

Epidemiological Studies of Low-dose Ionizing Radiation and Cancer: Rationale for the Monograph and Overview of Eligible Studies

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Abstract

Whether low-dose ionizing radiation can cause cancer is a critical, and long-debated question in radiation protection. Since the review by BEIRVII (2006) new publications from large, well-powered epidemiological studies of low-doses have reported positive dose-response relationships. It has been suggested, however, that biases could explain these findings. We conducted a systematic review of epidemiological studies with mean dose <100mGy published 2006-2017. We required individualized doses and dose-response estimates with confidence intervals. We identified 26 eligible studies (8 environmental, 4 medical and 14 occupational) including 71,000 solid cancers and 12,000 leukemias. Mean doses ranged from 0.1-82mGy. The excess relative risk/100mGy was positive for 17/22 solid cancer studies and 17/20 leukemia studies. The aim of this monograph is to systematically review the potential biases in these studies (including dose uncertainty, confounding and outcome misclassification) and to assess whether the sub-set of minimally biased studies provides evidence for cancer risks from low-dose radiation.

Introduction

Whether low-doses of ionizing radiation ($<100\text{mSv}$) can cause cancer is the most critical, and long-debated question for radiation protection standards (1). Currently the key sources of low-dose radiation exposure to the general population are diagnostic medical exposures like CT scans and natural background radiation (2). There are also about 20 million workers in the world who are exposed due to their occupation including medical workers, aircrew and nuclear workers (2).

The last major US review of the experimental and epidemiological evidence for cancer risks from low-dose exposures was conducted by the NAS BEIR VII committee in 2006 (3). The committee concluded that “the available scientific evidence is consistent with a linear dose-response relationship between ionizing radiation and the development of cancer in humans”. This conclusion has been questioned, however, as it was largely based on animal and mechanistic studies combined with epidemiological data from higher dose exposures ($>100\text{mGy}$), rather than direct data from populations exposed to doses $<100\text{mGy}$. The authors of the BEIR VII report highlighted the difficulty in providing direct human evidence, because the risks are likely to be small and very large studies, with minimal potential biases, are needed to detect them.

Since the BEIR VII report there have been a number of new publications from large, well powered epidemiological studies that have reported positive dose-response relationships, supporting excess cancer risks from low-dose and low-dose rate radiation exposure (4). These studies maximized statistical power to detect small excess risks by focusing on the most radiosensitive populations and outcomes (eg leukemia after childhood exposure), combining individual-level data from several studies (pooling) or using large-scale electronic record

linkage. Nevertheless, it has been suggested that biases such as confounding and dose error could explain the positive findings (5).

The aim of this monograph is to systematically assess the epidemiological evidence for excess cancer risks from low-dose/dose-rate radiation using the novel approach of conducting a formal assessment of the potential impact of biases for each study. For example, rather than a qualitative assessment that the risk estimates in nuclear workers could be confounded by uncontrolled smoking we review the related evidence from sub-studies of the cohorts that had collected smoking data, and then use models to assess the potential degree of confounding quantitatively. If no information is available then we used theoretical assessments of the strength of the relationship between the confounder and the disease, and prevalence of the confounder that would be required to completely explain the observed association (6). Similarly for dose error, we review sources of dose error and then formally assess the potential impact on the risk estimate. Again either by using directly related published information on dose error or theoretical assessments. In addition to confounding and dose uncertainty we review other sources of bias such as study power, follow-up bias, outcome uncertainty, selection bias and model misspecification. These are often overlooked despite their potential to bias the risk estimate and precision.

We reviewed studies published since the BEIR VII report in 2006, (3) including studies of environmental, medical and occupational radiation, childhood and adulthood exposures from acute or chronic exposures and outcomes including the most radiogenic cancers (leukemia, breast and thyroid cancer) as well as all solid cancers. Our findings will have important implications for radiation protection standards, which currently rely on the linear no-threshold assumption because of the lack of direct evidence for cancer risks from low-dose exposures. In

addition, our novel framework for the review where we formally and systematically assess the possible epidemiological biases for each study can serve as a model for reviewing epidemiological evidence for other exposures where there is controversy about the potential impact of biases.

Here we describe the criteria for including studies in our review, the search criteria and give a brief overview of each eligible study and summarize the main results. This provides the background for the manuscripts that will follow where we will evaluate 1) the dosimetry 2) confounding 3) outcome ascertainment 4) statistical power and interpretation of results. In our summary manuscript we bring together the findings from each of these in depth assessments and provide an overall assessment regarding the strength and direction of potential bias for each study. From that we draw conclusions about the current level of support from epidemiological studies of cancer risks from low-dose radiation exposure.

Study Eligibility

We conducted a systematic literature review of epidemiological studies published since the BEIR VII report in 2006 (3) and before 12.31.2017. Studies were eligible for inclusion if they were epidemiological studies of human populations exposed to low-dose radiation (mean dose < 100 mGy), predominantly, low-LET radiation exposure. We required individualized dose estimates for the study participants, and that the publications provided risk estimates and confidence intervals for the dose-response for cumulative radiation dose. The search strategy and results are described in detail in the Appendix.

Summary of Study Findings

We abstracted the excess relative risk at 100mGy (ERR at 100mGy) and confidence intervals (CI) from each eligible study for all cancers (or site-specific cancers where all cancers were not available) and leukemia (excluding CLL if possible), which is the most radiosensitive cancer. We converted risk estimates (and CIs) from Gy or mGy to 100mGy where necessary. Most of the studies of populations who received whole-body exposure reported results for all solid cancers and for leukemia separately. We have focused our review on these results rather than site-specific solid cancer analyses, which may lack power and are at risk from multiple testing. For non-uniform exposures the results are generally for specific cancer sites that were highly exposed and/or highly radiosensitive eg brain tumors after pediatric CT scans and breast cancer after medical occupational exposures.

Overview of the Eligible Studies

We identified 26 eligible studies including 8 studies of environmental, (7-14) 4 medical (15-18) and 14 studies of occupational exposure (19-35) (Table 1). Overall, the studies included 3.5 million individuals (although 2 million of these came from the Swiss population-based background study) of whom approximately 70,000 developed solid cancers and 12,000 leukemias. There is some overlap between studies as the UK NRRW (30), French and US workers are also included in the INWORKS cohort (28, 32) although the endpoints differed for the UK NRRW (cancer incidence versus cancer mortality). Mean doses ranged from 0.1mSv from the Three Mile Island accident (9) to 82mSv in Chernobyl liquidators.(34) Two studies included adults and children, (7, 10) seven of the studies focused on childhood exposure, (8, 11-

13, 15, 17, 18) and the majority evaluated adulthood exposure since they were occupational studies.

The ERR at 100mGy for all cancers (or the site-specific solid cancer) was positive (i.e., greater than zero) for 17 of the 22 independent studies that evaluated this end-point (Figures 1a and 1b). For leukemia the ERR at 100mGy was positive for 17 of the 20 independent studies with available data (Figures 2a and 2b). All of the studies reported dose-response risk estimates with 95% confidence intervals, with the exception of the Taiwanese(10), INWORKS (28, 32) and French nuclear workers (27), which reported 90% confidence intervals. For context when assessing the magnitude of the risk estimates, the ERR at 100mGy for solid cancers from an exposure at age 30 at attained age 70 would be in the range of 0.01 to 0.05.(36) In contrast, the ERR at 100mGy for leukemia following childhood exposure in the Life Span Study is approximately 4.5 and 2.2 for brain tumors.(37)

Environmental radiation exposure

Four of the eight eligible studies in this category were of natural background radiation exposure (11-14), and four were of populations exposed accidentally.(7-10)

Chernobyl residents childhood leukemia case-control study

This population-based case-control study of 421 cases of acute leukemia in children exposed <age 6 years to fall-out from the Chernobyl accident was conducted in Ukraine, Belarus and Russia (8). Two controls were selected from each case from polyclinics in the same residential area, matched on birth year, sex and residence at the time of the accident. Dose estimates were

based on questionnaire data from an in-person interviews with the parents. Mean dose in the controls was 6mGy vs 10mGy in the cases and the maximum was 391mGy. The ERR at 100mGy was positive and statistically significant.

Three Mile Island accident

This is a cohort based on a registry of 22,069 adults who lived within 5 miles of the Three Mile Island nuclear plant on the date of the accident in 1979(9). Dose estimation was based on residential location and the amount of time each person stayed in the 5-mile area during the 10 days following the accident. Mean dose was 0.25mSv with a maximum of approximately 1mSv. Cancer incidence was ascertained between 1982 and 1995 as follow-up of the cohort was completed in 1996. The ERR at 100mGy for all cancers (n=1643) was non-significantly negative, and was non-significantly positive for leukemia (n=55).

Chinese background radiation

This is a cohort of 31,604 adults of Guangdong Province in China, an area known for high background radiation from sources including thorium (14). During the study period of 1979 to 1998 the mean cumulative dose was 85mGy. Cancer mortality (n=956) was ascertained using active follow-up methods. The estimated ERR at 100mGy was non-significantly negative for cancer mortality (excluding leukemia) and was non-significantly positive for leukemia (n=15).

GB background radiation

This matched case-control study included 9,058 cases of childhood leukemia and 18,389 cases of other childhood cancers matched to 36,793 controls diagnosed in Great Britain (GB) between

1980 and 2006 (11). The cumulative mean red bone marrow dose from residential gamma and radon exposures was 4mSv with a maximum of 31mSv. Risks were estimated for gamma and radon doses separately, and on average radon only contributed about 10% of the total dose. There was a significant positive dose-response relationship for leukemia and red bone marrow dose, but no clear evidence of a relationship between other childhood cancers and background radiation exposure.

Swiss background radiation

A cohort of 2 million children was constructed using census data from 1990 and 2000 linked to the Swiss Childhood Cancer Registry (13). The census data were used to geocode residence and the mean cumulative radiation dose was 9mSv with a maximum of 49mSv. During the follow-up period to 2008 there were 530 childhood leukemias and 1,252 other childhood cancers diagnosed. There was a statistically significant dose-response relationship for childhood cancers (excluding leukemia) and background radiation and a borderline significant dose-response relationship for leukemia.

Techa river

Radioactive material was released into the Techa river by the Mayak nuclear weapons facility between 1949 and 1956. A cohort of 17,435 adults and children who were residents of the local villages was constructed who received external radiation exposure from gamma rays due to contamination of the river shoreline, and internal exposure from consumption of contaminated water, milk and food. The mean stomach dose was 52mGy with a maximum of 0.5Gy. There were 1,993 solid cancers ascertained up to 2007, and evidence of a statistically significant

positive dose-response relationship (7). The mean red bone marrow dose was above our threshold of 100mGy for this population and therefore the separate analysis of leukemia was ineligible.

Finnish background radiation

A Finnish study of childhood leukemia (n=1093) and matched controls (n=3279) used the Population Register to collect complete residential histories from birth (12). The estimated median cumulative red bone marrow dose from a combination of natural background radiation and fallout from Chernobyl was 2mSv with a maximum of 12mSv. The ERR at 100mGy was negative, but non-significant.

Taiwanese residents

This cohort of 6242 adults and children were accidentally exposed to chronic gamma irradiation from contaminated steel that was used to re-inforce their apartment buildings (10). The mean cumulative dose was 48mGy but exposures were as high as 2Gy. The exposures occurred between 1983 and 1992, when the contamination was discovered. Follow-up for cancer incidence (n=247) has been reported through 2012. There was a significant dose-response for all cancers (excluding leukemia) with an ERR at 100mGy of 0.04 (90%CI: 0.0 to 0.08) and for leukemia of 0.15 (90%CI: 0.03 to 0.24).

Medical radiation exposures

Canadian cardiac imaging

A hospital discharge database was used to ascertain a cohort of 82,861 patients who had an acute myocardial infarction (and no history of cancer) between 1996 and 2006 (16). Doses from cardiac imaging and therapeutic procedures were estimated for each patient with a mean dose of 5mSv with a maximum of >30mSv. Incident cancer diagnoses were ascertained using the same hospital databases. There was a significant dose-response for all cancers (n=12,020) with an ERR at 100mGy of 0.3 (95%CI: 0.2 to 0.4).

French pediatric CT study

This cohort of children (n=58,620) who had a CT scan before age 10 between 2000 and 2010 was linked to the French childhood cancer registry, which captures diagnoses up to age 15 years (17). During the follow-up period there were 12 leukemias and 15 brain tumors diagnosed. Mean doses were 9mGy to the red bone marrow and 23mGy to the brain and maximum doses of 50+mGy. After exclusion of children with cancer pre-disposing conditions there was a non-significant positive dose-response for leukemia and brain tumors in relation to cumulative organ doses from the CT scans.

UK pediatric CT

This is a cohort of 178,604 children and young adults (<age 22 years) who underwent CT scans in hospitals in the UK between 1985 and 2002. Cancer incidence was obtained by record linkage to the national cancer registry and with follow-up to 2008 there were 70 cases of leukemia/myelodysplastic syndrome and 112 brain tumors diagnosed after exclusion of cases

with cancer pre-disposing conditions or unreported brain tumors (15). The mean red bone marrow dose was 12mGy and mean brain dose was 43mGy with a maximum of more than 400mGy for children who underwent multiple head CT scans. There was a statistically significant dose-response relationship for brain tumors in relation to cumulative brain dose and leukemia in relation to red bone marrow dose from the CT scans.

PIRATES thyroid cancer pooling study

This pooled analysis of nine cohorts of 107,594 children included eight cohorts of medical exposures (including treatment for benign and malignant diseases) and the Japanese atomic bomb survivors. For this monograph we considered the results from the analysis that was restricted to children who received <200mGy to the thyroid, with a mean dose of 30mGy (18). This analysis included 394 incident thyroid cancers of which 137 were from the Life Span Study of Japanese atomic bomb survivors and 186 from the Israeli study of children treated with radiation for Tinea Capitis. Therefore, in our assessment of the potential biases that could have impacted this pooling project we have focused on the issues related to these two studies as they contributed 82% of the cases to the pooled analysis. There was a statistically significant linear dose-response relationship when doses were restricted to <200mGy, which was still significant and not materially altered when doses were restricted to <100mGy.

Occupational exposures

Korean radiation workers

This cohort included 79,679 workers from nuclear power, medical, research and other facilities who were under radiation surveillance and first exposed between 1984 and 2004 (19). The

mean recorded badge dose was 6mSv and the maximum was 159mSv. Follow-up was from 1992 (the period when cause of death was first available in the Korean registry) until 2004 and there were 141 cancer deaths including 7 leukemia deaths during this period. There was a non-significant dose-response relationship for all cancer deaths, and for the small number of leukemia deaths.

Chernobyl liquidators leukemia case-control study

A case-control study of clean-up workers from Belarus, Russia and the Baltic states was conducted by interviewing 19 eligible workers that developed (non-CLL) leukemia and 83 controls (24). The cases were ascertained from population-based cancer registries in each country. Red bone marrow doses were reconstructed from the interviews and the mean dose was approximately 40mGy with a maximum of >500mGy. The dose-response was positive but non-significant.

UK National Registry of Radiation Workers (UKNRRW)

This cohort of 174,451 workers with dose records includes individuals from the nuclear power, research, medical and defense industries (30). The mean occupational exposure was 25mSv and the maximum was >600mSv. The cohort was linked with UK cancer registration data and with follow-up to 2002 there were 11,113 incident cancers, including 362 leukemias. There was a statistically significant positive dose-response relationship for all cancers combined, and for leukemia.

Korean nuclear workers

This is a sub-cohort of nuclear workers within the larger Korean workers cohort described above who completed a questionnaire and clinical check-up between 1992 and 2005 (23). As there were few female employees the study focused on 16,236 males of which 8429 were radiation workers (they were issued with a dosimeter), and the remainder were classified as non-radiation workers. The cohort was linked to the national cancer registry and 203 incident cancers were ascertained up to 2005. The mean cumulative dose amongst the radiation workers was 20mSv, with a maximum of 480mSv. There was a positive but non-significant dose-response relationship for all incident cancers.

Rocketdyne workers

A cohort of workers employed at US nuclear research facilities between 1948 and 1999 included 41,169 workers involved in rocket testing and non-radiation activities and 5,801 involved in radiation activities (including 2,232 who received internal monitoring) (21). The mean external dose in the radiation workers was 13mSv but the maximum was 1Sv. Linkage to the national death index through 2008 identified 684 cancer deaths. There was a positive, but non-significant dose-response relationship for all cancers and leukemia.

Japanese radiation workers

This cohort is the third phase of the study and is comprised of 200,583 workers in the Radiation Dose Registration Center with mortality information from the national death registry from 1991-2002 (20). The mean occupational dose was 12mSv with a maximum of 100+mSv. There were

2703 cancer deaths including 80 from leukemia during the follow-up period. There was a borderline significant dose-response relationship for total cancer mortality, and a non-significant negative dose-response relationship for leukemia and occupational radiation exposure.

Canadian nuclear workers

This cohort of nuclear workers was created by linking employment records with the Canadian National Dose Registry and included 45,316 participants employed between 1956 and 1994 (35). The mean cumulative occupational dose was 22mSv and the maximum was 679mSv. Because of evidence of incomplete dose records for workers employed before 1965 the “best estimates” of radiation risk in the most recent analysis excluded these earliest workers. In the 42,228 workers employed 1965+ there were 347 solid cancer deaths and 13 leukemia deaths during the follow-up period, 1956-1994. There was a non-significant negative dose-response relationship for all solid cancer mortality and non-significant increased risk of leukemia mortality with occupational dose.

Ukrainian Chernobyl liquidators leukemia case-control study

A nested case-control study of 52 cases of (non-CLL) leukemia diagnosed between 1986 and 2006 and 863 controls was conducted from a cohort of Ukrainian clean-up workers (34). Occupational radiation exposure was reconstructed using questionnaire data. In the controls the estimated mean red bone marrow dose was 82mGy and the maximum was 2.5+Gy. There was a statistically significant, positive dose-response relationship with estimated red bone marrow dose.

German nuclear workers

The cohort was comprised of 8,746 workers from 17 nuclear power plants in West Germany who were employed in 1991 (when medical examinations were initiated) or started employment before 2009 (29). Follow-up for cancer mortality was via local population registries and by 2009 there were 126 cancer deaths ascertained. The mean cumulative dose was 30mSv and 8.5% had doses >100mSv. There was a non-significant negative dose-response for all solid cancer mortality and a non-significant positive dose-response for leukemia mortality and occupational dose.

US nuclear workers

This is a pooled study of four cohorts of 119,195 workers from US nuclear weapons facilities who started work as early as 1944 and were followed up to 2005 (33). The mean dose was 20mSv although some received up to 700mSv, but only 1.9% had confirmed internal exposures. There were 11,332 cancer deaths during the follow-up period. There was a non-significant positive dose-response relationship for leukemia mortality and for all cancer mortality (excluding leukemia).

INWORKS

The International Nuclear Workers Study (INWORKS) comprises data from the US and French nuclear workers studies combined with the UK NRRW to form a cohort of 308,297 workers (28, 32). The mean colon dose was 21mGy versus 16mGy to the red bone marrow with a maximum of 1+Gy. Overall there were 17,957 solid cancer deaths and 531 leukemia deaths during the

follow-up. Based on 90% confidence intervals there were statistically significant positive dose-response relationships for all solid cancer and leukemia mortality in relation to occupational radiation exposure.

US atomic veterans

A cohort of 114,270 military veterans were followed up for cancer mortality until 2010 (22). The estimated mean red bone marrow dose was 3mGy with a maximum of 500mGy. A dose-response analysis was conducted for leukemia deaths (n=27) and was found to be negative, but not statistically significant.

USRT

US radiologic technologists who were certified for at least two years between 1926 and 1982 were sent a series of questionnaires about their work history, lifestyle and self-reported cancer diagnoses. A series of site-specific cancer analyses have been conducted for the most radiosensitive cancer sites. In the cohort of approximately 110,000 workers there were 1922 breast cancer diagnoses, 3615 skin cancers and 193 brain tumor deaths (25, 26, 31). The mean cumulative breast dose was 37mGy, mean skin dose was 56 mGy and mean brain dose was 12mGy with maximum doses over 1Gy in those that worked during the earliest periods. Overall, there was a positive non-significant dose-response relationship for breast cancer and occupational radiation exposure but no clear relationship for brain tumor deaths or skin cancers.

French nuclear workers

Workers from French nuclear facilities who were employed between 1950 and 2004 were followed from 1968, when the national death registry was established (27). In the 59,004 workers there were 2536 deaths from solid cancer and 56 from leukemia by 2004. Among the 72% of the cohort that had non-zero badge doses the mean dose was 26mSv, with a maximum of 669mSv. There were positive, but non-significant, dose-response relationships for all solid cancer and leukemia mortality in relation to occupational dose.

Ineligible studies

When considering epidemiological studies published since 2006, there were 13 radiation dose-response studies that were excluded for failing just one criterion (Table 2). These included: 7 studies with a mean dose $>100\text{mGy}$ (38-44), five studies were ineligible because they only published risk estimates for categories of dose rather than a dose-response (45, 46) and two background radiation studies were excluded because dose rate rather than cumulative dose was assessed (47, 48). Five of the six studies that were excluded due to the mean dose exceeding 100mGy reported statistically significant ($p>0.1$) positive dose-response relationships. Six of the seven remaining studies were mostly null; the exception was the French biology researchers which found a significant dose-response for all solid cancers ($p\text{-trend}=0.03$) but did not report the dose-response coefficient (49).

Discussion

We identified a large body of epidemiological data published since 2006 that has assessed the evidence of cancer risks following low-dose radiation exposures. The majority of the 26 eligible

studies (mean dose of <100mGy) reported positive dose-response relationships for solid cancer risks and/or leukemia.

Major international and national organizations routinely review the epidemiological studies of cancer risks from ionizing radiation exposure including the US National Academy of Science BEIR reports (3), the United Nations UNSCEAR(1) and the UK AGIR committees.(50). These are comprehensive reviews, but all follow the traditional model of summarizing the findings of each study accompanied by a brief description of the strengths and weaknesses and potential biases. They have universally concluded that there is ample evidence that ionizing radiation is a carcinogen and that most types of cancer can be caused by radiation exposure. The inclusion criteria for our review are similar to that used by many of these organizations; focusing on studies that have evaluated the dose-response relationship; one of the Bradford Hill criteria for causality.(51) In this monograph we will take the novel approach to review the data by using statistical and epidemiological methods to systematically assess the evidence for bias. We then base our final assessment of whether there is direct epidemiological evidence for cancer risks from low-dose radiation exposures on the sub-set of studies that are considered to be minimally biased. Further discussion of our findings and comparison with the results and methods from previous reviews of the epidemiological evidence will be presented in the summary manuscript, after our detailed evaluation of the potential biases.

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References

1. UNSCEAR. Summary of low-dose radiation effects on health. In. New York: United Nations; 2011.
2. Radiation UNSCotEoA. Sources and effects of ionizing radiation In. New York: United Nations; 2008.
3. Council NR. *Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII Phase 2*. Washington, DC: The National Academies Press; 2006.
4. Kitahara CM, Linet MS, Rajaraman P, et al. A New Era of Low-Dose Radiation Epidemiology. *Curr Environ Health Rep* 2015;2(3):236-49.
5. Measurements NCoRPa. Implications of Recent Epidemiologic Studies for the Linear-Nonthreshold Model and Radiation Protection. NCRP commentary; no.27. In. Bethesda, MD: National Council on Radiation Protection and Measurements; 2018.
6. Axelson O, Steenland K. Indirect methods of assessing the effects of tobacco use in occupational studies. *Am J Ind Med* 1988;13(1):105-18.
7. 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.
8. Davis S, Day RW, Kopecky KJ, et al. 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):386-96.
9. 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):1230-5.

10. 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.
11. 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.
12. 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):1975-82.
13. Spycher BD, Lupatsch JE, Zwahlen M, et al. Background ionizing radiation and the risk of childhood cancer: a census-based nationwide cohort study. *Environ Health Perspect* 2015;123(6):622-8.
14. 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):173-81.
15. 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):388-94.
16. 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):430-6.
17. Journy N, Roue T, Cardis E, et al. Childhood CT scans and cancer risk: impact of predisposing factors for cancer on the risk estimates. *J Radiol Prot* 2016;36(1):N1-7.

18. 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.
19. 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.
20. 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.
21. 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):244-58.
22. 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.
23. 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.
24. Kesminiene A, Evrard AS, Ivanov VK, et al. Risk of hematological malignancies among Chernobyl liquidators. *Radiat Res* 2008;170(6):721-35.
25. 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.

26. 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):862-9.
27. Leuraud K, Fournier L, Samson E, et al. Mortality in the French cohort of nuclear workers. *Radioprotection* 2017;52(3):199-210.
28. 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.
29. 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):405-16.
30. 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):206-12.
31. 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.
32. 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.
33. 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):620-31.

34. Zablotska LB, Bazyka D, Lubin JH, et al. Radiation and the risk of chronic lymphocytic and other leukemias among Chernobyl cleanup workers. *Environ Health Perspect* 2013;121(1):59-65.
35. 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):214-23.
36. Grant EJ, Brenner A, Sugiyama H, et al. Solid Cancer Incidence among the Life Span Study of Atomic Bomb Survivors: 1958-2009. *Radiat Res* 2017;187(5):513-537.
37. Pearce MS, Salotti JA, Little MP, et al. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. *Lancet* 2012;380(9840):499-505.
38. Kashcheev VV, Chekin SY, Maksioutov MA, et al. Incidence and mortality of solid cancer among emergency workers of the Chernobyl accident: assessment of radiation risks for the follow-up period of 1992-2009. *Radiat Environ Biophys* 2015;54(1):13-23.
39. Krestinina LY, Davis FG, Schonfeld S, et al. Leukaemia incidence in the Techa River Cohort: 1953-2007. *Br J Cancer* 2013;109(11):2886-93.
40. Nair RR, Rajan B, Akiba S, et al. Background radiation and cancer incidence in Kerala, India-Karanagappally cohort study. *Health Phys* 2009;96(1):55-66.
41. Ronckers CM, Doody MM, Lonstein JE, et al. Multiple diagnostic X-rays for spine deformities and risk of breast cancer. *Cancer Epidemiol Biomarkers Prev* 2008;17(3):605-13.
42. Sokolnikov M, Preston D, Stram DO. Mortality from solid cancers other than lung, liver, and bone in relation to external dose among plutonium and non-plutonium workers in the Mayak Worker Cohort. *Radiat Environ Biophys* 2017;56(1):121-125.

43. Sun Z, Inskip PD, Wang J, et al. Solid cancer incidence among Chinese medical diagnostic x-ray workers, 1950-1995: Estimation of radiation-related risks. *Int J Cancer* 2016;138(12):2875-83.
44. Kesminiene A, Evrard AS, Ivanov VK, et al. Risk of thyroid cancer among chernobyl liquidators. *Radiat Res* 2012;178(5):425-36.
45. Matanoski GM, Tonascia JA, Correa-Villasenor A, et al. Cancer risks and low-level radiation in U.S. shipyard workers. *J Radiat Res* 2008;49(1):83-91.
46. Wang FR, Fang QQ, Tang WM, et al. Nested Case-control Study of Occupational Radiation Exposure and Breast and Esophagus Cancer Risk among Medical Diagnostic X Ray Workers in Jiangsu of China. *Asian Pac J Cancer Prev* 2015;16(11):4699-704.
47. Demoury C, Marquant F, Ielsch G, et al. Residential Exposure to Natural Background Radiation and Risk of Childhood Acute Leukemia in France, 1990-2009. *Environ Health Perspect* 2017;125(4):714-720.
48. Spix C, Grosche B, Bleher M, et al. Background gamma radiation and childhood cancer in Germany: an ecological study. *Radiat Environ Biophys* 2017;56(2):127-138.
49. Guseva Canu I, Rogel A, Samson E, et al. Cancer mortality risk among biology research workers in France: first results of two retrospective cohorts studies. *Int Arch Occup Environ Health* 2008;81(6):777-85.
50. Radiation AGoI. RCE-19: Risk of solid cancers following radiation exposure - estimates for the UK population. In. Chilton, UK: Health Protection Agency; 2011.
51. Hill AB. The environment and disease: association or causation? 1965. *J R Soc Med* 2015;108(1):32-7.

Table 1: Description of the eligible studies

Study	Age at exposure	Mean dose	Dose range	Design	Solid cancers	Leukemia	Cohort size
Environmental							
Chernobyl residents (leukemia)	Childhood	6mGy	0-265mGy	C-C	-	421	-
Three mile Island	Adulthood	0.1mSv	0-0.8mSv	Cohort	1,643	55	21,494
Chinese background	Adulthood	66mGy	0-125+mGy	Cohort	941	15	31,604
GB Background	Childhood	4mSv	0-31mSv	C-C	18,389	9,058	-
Swiss background	Childhood	9mSv	0-49mSv	Cohort	1,252	530	2,093,660
Techa river	All ages	52mGy	0-0.5Gy	Cohort	1,093	-	17,435
Finnish background	Childhood	2mSv*	0-12mSv	C-C	-	1,093	-
Taiwanese residents	All ages	48mGy	0-2+Gy	Cohort	274	11	6,242
Medical							
Canadian cardiac imaging	Adulthood	5mSv	0-30+mSv	Cohort	12,020	-	82,861
French Pediatric CT	Childhood	9/23mGy**	0-100+mGy	Cohort	15**	12	58,620
UK Pediatric CT	Childhood	12/43mGy**	0-400+mGy	Cohort	112**	70	178,604
PIRATES (low-dose)	Childhood	30mGy	0-200mGy	Cohort	394	-	107,594
Occupational							
Korean workers	Adulthood	6mSv	0-50+mSv	Cohort	134	7	79,679
Chernobyl liquidators (leukemia)	Adulthood	51mGy	0-500mGy	C-C	-	19	-
UKNRRW	Adulthood	25mSv	0-600+mSv	Cohort	11,133	362	174,541
Korean nuclear workers	Adulthood	20mSv	0-480mSv	Cohort	203	-	16,236
Rocketdyne workers	Adulthood	14mSv	0-1000mSv	Cohort	647	25	46,970
Japanese workers	Adulthood	12mSv	0-<450mSv	Cohort	2,636	80	200,583
Canadian nuclear workers	Adulthood	22mSv	0-679mSv	Cohort	437	21	45,316
Ukrainian Chernobyl liquidators (leukemia)	Adulthood	82mGy	0-2.5+Gy	C-C	-	52	-
German nuclear workers	Adulthood	30mSv	0-100+mSv	Cohort	10,877	7	8,972
US nuclear workers	Adulthood	20mSv	0-0.7+ Gy	Cohort	17,957	369	119,195
INWORKS	Adulthood	21/16mGy‡	0-1332 mGy	Cohort	3,615	531	308,297
US atomic veterans	Adulthood	6mGy	0-580mGy	Cohort	1,922	27	114,270
USRT (breast/skin/brain cancers)	Adulthood	37/56/12mG¶	0-1+ Gy	Cohort	1922/2536/193¶	-	110,000
French nuclear workers	Adulthood	26mSv	0-669mSv	Cohort	2,536	57	59,004

*median dose. **brain tumors/leukemia. ‡solid cancers/leukemia. ¶breast/skin/brain cancers. C-C: case-control.

Table 2: Descriptive characteristics of the ineligible studies and reason for exclusion

Population	1st author	Publication Year	Reason for exclusion	Findings for solid cancers and leukemia (or primary cancer site)
Breast cancer in US scoliosis	Ronckers	2008	Mean dose = 120mGy	Borderline significant positive dose-response relationship for breast cancer (p-trend=0.06).
Kerala background	Nair	2009	Mean dose = 161mGy	Non-significant negative dose-response for all solid cancers (excluding leukemia) p-trend>0.5.
Chernobyl clean-up workers	Kesminiene	2012	Mean dose =100-200mGy	Significant positive dose-response for thyroid cancer.
Techa river	Krestinina	2013	Mean dose = 410mGy	Significant positive dose-response for all leukemias (p-trend<0.001).
Mayak workers	Solkinokov	2015	Mean dose = 354mGy	Significant positive dose-response for all solid cancers (excluding lung, liver and bone cancers) p-trend=0.01.
Chernobyl clean-up workers	Kashcheev	2015	Mean dose = 132mGy	Significant positive dose-response for total cancer incidence (p-trend=0.034) and mortality (p-trend=0.05).
Chinese medical workers	Sun	2016	Mean dose = 250mGy	Significant positive dose-response for all solid cancer incidence (p-trend=0.002).
US Shipyard workers	Matanoski	2008	Categorical risk estimates	Non-significant increased risk of leukemia in highest dose category. No trend tests presented.
Australian nuclear test	Gun	2008	Categorical risk estimates	No increased risk of solid cancer or leukemia across dose-categories (p-trend>0.05).
French biology researchers	Guseva	2008	Categorical risk estimates	Significant increasing trend for all cancer deaths across dose-categories (p=0.03 5- year lag).
Finnish reindeer herders	Kurtio	2009	Categorical risk estimates	No overall increased risk of cancer across dose-categories (p-trend=0.28), but significant increased risk with dose for exposure <age 15 (p-trend=0.003).
Childhood X-rays	Hammer	2009	Categorical risk estimates	No increased risk of solid cancer (p-trend=0.32) or leukemia (p-trend=0.26) across dose-categories.
French background (Geocap case-control)	Demoury	2016	Risk for dose rate not cumulative dose	Acute leukemia not related to background radiation exposure (p-trend>0.05).