, we reviewed each manuscript's Discussion section to collect information on plausibility of substantial confounding by the major uncontrolled confounders identified.

Finally, when studies lacked data on factors that could plausibly confound, we applied an extension of the Axelson indirect adjustment method to evaluate the impact of the factor to materially influence a trend in radiation risks (2,8,9). Several approaches have been proposed for calculating externally corrected relative risks (RRs) or the maximum potential confounding bias (1,10,11). Our calculations illustrate the range of a potential bias in estimates of radiation–cancer associations under assumptions about the magnitudes of the confounder–exposure and confounder–disease associations (1). Briefly, suppose $RR_D^{OBS}(i)$ is the observed RR for category i of radiation dose (D) relative to category 0, $i = 0, \ldots, I$. For our evaluations, we further suppose that the confounder (C) is binary. Assuming a multiplicative model and that the parameters in the equations do not depend on important determinants of the outcome, such as age, we can express $RR_D^{OBS}(i)$ as

$$RR_D^{OBS}(i) = RR_D(i)\,\frac{1 + \pi_{1|i}\,(RR_C - 1)}{1 + \pi_{1|0}(RR_C - 1)} \quad \text{Equation (1),}$$

where $\pi_{1|i} = P(C = 1|D = i)$ is the conditional probability of the confounder at radiation level i, and $RR_D(i)$ and RR_C are the "true" RR and the confounder RR at the referent level of the other. From equation (1), the indirectly adjusted associations for radiation exposure are thus given by

$$RR_D(i) = RR_D^{OBS}(i) / \frac{1 + \pi_{1|i}\,(RR_C - 1)}{1 + \pi_{1|0}\,(RR_C - 1)} \quad \text{Equation (2).}$$

Given external information on $\pi_{1|i}$ and RR_C, equation (2) provides indirectly adjusted estimates of the true radiation RRs

$RR_D(i)$. Additionally, suppose we assume there is no radiation association, that ia, $RR_D(i) = 1$ for all i. Then given $RR_D^{OBS}(i)$, equation (2) yields a solution for $\pi_{1|i}$, the probability of the confounder at exposure i, in terms of $\pi_{1|0}$ and RR_C:

$$\pi_{1|i} = \frac{RR_D^{OBS}(i)\ \{1 + \ \pi_{1|0}(RR_C - 1)\} \ - \ 1}{RR_C - 1} \text{ Equation (3),}$$

or equivalently the odds ratios for D and C, $OR_{D,C}(i) = \pi_{1|i}(1 - \pi_{1|0})/\pi_{1|0}(1 - \pi_{1|i})$. Equation (3) enables an assessment of the plausibility that a binary factor C fully explains the observed radiation–disease association. The equation holds for any joint association (eg, multiplicative, submultiplicative, additive) between dose and C because the true joint model no longer involves dose when $RR_D(i) = 1$ for all i [(11); Mark Little, unpublished data].

Equations (2) and (3) provide adjustment formulae for observed RRs of a categorical exposure in the presence of a categorical confounder. Given an observed linear excess RR (ERR) model, $RR^{Obs}(D) = 1 + \beta\ D$, where β is the ERR per milligray, we did not directly evaluate bias of an ERR-per milligray estimate, because with non-null confounding the adjusted "true" association is no longer linear. Although we are not aware of a published formula, we can assume that the dose category–specific confounder prevalences $\pi_{1|i}$ needed to fully explain the observed $RR_D^{OBS}(i)$ in the absence of a radiation effect would be approximately similar to those required to explain the observed linear ERR per milligray under a linear model. The inputs to this evaluation for pediatric computed tomography (CT) and nuclear worker studies were very similar to those published previously (1), except that here we calculated the radiation risks using fitted linear ERR models rather than a categorical model as in Lubin et al. (1). For the CT studies, we rounded the prevalence of Down syndrome to 0.002 and for the nuclear worker study we used a slightly different collapsing of dose categories to simplify the table presentation.

To assess potential confounding from smoking status in nuclear worker studies, we used equation (3) to calculate the dose-specific proportions of ever-smokers, $P(C = 1|X = i)$, for a given overall smoking prevalence $P(C = 1)$, and the RR_C for all cancers except leukemia by smoking status. [Notably, the prevalence of ever-smokers was 0.55–0.70 among US veterans in 1954–1957 (12) and among males in the Behavior Risk Factor Surveillance System for 1984 and 1990, 0.75 in controls in German Wismut uranium miners (13), and 0.70–0.80 in a pooling of underground uranium miners' cohorts (14). The RR for ever-smoking was 1.6 in US veterans (12) and in a meta-analysis of international studies (15).]

To evaluate possible confounding by asbestos exposure in nuclear worker studies, we assumed that high exposure to asbestos increases the risk of death from all cancers except leukemia by 1.3-fold and that about 10% of nuclear workers might have been highly exposed to asbestos. This RR estimate is based on pooling the all-cancer standardized mortality ratios observed in two cohorts of textile workers highly exposed to (chrysotile) asbestos (16,17). The prevalence of asbestos exposure was from that observed in a nested lung cancer case-control study among Portsmouth Naval Shipyard workers [≥2 Threshold Limit Value-10, which = 240 fiber-days/cm^3 = 0.1 fiber/cm^3/d*240 working d/y*10 years (18)].

Results

Eligible Studies

We identified 26 eligible studies including eight studies of environmental, four of medical, and 14 of occupational exposure. The studies of environmental exposures included residents near the sites of the Chornobyl and Three Mile Island nuclear plant accidents (19,20), residents of villages along the Techa River contaminated by radioactive waste from the Mayak nuclear weapons facility in Russia (21), and residents of a building in Taiwan, China, contaminated with cobalt-60 (22). Four studies evaluated populations from China (23), Finland (24), Switzerland (25), and the United Kingdom (26) exposed to background radiation (Table 1). The Chinese study assessed cancer risk in adults, and the other three studies focused on the risk of cancer in children.

Eligible studies of medical exposures included cancers in patients undergoing diagnostic procedures [adults in Canada for cardiovascular conditions (27) and children in the United Kingdom (29) and France (28) undergoing CT] and a pooled study of thyroid cancer incidence following pediatric low-dose diagnostic or therapeutic radiation procedures (30).

Fourteen studies of occupationally exposed populations examined leukemia and/or other cancer incidence or mortality, including nuclear workers in Canada (37), France (47), Germany (39), Japan (36), Korea (31,34), United Kingdom (33), United States (35,40), and a pooled study (the International Nuclear Workers Study [INWORKS]) of studies from France, the United Kingdom, and the United States (41,42); Chornobyl accident recovery workers in Baltic countries, Belarus, Russia (32), and Ukraine (38); and atomic test participants (43) and radiological technologists in the United States (44–46).

Measured Confounders

Studies of environmental exposures and cancers in adulthood generally controlled for potential confounders such as age and birth cohort (or, roughly equivalently, calendar time and age) and sex (Table 1). Studies of environmental contamination (ie, Chornobyl and Techa River studies) often controlled for region of residence or background radiation, whereas studies of natural background radiation typically controlled for lifestyle-related factors (eg, smoking, education, or SES). Childhood leukemia studies controlled for age, sex, parental smoking behavior (or surrogates) and (in one study) Down syndrome, a cancer-predisposing condition. Studies of medical exposures typically adjusted for age, sex, calendar period, and time since exposure and excluded children with conditions predisposing to cancer [as a potential source of confounding by indication (CBI)]. Studies of occupational exposures generally adjusted for sex, age, birth cohort, and SES (as a means of controlling for confounding by lifestyle factors such as smoking or alcohol consumption or by occupational exposure to other carcinogens). Most studies also adjusted for employment duration as a means of controlling for healthy worker survivor bias (HWSB), because the HWSB is a type of bias that can lead to attenuation of the cumulative dose response in occupational cohort studies.

Unmeasured Confounders and Selection Bias

The population-based environmental studies exhibited limited potential for confounding or selection bias (Table 1). Two exceptions may be the Chornobyl residential study and the Techa River study. In the Chornobyl study, the authors reported evidence of control selection bias for Ukraine that may have caused an upward bias in risk estimate (19). The Techa River study experienced migration among 21% of cohort members outside (and back into) the cancer registry catchment area;

Table 1. Measured and unmeasured confounders reported in key studies*

Study no.	Study name	Reference	Outcome	Measured covariates	Uncontrolled potential confounders or potential for selection bias
Environmental studies					
1	Chornobyl residents	Davis et al. 2006 (19)	Childhood acute leukemia incidence	Calendar time, sex, birth year, and residence (matching)	SES/selection of controls differed by country and results suggest possible selection bias in Ukraine
2	Three Mile Island	Han et al. 2011 (20)	Cancer incidence (all, leukemia)	Age, race (restriction), education, smoking, background radiation, and sex	Other adulthood cancer risk factors, eg, alcohol, BMI
3	China background	Tao et al. 2012 (23)	Cancer mortality	Age, sex	Occupation, smoking, and other lifestyle factors potentially related to residential location, radon
4	GB background	Kendall et al. 2013a (26)	Childhood leukemia incidence	Age, sex, radon concentration, SES (Carstairs score, father's social class)	
5	Swiss background	Spycher et al. 2015 (25)	Childhood cancer incidence	Sex, birth year, distance to nearest highway, electromagnetic fields from radio and TV transmitters (based on a geographic model) and from high-voltage power line, degree of urbanization of municipality, SES, education of household reference person and number of persons per room, birth weight, and birth order of child	Radon
6	Techa River	Davis et al. 2015 (21)	Cancer incidence	Sex, ethnicity (Slav, Tartar/Bashkir), smoking status (ever/never/unknown), birth cohort, calendar period of follow-up, attained age, time since exposure, and age at exposure	Residual smoking confounding (unknown status for 54%), chemical exposures from contaminants from river. Possible bias from migration outside catchment area.
7	Finnish background	Nikkila et al. 2016 (24)	Childhood leukemia incidence	Age, sex, Down syndrome, maternal smoking during pregnancy, large birth weight	Radon
8	Taiwanese residents	Hseih et al. 2017 (22)	Cancer incidence (all excl leukemia, leuk excl CLL)	Age-matching (risk sets), sex, birth cohort (used log-linear model)	
Medical studies					
9	Canadian cardiac imaging	Eisenberg et al. 2011 (27)	Cancer incidence	Age, sex, and other diagnostic medical radiation exposures	Smoking, indication
10	French Pediatric CT	Journy et al. 2016 (28)	Childhood (<15 y) cancer incidence (1st primary)	Age, sex, calendar period of birth, time since entry, cancer predisposing conditions	Residual confounding by indication
11	UK Pediatric CT	Berrington et al. 2016 (29)	Cancer incidence (1st primary)	Age at exposure, sex, SES, time since first exposure, cancer predisposing syndromes, and unrecorded previous cancer. Attained age was the underlying time variable.	Residual confounding by indication

(continued)

Table 1. (continued)

Study no.	Study name	Reference	Outcome	Measured covariates	Uncontrolled potential confounders or potential for selection bias
12	PIRATES	Lubin et al. 2017 (30)	Incident thyroid cancer	Age, sex, study, age at exposure, calendar year of FU, number of radiation treatments, for Israel Tinea Capitis Study country of origin and referent type (North African/others), for Rochester Thymus Study presence of goiter and Jewish religion, for Atomic Bomb Survivors city of exposure (Hiroshima/Nagasaki), not in city and enrollment in Adult Health Study, for Childhood Cancer Survivors' Studies type of first cancer (Hodgkin Disease/other) and chemotherapy treatment	
Occupational studies					
13	Korean workers	Ahn et al. 2008 (31)	All-cancer mortality	Age, calendar year, sex	HWSB, smoking, SES, other occupational exposures, minor potential for prevalent hire bias
14	Chornobyl liquidators: Belarus, Russia, & Baltic countries	Kesminiene et al. 2008 (32)	Leukemia, lymphoma, and thyroid cancer incidence	Region of residence (matching), age at time of accident (matching)	Survival bias (some deceased workers were excluded due to lack of proxy respondent), other occupational exposures
15	UK NRRW	Muirhead et al. 2009 (33)	Cancer mortality and incidence (all cancer excl leukemia; leukemia excl CLL	Age, sex, calendar period, first employer industrial classification (industrial, nonindustrial, unknown)	HWSB, smoking, other occupational exposures (eg, asbestos or benzene)
16	Korean nuclear workers	Jeong et al. 2010 (34)	Cancer incidence	Age, year of birth, smoking status	HWSB, other occupational exposures
17	Rocketdyne nuclear workers	Boice et al. 2011 (35)	Cancer mortality (all cancers excl leukemia and leuk excl CLL)	Age-matching (risk sets), year of birth, year of hire, sex, pay type, duration of employment, work as a test stand mechanic	HWSB, smoking, other occupational exposures (eg, asbestos or benzene)
18	Japanese nuclear workers	Akiba et al. 2012 (36)	Cancer mortality (all cancer excl leukemia; leukemia)	Age, calendar year, areas of residence	HWSB/duration of employment, SES, other occupational exposures, major potential for prevalent hire bias, since follow-up began decades after exposures
19	Canadian nuclear workers	Zablotska et al. 2014 (37)	Cancer mortality (solid cancer and leukemia)	Age, sex, SES, calendar time, and duration of monitoring by stratification (analyses of leukemia additionally adjusted for facility and monitoring status)	HWSB, other occupational exposures
20	Chornobyl liquidators Ukraine	Zablotska et al. 2013 (38)	Leukemia incidence	Year of birth (matching), region of residence (matching)	Other occupational exposures
21	German nuclear workers	Merzenich et al. 2014 (39)	Cancer mortality (all cancer excl leukemia; leukemia excl CLL)	Age; restricted to males	HWSB, smoking (did not adjust for birth cohort, calendar year or SES), other occupational exposures, major potential for prevalent hire bias, since follow-up began decades after highest exposures

(continued)

Table 1. (continued)

Study no.	Study name	Reference	Outcome	Measured covariates	Uncontrolled potential confounders or potential for selection bias
22	US nuclear workers	Schubauer-Berigan et al. 2015 (40)	Cancer mortality (all cancer excl leukemia; leukemia excl CLL)	Age, sex, race, birth cohort, SES based on first job, facility, employment duration	HWSB, smoking, other occupational exposure (eg, asbestos or benzene)
23	INWORKS	Leuraud et al. 2015 (41); Richardson et al. 2015 (42)	Cancer mortality	Age, country, sex, decade of birth, SES, duration of employment, neutron monitoring status	HWSB, smoking, other occupational exposures (eg, asbestos or benzene)
24	Smoky Nuclear Test	Caldwell et al. 2016 (43)	Leukemia excl CLL mortality	Age, year of birth, year of first test participation, service and rank (considered a proxy for SES)	Smoking (authors suggest Smoky veterans had some unknown characteristics that increased their mortality risks, overall and for selected causes of death)
25	USRT	Preston et al. 2016 (breast) (44); Kitahara et al. 2017 (brain) (45); Lee et al. 2015 (BCC) (46)	Cancer incidence & mortality (breast, brain, BCC)	Breast: age, birth cohort, number of live births, menopausal status, BMI, family history of breast cancer, alcohol consumption, hormone replacement therapy Brain: age, sex BCC: age, sex, calendar year, sunburn history, complexion, BMI, skin reaction to sunlight, UVR score, exercise, income, dental x-rays, eye color, cigarette smoking, alcohol consumption, education	HWSB, possible selection bias in questionnaire (68–73% response rate)
26	French nuclear workers	Leuraud et al. 2017 (47)	Cancer mortality (all cancer excl leukemia; leukemia excl CLL)	Age, sex, SES, company, duration of employment, calendar period	HWSB, smoking, other occupational exposures (eg, asbestos or benzene)

*BCC = basal cell carcinoma; BMI = body mass index; CLL = chronic lymphocytic leukemia; CT = computed tomography; FU = follow-up; GB = Great Britain; HWSB = healthy worker survivor bias; INWORKS = International Nuclear Workers Study; NRRW = National Registry for Radiation Workers; PIRATES = Pooled International Radiation and Thyroid Cancer Epidemiology Studies; SES = socioeconomic status; USRT = US Radiologic Technologists; UVR = ultraviolet radiation.

however, the authors asserted that such migration would be expected to result in a loss of power without causing bias in the risk estimates (21).

Among the medical studies, the Canadian cardiac imaging study (27) did not control for CBI, and the CT studies (28,29) used information on cancer susceptibility syndromes (CSS) available for all or a subset of participants.

For the occupational studies, adjusting for duration of employment was an important means of partially controlling for the HWSB (Table 2): adjustment was found to increase the magnitude of the ERR–per unit dose for all cancers excluding leukemia in the United Kingdom (33) and US nuclear worker studies (40) and therefore in INWORKS (42). A greater potential for uncontrolled confounding from HWSB existed for the Korean worker (31) and Japanese nuclear worker (36) studies, which did not adjust for SES or duration of employment, and the German nuclear worker study (39), which did not adjust for birth cohort and SES. Prevalent hire bias is a form of selection bias in which follow-up begins after the start of exposure, which could result in unobserved exposure-related dropout of the most susceptible workers. This type of bias potentially existed for the German (39) and Japanese worker studies (36), because follow-up began decades after the highest exposures occurred and to a lesser extent for the French (47) and Korean worker studies (31) because follow-up began sooner after doses began accruing. All occupational studies involving hazardous exposures are potentially susceptible to residual confounding bias from the HWSB; standard analytical techniques, such as adjustment for duration of employment in a regression model, provide incomplete adjustment for this source of bias. Little evidence of selection bias was observed from incomplete questionnaire response in the US Radiologic Technologists study (44–46) (Table 2). Studies of nuclear workers are also potentially confounded by coexposures to other carcinogenic agents in the workplace, including benzene and asbestos, discussed below.

Direct and Indirect Assessments of Confounding

Some studies reported the change in estimate of the radiation dose-cancer association on adjustment for measured covariates. Tables 2 and 3 summarize the impact of adjusting for confounding factors on ERR–per unit dose estimates and give indirect evidence about the likelihood of confounding for factors not directly controlled for, which were abstracted from related studies.

Among the environmental studies, no factors were found to have substantial confounding impact on the risk per unit dose for either all cancers combined or leukemia. SES, for example, was weakly related to background radiation dose in the UK case-control study, and adjustment for smoking in the Techa river cohort reduced the ERR–per unit dose by only 11%. Among the medically exposed populations, most known risk factors for brain cancer and leukemia were unlikely to be associated with radiation dose and therefore are not likely to be confounders. We found little evidence of residual CBI through CSS because these conditions were very rare and not strongly related to number of CT scans. Exclusion of patients with previous unreported cancers in the UK pediatric CT study reduced the ERR–per unit dose for leukemia by 15% and for brain tumors by 30% (29). Lack of adjustment for SES is not expected to cause positive confounding of the ERR–per unit dose for leukemia, because participants from high-SES households have fewer CT scans and a higher baseline risk of leukemia (66,67). Other countries show little association between CT scans and SES (70). In the UK study and a Dutch study (52), SES adjustment did not materially affect the leukemia or brain tumor results.

Information for an indirect assessment of confounding in the environmental and medical studies was available either from secondary analyses of those studies or from external studies (54). In the study of cardiovascular imaging, there was indirect evidence of CBI, because there was a much weaker ERR–per unit dose for radiation exposure from other imaging and cancer risk than for cardiovascular imaging (27). An evaluation of the reason for pediatric CT scans in the UK study, based on a subset of all CTs, found that most CTs were unrelated to cancer suspicion. The main indication for repeated head scans over time was management of hydrocephalus (54). In addition, the start of follow-up in these studies is several years after the first CT, suggesting that the reason for the CT does not confound risk estimates. Meulepas et al. (53) calculated confounding bias in CT studies due to CSS under various scenarios and concluded that radiation risks for leukemia or brain tumors are unlikely substantially confounded. Direct adjustment for tuberous sclerosis complex, a brain tumor susceptibility syndrome and potential confounder as patients undergo routine brain imaging from time of diagnosis, changed the brain tumor ERR–per unit dose very little in a Dutch study of CT-related radiation risks (52).

In the occupational studies, adjustment for sex, age, birth cohort, and SES was performed to indirectly control potential confounding from smoking and occupational coexposures (Table 2); after doing so, there was little evidence of positive confounding by smoking in studies of nuclear workers (eg, chronic obstructive pulmonary disease was negatively associated with radiation in the UK, US, and INWORKS studies, and the ERR–per unit dose was similar for lung cancer and for all solid cancers). In the US nuclear worker study, liver cirrhosis was positively associated with radiation dose (although to a much lesser extent than all nonsmoking related cancers), indicating that in this study alcohol intake could be a positive confounder for liver cancer. In the US and UK cohorts, pleural cancer and other mesothelioma were strongly positively associated with dose, suggesting that asbestos exposure may be a positive confounder for lung cancer in these studies and INWORKS. For leukemia, we found little evidence of confounding by benzene or other leukemogens based on information from related studies in US workers (60,69,71).

Tables 4 and 5 summarize our assessment of the evidence regarding confounders for each study based on the information provided in Tables 2 and 3, respectively. For most environmental studies, potential confounders were generally either adjusted for or found not likely to actually cause bias. An exception is the study of background radiation in China, which did not adjust for lifestyle-related factors. The pediatric medical studies exhibited some potential for residual confounding from predisposing factors. For the occupational studies, direct and indirect evidence suggests that smoking, alcohol consumption, and other occupational exposures might cause confounding, especially those that did not adjust for birth cohort and SES.

Quantifying Potential Bias Due to Unmeasured Confounders

Using indirect methods, we evaluated potential confounding from smoking status in nuclear worker studies. In Table 6, we assumed no radiation association and calculated the distribution of smoking required to explain the dose response observed

Table 2. Direct and indirect assessments of confounding reported in studies of all cancers excluding leukemia*

Relevant study no.	Relevant study name (reference)	Confounder(s) considered	Outcome(s) for confounding	Effect of adjustment on ERR	Comment	Reference for confounding
Environmental studies						
3	China background (23)	Diet and nutrition, drinking water, pesticide residue, and Aflatoxin B1 in food, medical exposures, tobacco smoking, alcohol consumption	All cancers excluding leukemia	Not reported	Distributions of these potential confounding factors did not differ much between high background radiation and control areas	Tao 1996 (48); Zha et al. 1997 (49); Tao et al. 2012 (23)
5	Swiss background (25)	Residential mobility	Childhood cancer	+43% when restricting to children with stable residence	Main risk estimate is not adjusted for residence	Spycher et al. 2015 (25)
		Radon	Childhood cancer	Not reported	In a separate study, radon exposure was not associated with all childhood cancers combined (HR at 90% radon percentile = 0.93, 95% CI = 0.74 to 1.16, compared with median radon)	Hauri et al. 2013 (50)
6	Techa River (21)	Smoking	Solid cancer	−11%	Smoking status available for 46% of the cohort; 33% of men vs 2% of women reported ever smoking	Davis et al. 2015 (21)
		Chemicals	Solid cancer	Not reported	Reference states potentially prevalent chemicals are not known to be carcinogenic	Krestinina et al. 2005 (51)
Medical studies						
9	Canadian cardiac imaging (27)	Indication	All cancer	Not reported	Dose–response relationships observed for cardiac and noncardiac procedures	Eisenberg et al. 2011 (27)
10, 11	French & UK pediatric CT (28, 29)	SES	Brain tumors	None	No consistent evidence that brain tumors in children or young adults are associated with SES	
		SES	Brain tumors	+2%	SES approximated by quintiles of household income per postal area (average population, 40 persons)	Meulepas et al 2019 (52)
		CSS	Brain tumors	None	Simulations found radiation risks unlikely substantially confounded	Meulepas et al. 2016 (53)
		Tuberous sclerosis complex (a CSS)	Brain tumors	Not reported	ERR decreased by 8% when 66 TSC patients were excluded	Meulepas et al 2019 (52)
10	French pediatric CT (28)	CSS	Brain tumors	–45%	Adjustment for presence of any brain tumor-specific CSS	Journy et al. 2016a (28); Journy et al. 2016b (54)
11	UK pediatric CT (29)	CSS	Brain tumors	None	Exclusion of patients with CSS did not alter dose–response relationship	Berrington et al. 2016 (29)
		Previous unreported cancers	Brain tumors	−30%	Based on confounder data for 40% of cohort	Berrington et al. 2016 (29)
		Indication	Brain tumors	Not reported	Most head CTs were unrelated to cancer suspicion. Main indication for repeated head scans over time was management of hydrocephalus.	Journy et al. 2016a (28)

(continued)

Table 2. (continued)

Relevant study no.	Relevant study name (reference)	Confounder(s) considered	Outcome(s) for confounding	Effect of adjustment on ERR	Comment	Reference for confounding
12	PIRATES (30)	See Table 1	Thyroid cancer	Not reported	Only radiation and body fatness are established risk factors; some studies show subtle inverse associations with alcohol and smoking	Lauby-Secretan et al. 2016 (55)
Occupational studies						
15	UK NRRW (33)	Smoking	COPD mortality (smoking-related cancer)	NA (indirect evidence based on comparison of ERR/Sv)	Strongly negative ERR/Sv for COPD in full cohort	Muirhead et al. 2009b (56)
		Asbestos exposure	Pleura cancer (asbestos-related lung cancer)	NA (indirect evidence based on comparison of ERR/Sv)	Positive ERR/Sv for pleura cancer mortality, about 4.1× higher that of all cancers excluding leukemia, pleura, lung	Muirhead et al. 2009b (56)
		SES	All cancers other than leukemia	−25% with adjustment for SES	Authors state that effect of SES adjustment was lower when excluding lung cancer and pleura	Muirhead et al. 2009b (56)
16	Korean nuclear workers (34)	Smoking	Lung cancer		After adjustment for smoking, lung cancer dose response was statistically nonsignificantly negative.	Jeong et al. 2010 (34)
17	Rocketdyne nuclear workers (35)	Internal radiation	Solid cancer	Not reported	Authors state "other than for lung dose and bone marrow dose, the contribution of internal radiation dose to organs or tissues was not appreciable"	Boice et al. 2011 (35)
18	Japanese nuclear workers (36)	Smoking, alcohol	Solid cancer	Not reported	Conducted survey on alcohol and smoking among workers and observed positive correlation with dose. Indirectly evaluated confounding by smoking and alcohol by analyzing smoking-related and alcohol-related cancers. Found positive and high ERR/Sv for alcohol- and smoking-related cancers. No association persisted after exclusion of smoking- and alcohol-related cancers. Concluded that results for cancer confounded by smoking and alcohol drinking	Kudo et al. 2018 (57)
15, 22, 23, 26	UK, US, and French nuclear workers/ INWORKS (33, 40, 42, 47)	Smoking	COPD mortality (smoking-related cancer)	NA (indirect evidence based on comparison of ERR/Sv)	Statistically nonsignificant negative association between radiation dose and COPD mortality in INWORKS	Gillies et al. 2017 (58)
22, 23	US nuclear workers/ INWORKS (40, 42)	Smoking	COPD mortality (smoking-related cancer)	NA (indirect evidence based on comparison of ERR/Sv)	No association between duration of work and COPD mortality in cohort of US nuclear workers. Slightly negative ERR/Sv for COPD in full cohort, providing indirect evidence for minimal confounding by smoking.	Schubauer-Berigan et al. 2015 (40)

(continued)

Table 2. (continued)

Relevant study no.	Relevant study name (reference)	Confounder(s) considered	Outcome(s) for confounding	Effect of adjustment on ERR	Comment	Reference for confounding
		Smoking	Lung cancer	+56% (10-y lagged dose)	After adjusting for year of birth, found no association between cumulative dose and smoking	Petersen et al. 1990 (59)
		Smoking	Smoking-related cancer	NA (indirect evidence based on association of smoking with dose)	Authors state "…smoking was not strongly associated with either leukemia or dose in this study for workers with nonimputed smoking data…."	Schubauer-Berigan et al. 2007 (60)
		Alcohol consumption	Liver cirrhosis mortality (alcohol-related cancer)	NA (indirect evidence based on comparison of ERR/Sv)	Positive ERR/Sv for cirrhosis of liver, about same magnitude as that of all cancers	Schubauer-Berigan et al. 2015 (40)
		Asbestos exposure	Mesothelioma (asbestos-related lung cancer)	NA (indirect evidence based on comparison of ERR/Sv)	Positive ERR/Sv for mesothelioma, about 3.6× that of all nonsmoking-related cancers	Schubauer-Berigan et al. 2015 (40)
25	USRT (44–46)	Smoking	Breast cancer	None	Smoking not included in primary analysis of breast cancer incidence in USRT cohort as inclusion neither improved model fit nor had appreciable effect on inference about radiation dose–response association	Preston et al. 2016 (46)
		BMI	Breast cancer	Not reported	BMI was included in the primary analysis of breast cancer incidence in USRT cohort as inclusion either improved model fit or had appreciable effect on inference about radiation dose–response association	Preston et al. 2016 (46)
		Alcohol	Breast cancer	Not reported	Alcohol not included in primary analysis of breast cancer incidence in USRT cohort as inclusion had almost no effect on inference about radiation dose–response association	Preston et al. 2016 (46)
		SES	Breast cancer	None	Confounding unlikely because SES relatively homogeneous among radiologic technologists	
		Alcohol, BMI, height, race, smoking, marital status, reproductive history	Brain cancer	Not reported	Authors report no evidence of confounding by numerous covariates (eg, race, marital status, BMI, height, alcohol consumption, smoking, reproductive history)	Kitahara et al. 2017 (44)
		Education, income, smoking, alcohol, BMI, exercise, eye color, complexion, sunburn history, dental x-rays, solar UV score	Basal cell carcinoma	−133%	Unclear which confounders effected greatest change in ERR/Gy. Significant heterogeneity by age at exposure (Err/Gy positive for age <30 y and negative for older ages)	Lee et al. 2015 (45)

(continued)

Table 2. (continued)

Relevant study no.	Relevant study name (reference)	Confounder(s) considered	Outcome(s) for confounding	Effect of adjustment on ERR	Comment	Reference for confounding
		Duration of employment (HWSB)	Basal cell carcinoma	Not reported	Authors state that inclusion of employment duration changed results little	Lee et al. 2015 (45)
		Selection bias from 68–73% response rate	All cancers excluding nonmelanoma skin; melanoma	−2.7%; +1.3%	Found little effect of accounting for nonresponse rate on SIR estimates	Rao et al. 2005 (61)
26	French nuclear workers (47)	Smoking	COPD mortality	NA (indirect evidence based on ERR/Sv)	Statistically nonsignificant positive association between radiation and COPD in French nuclear workers positively confounded radiation-lung cancer association	Richardson et al. 2014 (62)
26	French nuclear workers (47)	Alcohol	Solid cancer (liver cirrhosis mortality)	Not reported	Significant deficit of deaths due to liver cirrhosis, psychosis, and other alcohol-related diseases (SMR = 0.27) in TRACY cohort of French uranium cycle workers. This cohort not included in French nuclear workers study nor in French contribution to INWORKS, although it is comparable with regard to SES and lifestyle	Samson et al. 2016 (63)
		Alcohol	Solid cancer (liver cirrhosis mortality)	Not reported	Significant deficit of liver cirrhosis mortality (SMR = 0.28)	Leuraud et al 2017 (47)
		Environmental radiation exposure	Solid cancer	0 to −18%	Scenarios based on place of place of birth and place of residency during work, and French maps of radon, telluric, and cosmic radiation exposure	Fournier et al. 2018 (64)

*BMI = body mass index; CI = confidence interval; COPD = chronic obstructive pulmonary disease; CSS = cancer susceptibility syndrome; CT = computed tomography; ERR = excess relative risk; ERR/Gy = excess RR per Gray; ERR/Sv = excess RR per Sievert; HR = hazard ratio; HWSB = healthy worker survivor bias; NA = not applicable; INWORKS = International Nuclear Workers Study; NRRW = National Registry for Radiation Workers; PIRATES = Pooled International Radiation and Thyroid Cancer Epidemiology Studies; SES = socioeconomic status; SIR = standardized incidence ratio; SMR = standardized mortality ratio; USRT = US Radiologic Technologists; UV = ultraviolet.

Table 3. Direct and indirect assessments of confounding reported in studies of leukemia*

Relevant study no.	Relevant study name (reference)	Confounder(s) considered	Outcome(s) for confounding	Effect of adjustment on ERR	Comment	Reference for confounding
Environmental studies						
1	Chornobyl residents (19)	SES	Leukemia	Not reported	Generally similar education level of parents (as a proxy for SES) for cases and controls	Davis et al. 2006 (19)
4	GB background (26)	SES (Carstair's deprivation index based on census ward and father's occupation)	Childhood leukemia	−32% to +32%, depending on SES metric	Main risk estimate adjusted for SES. May be relevant for similar studies	Kendall et al. 2013b (65)
		Radon	Childhood leukemia	−42%	A model including both gamma and radon dose to red bone marrow showed reduced ERR/Sv compared with model with just gamma dose	Kendall et al. 2013a (26)
3	China background (23)	Diet and nutrition, drinking water, pesticide residue, and Aflatoxin B1 in food, medical exposures, tobacco smoking, alcohol consumption	Leukemia	Not reported	Distributions of those potential confounding factors did not differ much between high background radiation and control areas	Tao et al. 2012 (23); Tao et al. 1996 (48); Zha et al. 1997 (49)
5	Swiss background (25)	Residential mobility	Childhood leukemia	+28% when restricting to children with stable residence	Main risk estimate is not adjusted for residence	Spycher et al. 2015 (25)
		Radon	Childhood leukemia	Not reported	In a separate study, radon exposure not associated with childhood leukemia (HR at 90% radon percentile = 0.93, 95% CI = 0.74 to 1.16, compared with median radon)	Hauri et al. 2013 (50)
7	Finnish background (24)	Down syndrome, birth weight (large for gestational age), maternal smoking, CT	Leukemia and leukemia subtypes	Not reported	Little change when accounting for these factors	Nikkila et al. 2016 (24)
Medical studies						
10,11 (11 adjusted for SES)	French & UK pediatric CT (28, 29)	SES	Leukemia	Not reported	Lower frequency of CT scans among higher SES groups; leukemia incidence appears somewhat higher among children from households with higher SES (ie, SES confounding would attenuate ERR)	Pearce et al. 2012 (66); Meulepas et al. 2017 (67)
		SES	Leukemia	<2%	RRs for dose categories differed by <2% when adjusted for quintiles of household income per postal area (average population, 40 persons)	Meulepas et al. 2019 (52)
		CSS	Leukemia	None	Radiation risks unlikely substantially confounded by CSS	Meulepas et al. 2016 (53)
10	French pediatric CT (28)	CSS	Leukemia	−18%	Adjustment for presence of any leukemia-specific CSS (mean cumulative bone marrow dose = 8.8 mGy and 10.4 mGy among children with and without leukemia-specific CSS). HR per bone marrow dose did not change when children with leukemia-specific CSS were excluded	Journy et al. 2016a (28); Journy et al. 2016b (54)

(continued)

Table 3. (continued)

Relevant study no.	Relevant study name (reference)	Confounder(s) considered	Outcome(s) for confounding	Effect of adjustment on ERR	Comment	Reference for confounding
11	UK pediatric CT (29)	CSS	Leukemia	None	Exclusion of patients with CSS did not alter dose–response relationship	Berrington et al. 2016 (29)
		Previous unreported cancers	Leukemia	−15%	Based on confounder data for 40% of cohort	Berrington et al. 2016 (29)
Occupational studies						
14	Chornobyl liquidators: Belarus, Russia, & Baltic countries (32)	Education, smoking, alcohol use, occupational and medical history, organization that sent liquidator to Chornobyl, date of start of mission, duration of mission, work on industrial site, personal monitoring of dose, use of protective measures, marital status	Leukemia/lymphoma incidence	Not reported	Authors state that none of these factors modified OR by 10% or more	Kesmeniene et al. 2012 (68)
20	Chornobyl liquidators: Ukraine (38)	Education, smoking, alcohol use, medical or diagnostic radiation exposures, occupational exposures to chemicals or radiation before and after Chornobyl accident, urban/rural residential status at interview, age and year of first cleanup mission, type of work, total number of missions	Leukemia incidence	Not reported	Authors state that distribution of these factors did not significantly differ between cases and controls	Zablotska et al. 2013 (38)
17	Rocketdyne nuclear workers (35)	Internal radiation	Leukemia	Not reported	Authors state "other than for lung dose and bone marrow dose, the contribution of internal radiation dose to organs or tissues was not appreciable"	Boice et al. 2011 (35)
22,23	US nuclear workers/ INWORKS (40, 41)	Benzene; cigarette smoking; plutonium dose	Leukemia	−16% to −41%; −9%; +4%	Benzene confounding greatest for early employment years and leukemias of uncertain subtype	Schubauer-Berigan et al. 2007 (60)
		Benzene; SES	Leukemia (non-CLL)	<15% (direction not reported)	<15% change in ERR when adjusting for benzene or SES exposure in leukemia case-control study among US nuclear workers	Daniels et al. 2013 (69)
15	UK NRRW (33)	SES	Leukemia	Not reported	Authors state that omitting SES adjustment had little impact on ERR/Sv	Muirhead 2009b (56)

*CI = confidence interval; CLL = chronic lymphocytic leukemia; CSS = cancer susceptibility syndrome; CT = computed tomography; ERR = excess relative risk; ERR/Sv = excess relative risk per Sievert; GB = Great Britain; HR = hazard ratio; INWORKS = International Nuclear Workers Study; NRRW = National Registry for Radiation Workers; SES = socioeconomic status; USRT = US Radiologic Technologists.

Table 4. Summary of empirical evidence on potential confounding reported in studies of all cancers excluding leukemia*

No.	Study name (reference)	Confounder: Lifestyle Smoking	Alcohol	BMI	SES	Occupational Chemical	Medical Indication/predisposing factors
Environmental							
2	Three Mile Island (20)	Adj			Adj		NA
3	China background (23)	No	No			NA	NA
5	Swiss background (25)	NA	NA	NA	Adj	NA	NA
6	Techa River (21)	Adj				No	NA
8	Taiwanese residents (22)					NA	NA
Medical							
9	Canadian cardiac imaging (27)					NA	No
10	French Pediatric CT (28) (brain/CNS)	NA	NA	NA	NA	NA	Some (CSS)
11	UK Pediatric CT (29) (brain/CNS)	NA	NA	NA	NA	NA	No (CSS), some (previous cancers)
12	PIRATES (30) (thyroid)	NA	NA	NA	NA	NA	
Occupational							
13	Korean workers (31)	Possibly	Possibly		Yes	Possibly	NA
15	UK NRRW (33)	No			Adj	Possibly	NA
16	Korean nuclear workers (34)	Adj			Yes	Possibly	NA
17	Rocketdyne nuclear workers (35)				Adj	Possibly	NA
18	Japanese nuclear workers (36)	Yes	Yes		Yes	Possibly	NA
19	Canadian nuclear workers (37)				Adj	Possibly	NA
21	German nuclear workers (39)	Possibly	Possibly		Yes	Possibly	NA
22	US nuclear workers (40)	No	Possibly		Adj	Possibly	NA
23	INWORKS (42)	No	Possibly		Adj	Possibly	NA
25	USRT (breast) (44)	No	No	Adj	No	NA	NA
25	USRT (brain) (45)	No	No	Adj	NA	NA	NA
25	USRT (BCC) (46)	Adj	Adj	Adj	Adj	NA	NA
26	French nuclear workers (47)	Possibly	No		Adj	Possibly	NA

*Adj = risk estimate from study was adjusted for potential confounder (see Table 1); BCC = basal cell carcinoma; BMI = body mass index; CNS = central nervous system; CSS = cancer susceptibility syndrome; CT = computed tomography; INWORKS = International Nuclear Workers Study; NA = confounder is not an established risk factor for all cancer excluding leukemia or is not prevalent in the study population; No, Yes, and Possibly = assessment of likelihood of substantial confounding based on evidence presented in Table 2; NRRW = National Registry for Radiation Workers; PIRATES = Pooled International Radiation and Thyroid Cancer Epidemiology Studies; SES = socioeconomic status; USRT = US Radiologic Technologists.

Table 5. Summary of empirical evidence on potential confounding reported in studies of leukemia*

No	Study name (reference)	Confounder: Lifestyle Smoking	SES	Occupational Chemical	Medical Indication/predisposing factor
Environmental					
1	Chornobyl residents (19)	NA	No	NA	NA
2	Three Mile Island (20)	Adj	Adj		NA
3	China background (23)	No		NA	NA
4	GB background (26)	NA	Adj	NA	NA
5	Swiss background (25)	NA	Adj	NA	NA
7	Finnish background (24)	No		NA	No
8	Taiwanese residents (22)			NA	NA
Medical					
10	French Pediatric CT (28)	NA	Possibly	NA	No (CSS)
11	UK Pediatric CT (29)	NA	No	NA	No (CSS)
Occupational					
13	Korean workers (31)		Yes	Possibly	NA
14	Chornobyl liquidators: Belarus, Russia, & Baltic countries (32)	No	No	No	NA
15	UK NRRW (33)		No	Possibly	NA
17	Rocketdyne nuclear workers (35)		Adj	Possibly	NA
18	Japanese nuclear workers (36)		Yes	Possibly	NA
19	Canadian nuclear workers (37)		Adj	Possibly	NA
20	Chornobyl liquidators: Ukraine (38)	No	No	No	NA
21	German nuclear workers (39)		Yes	Possibly	NA
22	US nuclear workers (40)	No	Adj	Possibly	NA
23	INWORKS (41)	No	Adj	Possibly	NA
24	Smoky nuclear test (43)		Adj		NA
26	French nuclear workers (47)	Possibly	Adj	Possibly	NA

*Adj = risk estimate form study was adjusted for potential confounder (see Table 1); CSS = cancer susceptibility syndrome; CT = computed tomography; INWORKS = International Nuclear Workers Study; No, Yes and Possibly = assessment of likelihood of substantial confounding based on evidence presented in Table 3; NA = confounder is not an established risk factor for leukemia or is not prevalent in the study population; NRRW = National Registry for Radiation Workers; SES = socioeconomic status.

for all cancer mortality except leukemia in the INWORKS study of nuclear workers (42). For overall smoking prevalences of 50–70% and a smoking-related all cancer RR of 1.6, calculated smoking prevalences in the highest dose categories exceeded 1.0, indicating smoking status cannot explain the full range of observed radiation risks (Table 6). At an overall smoking prevalence of 50%, a minimum RR for smoking of 1.81 is required for valid probabilities in all categories. In this case, smoking prevalences increasing from slightly below 50% for low-dose categories to almost 100% at 500 mGy or more are required to entirely explain the observed association with radiation exposure. Results support the authors' conclusion that smoking could not explain the RR trend.

Assuming heavy asbestos exposure increases all cancer risk 1.3-fold, the prevalence of exposure would have to increase with radiation dose from 6% in the lowest radiation dose category to greater than 100% in the highest radiation dose category in order to explain the observed radiation dose–response association for all cancer excluding leukemia in INWORKS. This is impossible. If the asbestos-related RR were 1.6, asbestos prevalence would have to increase from 8% to 61% in the highest dose category, which is implausible; even in the US site with highest asbestos exposure (the Portsmouth Naval Shipyard), the correlation between asbestos and occupational radiation dose was quite low ($r = 0.09$) (18).

For studies of leukemia following radiation dose from pediatric CT exams, an evaluation of bias shows that for a CSS such as Down syndrome, which carries a 20-fold increased leukemia risk (72), prevalence would have to increase from the population level of 0.2% (53) in the lowest dose category to 4% in the highest dose category to fully explain the observed radiation dose response (Table 7). This is implausible, because the UK study found a Down syndrome prevalence of just 0.03% and no evidence of association with radiation dose (29).

Summary Regarding Potential Biases

After considering evidence from direct and indirect confounding assessment as well as theoretical assessment of the potential impact of confounding, Table 8 summarizes our results with respect to potential biases and provides an overall assessment of the likelihood and direction of possible confounding and selection bias for each study. Few studies exhibited serious potential for confounding (eg, a change in dose response estimate of >20%) or selection bias. The most consistent finding across studies is the likelihood of downward bias (towards the null) in nuclear worker studies due to a HWSB of unknown magnitude, because direct adjustment is not possible with conventional statistical methods. Although confounding from coexposures was not directly evaluated in most occupationally exposed cohorts, our hypothetical adjustments in Table 6 using INWORKS as an example suggest that these coexposures are unlikely to cause serious confounding, particularly after adjustment for birth cohort and SES.

Discussion

All epidemiological studies have strengths and limitations that may affect their ability to quantify the association between radiation and cancer risk, especially at low doses and low dose rates (73–75). Confounding and selection bias are important considerations in observational epidemiology, particularly in low-dose radiation studies, where the excess risk at average study doses may be quite small. We have reviewed recent literature on low-radiation dose–cancer associations with regard to potential confounders and summarized the measured confounders that were included in these analyses as well as considered the impact of unmeasured confounding on radiation risk estimates for solid cancers and leukemia. Overall, we found little evidence that confounding or selection bias was likely to entirely explain the observed positive relationships between low-dose radiation and cancer. For confounding, this was either because the relationship between the confounder and radiation exposure was relatively weak or the confounder was only a weak risk factor for all solid cancers or leukemia, the two outcomes of primary interest in this monograph.

For confounding to occur, there must be imbalance between exposure groups in the distribution of the confounding factor. How might such imbalance arise? One possibility is that the potential confounder is a cause of radiation exposure. For example, in Table 1, we reviewed several studies of medical radiation exposures for diagnostic procedures in which there was concern that clinical conditions associated with an increased cancer risk might also lead to more diagnostic radiation exposure. Another possibility is that there is common cause of both radiation exposure and the confounding factor. For example, in Table 1 we pointed to potential concerns in occupational studies that employment in a specific work location might lead to benzene exposure and radiation exposure. However, our evaluation of confounding by other occupational carcinogens suggests that such bias is likely to be modest, particularly after adjusting for sex, attained age, birth cohort, and SES (which are related to exposure to other occupational carcinogens).

A confounding factor must also cause (or be associated with another cause of) the disease of interest. Therefore, it is incorrect to assert, in general, that a factor is an important confounder of radiation effects for all diseases: a factor may be an important confounder in analysis of one disease and irrelevant as a confounder in analysis of a different disease. Accordingly, judgment regarding potential for confounding depends on the outcome under study. For example, cigarette smoking is a strong risk factor for lung cancer and is often viewed as an important potential confounding factor in investigations of lung cancer. The RR of lung cancer for moderate to heavy smokers generally exceeds 10 (76) and is greater than the RR associated with exposure to relatively high doses of radiation, which rarely exceeds 2 (United Nations Scientific Committee on the Effects of Atomic Radiation) (77). Therefore, even moderate associations between radiation dose and smoking can lead to potentially important bias in studies of radiation–lung cancer associations. In contrast, the smoking-related RR of most other cancers generally does not exceed 2, and is 1 (ie, null) for cancers that are not smoking related; therefore, much stronger radiation–smoking associations would be required for smoking-related cancers other than lung cancer to induce substantial confounding bias (and no bias would be expected for nonsmoking related cancers). In Tables 2 and 3, we separated our considerations of confounders of the radiation associations with cancers other than leukemia and leukemia.

Confounding can lead to bias toward the null or away from the null. A disease risk factor that is distributed more frequently among the exposed than unexposed may lead to spurious evidence of a positive association between radiation and cancer where none exists (or lead to exaggerated evidence regarding the magnitude of association between radiation and cancer where an association exists). Conversely, a risk factor that is distributed more frequently among the unexposed than

Table 6. Degree of imbalance between categories of radiation dose in the distribution of an unmeasured confounding factor (e.g., ever smoking) of varying strengths required to explain the observed radiation dose-response association for all cancers excluding leukemia in the International Nuclear Workers Study (INWORKS).*†

	Radiation dose D (mGy)						
	<5	5 to <20	20 to <100	100 to <200	200 to <300	300 to <500	≥500
				Observed result‡			
Mean dose	0.6	10.6	44.2	138.1	240.6	368.0	630.8
RR_D^{OBS}	1.00	1.00	1.02	1.07	1.12	1.18	1.30
RR_C			For fixed P(C = 1) = 0.10‖, computed P(C = 1|D = i), I = 1,. . .,6				
1.3	0.06	0.08	0.13	0.29	0.45	0.66	(>1.00)§
1.6	0.08	0.09	0.12	0.20	0.28	0.39	0.61
2.0	0.09	0.09	0.11	0.16	0.21	0.28	0.42
3.0	0.09	0.10	0.11	0.13	0.16	0.20	0.27
4.0	0.10	0.10	0.11	0.12	0.15	0.17	0.23
RR_C			For fixed P(C = 1) = 0.20‖, computed P(C = 1|D = i), I = 1,. . .,6				
1.3	0.16	0.18	0.24	0.40	0.56	0.78	(>1.00)§
1.6	0.18	0.19	0.22	0.30	0.39	0.51	0.74
2.0	0.19	0.19	0.21	0.27	0.32	0.40	0.55
3.0	0.19	0.20	0.21	0.24	0.27	0.32	0.40
4.0	0.19	0.20	0.21	0.23	0.25	0.29	0.35
RR_C			For fixed P(C = 1) = 0.30‖, computed P(C = 1|D = i), i = 1,. . .,6				
1.3	0.26	0.28	0.34	0.50	0.67	0.90	(>1.00)§
1.6	0.28	0.29	0.32	0.41	0.50	0.62	0.87
2.0	0.29	0.29	0.31	0.37	0.43	0.51	0.67
3.0	0.29	0.29	0.31	0.34	0.38	0.43	0.53
4.0	0.29	0.30	0.31	0.34	0.37	0.40	0.48
RR_C			For fixed P(C = 1) = 0.50‖, computed P(C = 1|D = i), i = 1,. . .,6				
1.3	0.46	0.48	0.54	0.71	0.89	(>1.00)§	(>1.00)§
1.6	0.48	0.49	0.52	0.62	0.72	0.86	(>1.00)§
2.0	0.48	0.49	0.51	0.58	0.65	0.75	0.93
3.0	0.49	0.49	0.51	0.55	0.60	0.66	0.79
4.0	0.49	0.49	0.51	0.55	0.58	0.64	0.74
RR_C			For fixed P(C = 1) = 0.70‖, computed P(C = 1|D = i), i = 1,. . .,6				
1.3	0.66	0.68	0.74	0.92	(>1.00)§	(>1.00)§	(>1.00)§
1.6	0.67	0.68	0.72	0.83	0.94	(>1.00)§	(>1.00)§
2.0	0.68	0.69	0.72	0.79	0.87	0.98	(>1.00)§
3.0	0.69	0.69	0.71	0.77	0.82	0.90	(>1.00)§
4.0	0.69	0.69	0.71	0.76	0.81	0.87	1.00

*Prevalence of a potential confounding factor (eg, ever-smoker, C) by radiation dose (D) categories [assuming the true RRs are null, $RR_D(i) = 1$ for all i and a multiplicative model for the joint association of D and C], and observed RRs $RR_D^{OBS}(i)$ for all cancer mortality, except leukemia, by radiation dose for pooled data of studies of nuclear workers (INWORKS). Entries based on selected values for P(C = 1) and the RR of C in the lowest dose category, RR_C †mGy = milligray; RR = relative risk; ERR/mGy = excess RR per mGy.

‡Exposure information and observed RRs for all cancers excluding leukemia based on fitted ERR/mGy from the INWORKS study of nuclear radiation workers, $RR_D^{OBS}(d) = 1 + 0.00048\ d$, with several adjacent categories combined for clarity and with category-specific RRs adjusted to the lowest exposure category, ie, divided by (1 + 0.00048 × 0.6) (33).

‖Designated overall probability of the confounder.

§Parentheses denote invalid probability. For P(C = 1) = 0.10, $RR_C = 1.33$ is the minimum confounder RR admitting valid probability values for all P(C = 1|D = i), 0.07, 0.08, 0.13, 0.27, 0.42, 0.61, 1.00, respectively; for P(C = 1) = 0.20, $RR_C = 1.39$ is the minimum confounder RR admitting valid probability values for all P(C = 1|D = i), 0.17, 0.18, 0.23, 0.35, 0.49, 0.66, 1.00, respectively; for P(C = 1) = 0.30, $RR_C = 1.47$ is the minimum confounder RR admitting valid probability values for all P(C = 1|D = i), 0.28, 0.29, 0.33, 0.44, 0.55, 0.70, 1.00, respectively; for P(C = 1) = 0.50, $RR_C = 1.81$ is the minimum confounder RR admitting valid probability values for all P(C = 1|D = i), 0.48, 0.49, 0.52, 0.60, 0.68, 0.78, 1.00, and for P(C = 1) = 0.70, $RR_C = 4.00$ is the minimum confounder RR admitting valid values for all P(C = 1|D = i), 0.69, 0.69, 0.71, 0.76, 0.81, 0.87, 1.00 [Lubin et al. 2018 (1)].

exposed may obscure evidence of a positive association between radiation and cancer, or even lead to spurious evidence of an inverse association between radiation and cancer. For example, in some nuclear facilities, higher radiation doses tend to be accrued in areas where people are prohibited from smoking cigarettes, whereas lower radiation doses tend to be accrued in areas where smoking may be permitted (56,78).

Concerns regarding the impact of confounding on a radiation–cancer association tend to be greater when investigating an association of small magnitude than when investigating associations of large magnitude because modest imbalances in confounding factors between radiation exposure groups may be sufficient to lead to meaningful distortion in the former. We reviewed external evidence regarding the strength of the association between the confounding factor and disease. Under the assumption of no radiation association, we calculated the degree of imbalance in the distribution of unmeasured confounding factors between categories of radiation dose required to explain the observed radiation dose–response association. Even for these small effects, for example, for low-dose occupational radiation and all solid cancers, we showed from these theoretical calculations that confounders were unlikely to completely

Table 7. Degree of imbalance between categories of radiation dose in the distribution of an unmeasured confounding factor (e.g., cancer predisposing conditions) of varying strengths required to explain the observed radiation dose-response association for leukemia in pediatric CT studies.*†

	Radiation dose D (mGy)					
	<5	5–9	10–14	15–19	20–29	≥30
			Observed results ‡			
Mean dose	2.3	7.1	12.3	16.5	24.7	51.1
RR_D^{OBS}	1.00	1.15	1.31	1.44	1.69	2.50
RR_C			For fixed P(C=1|D=0)=0.002‖, computed P(C=1|D=i), i=1,. . .,5			
2.5§	0.002	0.10	0.21	0.29	0.46	1.00
10.0	0.002	0.02	0.04	0.05	0.08	0.17
20.0	0.002	0.01	0.02	0.03	0.04	0.08
RR_C			For fixed P(C=1|D=0)=0.005‖, computed P(C=1|D=i), i=1,. . .,5			
2.5§	0.005	0.10	0.21	0.29	0.46	1.00
10.0	0.005	0.02	0.04	0.06	0.08	0.18
20.0	0.005	0.01	0.02	0.03	0.04	0.09
RR_C			For fixed P(C=1|D=0)=0.01‖, computed P(C=1|D=i), i=1,. . .,5			
2.5§	0.01	0.11	0.21	0.30	0.46	1.00
10.0	0.01	0.03	0.05	0.06	0.09	0.19
20.0	0.01	0.02	0.03	0.04	0.05	0.10
RR_C			For fixed P(C=1|D=0)=0.10‖, computed P(C=1|D=i), i=1,. . .,5			
3.0§	0.10	0.19	0.28	0.36	0.51	1.00
10.0	0.10	0.13	0.16	0.19	0.24	0.42
20.0	0.10	0.12	0.15	0.17	0.20	0.33
RR_C			For fixed P(C=1|D=0)=0.20‖, computed P(C=1|D=i), i=1,. . .,5			
4.0§	0.20	0.24	0.36	0.43	0.57	1.00
10.0	0.20	0.25	0.30	0.34	0.41	0.67
20.0	0.20	0.27	0.28	0.31	0.37	0.58

*Prevalence of a potential confounding factor (eg, prevalence of any cancer predisposing conditions, C) by radiation dose (D) categories [assuming the true RRs are null, $RR_D(i) = 1$ for all i and a multiplicative model for the joint association of D and C], and observed RRs $RR_D^{OBS}(i)$for leukemia by radiation dose in a study of pediatric CT scanning. Entries based on selected values for P(C = 1|X = 0) and the RR of C in the lowest dose category, RR_C

†mGy = milligray; RR = relative risk; ERR/mGy = excess RR per mGy.

‡Exposure information and observed RRs for leukemia and myelodysplastic syndrome based on fitted ERR/mGy from the reanalysis of the UK/NCI Study of Pediatric CT Scanning, $RR_D^{OBS}(d) = 1 + 0.033\ d$, with category-specific RRs adjusted to the referent category, ie, divided by (1 + 0.033 x 2.3) (20).

‖Designated overall probability of the confounder, P(C = 1). Value of 0.002 refers to Down syndrome.

§For designated P(C = 1|D = 0), minimum confounder RR_C admitting valid probability values for all P(C = 1|D = i).

explain positive findings. This is because the degree of confounding depends, in part, on the prevalence of the confounder among the exposed and unexposed. We illustrate this in Tables 6 and 7. Exposures or conditions that are rarely observed in a study population are unlikely to be strong confounders. For example, it has been suggested that CSS may confound studies of cancer risk following pediatric CT examinations. However, in Table 7 we show that such predisposing conditions are rare among patients in the French and UK pediatric CT studies, suggesting that the degree of confounding due to predisposing conditions is likely to be small. Another example pertains to smoking or asbestos exposure in nuclear workers: several studies have found that smoking is only weakly positively or even negatively associated with radiation dose in the cohorts included in the US pooled nuclear worker study (18,59,60,79). Directly adjusting for smoking in a lung cancer study among Hanford workers (59) and for asbestos exposure among Portsmouth Naval Shipyard workers (18) changed risk estimates little.

Confounding may be handled through various approaches to account for the effect of the factor itself (if the study collected information on the factor) or to control for variables that are associated with that factor. For example, in a study that lacks individual information on smoking, an investigator might adjust for variables that are associated with smoking (eg, SES and birth cohort) and thereby reduce potential confounding of the radiation dose–cancer association by smoking. Similarly, although body mass index was not adjusted for in most occupational studies, it is unlikely to be associated with radiation dose, particularly after adjusting for birth cohort and SES. However, it is important to distinguish between factors that are potential confounders and factors that are associated with radiation exposure because they are effects of exposure. Control for the former may reduce bias due to confounding, whereas control for the latter may induce bias. One example of the latter is an exposure (or other factor) intermediate in the chain of causation from radiation exposure to the disease of interest. Careful consideration, rather than statistical tests, is needed to distinguish between variables that are confounders and those that are intermediate variables; these judgments are central to deciding whether to control for a factor. Temporality often is an important consideration. For example, knowledge that one was exposed to radiation may lead to subsequent behavior changes later in life (eg, change in alcohol consumption or smoking behavior). In such a setting, current smoking status is a risk factor for cancer and associated with prior radiation exposure, but it is not a confounder. Rather, it is an indirect effect of prior radiation exposure operating via a pathway that involves behavioral changes affected by the conditions that also led to radiation exposure. In such a setting, it is possible to estimate the direct effect of radiation on cancer, separate from any indirect effects, but such models often require strong assumptions.

Table 8. Overall assessment of likelihood of uncontrolled confounding in studies of low-dose radiation and cancer

Study (reference)	No.	Overall likelihood (direction*) of uncontrolled confounding?		Overall likelihood (direction*) of selection bias?		Comment
		All cancers excluding leukemia	Leukemia	All cancers excluding leukemia	Leukemia	
Environmental						
Chornobyl residents (19)	1	NA	Unlikely	NA	Likely ↑	Exclusion of subgroup with potential recall bias substantially reduced risk estimates
Three Mile Island (20)	2	Unlikely	Unlikely	Unlikely	Unlikely	No information on confounding by alcohol and BMI for all cancers excluding leukemia
China background (23)	3	Unlikely	Unlikely	Unlikely	Unlikely	
GB background (26)	4	NA	Unlikely	NA	Unlikely	
Swiss background (25)	5	Unlikely	Unlikely	Unlikely	Unlikely	Study directly assessed many factors
Techa River (21)	6	Unlikely	NA	Unlikely	NA	No information on confounding by alcohol, SES, and BMI
Finnish background (24)	7	NA	Unlikely	NA	Unlikely	No information on confounding by SES
Taiwanese residents (22)	8	Unlikely	Unlikely	Unlikely	Unlikely	No information on confounding by smoking, alcohol, SES, and BMI
Medical						
Canadian cardiac imaging (27)	9	Likely ↑↓	Unlikely	Unlikely	Unlikely	Lifestyle factors causing uncertain bias direction
French Pediatric CT (28)	10	Unlikely	Unlikely	Unlikely	Unlikely	
UK Pediatric CT (29)	11	Unlikely	Unlikely	Unlikely	Unlikely	Indirect adjustment suggests predisposing factors cause little bias
PIRATES (30)	12	Unlikely	Unlikely	Unlikely	Unlikely	
Occupational						
Korean workers (31)	13	Likely ↓	Unlikely	Likely ↓	Likely ↓	HWSB and prevalent hire bias
Chornobyl liquidators: Belarus, Russia, & Baltic countries (32)	14	Unlikely	Unlikely	Unlikely	Unlikely	
UK NRRW† (33)	15	Likely ↓	Unlikely	Unlikely	Unlikely	HWSB
Korean nuclear workers (34)	16	Likely ↓	NA	Unlikely	NA	HWSB
Rocketdyne nuclear workers (17)	17	Likely ↓	Unlikely	Unlikely	Unlikely	HWSB
Japanese nuclear workers (36)	18	Likely ↑↓	Unlikely	Likely ↓	Likely ↓	Smoking, HWSB, prevalent hire bias
Canadian nuclear workers (37)	19	Likely ↓	Unlikely	Unlikely	Unlikely	HWSB
Chornobyl liquidators: Ukraine (38)	20	Unlikely	Unlikely	Unlikely	Unlikely	
German nuclear workers (39)	21	Likely ↓	Unlikely	Likely ↓	Likely ↓	HWSB and prevalent hire bias
US nuclear workers† (40)	22	Likely ↓	Unlikely	Unlikely	Unlikely	HWSB
INWORKS (41, 42)	23	Likely ↓	Unlikely	Unlikely	Unlikely	HWSB
Smoky nuclear test (43)	24	NA	Unlikely	NA	Unknown	
USRT (BCC) (46)	25	Unlikely	NA	Unlikely	NA	
USRT (breast cancer) (44)	25	Unlikely	NA	Unlikely	NA	
USRT (brain tumors) (45)	25	Unlikely	NA	Unlikely	NA	
French nuclear workers† (47)	26	Likely ↓	Unlikely	Likely ↓	Likely ↓	HWSB and prevalent hire bias

*↑ indicates upward bias (away from null for positive point estimate, toward null for negative point estimate), ↓ indicates downward bias (toward null for positive point estimate, away from null for negative point estimate). BCC = basal cell carcinoma; BMI = body mass index; CT = computed tomography; GB = Great Britain; HWSB = healthy worker survivor bias; INWORKS = International Nuclear Workers Study; NA = not applicable; NRRW = National Registry for Radiation Workers; PIRATES = Pooled International Radiation and Thyroid Cancer Epidemiology Studies; SES = socioeconomic status; USRT = US Radiologic Technologists.
†Studies were part of INWORKS.

It is also unwise to adjust for factors that are related to exposure but not plausibly independently related to disease risk. For example, in occupational studies one might control for calendar period, or time period of hire, in a model for lung cancer that also adjusts for birth cohort and attained age (ostensibly as an approach to reduce bias due to secular changes in smoking patterns). Occupational exposure is frequently higher in earlier time periods before hazard and control methods were well understood. Yet, after adjusting for important correlates of smoking, like age and birth cohort, time period of hire would not be expected to be associated with smoking, and adjustment could inflate variance estimates and distort risk estimates for the exposure of interest.

A potential source of confounding that has not been fully considered in the occupational studies is bias due to healthy worker survivorship. The HWSB occurs when workplace exposures cause ill health or other conditions that lead to early departure from the workforce and thereby eliminate the potential for future radiation exposure [eg, see (80)] and is especially important when studying hazardous or highly selective workplaces where dose is accrued over a working lifetime. Furthermore, due to the highly sensitive nature of nuclear weapons work, these workers are subject to initial and ongoing stringent medical and security screening (81), which may exacerbate the HWSB. Although conventional statistical methods (eg, regression modelling) are not currently capable of adjusting for the HWSB, this is an area of active research (82), including in radiation-exposed worker populations (83).

The indirect adjustment approach employed here did not estimate the impact of bias correction on the precision of the effect estimate. Although the application of the indirect adjustment approach to adjust the observed confidence limits is possible, a full and comprehensive adjustment requires knowledge of the uncertainties associated with the joint distribution of the confounder and radiation dose as well as of the rate ratio, and the methodological approaches are not straightforward (1,84). We considered this to be beyond the scope of this article, because the required information does not exist for most studies, but recognize that it is an area of active research.

In our review, we found that epidemiological analyses controlled for relatively few factors (Table 1). The primary reason for this is the study design in radiation epidemiology, which is most commonly a retrospective study conducted via record linkage rather than direct participant contact. This design is used to facilitate the large sample size needed for studying low doses and because radiation-related cancers can take many decades to occur. The disadvantage as we have shown here is that this often limits the ability to collect information on confounding factors unless they are also available in historical records. It is common in systematic reviews to evaluate quality of studies based on whether they address sources of potential bias and then to exclude or consider uninformative studies that are evaluated as low quality. Based purely on such quality assessment, many of the studies we evaluated might be considered low quality because they did not have direct information on potential confounders like smoking. However, this approach does not consider the direction and magnitude of the potential bias. We have shown that there are a number of approaches to assess the potential for bias via substudies, other outcomes known to be related to the confounder but unlikely related to radiation or indirect calculations via the Axelson approach. Our in-depth analysis showed that confounding was generally unlikely to be a major source of bias in these recent studies of low-dose radiation and cancer. Nevertheless, we urge authors to publish the impact of adjustment for potential confounders to facilitate the assessment of confounding in their own and other related studies. We have also laid out a rigorous approach for assessing the potential for confounding using a variety of data sources and methods that can be used more broadly in systematic reviews of observational data.

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