Review of the risk of cancer following low and moderate doses of sparsely ionising radiation received in early life in groups with individually estimated doses

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Abstract

Background: The detrimental health effects associated with the receipt of moderate (0.1–1 Gy) and high (>1 Gy) acute doses of sparsely ionising radiation are well established from human epidemiological studies. There is accumulating direct evidence of excess risk of cancer in a number of populations exposed at lower acute doses or doses received over a protracted period. There is evidence that relative risks are generally higher after radiation exposures in utero or in childhood.

Methods and findings: We reviewed and summarised evidence from 60 studies of cancer or benign neoplasms following low- or moderate-level exposure in utero or in childhood.

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Declaration of Competing Interest
The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2021.106983.
from medical and environmental sources. In most of the populations studied the exposure was predominantly to sparsely ionising radiation, such as X-rays and gamma-rays. There were significant ($p < 0.001$) excess risks for all cancers, and particularly large excess relative risks were observed for brain/CNS tumours, thyroid cancer (including nodules) and leukaemia.

**Conclusions:** Overall, the totality of this large body of data relating to *in utero* and childhood exposure provides support for the existence of excess cancer and benign neoplasm risk associated with radiation doses < 0.1 Gy, and for certain groups exposed to natural background radiation, to fallout and medical X-rays *in utero*, at about 0.02 Gy.

**Keywords**

Radiation; Childhood; *In utero*; Cancer risk; Radiobiology

1. **Introduction**

Although moderate and high doses of sparsely ionising radiation (such as X-rays and gamma-rays), when received at a high dose-rate, are known to be associated with elevated cancer risks (Armstrong et al. 2012; Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation 2006; International Commission on Radiological Protection (ICRP) 2007; United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2008), less is known about any risks arising from exposures at lower doses and dose rates.

There is growing evidence in the Japanese atomic bomb survivors (Grant et al. 2017; Little et al. 2020) and in groups receiving medical diagnostic exposures or radiation therapy of an excess risk of cancer following lower levels of exposure to radiation, particularly among those exposed in childhood (Little et al. 2018b; Lubin et al. 2017). The pioneering case-control study of Stewart *et al* (Bithell and Stewart 1975; Stewart *et al* 1956; Stewart *et al* 1958), which became known as the Oxford Survey of Childhood Cancers (OSCC), suggested that there might be excess risk of most types of childhood cancer associated with antenatal exposure to doses of about 0.01–0.03 Gy of X-rays; however, the interpretation of the association found by this and similar case-control studies has been controversial, with potential for recall and selection biases and for confounding (Brent 2014; International Commission on Radiological Protection (ICRP) 2003; United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2008). More recently there have been a number of studies of childhood cancer associated with natural background exposure to gamma radiation (with cumulative doses generally in the range of at most a few tens of mGy), some (but not all) of which have observed excess cancer risks (Kendall *et al* 2021; Mazzei-Abba *et al* 2020).

By far the largest part (>80%) of man-made radiation exposure (apart from patients receiving radiotherapy) to children in the US is from computed tomography (CT) scan use, comprising a collective effective dose of about 18,000 person Sv in 2016, with much smaller contributions from conventional radiography (~1300 person Sv), fluoroscopy (~700 person Sv), nuclear imaging (~700 person Sv), and image-guided interventions (~300 person Sv) (National Council on Radiation Protection and Measurements (NCRP) 2019). Both in the
US and Canada rates of CT scan use in children have stabilised since the early 2000s, with some signs of reduction since about 2006 (Smith-Bindman et al. 2019), in contrast to trends in the adult population in the US and elsewhere where rates have carried on increasing (National Council on Radiation Protection and Measurements (NCRP) 2009; 2019; Smith-Bindman et al. 2019). There have been a number of studies evaluating risks of cancer after CT scanning in childhood, many of which have indicated some excess risk (Berrington de Gonzalez et al. 2016; Journy et al. 2015; Journy et al. 2016; Kojimahara et al. 2020; Krille et al. 2015; Mathews et al. 2013; Meulepas et al. 2019; Pearce et al. 2012) although the interpretation of these findings is not straightforward (Boice 2015; Walsh et al. 2014).

There have been a number of recent reviews of this low and moderate dose literature, in particular by the National Council on Radiation Protection and Measurements (NCRP) (National Council on Radiation Protection and Measurements (NCRP) 2018; Shore et al. 2018; Shore et al. 2019) and by a large group of collaborators coordinated by the National Cancer Institute (NCI) (Berrington de Gonzalez et al. 2020; Daniels et al. 2020; Gilbert et al. 2020; Hauptmann et al. 2020; Linet et al. 2020; Schubauer-Berigan et al. 2020), although most studies surveyed in both cases related to exposure in adulthood.

Childhood cancers have never been common diseases and recent decades have seen great improvements in therapy (Stiller 2007). Nevertheless, they remain diseases of concern, particularly due to the temporal and spatial variations in incidence (“clusters”) that have been observed in, for example, childhood leukaemia (Steinmaus et al. 2004). In this paper we shall review cancer risks following exposure to sparsely ionising (low linear energy transfer (LET)) radiation exposure early in life (in utero and in childhood) in many of these low and moderate dose studies, and by a meta-analysis quantitatively assess the degree of compatibility of relative risk estimates derived from the main studies. As such, the focus of this review is quite distinct from the recent reviews of low dose risk by the NCRP (National Council on Radiation Protection and Measurements (NCRP) 2018) and by the NCI (Berrington de Gonzalez et al. 2020; Daniels et al. 2020; Gilbert et al. 2020; Hauptmann et al. 2020; Linet et al. 2020; Schubauer-Berigan et al. 2020), which concentrated on all-age exposure with the former conducted in the context of radiological protection, and specifically did not assess in utero exposure in any depth; however, the issue of risks after radiation exposure in childhood has been dealt with in a number of other reviews (Linet et al. 2009; United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2013). In the Discussion we shall also briefly review the radiobiology to assess the biological plausibility of these epidemiological associations.

2. Methods

2.1. Literature review

A literature search of PubMed was last performed on 16th May 2021 using the search terms given in the Supplementary Methods. Additionally, recent UNSCEAR reports (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2008; 2013; 2018) were scanned to assess additional literature, as well as recent review articles (Kendall et al. 2021; Linet et al. 2009; Linet et al. 2012; Wakeford and Bithell 2021). We restricted
attention to those studies of persons exposed *in utero* or in childhood (age 20 y or less) and with individually estimated organ/tissue doses. A further restriction was either that maximum cumulative doses (or if this could not be determined, mean cumulative doses) should not exceed the conventional definitions of low doses, <0.1 Gy, or moderate doses, 0.1–1 Gy (Harrison et al. 2021; Little et al. 2021a; United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2015), or that the maximum dose rate should not exceed 0.005 Gy per hour (the conventional upper limit for low dose rate (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2018) or 0.1 Gy per hour (which we take as the upper limit for moderate dose rate). Justification for these limits will be found in the Supplementary Methods.

### 2.2. Meta-analysis

Meta-analysis was conducted of the studies, of *in utero* and postnatal exposures, outlined in Tables 1–5; the basis of all estimations of radiation risk in this latter analysis is the value of excess relative risk (ERR) per unit of absorbed dose of radiation exposure (ERR per Gy). For absorbed dose, most publications employed unweighted radiation dose (Gy), but some use weighted dose, for example in the LSS to account for the higher biological effectiveness of neutrons compared with photons (Shimizu et al. 2010; Grant et al. 2017). Wherever possible the OR, RR or ERR were taken directly from the relevant publication; further details are given in Tables 1–5 and Supplementary Tables S1–S2. There are grounds for thinking that risks of thyroid nodule and thyroid cancer are not dissimilar, as for example suggested by the Ukraine *in utero* data of Hatch *et al.* (Hatch et al. 2019), likewise among postnatally exposed groups in Belarus (Cahoon et al. 2017a; Zablotska et al. 2011). For this reason we group thyroid cancer and thyroid nodules together in all meta-analyses. Further details of data exclusions and of how the data abstraction was performed for particular studies are given in the Supplementary Methods.

An aggregate estimate of ERR per Gy was computed across subsets of these studies using random effects models and standard statistical methods. Random effects models were fitted by restricted maximum likelihood (REML) because of the theoretically superior performance, in particular, the absence of bias in the estimate of variance (Bartlett and Fowler 1937; Viechtbauer 2005). Results are given in Table 6 and Supplementary Tables S3, S4. However, for certain analyses (Table 7, Supplementary Tables S5) maximum-likelihood fits were used, as these facilitate comparison of nested models (in particular, to test against improvement over the null). Values of ERR per Gy derived from the meta-analysis are given in Tables 6, 7 and Supplementary Tables S3–S5 for major cancer subtypes (leukaemia, lymphoma, brain/central nervous system (CNS), etc.), by *in utero* vs postnatal exposure and by level of maximum dose or maximum dose rate, into low (L), medium (M), or high (H), using the classification by dose (L/M/H) and dose rate (L/M/H) in columns 3 and 5, respectively, of Tables 1–5. We undertook sensitivity analyses in which we refitted:

- **a.** thyroid nodule data < 0.799 Gy of Hatch *et al.* (Hatch et al. 2019);
- **b.** thyroid cancer data < 0.284 Gy of Kopecky *et al.* (Kopecky et al. 2006);
- **c.** Cardis *et al.* (Cardis et al. 2005) thyroid cancer data using a linear model restricted to < 1 Gy;

*Environ Int.* Author manuscript; available in PMC 2022 May 19.
d. Lubin et al (Lubin et al. 2017) data restricted to < 0.1 Gy;

e. Preston et al (Preston et al. 2007) brain/CNS and breast cancer data restricted to < 0.1 Gy;

f. Cahoon et al (Cahoon et al. 2017b) lung cancer data restricted to < 0.1 Gy.

These we term the “lower dose risks”. These we contrasted with using instead:

a. the full dose range thyroid nodule data of Hatch et al (Hatch et al. 2019);

b. the full dose range thyroid cancer data of Kopecky et al (Kopecky et al. 2006);

c. Cardis et al (Cardis et al. 2005) thyroid cancer data using a linear model restricted to < 2 Gy;

d. Lubin et al (Lubin et al. 2017) data restricted to < 0.2 Gy;

e. Preston et al (Preston et al. 2007) brain/CNS and breast cancer data restricted to < 1 Gy; and

f. Cahoon et al (Cahoon et al. 2017b) lung cancer data restricted to < 1 Gy.

These we term the “higher dose risks”.

All statistical models were fitted using the metafor package (Viechtbauer 2010; 2020) in R (R Project version 3.6.1 2019). Further details of the statistical methods are given in the Supplementary Methods.

3. Results

The second stage of the literature review yielded 49 studies in which radiation exposure has been quantitatively assessed, whether in utero or in childhood (Tables 1–5). Supplementary Table S6 gives details of a further 11 studies of natural background radiation that are not included in Table 1, generally because they were not informative or because their results were effectively subsumed within larger studies; also given in Supplementary Table S6, for completeness, are details of those 6 studies that are also included in Table 1.

3.1. Risks of in utero exposure

There are strong estimates of excess risk of cancer in childhood in the OSCC study of Bithell and Stiller (Bithell and Stiller 1988) and of Bithell (Bithell 1993) (Table 2, Supplementary Table S7), at doses that likely do not exceed 0.03 Gy, and borderline significant indications of excess risk for lympho-haematopoietic malignancies in the range of attained ages up to 61 years in the Southern Urals study of Schüz et al (Schüz et al. 2017) and for all thyroid nodules (mainly benign) at an attained age of 25–30 years in the Ukraine 131I-exposed cohort of Hatch et al (Hatch et al. 2019) (Table 3, Supplementary Table S7). There are weaker indications of excess brain tumour risk in a case-control study of medical diagnostic exposures (Pasqual et al. 2020) (Table 2, Supplementary Table S7), for solid cancer in the in utero exposed Japanese atomic bomb survivors in the incidence study of Preston et al (Preston et al. 2008) at attained age of 12–55 years and in the mortality study of Sugiyama et al (Sugiyama et al. 2021) at attained age of 5–67 years (Table 4, Supplementary
Table S7), and for lymphoma, leukaemia and solid cancer in the offspring of US radiologic technologists (Johnson et al. 2008) at attained age up to 20 years (Table 3, Supplementary Table S7).

3.2. Risks of radiation exposure in childhood

3.2.1. Risks associated with environmental radiation exposure

3.2.1.1. Naturally occurring environmental exposures:

A large number of studies of natural background radiation and childhood cancer have been conducted, as shown in Table 1 and Supplementary Table S6. The maximum doses are generally very low, in no case exceeding 0.05 Gy (Table 1). Among the main studies listed in Table 1, all are of natural background gamma radiation, but some also include assessment of the risks of radon exposure (Berlivet et al. 2021; Berlivet et al. 2020; Demoury et al. 2017; Kendall et al. 2013). All these studies, and two studies that assessed only gamma radiation (Nikkilä et al. 2016; Spycher et al. 2015) are of European national populations, and are register based. Most studies do not yield significant excess risks, the only exceptions being the British study of Kendall et al (Kendall et al. 2013) and the Swiss study of Spycher et al (Spycher et al. 2015). We note that since the original database search was conducted an updated Swiss study has been published (Mazzei-Abba et al. 2021), which reported very similar relative risk estimates to those of Spycher et al (Spycher et al. 2015) and we judge that the meta-analysis would be little affected. The small Finnish study of Nikkilä et al (Nikkilä et al. 2016) is probably of limited statistical power, but the French studies are of much larger populations (Berlivet et al. 2021; Berlivet et al. 2020; Demoury et al. 2017). The small size of most of the studies in Supplementary Table S6 means that they have little realistic chance of detecting an effect of radiation exposure.

3.2.1.2. Exposures due to man-made environmental contamination:

The Chernobyl nuclear accident in northern Ukraine in 1986 resulted in large releases of radioisotopes of iodine and caesium, and other radionuclides to a lesser extent, resulting in a mixture of internal and external exposure, particularly to parts of the populations of Ukraine, Belarus and Russia (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2011). One of the main health consequences has been the markedly elevated incidence of thyroid cancer, largely due to intakes of radioiodine by children (Brenner et al. 2011). However, as noted in the Methods, the thyroid doses in most of these studies include both high doses and high dose rates; an exception in this respect is the Belarus and Russia thyroid cancer case-control study of Cardis et al (Cardis et al. 2005), which did consider risks over lower dose (and dose rate) ranges (Table 5).

More relevant to the present review are two case-control studies of childhood leukaemia among those exposed in utero or under the age of 6 years while living in heavily contaminated areas of the former USSR at the time of the Chernobyl accident; the mean dose to the active bone marrow (ABM) was around 10 mGy (Davis et al. 2006; Noshchenko et al. 2010). There are modest excess risks in the Russian and Belarusian components of the study of Davis et al (Davis et al. 2006) and the Ukrainian study of Noshchenko et al (Noshchenko et al. 2010), only the second of these significant (Table 5). Raised, albeit non-significant, risks were observed in a study of childhood leukaemia in Utah and fallout
from the Nevada Test Site (Stevens et al. 1990) (Table 5). A cohort study in Utah, Nevada and Arizona of thyroid disease and childhood exposure to fallout from the Nevada Test Site found a positive association for thyroid neoplasms (Lyon et al. 2006) (Table 5). By contrast, a cohort study of persons exposed in early life to $^{131}$I releases from the Hanford nuclear site (Davis et al. 2004) yielded virtually no excess risks of thyroid cancer or benign thyroid nodules (Table 5), but this study probably had only limited power to detect the increased risks predicted by studies of external exposure in childhood (Table 4).

3.2.2. Risks associated with medical diagnostic exposure and other low and moderate dose radiation exposure—There have been a number of studies evaluating risks of cancer after diagnostic CT scan exposure in childhood, some of which have yielded excess risks of various cancers (Berrington de Gonzalez et al. 2016; Journy et al. 2015; Journy et al. 2016; Kojimahara et al. 2020; Krille et al. 2015; Mathews et al. 2013; Meulepas et al. 2019; Nikkilä et al. 2018; Pearce et al. 2012), and summarised in Table 2. Most studies only assessed risk of leukaemia and brain tumours (Table 2). Only in the Finnish case-control study (Nikkilä et al. 2018), the Australian study (Mathews et al. 2013) and the UK study (Pearce et al. 2012), the low dose part of which is subsumed in the study of Little et al (Little et al. 2018b), was the excess risk of leukaemia statistically significant. In the UK study (Berrington de Gonzalez et al. 2016; Pearce et al. 2012), the Australian study (Mathews et al. 2013), the German study (Krille et al. 2015) and the Dutch study (Meulepas et al. 2019) there were significant excess risks of brain tumours (Table 2).

Table 2 shows leukaemia risks in the < 0.1 Gy pooled dataset of Little et al (Little et al. 2018b), also thyroid cancer incidence following external exposure in childhood at thyroid doses of < 0.2 Gy and < 0.1 Gy (Lubin et al. 2017). Risks in both studies are statistically significantly elevated (Table 2). Table 4 shows the paediatrically exposed moderate dose range brain and breast cancer data of Preston et al (Preston et al. 2007), the lung cancer data of Cahoon et al (Cahoon et al. 2017b) and the solid cancer data of Grant et al (Grant et al. 2017), all from the LSS cohort. The risks in these datasets are generally compatible with those in the medical diagnostic studies, although the central estimates of risk tend to be higher in the LSS (Tables 2, 4).

3.3. Meta-analysis of cancer risks associated with radiation exposure in early life

3.3.1. Restricted maximum likelihood (REML) and maximum likelihood analyses—The REML analysis of Table 6 in relation to postnatal exposure suggests that, overall, there were significantly elevated risks of all cancers and brain/CNS tumours ($p < 0.05$), with marginally significant ($p = 0.108$) elevation of risk for leukaemia. Risks for lymphoma and the remainder category (cancers other than leukaemia, lymphoma, brain/CNS tumours) were markedly lower, and were not statistically significant ($p > 0.5$). In relation to in utero exposure there was (at least using the lower dose analysis) significant excess risk for thyroid cancer and thyroid nodules ($p < 0.05$), and large (but non-significant ($p > 0.2$)) excess risks for brain/CNS tumours. [Note: the meaning of “higher dose” studies and “lower dose” studies is defined in the Methods.] For most postnatal exposure endpoints there was significant inter-study heterogeneity, as indicated by the $Q$ statistic, although that was not the case in relation to in utero exposure (Table 6). The $F$ statistic was often substantial for many
postnatal exposure endpoints, a number above 40%, implying that a material proportion of the variance was due to inter-study heterogeneity; however, this was generally not the case for in utero exposure. Analysis of the data for in utero exposed subjects using adjustments to the ERR for attained age yielded much larger risks (Supplementary Table S4) than those using the unadjusted data (Table 6), but only for thyroid nodules was there a significant positive trend when using the lower dose estimates ($p = 0.033$).

Further maximum likelihood analyses were performed in order to assess the significance of certain contrasts between lower and higher dose meta-analyses, exhibited in Table 7. These suggest that for thyroid cancer (including thyroid nodules) there was significantly lower risk ($p = 0.033$) associated with postnatal exposure compared with in utero exposure when using the lower dose estimates. Lung cancer and thyroid (including nodules) risk were significantly higher at lower levels of dose ($p = 0.031$, $p = 0.001$ respectively) using the lower dose set of risk estimates. Lung cancer risk was significantly higher for low dose-rate exposures than for moderate and high dose-rate exposures ($p = 0.031$), although information was only available for the lower dose set of risk estimates, whereas for thyroid (including nodules) risks were significantly higher ($p < 0.001$) for the moderate and high dose-rate exposures than for lower dose-rate exposure. However, the problems of convergence with all the thyroid cancer/thyroid nodules model fits complicate interpretation of all these findings for this endpoint and caution in interpretation is required. There was significant ($p < 0.05$) inter-study heterogeneity for certain endpoints for certain of these contrasts, a generally consistent feature of the analyses of leukaemia, brain/CNS tumours and thyroid cancer (including nodules) (Table 7). The $I^2$ statistic was somewhat variable, generally near 0, but for brain/CNS tumours consistently above 50%, implying that a relatively large amount of the variance for this endpoint was accounted for by inter-study heterogeneity.

The analysis of Supplementary Tables S3 and S5, in which inverse-variance weighted linear models were employed to refit thyroid nodule data < 0.799 Gy of Hatch et al (Hatch et al. 2019), leukaemia data of Stevens et al (Stevens et al. 1990), and thyroid cancer data < 0.284 Gy of Kopecky et al (Kopecky et al. 2006) yielded generally similar findings, although the postnatal risk of leukaemia reduced but became (at least when using the lower dose set of risk estimates) highly significantly increasing ($p < 0.001$) (Supplementary Table S3). Additional analysis suggested that when using the lower dose study estimates there was highly significant heterogeneity in risk by endpoint (using the 6-endpoint split of Tables 6 and 7) overall (combining postnatal and in utero exposures) ($p < 0.001$), and also considering only studies of post-natal exposure ($p < 0.001$), but not for studies only of in utero exposure ($p = 0.194$) (results not shown). When using the higher dose study estimates there was highly significant heterogeneity in risk by endpoint overall (combining postnatal and in utero exposures) ($p < 0.001$), but not when considering only studies of postnatal exposure ($p = 0.461$), or for studies only of in utero exposure ($p = 0.266$) (results not shown). A complication with the analyses overall and for postnatal exposure only is that there were indications of non-convergence, whether using the lower or the higher risk estimates.

### 3.3.2. Possible selection bias

Although the general symmetry of the funnel plots does not suggest any marked selection bias (Supplementary Figure S1), nevertheless the
formal analysis of selection bias in Supplementary Table S8 implies that for many endpoints, in particular all postnatal endpoints, leukaemia, thyroid cancer (including nodules) and all cancer other than thyroid cancer (including nodules) there is significant selection bias ($p < 0.05$). However, the analysis of Supplementary Table S8 also demonstrates that adjusting for selection bias using the trim-and-fill method of Duval and Tweedie (Duval and Tweedie 2000) does not in general lead to marked changes in the central estimates, whether using the lower or higher set of risk estimates – only for lymphoma does the adjustment for selection bias lead to a marked reduction in ERR, although for the lower dose risk estimates the risk for all post-natal studies substantially increases after adjustment.

4. Discussion

4.1. General remarks

While understanding of the development of cancer at a cellular and sub-cellular level is very important and steadily increasing, and can inform risk extrapolation, epidemiology provides the human evidence most directly relevant to estimate radiation-related cancer risk. Because we are interested in the effects of low doses, large study populations are required to achieve sufficient statistical power. Studies of cancer after exposure in childhood have decisive advantages over studies of adult cancers: the frequency of cancer at young ages is relatively low and the ERR per unit dose is generally substantially higher than for exposure in adulthood (Grant et al. 2017; United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2008; 2013). Most of the risk factors apart from radiation for the common childhood cancers are familial or genetic (Roman et al. 2018); there are few other risk factors that substantially modify risk at a population level in childhood (Linet et al. 2018). However, about 20% of childhood leukaemia could be attributed to natural background radiation on the basis of conventional risk estimates (Wakeford 2004; Wakeford et al. 2009).

The meta-analyses that we have undertaken combine studies that consider different ranges of attained ages. Many are of childhood cancers, but some extend into adulthood. We have attempted to allow for this in the analyses, in particular the analyses of exposures in utero (Supplementary Tables S4, S7), but this point should be borne in mind. In addition, as noted above, for many postnatal exposure endpoints (but not for studies of in utero exposure) a large proportion of the total variance is accounted for by inter-study heterogeneity, which complicates interpretation of the findings. Nevertheless, the meta-analysis of Table 6 using REML models suggests that there are significant risks for all cancers in relation to postnatal exposure ($p < 0.01$), with particularly large relative risks for brain/CNS tumours and leukaemia, whereas in relation to in utero exposure the strongest evidence of excess is for thyroid cancer (including nodules) ($p = 0.033$), although this is based on one study (Hatch et al. 2019). The meta-analysis using maximum-likelihood fitted models in Table 7 implies that for thyroid cancer (including nodules) there is significantly higher relative risk associated with in utero exposure compared with postnatal exposure. There are significant variations by dose and dose rate for certain endpoints, so that lung cancer relative risk appears to be highest for low dose-rate exposures, although the data are limited. There are suggestions of significant variation in relative risk between the cancer endpoints overall, but not when
postnatal and in utero exposures are considered separately. The findings of selection bias in the data are somewhat troubling. Nevertheless, although statistically significant for a few endpoints (in particular leukaemia and thyroid), adjustment for such bias does not generally change the ERR estimates (Supplementary Table S8).

It is important to recognise that although relative risks for childhood exposure are relatively high, the absolute risks associated with exposure are quite low. For example, in the pooled analysis of leukaemia after childhood exposure the excess cases or deaths after 0.1 Gy were in the range 0.1–0.4 per 10,000 person-years of follow up (Little et al. 2018b). It is also important to recognize that there has been evidence for some time that relative risks associated with exposure in utero and in childhood are very likely not constant with attained age (Little et al. 1991). We have attempted to adjust for this at least in relation to the studies of in utero exposure (Supplementary Tables S5, S7), from which can be seen the substantial difference that is made. It is possible that such attained age effects could explain part of the heterogeneity observed in studies of postnatal exposure; unfortunately, it was less easy to get useful information on attained age in all of these studies.

### 4.2. Studies of atomic bomb survivors

The survivors of the Japanese atomic bombings offer a unique cohort which can throw light on low-dose effects as well as effects at higher doses – around two-thirds of the survivors received doses < 0.1 Gy. Cancer relative risks in the LSS (Table 4) are not very dissimilar in magnitude to those in diagnostically exposed groups (Table 2). There are suggestions that in utero relative risks in the atomic bomb survivors (Table 4) may be lower than those in some other groups, in particular, for endpoints such as lymphoma and brain/CNS tumours (Tables 2, 3, Supplementary Table S7), as is also indicated by the results of the meta-analysis (Table 7). It should be noted that there are limited numbers of cases and deaths among the in utero exposed occurring in childhood (age < 15 years), specifically one death from liver cancer (Delongchamp et al. 1997) and a non-fatal case of Wilms’ tumour (Yoshimoto et al. 1988). The first case of leukaemia, also the first death from this cause, occurred at age 18 years (Delongchamp et al. 1997; Yoshimoto et al. 1988).

For leukaemia there are indications of lower relative risk among those exposed in utero during the atomic bombings, with an average dose of ~ 0.12 Gy (Sugiyama et al. 2021), than in the OSCC (Table 2) and in other case-control studies of intrauterine medical diagnostic exposure. This may be because of elevated sensitivity of the active bone marrow (ABM) to the competing effects of moderate doses of acutely delivered radiation in utero. It is notable that there are no leukaemia cases or deaths observed in childhood among the in utero exposed cohort, although the expected numbers are small (Delongchamp et al. 1997; Wakeford and Little 2003; Yoshimoto et al. 1988). The study of Ohtaki et al (Ohtaki et al. 2004) may have some bearing on this, as it suggested that stable chromosome translocations among the in utero exposed survivors exhibited a biphasic response, steeply increasing below about 0.1 Gy then involuting above that dose, indicating that haematopoietic cells may be damaged irreparably by moderate doses and replaced by viable cells.

Recent studies in the LSS have demonstrated that radiation incidence relative risk of female breast cancers is highest for exposure around menarche (Brenner et al. 2018) and that
significantly increased radiation incidence risk of uterine corpus cancers is found only for exposure during the mid-pubertal period preceding menarche (Utada et al. 2019). During puberty, rapid stem cell proliferation of the terminal end buds mediates development of the mammary gland into a highly branched epithelial network (Scheele et al. 2017). Likewise, a dramatic increase in uterine volume and endometrial thickness occur during puberty prior to menarche (Hagen et al. 2015). A narrow age at exposure window for cancer radiosensitivity in the breast and uterine corpus may be related to radiation exposure during a period of such increased cell proliferation, and have significant implications for radiological protection.

4.3. Studies of in utero irradiation

The association between cancer in childhood and a prior radiographic examination of the abdomen of the pregnant mother identified by case-control studies such as those of Stewart et al (Bithell and Stewart 1975; Stewart et al. 1956) and many others (Wakeford 2008) (see Little et al (Little et al. 2021b, submitted)) provides epidemiological evidence that externally delivered doses of ionising radiation of the order of 0.005–0.030 Gy of X-rays increase the risk of cancer (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2008). This level of dose is somewhat lower than the lowest doses producing significantly increased risks of cancer in all other epidemiological studies, apart from the natural background radiation studies that we discuss below (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2008). Case-control studies have often been used in this setting, which can be subject to a number of biases, in particular selection, participation and recall biases, which can make them a poor choice for studies of medical exposure; however, with care, large case-control studies have been used in a medical setting without appreciable bias (MacMahon 1962). Nevertheless, the interpretation of the associations in this group of studies has been controversial. Doll and Wakeford (Doll and Wakeford 1997), after reviewing the available evidence, concluded that there are strong grounds for a causal interpretation of the association, and although this is still not universally accepted (International Commission on Radiological Protection (ICRP) 2003; National Council on Radiation Protection and Measurements (NCRP) 2013) there has been a degree of consensus in recent years (Armstrong et al. 2012; Wakeford and Little 2003) that this association may represent a cause-and-effect relationship.

As well as the medical diagnostic studies without assessed doses (which are reviewed in a separate paper (Little et al. 2021b, submitted)), there is information in a large number of studies of various exposed groups in which individual dose estimates are available (Tables 2, 3, Supplementary Table S7). One of the more intriguing findings of the meta-analysis are the indications of difference for certain endpoints in the magnitude of relative risk for exposures in utero and in the postnatal period (Tables 6, 7). In particular the analysis of Table 7 highlights the significant difference between these two types of exposure for thyroid cancer (including nodules), with relative risks tending to be higher for in utero than for postnatal exposure. Although not formally statistically significant there are also indications of much higher risks of lymphoma and brain/CNS associated with exposure in utero than for postnatal exposure (Table 7).
4.4. Studies of natural background radiation

As discussed by Kendall et al (Kendall et al. 2021), many of the early studies concentrated on effects of exposure from inhaled radon (an alpha-particle emitting noble gas) and its radioactive progeny, but as time went on, there was an increasing focus on studies of gamma radiation as well as, or instead of, radon, possibly driven by the realisation that doses from penetrating gamma radiation almost certainly accounted for most of the predicted radiation-related absolute risk of cancers in childhood (Kendall et al. 2021). A large number of studies of natural background radiation and childhood cancer have been conducted (Supplementary Table S6). The early studies tended to be ecological, but as time went on there was a preference for the more reliable case-control design. Insufficient statistical power is a particular problem for case-control studies, as realistically sized interview-based studies, with usually at most a few thousand cases, can never have high (>80%) statistical power to detect realistic excess risks (Little et al. 2010). As shown by Land (Land 1980) if a low power study produces a statistically significant positive trend it is almost always bound to be upwardly biased. Studies reporting positive associations are also more likely than negative ones to be written up and published, leading to a reporting bias. However, Hauptmann et al (Hauptmann et al. 2020) judged that most studies that are set up to study cancer and are of reasonable size would be published, whether null or not. Kendall et al (Kendall et al. 2021) discuss various other issues, in particular the problems of selection bias that may affect case-control studies. Largely in response to these two problems, of lack of statistical power and potential bias, a number of register-based national studies have been conducted over the last decade or so, and the advantages and disadvantages of these are discussed by Kendall et al (Kendall et al. 2021). Although free of selection, participation and recall bias, inevitably registry-based studies will lack individual dose estimates and many other individual covariates that can be collected by an interview-based case-control study. However, surrogates for some of these, for example indicators of socioeconomic status, are included in many datasets, and as noted above there are few large risks factors that operate at a population level for most childhood cancers. Therefore, this loss of information is perhaps not a large concern. There have been a number of European national register-based studies (Berlivet et al. 2021; Berlivet et al. 2020; Demoury et al. 2017; Kendall et al. 2013; Mazzei-Abba et al. 2021; Nikkilä et al. 2016; Spix et al. 2017; Spycher et al. 2015), recently reviewed by Mazzei-Abba et al (Mazzei-Abba et al. 2020) and by Kendall et al (Kendall et al. 2021). Most of these studies remain underpowered; only the British study (Kendall et al. 2013) and the French study (Berlivet et al. 2021; Demoury et al. 2017) have reasonable power, of 50% or more, to detect the predicted excess risk.

4.5. Studies of exposures due to man-made environmental contamination

In terms of population exposure, the Chernobyl reactor accident in northern Ukraine in 1986 was by far the largest nuclear accident, in particular, leading to significant intakes of internally deposited radio-active iodine among the populations of the former USSR (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2011). As noted in the Supplementary Methods, many thyroid doses and dose rates were very high, so that the screening studies of these populations, recently reviewed by Hatch and Cardis (Hatch and Cardis 2017) are outside the scope of the present review. The mean ABM dose from Chernobyl exposure, mainly external gamma radiation from deposited...
radioceasium, was just 10 mGy and the study of childhood leukaemia in the Chernobyl-exposed populations has been problematical (Davis et al. 2006); there were concerns about the representativeness of the controls in the Ukrainian part of the study (Davis et al. 2006; Moysich et al. 2011), which led to a further case-control study being conducted in Ukraine that produced a substantially lower risk estimate (Noshchenko et al. 2010) (Table 5). The positive findings for thyroid cancer and benign neoplasms in the Nevada fallout study (Lyon et al. 2006) are also consistent with studies of exposures at slightly higher (but still low) levels of external dose (Lubin et al. 2017) (Tables 2, 5). They are also consistent with risks in the Chernobyl screening studies, although doses and dose rates here are high (Brenner et al. 2011; Little et al. 2014; Little et al. 2015). Both comparisons suggest that internal exposure or low dose rate exposure are unlikely to be the reason for the absence of thyroid cancer risks in the Hanford study (Davis et al. 2004). It is possible that the statistical power in the Hanford study is low.

The Fukushima Dai-ichi nuclear accident in Japan in 2011 also released radioactive iodine, but an order of magnitude less than the release during the Chernobyl accident, and thyroid doses were estimated to be much less than those received by children living around Chernobyl (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2014; 2021b). As yet, no studies of populations exposed from Fukushima have incorporated individual dosimetry; in particular this is the case for studies of thyroid cancer by Tsuda et al. (Tsuda et al. 2016) and by Ohira et al. (Ohira et al. 2020) (see Table 5); the study of Tsuda et al. (Tsuda et al. 2016) has been much criticised on other grounds (Wakeford et al. 2016).

4.6. Studies of computed tomography (CT) in children

Large datasets of persons receiving substantial doses from CT examinations in childhood have been assembled (Bernier et al. 2019; Berrington de Gonzalez et al. 2016; Journy et al. 2015; Journy et al. 2016; Kojimahara et al. 2020; Krille et al. 2015; Mathews et al. 2013; Meulepas et al. 2019; Nikkilä et al. 2018; Pearce et al. 2012). In these CT studies there is some assessed potential for bias associated with reverse causation (Boice 2015; Walsh et al. 2014), that is that the CT scan might have been taken because of early symptoms from pre-existing (latent) disease and was therefore not a cause of the disease (Schubauer-Berigan et al. 2020; Walsh et al. 2014). A priori it is unlikely that reverse causation would have much role to play for leukaemia, as most cases are acute. Confounding by indication, in other words the possibility that high-risk conditions lead to increase in prevalence of CT imaging, is also a concern in these studies (Schubauer-Berigan et al. 2020; Walsh et al. 2014). Confounding by indication is quite distinct from reverse causation, although the two terms are often used interchangeably (Kummeling and Thijs 2008). Recent studies have demonstrated that although there is evidence of confounding by indication in the UK (Berrington de Gonzalez et al. 2016), French (Journy et al. 2015), Dutch (Meulepas et al. 2019) and Finnish (Nikkilä et al. 2018) studies, excluding patients with possibly predisposing syndromes (PS) did not much affect the trends with dose. A number of different methods were employed: in the UK study pathology reports from the cancer registries and radiologists’ notes were used to determine whether the cases and non-cases had any of a large number of PS (Berrington de Gonzalez et al. 2016); in the French study...
patient data from the hospital discharge data was used to diagnose patients with these PS, using a slightly smaller list (Journy et al. 2015); in the Dutch study only patients with tuberous sclerosis (one of the PS ascertained in the British but not in the French study) were ascertained via linkage with two hospitals treating most of the patients; and in the Finnish study (Nikkilä et al. 2018) only patients with Down syndrome were ascertained (one of the PS ascertained in the British and French studies). The theoretical study of Meulepas et al. examined plausible scenarios for confounding by indication, via inclusion of individuals with cancer susceptibility syndromes, and suggested that confounding by indication associated with inclusion of such persons was not expected to be substantial (Meulepas et al. 2016). Another theoretical study suggested that reverse causation is unlikely to result in bias away from the null for brain cancer (Little et al. 2021c in press). However, the study of Mathews et al. (Mathews et al. 2013) suggests that care is required in the design and conduct of CT scan studies if confounding by indication is to be avoided.

4.7. Doses and dose rates in the studies considered and for in vivo radiobiological data

Doses from natural background radiation (Table 1, Supplementary Table S6), the medical in utero studies (Table 2) and the studies of fallout (Table 5) are exceptionally low (generally < 0.03 Gy), but in all studies considered here the dose rates are generally low or moderate – the highest dose rates were generally in the CT scan studies and in a study of persons receiving multiple fluoroscopic exposures as part of the monitoring of tuberculosis treatment (Little and Boice 1999), approach 0.1 Gy per hour; only in the study of Swedish children treated for skin haemangioma (Lundell et al. 1999) did dose rates greatly exceed 0.1 Gy per hour (Table 2). Natural background radiation exposures are ubiquitous and adequately sized cohorts can be assembled, though the studies need to be at a national or super-national scale in order to achieve reasonable statistical power (Little et al. 2010).

A particularly interesting finding is that relative risks associated with lung cancer were significantly lower in the moderate and high dose-rate studies than in the low dose-rate studies, also lower in the moderate and high dose studies than in the low dose studies (Table 7, Supplementary Table S5). This is not what would be expected conventionally, running somewhat counter to the general observation, based largely on radiobiological data, that cancer risks following low dose and low dose rate radiation would be below those at high dose rate (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 1993; 2008). These results took no account of smoking data in the relevant datasets (Cahoon et al. 2017b; Ronckers et al. 2010), which could conceivably confound; nevertheless, analyses concentrating on lifelong smokers, or in which the baseline rates in the LSS were adjusted for smoking status and numbers of cigarettes per day smoked yielded ERR that were fairly close to the unadjusted ERR (Table 4). However, recent reanalysis of some large animal datasets did not yield very strong evidence for the ameliorating effects of low dose-rate or low dose exposure on cancer risk (Tran and Little 2017), although evidence of such dose rate effects is stronger when the less relevant endpoint of life shortening is used (Haley et al. 2015). This evidence relating to possible effects of dose rate is fairly weak, since we are comparing risks in moderate and high dose rate studies with those at low dose rate among very different study populations, with different periods of follow-up; nevertheless, what we have done is in the spirit of similar exercises that have been conducted
in the epidemiological literature that attempt to assess dose rate effects (Hoel 2018; Jacob et al. 2009; Kocher et al. 2018; Little et al. 2021d; Shore et al. 2017; Walsh et al. 2021).

### 4.8. Other reviews of the literature

A group of NCI collaborators conducted a systematic review of 26 recently published epidemiological studies with mean doses < 0.1 Gy (range 0.0001–0.082 Gy). These comprised eight environmental, four medical, and 14 occupational studies (Berrington de Gonzalez et al. 2020; Daniels et al. 2020; Gilbert et al. 2020; Hauptmann et al. 2020; Linet et al. 2020; Schubauer-Berigan et al. 2020). The review included six studies of cancer after childhood exposure, all included here. The review considered a critical appraisal of dosimetry methods, confounding and selection bias, outcome assessment problems and the effects of dose measurement errors. Meta-analysis was conducted of leukaemia risk after childhood exposure (Hauptmann et al. 2020). Both for solid cancers and for leukaemia, the majority of the studies reported positive ERRs per unit dose. Several limitations were identified, but only a few positive studies were potentially biased away from the null. These studies therefore directly supported excess cancer risks from low-dose ionising radiation (Berrington de Gonzalez et al. 2020; Daniels et al. 2020; Gilbert et al. 2020; Hauptmann et al. 2020; Linet et al. 2020; Schubauer-Berigan et al. 2020), and the magnitude of cancer risks was statistically compatible with those in the LSS (Hauptmann et al. 2020).

It is interesting to note how little overlap there is between the datasets considered in the NCI review (Hauptmann et al. 2020) and the present one, specifically six studies (Davis et al. 2006; Journy et al. 2015; Kendall et al. 2013; Lubin et al. 2017; Nikkilä et al. 2016; Spycher et al. 2015), although the version of the UK CT study used in the NCI review (Berrington de Gonzalez et al. 2016) is substantially the same as that employed here (Pearce et al. 2012). There is rather more overlap with the studies considered in a recent review by NCRP (National Council on Radiation Protection and Measurements (NCRP) 2018), specifically eleven studies (Akleyev et al. 2016; Demoury et al. 2017; Kendall et al. 2013; Krille et al. 2015; Little and Boice 1999; Lubin et al. 2017; Nikkilä et al. 2016; Pearce et al. 2012; Preston et al. 2008; Ronckers et al. 2008; Schüz et al. 2017). The fact that there is not greater overlap can be explained by a number of factors, specifically the fact that the NCI review omitted all studies published before 2006 and after 2017, and because of when it was done, the NCRP study (National Council on Radiation Protection and Measurements (NCRP) 2018) effectively did not include any studies published after 2017. The NCI study was limited to those datasets (excluding the Mayak workers and the Kerala natural background radiation studies) in which the mean dose was under 0.1 Gy (Hauptmann et al. 2020), unlike the present review, which limited coverage based on a combination of the maximum cumulative dose and maximum dose rate, so that studies which had dose rate > 0.1 Gy/hour and maximum dose > 1 Gy were excluded. The NCRP review was likewise limited to “a comprehensive review of recent (within ~ 10 y) relevant epidemiologic studies with quantitative dose–response analyses” (National Council on Radiation Protection and Measurements (NCRP) 2018). Nevertheless, as inspection of Tables 1–5 demonstrates there are certain other studies that might have been included in previous reviews. For example, the lung cancer mortality part of the scoliosis study of Ronckers et al (Ronckers et al. 2010) and the German CT study of Krille et al (Krille et al. 2015) were both apparently eligible.
for inclusion in the NCI review, but were both excluded because of the abstract-based screening employed there. Likewise the mortality part of the scoliosis study of Ronckers et al. (Ronckers et al. 2010) was apparently not considered for inclusion in the NCRP review. This highlights the difficulty of reviews based on automatic searches of databases such as PubMed, but may also reflect exclusions made in reviewing the searched articles using established criteria that were not made clear in the publications. Bearing on this it should be noted that a very large number of the papers we reviewed were not found in our PubMed search, but were found from assessments of other literature (see Supplementary Methods).

4.9. Biological data pertaining to the plausibility of low dose cancer risk

In this section we consider biological data that may support linearity of dose response for cancer, and why departures from linearity can be expected, as well as dose rate effects. The discussion here is mostly quite general, and is applicable to exposures at any age. Although curvature of dose response is not addressed in the low dose/low dose rate data considered in this paper, it is certainly observed at slightly higher levels of dose (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 1993; 2008), and the presence of curvature is the reason why it is important that attention be paid to low dose or low dose rate effects – otherwise one would just consider the full dose range.

Cancer is thought to result from mutagenic damage to a single cell, specifically to its nuclear DNA, which in principle could be caused by a single radiation track, and this argues against the existence of a threshold of dose below which cancer risk is not elevated, as discussed elsewhere (Little et al. 2009). A more recent evaluation of the biological mechanisms relevant for low dose radiation cancer risk inference concluded that ‘There remains good justification for the use of a nonthreshold model for risk inference for radiation protection purposes, given the present robust knowledge on the role of mutation and chromosomal aberrations in carcinogenesis’ and, in relation to the potential targets in addition to nuclear DNA, ‘The potential contributions of phenomena such as transmissible genomic instability, bystander phenomena, induction of abscopal effects and adaptive response remain unclear.’ (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2021a). A low LET radiation dose of 0.001 Gy corresponds to about one electron track hitting a cell nucleus (National Council on Radiation Protection and Measurements (NCRP) 2001; United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 1993). This suggests that at low doses (0.01 Gy or less spread over a year) it is unlikely that temporally and spatially separate electron tracks could cooperatively produce DNA damage (Brenner et al. 2003), so that in this very low dose region DNA damage at a cellular level would be proportional to dose. It is known that the efficiency of cellular repair processes varies with dose and dose rate (National Council on Radiation Protection and Measurements (NCRP) 2001; United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 1993), and this may be the reason for the curvature that is observed in the cancer dose response at higher levels of dose (e.g. for leukaemia (Hsu et al. 2013) and some solid cancers (Little et al. 2020)) and dose rate effects observed in epidemiological (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2008) and animal (Haley et al. 2015; Tran and Little 2017; United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 1993) data. DNA double
strand breakage, and clustered damage (two or more lesions in close proximity) (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 2012) are thought to be the most critical lesion induced by radiation (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 1993). Repair of DNA double strand breaks (DSBs) relies on a number of pathways, even the most accurate of which, homologous recombination, is prone to errors (National Council on Radiation Protection and Measurements (NCRP) 2001); other repair pathways, e.g., non-homologous end joining, single-strand annealing, are intrinsically much more error prone (International Commission on Radiological Protection (ICRP) 2006; National Council on Radiation Protection and Measurements (NCRP) 2001). The variation in efficacy of repair that undoubtedly occurs will affect the magnitude of unrepaired and misrepaired damage and, whereas unrepaired damage is likely to result in cell death, non-lethal misrepaired damage by definition results in mutation. Some information is available on the age-dependence of induction of DNA and chromosomal damage, and while not many studies are available, any differences between the young and adults are not great (Gomolka et al. 2018; Oestreicher et al. 2018).

5. Conclusions

Here we have considered the overall question of the relationship between low-level exposure to low LET radiation in childhood and the consequent risk of cancer. Attention was mainly focused on leukaemia, the most common and best studied of the childhood cancers, but we have also presented evidence of excess risk of brain/CNS and thyroid cancer and thyroid nodule risk. The data presented here, particularly that in Tables 1 and 2, indicate that there is now little reasonable doubt that the childhood leukaemia risk extends into the low dose range conventionally considered to be doses<0.1 Gy of low LET radiation. We would suggest that the evidence for elevated leukaemia risk now extends down to 0.05 Gy, and indeed for acute lymphoblastic leukaemia, as shown in a recent pooling study of low dose studies, excess risk extends down to around 0.02 Gy (Little et al. 2018b). These studies (Little et al. 2018b) and studies of natural background radiation (Kendall et al. 2013; Mazzei-Abba et al. 2021; Spix et al. 2017; Spycher et al. 2015) and of medical diagnostic exposures (Berrington de Gonzalez et al. 2016; Journy et al. 2015; Journy et al. 2016; Krille et al. 2015; Mathews et al. 2013; Meulepas et al. 2019; Pearce et al. 2012) offer strong suggestions of excess risks for certain types of cancer at around the same level of dose, about 0.02 Gy. Studies should concentrate on all these endpoints (leukaemia, thyroid cancer and brain/CNS tumours), because in these the excess risk will be most clearly established, and at lower levels of dose, although it is likely that different patterns of low-dose response may emerge. Mechanistic understanding of the development of cancer at a cellular and molecular level makes such a possibility biologically plausible. Further integration of information, particularly quantitative information, on the biological mechanisms of radiation carcinogenesis and leukaemogenesis making use of the adverse outcome pathway framework (National Council on Radiation Protection and Measurements (NCRP) 2020) with the further refinement of epidemiological investigations such as those reviewed here will serve to characterise radiation-related cancer risks more precisely.
Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgements

This work was supported by the Intramural Research Program of the National Institutes of Health, National Cancer Institute, Division of Cancer Epidemiology and Genetics. The authors are grateful for the detailed and helpful comments of Dr. Jay Lubin, also for those of the four referees.

References

Akleyev A, Deltour I, Krestinina L, Sokolnikov M, Tsareva Y, Tolstykh E, Schütz J, 2016. Incidence and mortality of solid cancers in people exposed in utero to ionizing radiation: pooled analyses of two cohorts from the Southern Urals, Russia. PloS One 11, e0160372.

Armstrong B, Brenner DJ, Baverstock K, Cardis E, Green A, Guilmette RA, Hall J, Hill MA, Hoel D, Krewski D, Little MP, Marshall M, Mitchel REJ, Muirhead CR, Priest ND, Richardson DB, Riddell AE, Sabatier L, Sokolnikov ME, Tomasek L, Ullrich RL, 2012. Radiation. Volume 100D. A review of human carcinogens. International Agency for Research on Cancer, Lyon, France, pp. 1–341.

Bartlett MS, Fowler RH, 1937. Properties of sufficiency and statistical tests. Proc. Royal Soc. Lond. Ser. A – Mathem. Phys. Sci. 160, 268–282.

Berlivet J, Hémon D, Cléro É, Ielsch G, Laurier D, Faure L, Clavel J, Goujon S, 2021. Residential exposure to natural background radiation at birth and risk of childhood acute leukemia in France, 1999–2009. J. Environ. Radioact. 233, 106613.

Berlivet J, Hémon D, Cléro É, Ielsch G, Laurier D, Guissou S, Lacour B, Clavel J, Goujon S, 2020. Ecological association between residential natural background radiation exposure and the incidence rate of childhood central nervous system tumors in France, 2000–2012. J. Environ. Radioact. 211, 106071.

Bernier M-O, Baysson H, Pearce MS, Moissonnier M, Cardis E, Hauptmann M, Struelens L, Dabin J, Johansen C, Journy N, Laurier D, Blettner M, Le Cornet L, Pokora R, Gradowska P, Meulepas JM, Kjaerheim K, Istad T, Olerud H, Sovik A, Bosch de Basea M, Thierry-Chef I, Kajiser M, Nordenskjöld A, Berrington de Gonzalez A, Harbon RW, Kesminiene A, 2019. Cohort Profile: the EPI-CT study: a European pooled epidemiological study to quantify the risk of radiation-induced cancer from paediatric CT. Int. J. Epidemiol. 48, 379–381g. [PubMed: 30388267]

Berrington de Gonzalez A, Daniels RD, Cardis E, Cullings HM, Gilbert E, Hauptmann M, Kendall G, Laurier D, Linet MS, Little MP, Lubin JH, Preston DL, Richardson DB, Stram D, Thierry-Chef I, Schubauer-Berigan MK, 2020. Epidemiological Studies of Low-Dose Ionizing Radiation and Cancer: Rationale and Framework for the Monograph and Overview of Eligible Studies. J. Natl. Cancer Inst. Monogr. 2020, 97–113. [PubMed: 32657348]

Berrington de Gonzalez A, Journy N, Lee C, Morton LM, Harbon RW, Stewart DR, Parker L, Craft AW, McHugh K, Little MP, Pearce MS, 2017. No Association between Radiation Dose from Pediatric CT Scans and Risk of Subsequent Hodgkin Lymphoma. Cancer Epidemiol. Biomarkers Prevent. 26, 804–806.

Berrington de Gonzalez AB, Salotti JA, McHugh K, Little MP, Harbon RW, Lee C, Ntowe E, Braganza MZ, Parker L, Rajaraman P, Stiller C, Stewart DR, Craft AW, Pearce MS, 2016. Relationship between paediatric CT scans and subsequent risk of leukaemia and brain tumours: assessment of the impact of underlying conditions. Br. J. Cancer 114, 388–394. [PubMed: 26882064]

Bithell JF, 1993. Statistical issues in assessing the evidence associating obstetric irradiation and childhood malignancy. In: Lengfelder E, Wendhausen H (Eds.), Neue Bewertung des Strahlenrisikos: Niedrigdosis-Strahlung und Gesundheit. MMV Medizin Verlag, Munich, pp. 53–60.

Bithell JF, Stewart AM, 1975. Pre-natal irradiation and childhood malignancy: a review of British data from the Oxford Survey. Br. J. Cancer 31, 271–287. [PubMed: 1156514]
Bithell JF, Stiller CA, 1988. A new calculation of the carcinogenic risk of obstetric X-raying. Stat. Med. 7, 857–864. [PubMed: 3413365]

Boice JD Jr., 2015. Radiation epidemiology and recent paediatric computed tomography studies. Annals ICRP 44 (1 suppl), 236–248.

Brenner AV, Preston DL, Sakata R, Sugiyama H, Berrington de Gonzalez A, French B, Utada M, Cahoon EK, Sadakane A, Ozasa K, Grant EJ, Mabuchi K, 2018. Incidence of breast cancer in the Life Span Study of atomic bomb survivors: 1958–2009. Radiat. Res. 190, 433–444. 10.1667/RR15015.1. [PubMed: 30044713]

Brenner AV, Tronko MD, Hatch M, Bogdanova TI, Oliynyk VA, Lubin JH, Zablotska LB, Tereschenko V, McConnell RJ, Zamotaeva GA, O’Kane P, Bouville AC, Chaykovskaya LV, Greenebaum EM, Paster IP, Shpak VM, Ron E, 2011. I-131 dose response for incident thyroid cancers in Ukraine related to the Chernobyl accident. Environ. Health Perspect. 119, 933–939. [PubMed: 21406336]

Brenner DJ, Doll R, Goodhead DT, Hall EJ, Land CE, Little MP, Preston DL, Preston RJ, Puskin JS, Ron E, Sachs RK, Samet JM, Setlow RB, Zaider M, 2003. Cancer risks attributable to low doses of ionizing radiation: assessing what we really know. Proc. Natl. Acad. Sci. USA 100, 13761–13766. [PubMed: 14610281]

Brent RL, 2014. Carcinogenic risks of prenatal ionizing radiation. Seminars Fetal Neonatal Med. 19, 203–213.

Bunch KJ, Muirhead CR, Draper GJ, Hunter N, Kendall GM, O’Hagan JA, Phillipson MA, Vincent TJ, Zhang W, 2009. Cancer in the offspring of female radiation workers: a record linkage study. Br. J. Cancer 100, 213–218. [PubMed: 19127273]

Cahoon EK, Nadyrov EA, Polianskaya ON, Yauseyenka VV, Veyalkin IV, Yeudakhova TI, Maskivicheva TI, Minenko VF, Liu W, Drozdovitch V, Mabuchi K, Little MP, Zablotska LB, McConnell RJ, Hatch M, Peters KO, Rozhko AV, Brenner AV, 2017a. Risk of Thyroid Nodules in Residents of Belarus Exposed to Chernobyl Fallout as Children and Adolescents. J. Clin. Endocrinol. Metab. 102, 2207–2217.

Cahoon EK, Preston DL, Pierce DA, Grant E, Brenner AV, Mabuchi K, Utada M, Ozasa K, 2017b. Lung, laryngeal and other respiratory cancer incidence among Japanese atomic bomb survivors: An updated analysis from 1958 through 2009. Radiat. Res. 187, 538–548. 10.1667/RR14583.1. [PubMed: 28323575]

Cardis E, Kesminiene A, Ivanov V, Malakhova I, Shibata Y, Khrouch V, Drozdovitch V, Maceika E, Zvonova I, Vlassok O, Bouville A, Goulo K, Hoshi M, Abrosimov A, Anoshko J, Astakhova L, Chekin S, Demidchik E, Galanti R, Ito M, Korobova E, Lushnikov E, Maksioutov M, Masyakin V, Nerovnia A, Parshin V, Parshkov E, Pilipetsevich N, Pinchera A, Polyakov S, Shabeka N, Suonio E, Tenet V, Tsyb A, Yamashita S, Williams D, 2005. Risk of thyroid cancer after exposure to 131I in childhood. J. Natl. Cancer Inst. 97, 724–732. [PubMed: 15900042]

Committee to Assess Health Risks from Exposure to Low Levels of Ionizing Radiation, NRC. Health Risks from Exposure to Low Levels of Ionizing Radiation: BEIR VII - Phase 2. p.1–406. Washington, DC, USA, National Academy Press, 2006.

Daniels RD, Kendall GM, Thierry-Chef I, Linet MS, Cullings HM, 2020. Strengths and Weaknesses of Dosimetry Used in Studies of Low-Dose Radiation Exposure and Cancer. J. Natl. Cancer Inst. Monogr. 2020, 114–132. [PubMed: 32657346]

Davis S, Day RW, Kopecky KJ, Mahoney MC, McCarthy PL, Michalek AM, Moysich KB, Onstad LE, Stepanenko VF, Voillequé PG, Chegerova T, Falkner K, Kulikov S, Maslova E, Ostapenko V, Rivkind N, Shevchuk V, Tsyb AF, 2006. 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. 35, 386–396. [PubMed: 16295488]

Davis S, Kopecky KJ, Hamilton TE, Onstad L, 2004. Thyroid neoplasia, autoimmune thyroiditis, and hypothyroidism in persons exposed to iodine 131 from the Hanford nuclear site. JAMA 292, 2600–2603. [PubMed: 15572718]

Delongchamp RR, Mabuchi K, Yoshimoto Y, Preston DL, 1997. Cancer mortality among atomic bomb survivors exposed in utero or as young children, October 1950-May 1992. Radiat. Res. 147, 385–395. [PubMed: 9052687]

Demoury C, Marquant F, Ielsch G, Goujon S, Debayle C, Faure L, Coste A, Laurent O, Guillevic J, Laurier D, Hémon D, Clavel J, 2017. Residential Exposure to Natural Background Radiation
and Risk of Childhood Acute Leukemia in France, 1990–2009. Environ. Health Perspect. 125, 714–720. [PubMed: 27483500]

DerSimonian R, Laird N. 1986. Meta-analysis in clinical trials. Control Clin. Trials 7, 177–188. [PubMed: 3802833]

Doll R, Wakeford R. 1997. Risk of childhood cancer from fetal irradiation. Br. J. Radiol. 70, 130–139. [PubMed: 9135438]

Duval S, Tweedie R. 2000. A nonparametric “trim and fill” method of accounting for publication bias in meta-analysis. J. Am. Stat. Assoc. 95, 89–98.

Gilbert ES, Little MP, Preston DL, Stram DO. 2020. Issues in Interpreting Epidemiologic Studies of Populations Exposed to Low-Dose, High-Energy Photon Radiation. J. Natl. Cancer Inst. Monogr. 2020, 176–187. [PubMed: 32657345]

Gilman EA, Kneale GW, Knox EG, Stewart AM. 1988. Pregnancy x-rays and childhood cancers: effects of exposure age and radiation dose. J. Radiol. Prot. 8, 3–8.

Gomolka M, Oestreichel U, Rößler U, Samaga D, Endesfelder D, Lang P, Neumaier K, Belka C, Niemeyer M, Kiechle M, Hashargen U, Hübener C, Kirilum HJ, Kulka U, Rosenberger A, Walsh L, Baatout S, Kesminiene A, Lindholm C. 2018. Age-dependent differences in DNA damage after in vitro CT exposure. Int. J. Radiat. Biol. 94, 272–281. [PubMed: 29319401]

Grant EJ, Brenner A, Sugiyama H, Sakata R, Sadakane A, Utada M, Cahooon EK, Milder CM, Soda M, Cullings HM, Preston DL, Mabuchi K, Ozasa K. 2017. Solid Cancer Incidence among the Life Span Study of Atomic Bomb Survivors: 1958–2009. Radiat. Res. 187, 513–537. [PubMed: 28319463]

Hagen CP, Mouritsen A, Mieritz MG, Tinggaard J, Wohlfahrt-Veje C, Fallentien E, Brooks V, Sundberg K, Jensen LN, Juul A, Main KM. 2015. Uterine volume and endometrial thickness in healthy girls evaluated by ultrasound (3-dimensional) and magnetic resonance imaging. Fertil. Steril. 104, 452–459 e1-e2. [PubMed: 26051091]

Hagstrom RM, Glasser SR, Brill AB, Heyssel RM. 1969. Long term effects of radioactive iron administered during human pregnancy. Am. J. Epidemiol. 90, 1–10. [PubMed: 5794005]

Haley BM, Paunesku T, Grdina DJ, Woloschak GE. 2015. The increase in animal mortality risk following exposure to sparsely ionizing radiation is not linear quadratic with dose. PLoS ONE 10, e0140989. 10.1371/journal.pone.0140989.

Harrison JD, Balonov M, Bochud F, Martin CJ, Menzel H-G, Smith-Bindman R, Ortiz-López P, Simmonds JR, Wakeford R. 2021. The use of dose quantities in radiological protection: ICRP publication 147 Ann ICRP 50(1) 2021. J. Radiol. Prot. 41, 410–422.

Hatch M, Brenner AV, Cahooon EK, Drozdovitch V, Little MP, Bogdanova T, Shpak V, Bolshova E, Zamotayeva G, Terekhova G, Shkelkovoy E, Klochkova V, Mabuchi K, Tronko M. 2019. Thyroid Cancer and Benign Nodules After Exposure In Utero to Fallout From Chernobyl. J. Clin. Endocrinol. Metabol. 104, 41–48.

Hatch M, Cardis E. 2017. Somatic health effects of Chernobyl: 30 years on. Eur. J. Epidemiol. 32, 1047–1054. [PubMed: 28929329]

Hauptmann M, Daniels RD, Cardis E, Cullings HM, Kendall G, Laurier D, Litner MS, Little MP, Lubin JH, Preston DL, Richardson DB, Stram DO, Thierry-Chef I, Schubauer-Berigan MK, Gilbert ES, Barrington de Gonzalez A. 2020. Epidemiological Studies of Low-Dose Ionizing Radiation and Cancer: Summary Bias Assessment and Meta-Analysis. J. Natl. Cancer Inst. Monogr. 2020, 188–200. [PubMed: 32657347]

Hoel DG. 2018. Nuclear epidemiologic studies and the estimation of DREF. Int. J. Radiat. Biol. 94, 307–314. [PubMed: 29400635]

Hsu W-L, Preston DL, Soda M, Sugiyama H, Funamoto S, Kodama K, Kimura A, Kamada N, Dohy H, Tomonaga M, Iwanaga M, Miyazaki Y, Cullings HM, Suyama A, Ozasa K, Shore RE, Mabuchi K. 2013. The incidence of leukemia, lymphoma and multiple myeloma among atomic bomb survivors: 1950–2001. Radiat. Res. 179, 361–382. 10.1667/RR2892.1. [PubMed: 23398354]

International Commission on Radiological Protection (ICRP). 2006. Low-dose extrapolation of radiation-related cancer risk. ICRP Publication 99. Ann. ICRP 35(4), 1–140.

International Commission on Radiological Protection (ICRP). 2003. Biological effects after prenatal irradiation (embryo and fetus). ICRP publication 90. Ann. ICRP 33 (1–2), 1–206.
International Commission on Radiological Protection (ICRP), 2007. The 2007 Recommendations of the International Commission on Radiological Protection. ICRP publication 103. Ann. ICRP 37(2–4), 1–332.

Jacob P, Rühm W, Walsh L, Blettner M, Hammer G, Zeeb H, 2009. Is cancer risk of radiation workers larger than expected? Occup. Environ. Med. 66, 789–796.

Johnson KJ, Alexander BH, Doody MM, Sigurdson AJ, Linet MS, Spector LG, Hoffbeck RW, Simon SL, Weinstock RM, Ross JA, 2008. Childhood cancer in the offspring born in 1921–1984 to US radiologic technologists. Br. J. Cancer 99, 545–550. [PubMed: 18665174]

Journy N, Rehel J-L, Ducou Le Pointe H, Lee C, Brisse H, Chateil J-F, Caer-Lorho S, Laurier D, Bernier M-O, 2015. Are the studies on cancer risk from CT scans biased by indication? Elements of answer from a large-scale cohort study in France. Br. J. Cancer 112, 185–193. [PubMed: 25314057]

Journy N, Roué T, Cardis E, Ducou Le Pointe H, Brisse H, Chateil J-F, Laurier D, Bernier MO, 2016. Childhood CT scans and cancer risk: impact of predisposing factors for cancer on the risk estimates. J. Radiol. Prot. 36. N1-7.

Kendall GM, Little MP, Wakeford R, 2021. A review of studies of childhood cancer and natural background radiation. Int. J. Radiat. Biol. 97, 769–781. [PubMed: 33395329]

Kendall GM, Little MP, Wakeford R, Bunch KJ, Miles JCH, Vincent TJ, Meara JR, Murphy MFG, 2013. A record-based case-control study of natural background radiation and the incidence of childhood leukemia and other cancers in Great Britain during 1980–2006. Leukemia 27, 3–9. [PubMed: 22766784]

Kocher DC, Apostoaei AI, Hoffman FO, Trabalka JR, 2018. Probability distribution of dose and dose-rate effectiveness factor for use in estimating risks of solid cancers from exposure to low-LET radiation. Health Phys. 114, 602–622. [PubMed: 29697512]

Kojimahara N, Yoshitake T, Ono K, Kai M, Bynes G, Schüz J, Cardis E, Kesminiene A, 2020. Computed tomography of the head and the risk of brain tumours during childhood and adolescence: results from a case-control study in Japan. J. Radiol. Prot. 40, 1010–1023.

Kopecky KJ, Stepanenko V, Rivkind N, Voillegqué P, Onstad L, Shakhtranin V, Parshkow E, Kulikov S, Lushnikov E, Abrosimov A, Troshin V, Romanova G, Doroschenko V, Proshin A, Tsyb A, Davis S, 2006. Childhood thyroid cancer, radiation dose from Chernobyl, and dose uncertainties in Bryansk Oblast, Russia: a population-based case-control study. Radiat. Res. 166, 367–374. [PubMed: 16881738]

Krille L, Dreger S, Schindel R, Albrecht T, Asmussen M, Barkhausen J, Berthold JD, Chavan A, Claussen C, Forsting M, Gianicolo EAL, Jablonka K, Jahnken A, Langer M, Laniado M, Lotz J, Mentzel HH, Queisser-Wahrendorf A, Rompel O, Schlick I, Schneider K, Schumacher M, Seidenbusch M, Spix C, Spors B, Staatz G, Vogl T, Wagner J, Weisser G, Zeeb H, Blettner M, 2015. Risk of cancer incidence before the age of 15 years after exposure to ionising radiation from computed tomography: results from a German cohort study. Radiat. Environ. Biophys. 54, 1–12. [PubMed: 25567615]

Kummeling I, Thijs C, 2008. Reverse causation and confounding-by-indication: do they or do they not explain the association between childhood antibiotic treatment and subsequent development of respiratory illness? Clin. Exp. Allergy 38, 1249–1251. [PubMed: 18564329]

Land CE, 1980. Estimating cancer risks from low doses of ionizing radiation. Science 209, 1197–1203. [PubMed: 7408378]

Linet MS, Kim KP, Rajaraman P, 2009. Children’s exposure to diagnostic medical radiation and cancer risk: epidemiologic and dosimetric considerations. Pediatr. Radiol. 39 (Suppl 1), S4–S26. [PubMed: 19083224]

Linet MS, Morton LM, Devesa SS, Dores GM, 2018. Leukemias. In: Thun MJ, Linet MS, Cerhan JR, Haiman CA, Schottenfeld D (Eds.), Cancer epidemiology and prevention, Fourth edition. Oxford University Press, New York, NY, pp. 715–744.

Linet MS, Schubauer-Berigan MK, Berrington de Gonzalez A, 2020. Outcome Assessment in Epidemiological Studies of Low-Dose Radiation Exposure and Cancer Risks: Sources, Level of Ascertainment, and Misclassification. J. Natl. Cancer Inst. Monogr. 2020, 154–175. [PubMed: 32657350]

Environ Int. Author manuscript; available in PMC 2022 May 19.
Little MS, Slovis TL, Miller DL, Kleinerman R, Lee C, Rajaraman P, Berrington de Gonzalez A, 2012. Cancer risks associated with external radiation from diagnostic imaging procedures. CA: Cancer J. Clinicians 62, 75–100.

Little MP, Azizova TV, Hamada N, 2021a. Low- and moderate-dose non-cancer effects of ionizing radiation in directly exposed individuals, especially circulatory and ocular diseases: a review of the epidemiology. Int. J. Radiat Biol. 97, 782–803. [PubMed: 33471563]

Little MP, Boice JD Jr., 1999. Comparison of breast cancer incidence in the Massachusetts tuberculosis fluoroscopy cohort and in the Japanese atomic bomb survivors. Radiat. Res. 151, 218–224. [PubMed: 9952307]

Little MP, Hawkins MM, Shore RE, Charles MW, Hildreth NG, 1991. Time variations in the risk of cancer following irradiation in childhood. Radiat. Res. 126, 304–316. [PubMed: 2034788]

Little MP, Kukush AG, Masiuk SV, Shklyar S, Carroll RJ, Lubin JH, Kwon D, Brenner AV, Tronko MD, Mabuchi K, Bogdanova TI, Hatch M, Zablotska LB, Tereshchenko VP, Ostroumova E, Bouvile AC, Drozdovitch V, Chepurny MI, Kogvan LN, Simon SL, Shpak VM, Likhtarev IA, 2014. Impact of uncertainties in exposure assessment on estimates of thyroid cancer risk among Ukrainian children and adolescents exposed from the Chernobyl accident. PLoS ONE 9, e85723. 10.1371/journal.pone.0085723.

Little MP, Kwon D, Zablotska LB, Brenner AV, Cahoon EK, Rozhko AV, Polyanskaeva ON, Minenko VF, Golovanov I, Bouville A, Drozdovitch V, 2015. Impact of uncertainties in exposure assessment on thyroid cancer risk among persons in Belarus exposed as children or adolescents due to the Chernobyl accident. PLoS ONE 10, e0139826. 10.1371/journal.pone.0139826.

Little MP, Lim H, Friesen MC, Preston DL, Doody MM, Sigurdsson AJ, Neta G, Alexander BH, Chang LA, Cahoon EK, Simon SL, Linet MS, Kitahara CM, 2018a. Assessment of thyroid cancer risk associated with radiation dose from personal diagnostic examinations in a cohort study of US radiologic technologists, followed 1983–2014. BMJ Open 8 (5), e021536. 10.1136/bmjopen-2018-021536.

Little MP, Wakeford R, Bouffler SD, Abalo K, Hauptmann M, Hamada N, Kendall GM, 2021b. Cancer risks among studies of diagnostic radiation exposure in early life without quantitative estimates of dose. Environ. Internat. submitted.

Little MP, Patel A, Lee C, Hauptmann M, Berrington de Gonzalez A, Albert P, 2021c. Impact of reverse causation on estimates of cancer risk associated with radiation exposure from computerized tomography: a simulation study modeled on brain cancer. Am. J. Epidemiol. 10.1093/aje/kwab247 (in press).

Little MP, Pawel D, Misumi M, Hamada N, Cullings HM, Wakeford R, Ozasa K, 2020. Lifetime mortality risk from cancer and circulatory disease predicted from the Japanese atomic bomb survivor Life Span Study data taking account of dose measurement error. Radiat. Res. 194, 259–276. 10.1667/RR15571.1. [PubMed: 32942303]

Little MP, Pawel DJ, Abalo K, Hauptmann M, 2021d. Methodological improvements to meta-analysis of low dose rate studies and derivation of dose and dose-rate effectiveness factors. Radiat. Environ. Biophys. 60, 485–491. [PubMed: 34218328]

Little MP, Wakeford R, Corregio D, French B, Zablotska LB, Adams MJ, Allodji R, de Vathaire F, Lee C, Brenner AV, Miller JS, Campbell D, Pearce MS, Doody MM, Holmberg E, Lundell M, Sadetzki S, Linet MS, Berrington de Gonzalez A, 2018b. Leukaemia and myeloid malignancy among people exposed to low doses (<100 mSv) of ionising radiation during childhood: a pooled analysis of nine historical cohort studies. Lancet Haematol. 5, e346–e358. [PubMed: 30026010]

Little MP, Wakeford R, Lubin JH, Kendall GM, 2010. The statistical power of epidemiological studies analyzing the relationship between exposure to ionizing radiation and cancer, with special reference to childhood leukemia and natural background radiation. Radiat. Res. 174, 387–402. [PubMed: 20726729]

Little MP, Wakeford R, Tawn EJ, Bouffler SD, Berrington de Gonzalez A, 2009. Risks associated with low doses and low dose rates of ionizing radiation: why linearity may be (almost) the best we can do. Radiology 251, 6–12. [PubMed: 19332841]

Lubin JH, Adams MJ, Shore R, Holmberg E, Schneider AB, Hawkins MM, Robison LL, Inskip PD, Lundell M, Johansson R, Kleinerman RA, de Vathaire F, Damber L, Sadetzki S, Tucker M, Sakata
R, Veiga LHS, 2017. Thyroid cancer following childhood low-dose radiation exposure: a pooled analysis of nine cohorts. J. Clin. Endocrinol. Metab. 102, 2575–2583. [PubMed: 28323979]

Lundell M, 1994. Estimates of absorbed dose in different organs in children treated with radium for skin hemangiomas. Radiat. Res. 140, 327–333. 10.2307/3579109. [PubMed: 7972684]

Lundell M, Mattsson A, Karlsson P, Holmberg E, Gustafsson A, Holm L-E, 1999. Breast cancer risk after radiotherapy in infancy: a pooled analysis of two Swedish cohorts of 17,202 infants. Radiat. Res. 151, 626–632. [PubMed: 10319736]

Lyon JL, Alder SC, Stone MB, Scholl A, Reading JC, Holubkov R, Sheng X, White GL Jr., Hegmann KT, Anspaugh L, Hoffman FO, Simon SL, Thomas B, Carroll R, Meikle AW, 2006. Thyroid disease associated with exposure to the Nevada nuclear weapons test site radiation: a reevaluation based on corrected dosimetry and examination data. Epidemiology 17, 604–614. [PubMed: 17028502]

MacMahon B, 1962. Prenatal x-ray exposure and childhood cancer. J. Natl. Cancer Inst. 28, 1173–1191. [PubMed: 14468031]

Mathews JD, Forsythe AV, Brady Z, Butler MW, Goergen SK, Byrnes GB, Giles GG, Wallace AB, Anderson PR, Guiver TA, McGale P, Cain TM, Dowty JG, Bickerstaffe AC, Darby SC, 2013. Cancer risk in 680,000 people exposed to computed tomography scans in childhood or adolescence: data linkage study of 11 million Australians. BMJ 346, f2360.

Mazzei-Abba A, Folly CL, Coste A, Wakeford R, Little MP, Raaschou-Nielsen O, Kendall G, Hemon D, Nikkilä A, Spix C, Auvinen A, Spycher BD, 2020. Epidemiological studies of natural sources of radiation and childhood cancer: current challenges and future perspectives. J. Radiol. Prot. 40, R1–R23. [PubMed: 31751953]

Mazzei-Abba A, Folly CL, Kreis C, Ammann RA, Adam C, Brack E, Egger M, Kuehni CE, Spycher BD, 2021. External background ionizing radiation and childhood cancer: Update of a nationwide cohort analysis. J. Environ. Radioact. 238–239, 106734.

Meulepas JM, Ronckers CM, Merks J, Weijerman ME, Lubin JH, Hauptmann M, 2016. Confounding of the Association between Radiation Exposure from CT Scans and Risk of Leukemia and Brain Tumors by Cancer Susceptibility Syndromes. Cancer Epidemiol. Biomarkers Prevent. 25, 114–126.

Meulepas JM, Ronckers CM, Smets A, Nievelstein RAJ, Gradowska P, Lee C, Jahnken A, van Straten M, de Wit MY, Zonnenberg B, Klein WM, Merks JH, Visser O, van Leeuwen FE, Hauptmann M, 2019. Radiation Exposure From Pediatric CT Scans and Subsequent Cancer Risk in the Netherlands. J. Natl. Cancer Inst. 111, 256–263. [PubMed: 30020493]

Mole RH, 1990. Childhood cancer after prenatal exposure to diagnostic X-ray examinations in Britain. Br. J. Cancer 62, 152–168. [PubMed: 2202420]

Moysich KB, McCarthy P, Hall P, 2011. 25 years after Chernobyl: lessons for Japan? Lancet Oncol. 12, 416–418. [PubMed: 21514885]

National Council on Radiation Protection and Measurements (NCRP), 2001. Report No. 136. Evaluation of the linear-nonthreshold dose-response model for ionizing radiation. p.i-ix 1–287. Bethesda, MD, USA, National Council on Radiation Protection and Measurements (NCRP).

National Council on Radiation Protection and Measurements (NCRP), 2009. Report No. 160. Ionizing radiation exposure of the population of the United States. p.i-xv 1–387. Bethesda, MD, USA, National Council on Radiation Protection and Measurements (NCRP).

National Council on Radiation Protection and Measurements (NCRP), 2013. Report No. 174. Preconception and prenatal radiation exposure: health effects and protective guidance. p.i-xiii 1–371. Bethesda, MD, USA, National Council on Radiation Protection and Measurements (NCRP).

National Council on Radiation Protection and Measurements (NCRP), 2018. Implications of recent epidemiologic studies for the linear-nonthreshold model and radiation protection. NCRP Commentary no 27. p.i-ix 1–199. Bethesda, MD, USA, National Council on Radiation Protection and Measurements (NCRP).

National Council on Radiation Protection and Measurements (NCRP), 2019. Report No. 184. Medical radiation exposure of patients in the United States. p.i-xii 1–298. Bethesda, MD, USA, National Council on Radiation Protection and Measurements (NCRP).
National Council on Radiation Protection and Measurements (NCRP), 2020. Report No. 186. Approaches for integrating information from radiation biology and epidemiology to enhance low-dose health risk assessment. p.i–xi 1–296. Bethesda, MD, USA, National Council on Radiation Protection and Measurements (NCRP).

Nikkilä A, Erme S, Arvela H, Holmgren O, Raitanen J, Lohi O, Auvinen A, 2016. Background radiation and childhood leukemia: A nationwide register-based case-control study. Int. J. Cancer 139, 1975–1982. [PubMed: 27405274]

Nikkilä A, Raitanen J, Lohi O, Auvinen A, 2018. Radiation exposure from computerized tomography and risk of childhood leukemia: Finnish register-based case-control study of childhood leukemia (FRECCLE). Haematologica 103, 1873–1880. [PubMed: 29976736]

Noshchenko AG, Bondar OY, Drozdova VD, 2010. Radiation-induced leukemia among children aged 0–5 years at the time of the Chernobyl accident. Int. J. Cancer 127, 412–426. [PubMed: 19688829]

Oestreicher U, Endesfelder D, Gomolka M, Keszumiene A, Lang P, Lindholm C, Rößler U, Samaga D, Kulka U, 2018. Automated scoring of dicentric chromosomes differentiates increased radiation sensitivity of young children after low dose CT exposure in vitro. Int. J. Radiat. Biol. 94, 1017–1026. [PubMed: 30028637]

Ohira T, Shimura H, Hayashi F, Nagao M, Yasumura S, Takahashi H, Suzuki S, Matsuzuka T, Suzuki S, Iwadate M, Ishikawa T, Sakai A, Suzuki S, Nollet KE, Yokoya S, Ohto H, Kamiya K, 2020. Fukushima Health Management Survey, G. Absorbed radiation doses in the thyroid as estimated by UNSCEAR and subsequent risk of childhood thyroid cancer following the Great East Japan Earthquake. J. Radiat. Res. 61, 243–248. [PubMed: 32030428]

Ohtaki K, Kodama Y, Nakano M, Itoh M, Awa AA, Cologne J, Nakamura N, 2004. Human fetuses do not register chromosome damage inflicted by radiation exposure in lymphoid precursor cells except for a small but significant effect at low doses. Radiat. Res. 161, 373–379. [PubMed: 15038761]

Parkin DM, Clayton D, Black RJ, Masuyer E, Friedel HP, Ivanov E, Sinnaeve T, Tzvetansky CG, Geryk E, Storm HH, Rahu M, Pukkala E, Bernard JL, Carli PM, L'Huilier MC, Ménégoz F, Schaffer P, Schraub S, Kaatsch P, Michaelis J, Apjok E, Schuler D, Cropsigni P, Magnani C, Terracini B, Stengrevics A, Kriauciuinas R, Coebergh JW, Langmark F, Zatonski W, Tulbure R, Boukhny A, Merabishvili V, Plesko I, Krámarová E, Pompe-Kirn V, Barlow L, Endersle F, Levi F, Raymond L, Schüller G, Torhorst J, Stiller CA, Sharp L, Bennett BG, 1996. Childhood leukaemia in Europe after Chernobyl: 5 year follow-up. Br. J. Cancer 73, 1006–1012. [PubMed: 8611419]

Pasqual E, Castaño-Vinyals G, Thierry-Chef I, Kojihara N, Sim MR, Kundi M, Krewski D, Momoli F, Lacour B, Remen T, Radon K, Weinmann T, Petridou E, Moschovi M, Dikshit R, Sadetski S, Maule M, Farinotti M, Ha M, t Mannelt J, Alguacil J, Aragonés N, Vermeulen R, Kromhout H, Cardis E, 2020. Exposure to Medical Radiation during Fetal Life, Childhood and Adolescence and Risk of Brain Tumor in Young Age: Results from The MOBI-Kids Case-Control Study. Neuroepidemiology 54, 343–355. [PubMed: 32200380]

Pearce MS, Salotti JA, Little MP, McHugh K, Lee C, Kim KP, Howe NL, Ronckers CM, Rajaraman P, Craft AW, Parker L, Berrington de González A, 2012. Radiation exposure from CT scans in childhood and subsequent risk of leukaemia and brain tumours: a retrospective cohort study. Lancet 380, 499–505. [PubMed: 22681860]

Pottern LM, Kaplan MM, Reed Larsen P, Enrique Silva J, Koenig RJ, Lubin JH, Stovall M, Boice JD, 1990. Thyroid nodularity after childhood irradiation for lymphoid hyperplasia: a comparison of questionnaire and clinical findings. J. Clin. Epidemiol. 43, 449–460. [PubMed: 2324785]

Preston DL, Cullings H, Suyama A, Funamoto S, Nishi N, Soda M, Mabuchi K, Kodama K, Kasagi F, Shore RE, 2008. Solid cancer incidence in atomic bomb survivors exposed in utero or as young children. J. Natl. Cancer Inst. 100, 428–436. [PubMed: 18334707]

Preston DL, Ron E, Tokuoka S, Funamoto S, Nishi N, Soda M, Mabuchi K, Kodama K, 2007. Solid cancer incidence in atomic bomb survivors: 1958–1998. Radiat. Res. 168, 1–64. [PubMed: 17722996]

R Project version 3.6.1. R: A language and environment for statistical computing. https://www.r-project.org. Vienna, Austria: R Foundation for Statistical Computing.
Ronckers CM, Doody MM, Lonstein JE, Stovall M, Land CE, 2008. Multiple diagnostic X-rays for spine deformities and risk of breast cancer. Cancer Epidemiol. Biomarkers Prev. 17, 605–613. [PubMed: 18349278]

Roman E, Lightfoot T, Picton S, Kinsey S, 2018. Childhood cancers. In: Thun MJ, Linet MS, Cerhan JR, Haiman CA, Schottenfeld D (Eds.), Cancer epidemiology and prevention, fourth ed. Oxford University Press, New York, NY, pp. 1119–1153.

Ronckers CM, Land CE, Miller JS, Stovall M, Lonstein JE, Doody MM, 2010. Cancer mortality among women frequently exposed to radiographic examinations for spinal disorders. Radiat. Res. 174, 83–90. [PubMed: 20681802]

Ronckers CM, Land CE, Verduijn PG, Hayes RB, Stovall M, van Leeuwen FE, 2001. Cancer mortality after nasopharyngeal radium irradiation in the Netherlands: a cohort study. J. Natl. Cancer Inst. 93, 1021–1027. [PubMed: 11438568]

Scheele CLGJ, Hannezo E, Muraro MJ, Zomer A, Langedijk NSM, van Oudenaarden A, Simons BD, van Rheenen J, 2017. Identity and dynamics of mammary stem cells during branching morphogenesis. Nature 542, 313–317. [PubMed: 28135720]

Schubauer-Berigan MK, Berrington de Gonzalez A, Cardis E, Laurier D, Lubin JH, Hauptmann M, Richardson DB, 2020. Evaluation of Confounding and Selection Bias in Epidemiological Studies of Populations Exposed to Low-Dose, High-Energy Photon Radiation. J. Natl. Cancer Inst. Monogr. 2020, 133–153. [PubMed: 32657349]

Schüz J, Deltour I, Krestininia LY, Tsareva YV, Tolstykh EI, Sokolnikov ME, Akleyev AV, 2017. In utero exposure to radiation and haematological malignancies: pooled analysis of Southern Urals cohorts. Br. J. Cancer 116, 126–133. [PubMed: 27855443]

Self SG, Liang K-Y, 1987. Asymptotic properties of maximum likelihood estimators and likelihood ratio tests under nonstandard conditions. J. Am. Statist. Assoc. 82, 605–610.

Shimizu Y, Kodama K, Nishi N, Kasagi F, Suyama A, Soda M, Grant EJ, Sugiyama H, Sakata R, Moriwaki H, Hayashi M, Konda M, Shore RE, 2010. Radiation exposure and circulatory disease risk: Hiroshima and Nagasaki atomic bomb survivor data, 1950–2003. BMJ 340, b5349.

Shore R, Walsh L, Azizova T, Rühm W, 2017. Risk of solid cancer in low dose-rate radiation epidemiological studies and the dose-rate effectiveness factor. Int. J. Radiat Biol. 93, 1064–1078. [PubMed: 28421857]

Shore RE, Beck HL, Boice JD, Caffrey EA, Davis S, Grogan HA, Mettler FA, Preston RJ, Till JE, Wakeford R, Walsh L, Dauer LT, 2018. Implications of recent epidemiologic studies for the linear nonthreshold model and radiation protection. J. Radiol. Prot. 38, 1217–1233. [PubMed: 30004025]

Shore RE, Beck HL, Boice JD Jr., Caffrey EA, Davis S, Grogan HA, Mettler FA Jr., Preston RJ, Till JE, Wakeford R, Walsh L, Dauer LT, 2019. Recent Epidemiologic Studies and the Linear No-Threshold Model For Radiation Protection—Considerations Regarding NCRP Commentary 27. Health Phys. 116, 235–246. [PubMed: 30585971]

Smith-Bindman R, Kwan ML, Marlow EC, Theis MK, Bolch W, Cheng SY, Bowles EJA, Duncan JR, Greenlee RT, Kushi LH, Pole JD, Rahm AK, Stout NK, Weinmann S, Miglioretti DL, 2019. Trends in Use of Medical Imaging in US Health Care Systems and in Ontario, Canada, 2000–2016. JAMA 322, 843–856. [PubMed: 31479136]

Spix C, Grosche B, Bleher M, Kallesten P, Scholz-Kreisel P, Blettner M, 2017. Background gamma radiation and childhood cancer in Germany: an ecological study. Radiat. Environ. Biophys. 56, 127–138. [PubMed: 28337585]

Spycher BD, Lupatsch JE, Zwahlen M, Röösli M, Niggli F, Grotzer MA, Rishewski J, Egger M, Kuelhni CE, 2015. Background ionizing radiation and the risk of childhood cancer: a census-based nationwide cohort study. Environ. Health Perspect. 123, 622–628. [PubMed: 25707026]

Steinmaus C, Lu M, Todd RL, Smith AH, 2004. Probability estimates for the unique childhood leukemia cluster in Fallon, Nevada, and risks near other U.S. Military aviation facilities. Environ. Health Perspect. 112, 766–771. [PubMed: 15121523]

Stern H, Seidenbusch M, Hapfelmeier A, Meierhofer C, Naumann S, Schmid I, Spix C, Ewert P, 2020. Increased Cancer Incidence Following up to 15 Years after Cardiac Catheterization in Infants

Environ Int. Author manuscript; available in PMC 2022 May 19.
under One Year between 1980 and 1998-A Single Center Observational Study. J. Clin. Med. 9, 315.

Stevens W, Thomas DC, Lyon JL, Till JE, Kerber RA, Simon SL, Lloyd RD, Elghany NA, Preston-Martin S, 1990. Leukemia in Utah and radioactive fallout from the Nevada test site. A case-control study. JAMA 264, 585–591. [PubMed: 2366297]

Stewart A, Webb J, Giles D, Hewitt D, 1956. Malignant disease in childhood and diagnostic irradiation in utero. Lancet 268, 447.

Stewart A, Webb J, Hewitt D, 1958. A survey of childhood malignancies. Br. Med. J. 1, 1495–1508. [PubMed: 13546604]

Stiller C, 2007. Childhood cancer in Britain. Incidence, survival, mortality. Oxford University Press, Oxford, pp. 1–270.

Sugiyama H, Misumi M, Sakata R, Brenner AV, Utada M, Ozasa K, 2021. Mortality among individuals exposed to atomic bomb radiation in utero: 1950–2012. Eur. J. Epidemiol. 36, 415–428. [PubMed: 33492551]

Tran V, Little MP, 2017. Dose and dose rate extrapolation factors for malignant and non-malignant health endpoints after exposure to gamma and neutron radiation. Radiat. Environ. Biophys. 56, 299–328. [PubMed: 28939964]

Tsuda T, Tokinobu A, Yamamoto E, Suzuki E, 2016. Thyroid cancer detection by ultrasound among residents ages 18 years and younger in Fukushima, Japan: 2011 to 2014. Epidemiology 27, 316–322. [PubMed: 26441345]

United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), 1972. A report of the United Nations Scientific Committee on the Effects of Atomic Radiation to the General Assembly, with annexes. Levels and Effects. Report E.72. IX.18. p.1–447. New York, United Nations.

United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), 1993. Sources and effects of ionizing radiation. UNSCEAR 1993 report to the General Assembly, with scientific annexes. Report E.94.IX.2. p.1–922. New York, United Nations.

United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), 2008. UNSCEAR 2006 Report. Annex A. Epidemiological Studies of Radiation and Cancer. Report E.08.IX.6. p.13–322. New York, United Nations.

United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), 2011. UNSCEAR 2008 Report. Annex D. Health effects due to radiation from the Chernobyl accident. Report E.10.XI.3. p.1–173. New York, United Nations.

United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), 2012. Biological mechanisms of radiation actions at low doses. A white paper to guide the Scientific Committee’s future programme of work. Report V.12–57831. p.1–35. New York, United Nations.

United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), 2013. Volume II. Scientific Annex B: Effects of radiation exposure of children. Report E.14.IX.2. p.1–269. New York, United Nations.

United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), 2014. Sources, effects and risks of ionizing radiation. UNSCEAR 2013 Report. Volume I. Scientific Annex A: Levels and effects of radiation exposure due to the nuclear accident after the 2011 great east-Japan earthquake and tsunami. Report E.14.IX.1. p.1–311. New York, United Nations.

United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), 2015. Sources, effects and risks of ionizing radiation. UNSCEAR 2012 Report to the General Assembly with Scientific Annexes. Annex A. Attributing health effects to ionizing radiation exposure and inferring risks. Report E.16.IX.1. p.17–90. New York, United Nations.

United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), 2018. Sources, effects and risks of ionizing radiation. UNSCEAR 2017 report to the General Assembly. Scientific annexes A and B. Report E.18.IX.1. p.1–194. New York, United Nations.

United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), 2021a. Report of the United Nations Scientific Committee on the Effects of Atomic Radiation. Sixty-seventh session (2–6 November 2020). Report A/76/46 Part 1. p.1–22. New York, United Nations.
United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), 2021b. UNSCEAR 2020 Report. Annex B. Levels and effects of radiation exposure due to the accident at the Fukushima Daiichi Nuclear Power Station: implications of information published since the UNSCEAR 2013 Report. Report V.21–00572. p.1–243. New York, United Nations.

Utada M, Brenner AV, Preston DL, Cologne JB, Sakata R, Sugiyama H, Sadakane A, Grant EJ, Cahoon EK, Ozasa K, Mabuchi K, 2019. Radiation risks of uterine cancer in atomic bomb survivors: 1958–2009. JNCI Cancer Spectrum 2(4) pky081.

Viechtbauer W, 2005. Bias and efficiency of meta-analytic variance estimators in the random-effects model. J. Educ. Behav. Stat. 30, 261–293.

Viechtbauer W, 2010. Conducting meta-analyses in R with the metafor package. J. Statist. Software 36, 1–48.

Viechtbauer W metafor. Version 2.4–0. CRAN - The Comprehensive R Archive Network, 2020.

Wakeford R, 2004. The cancer epidemiology of radiation. Oncogene 23, 6404–6428. [PubMed: 15322514]

Wakeford R, 2008. Childhood leukaemia following medical diagnostic exposure to ionizing radiation in utero or after birth. Radiat. Prot. Dosim. 132, 166–174.

Wakeford R, Auvinen A, Gent RN, Jacob P, Kesminiene A, Laurier D, Schüz J, Shore R, Walsh L, Zhang W, 2016. Re: Thyroid Cancer Among Young People in Fukushima. Epidemiology 27, e20–e21. [PubMed: 26841059]

Wakeford R, Bithell JF, 2021. A review of the types of childhood cancer associated with a medical X-ray examination of the pregnant mother. Int. J. Radiat Biol. 97, 571–592. [PubMed: 33787450]

Wakeford R, Kendall GM, Little MP, 2009. The proportion of childhood leukaemia incidence in Great Britain that may be caused by natural background ionizing radiation. Leukemia 23, 770–776. [PubMed: 19151785]

Wakeford R, Little MP, 2003. Risk coefficients for childhood cancer after intrauterine irradiation: a review. Int. J. Radiat Biol. 79, 293–309. [PubMed: 12943238]

Walsh L, Shore R, Auvinen A, Jung T, Wakeford R, 2014. Risks from CT scans—what do recent studies tell us? J. Radiol. Prot. 34 (1), E1–E5. [PubMed: 24594968]

Walsh L, Shore R, Azizova TV, Rühm W, 2021. On the choice of methodology for evaluating dose-rate effects on radiation-related cancer risks. Radiat. Environ. Biophys. 60, 493–500. [PubMed: 34170393]

Yoshimoto Y, Kato H, Schull WJ, 1988. Risk of cancer among children exposed in utero to A-bomb radiations, 1950–84. Lancet 332, 665–669.

Zablotska LB, Ron E, Rozhko AV, Hatch M, Polynskaya ON, Brenner AV, Lubin J, Romanov GN, McConnell RJ, O’Kane P, Evseenko VV, Drozdovitch VV, Luckyyanov N, Menenko VF, Bouville A, Masyakin VB, 2011. Thyroid cancer risk in Belarus among children and adolescents exposed to radiodine after the Chornobyl accident. Br. J. Cancer 104, 181–187. [PubMed: 21102590]

Zidane M, Truong T, Lesueur F, Xhaard C, Cordina-Duverger E, Boland A, Blanché H, Ory C, Chevillard S, Deleuze J-F, Souchard V, Ren Y, Zemmache MZ, Canale S, Borson-Chazot F, Schwartz C, Mariné Barjoan E, Guizard A-V, Laurent-Puig P, Mulot C, Guibon J, Karimi M, Schlumberger M, Adajad E, Rubino C, Guenel P, Cazier J-B, de Vathaire F, 2021. Role of DNA Repair Variants and Diagnostic Radiology Exams in Differentiated Thyroid Cancer Risk: A Pooled Analysis of Two Case-Control Studies. Cancer Epidemiol. Biomarkers Prevent. 30, 1208–1217.
Table 1

Risks from childhood exposure in studies of natural background radiation.

| Reference                        | Mean dose (Gy) | Max dose (Gy) | Mean dose rate (Gy/h) | Max dose rate (Gy/h) | Description of study data                                                                 | Notes                                                      | Endpoint [incidence unless otherwise stated] | Number of cases / deaths | ERR / Gy (95% CI) |
|----------------------------------|----------------|---------------|-----------------------|----------------------|-----------------------------------------------------------------------------------------|----------------------------------------------------------|--------------------------------------------|------------------------------------------|-----------------------|
| (Kendall et al. 2013)            | 0.0040         | 0.0311 (L)    | NA                    | 1.597 × 10^{-7} (L)  | Great Britain NRCT study 1980–2006                                                        | Gamma only, mean equivalent ABM dose and range including dose from radon and gamma | Acute myeloid leukaemia 1316               | 40 (~ 110,210)             | 0.0040...
| (Spycher et al. 2015)            | 0.00906        | 0.0494 (L)    | 1.09 × 10^{-7} (L)    | 3.83 × 10^{-7} (L)   | Swiss Cancer Registry study, 1990–2008, children < 16 y                                 | Gamma only                                   | Leukaemia 530               | 36 (~ 3.77)                | 0.00906...
| (Nikkilä et al. 2016)           | 0.0019         | >0.011 (L)    | 6.64 × 10^{-8} (L)    | 1.40 × 10^{-7} (L)   | Finnish Cancer Registry study 1990–2011                                                  | median doses, dose rates in controls            | Acute lymphoblastic leukaemia 786   | –10 (~ 100,90)            | 0.0019...
| (Demoury et al. 2017)           | 0.0158         | 0.0402 (L)    | 9.82 × 10^{-8} (L)    | 2.608 × 10^{-7} (L)  | French Childhood Cancer Registry (RNCE) ecological study 1990–2000, and case-control study 2002–2007 | mean, max dose and mean, max dose rate estimated from controls age 15 in Geocap case-control study | Acute myeloid leukaemia 937             | –30 (~ 110,60)            | 0.0158...
| (Berlivet et al. 2020)          | 0.0063         | 0.0352 (L)    | 9.22 × 10^{-8} (L)    | 2.548 × 10^{-7} (L)  | French Childhood Cancer Registry (RNCE) ecological study 2000–2012                       | Brain/CNS                                    | Acute leukaemia 9056          | 0 (~ 10,10)                | 0.0063...
| (Berlivet et al. 2021)          | 0.0047         | 0.0324 (L)    | 9.08 × 10^{-8} (L)    | 2.548 × 10^{-7} (L)  | French Childhood Cancer Registry (RNCE) ecological study 1990–2009                       | Cumulative gamma dose                          | Acute leukaemia 6057          | –8 (~ 26,14)               | 0.0047...

CNS, central nervous system.

\(^a\) (L) = maximum dose consistent with low dose, (M) = maximum dose consistent with moderate dose but not with low dose, (H) = maximum dose consistent with high dose but not with moderate or low dose.
(L) = maximum dose rate consistent with low dose rate, (M) = maximum dose rate consistent with moderate dose rate but not with low dose rate, (H) = maximum dose rate consistent with high dose rate but not with moderate or low dose rate.
### Table 2

Risks from childhood and *in utero* exposure in studies of medical diagnostic radiation exposure.

| Reference | Mean dose (Gy) | Max dose (Gy) | Mean dose rate (Gy/h) | Max dose rate (Gy/h) | Description of study data | Notes | Endpoint (incidence unless otherwise stated) | Number of cases / deaths | ERR / Gy (95% CI) |
|-----------|---------------|---------------|-----------------------|----------------------|---------------------------|-------|---------------------------------------------|--------------------------|-----------------|
| **Postnatal exposure** | | | | | | | | | |
| (Pottern et al. 1990) | 0.1275 | 0.55 (M) | NA | NA (M) | Lymphoid hyperplasia cohort treated 1938–1969 at Children’s Hospital Medical Center, Boston | Questionnaire data, mean dose weighted sum of exposed and unexposed | Thyroid nodule | 54 | 64 (18,225) |
| | 0.1376 | 0.53 (M) | NA | NA (M) | | | | 81 | 7 (3,15) |
| (Little and Boice 1999) | 1.2 | 5.4 (H) | <0.01–0.1 | 0.1 (M) | Massachusetts TB fluoroscopy cohort, with exposure under age 20 | Adjustment for attained age (centred at age 50) | Breast | 78 | 0.062 (0.0005,0.93) |
| (Lundell et al. 1999) | 0.09171 | 1 (M) | NA | <600 (H) | Swedish haemangioma cohort irradiated for skin haemangioma at Radiumhemmet Stockholm 1920–1959 and Sahlgrenska University Hospital Göteborg 1930–1965 and followed up 1958–1993 | Refitted to data in paper < 1 Gy using a linear Poisson model, mean dose via breast year weighted mean, maximum dose rate from (Lundell 1994) | Breast | 215 | −0.4 (−1.1,0.7) |
| (Ronckers et al. 2001) | 0.004 | 0.03 (M) | NA | NA (M) | Dutch nasopharyngeal radium irradiated children treated for otitis serosa and frequency matched controls treated 1945–1981, followed 1982–1997 | | Lymphoproliferative and haematopoetic malignancy mortality | 23 | 450 (50,1690) |
| (Ronckers et al. 2008) | 0.121 | 1.11 (H) | 0.0045 | 0.0156 (M) | US scoliosis cohort of women diagnosed with scoliosis 1912–1965 and followed (via questionnaire) up to 1992, given multiple diagnostic X-radiographs | Mean and maximum dose rate based on the mean and maximum breast dose per radiograph | Breast | 78 | 2.9 (−0.1,8.6) |
| (Ronckers et al. 2010) | 0.109 | 1.703 (H) | 0.0045 | 0.0156 (M) | US scoliosis cohort of women diagnosed with scoliosis 1912–1965 and followed (via linkage) | Mean and maximum dose rate based on the mean and maximum breast dose | Breast mortality | 112 | 4.0 (1.0,9.4) |
| Reference | Mean dose (Gy) | Max dose (Gy)<sup>a</sup> | Mean dose rate (Gy/h) | Max dose rate (Gy/h)<sup>b</sup> | Description of study data | Notes | Endpoint [incidence unless otherwise stated] | Number of cases / deaths | ERR / Gy (95% CI) |
|-----------|----------------|---------------------------|----------------------|---------------------------|-----------------------------|-------|-----------------------------------------------|--------------------------|----------------|
| (Pearce et al. 2012) | 0.04463 | >0.3302 (M) | NA | >0.044 (M) | US scoliosis cohort of women diagnosed with scoliosis 1912–1965 and followed (via linkage with various registers) from 1992 (date of questionnaire) to 2004, given multiple diagnostic X-radiographs | | Lung mortality | 17 | −1.4 (−7.1, 3.1) |
| (Mathews et al. 2013) | 0.0059 | NA (M) | 0.0046 | NA (M) | Australian CT study of persons aged 0–19 years in 1/1985 or born after that point, 1985–2007 | 1 year lag, dose rates based on mean dose per scan | Leukaemia + MDS | 246 | 39 (14,70) |
| | 0.048 | NA (M) | 0.040 | NA (M) | | 5 year lag, dose rates based on mean dose per scan | Brain/CNS | 283 | 21 (14,29) |
| (Journy et al. 2015) | 0.0069 | >0.1 (M) | NA | NA (M) | French infant CT study, 2000–2011, age < 10 y at first CT, followed via RNCE | Median ABM dose - very similar to Journy et al (Journy et al. 2016) except this paper uses Poisson models with linear ERR model. 2 year exclusion | Leukaemia | 17 | 47 (−65,159) |
| | 0.0183 | >0.1 (M) | NA | NA (M) | Median brain dose - very similar to Journy et al (Journy et al. 2016) except this paper uses Poisson models with linear ERR model. 4 year exclusion | | Brain/CNS | 13 | −4 (−11,1) |
| | 0.0069 | >0.1 (M) | NA | NA (M) | Median ABM dose - very similar to Journy et al (Journy et al. 2016) except this paper uses Poisson models with linear ERR model. 2 year exclusion | | Lymphoma | 19 | 8 (−57,73) |
| Reference | Mean dose (Gy) | Max dose (Gy)<sup>a</sup> | Mean dose rate (Gy/h) | Max dose rate (Gy/h)<sup>b</sup> | Description of study data | Notes | Endpoint [incidence unless otherwise stated] | Number of cases / deaths | ERR / Gy (95% CI) |
|-----------|---------------|-----------------|---------------------|--------------------------|----------------------------|-------|--------------------------------------|--------------------------|------------------|
| (Krille et al. 2015) | 0.0117 | (M) | NA | NA | German infant CT study, 1980-2010, age < 15 y at first CT, lag 2 y | Using ABM dose | Leukaemia | 12 | 9 (−19,37) |
| | 0.0344 | (M) | NA | NA | Using brain dose | | | | |
| (Berrington de Gonzalez et al. 2017) | 0.012 | 0.689 (M) | NA | NA | UK-NCI paediatric CT cohort, age at first CT < 22 y, 1980-2008 | Using ABM dose, 2 y lag | Hodgkin lymphoma | 65 | −1 (−16,13) |
| (Lubin et al. 2017) | 0.02991 | 0.2 (M) | NA | NA | Pooled analysis of 9 datasets | Dose < 0.2 Gy | Thyroid cancer | 252 | 11.1 (6.6,19.7) |
| | 0.01730 | 0.1 (L) | NA | NA | | Dose < 0.1 Gy | Thyroid cancer | 184 | 9.6 (3.7,17.0) |
| (Little et al. 2018b) | 0.0196 | 0.1 (L) | NA | NA | 9 cohort pooled moderate dose medical + LSS analysis - dose < 0.1 Gy | | Acute myeloid leukaemia + MDS | 87 | 20.9(4,1,49.2) |
| | 0.0049 | 0.7949 (M) | NA | NA | US Radiologic Technologist cohort, followed up via four questionnaires administered 1983–2014 | Health endpoints and medical diagnostic exposure assessed via questionnaire. Risks for exposure aged 0–19 as part of model with separate windows for various age at exposure groups | Papillary thyroid cancer | 275 | 6.75 (−3.3,23.24) |
| | 0.00629 | 0.0332 (L) | NA | 0.0068 (M) | Finnish Cancer Registry based case-control study 1990-2011 | median dose for controls, using NCICT software | Thyroid cancer | 414 | 4.57 (−3.0,16.1) |
| (Meulepas et al. 2019) | 0.0385 | >0.22 (M) | NA | NA | Dutch CT study of children (age < 18 y) at first CT, 1979–2012 | Exclusion and lag 5 y, brain dose | | 84 | 8.6 (2.0,22.2) |
| | 0.0095 | >0.017 (L) | NA | NA | | | Brain/CNS | | |
| | 0.0095 | >0.017 (L) | NA | NA | Exclusion and lag 2 y, ABM dose | Leukaemia + MDS | 63 | 0.4 (−1.2,16.1) |
| Reference                          | Mean dose (Gy) | Max dose (Gy) | Mean dose rate (Gy/h) | Max dose rate (Gy/h) | Description of study data | Notes                                                                 | Endpoint [incidence unless otherwise stated] | Number of cases / deaths | ERR / Gy (95% CI) |
|----------------------------------|----------------|--------------|-----------------------|----------------------|--------------------------|-----------------------------------------------------------------------|-----------------------------------------------|--------------------------|-------------------|
| (Kojimahara et al. 2020)         | 0.025          | >0.032 (M)   | NA                    | NA (M)               | Case-control study of 120 cases and 360 appendicitis controls aged 10–24 y, 2011–2015 | Mean dose to controls, lag 2 y, adjusted for parental education, history of neurological disease and ADD/ADHD | Brain/CNS Gioma | 120               | 0 (−10,10)       |
| (Pasqual et al. 2020)            | 0.0002         | 0.217 (M)   | NA                    | NA (M)               | MOBI-Kids multinational case-control study of medical diagnostic radiation exposures among persons aged 10–24 y | Dose lag 2 y | Brain/CNS | 844               | 0 (0,10)          |
| (Stern et al. 2020)              | 0.029          | 0.75 (M)    | NA                    | NA (M)               | Cohort of children receiving catheterization at age < 1 y 1980–1998, linked to German Childhood Cancer Registry | Risk derived from given relative risk (and CI) for > 0.094 Gy group by dividing (RR-1) by 0.094 | All cancer | 16                | 27.7 (−22.3,77.6) |
| (Zidane et al. 2021)             | 0.00198        | 0.1942 (M)  | NA                    | NA (M)               | French CATHY three-centre case-control study, with focus on childhood medical diagnostic procedures 2002–2006 | Linear part of linear-quadratic-exponential dose response | Thyroid cancer | 1071              | 17 (0.6,35)       |

**In utero exposure**

| Reference                          | Mean dose (Gy) | Max dose (Gy) | Mean dose rate (Gy/h) | Max dose rate (Gy/h) | Description of study data | Notes                                                                 | Endpoint [incidence unless otherwise stated] | Number of cases / deaths | ERR / Gy (95% CI) |
|-----------------------------------|----------------|--------------|-----------------------|----------------------|--------------------------|-----------------------------------------------------------------------|-----------------------------------------------|--------------------------|-------------------|
| (Hagstrom et al. 1969)            | ~0.1           | ~0.15 (M)   | ~0.000065             | ~0.000097 (L)        | Women administered $^{59}$Fe in pregnancy at Vanderbilt University Hospital, 1945–1949 and followed up to 1967 | Dose rate estimated via theoretical calculation based on physical half life of $^{59}$Fe, excess relative risk derived via dividing excess odds ratio by mean dose | Leukaemia mortality | 1                | $^{+00}$ (−9.74, $^{+00}$) |
|                                   |                |              |                       |                      |                          | Solid tumour mortality                                                |                                               |                          |                   |
| (Bithell and Stiller 1988)        | NA             | <0.03 (L)   | NA                    | 0.018 (M)            | Oxford Survey of Childhood Cancers, case-control pairs born 1953–1972, estimated via jointly fitted log linear model of OR with log-linear model of dose based on UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 1972) estimates | Trimester 2, maximum dose rates from UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 1972) for 1943–1949 Trimester 3, maximum dose rates from UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) 1972) estimates | All cancer mortality | 8513              | 20.8 (0.27,61.8) |
|                                   |                |              |                       |                      |                          |                                                                       |                                               |                          | 28.8 (17.1,43.6)  |
| Reference | Mean dose (Gy) | Max dose (Gy)\(^a\) | Mean dose rate (Gy/h) | Max dose rate (Gy/h)\(^b\) | Description of study data | Notes | Endpoint [incidence unless otherwise stated] | Number of cases / deaths | ERR / Gy (95% CI) |
|-----------|----------------|---------------------|----------------------|-----------------------------|--------------------------|-------|---------------------------------|--------------------------|------------------|
| (Bithell 1993) | NA | <0.03 (L) | NA (L) | >0.0061 (M) | Oxford Survey of Childhood Cancers, case-control pairs born 1953–1979 | Estimated via log linear-quadratic model of OR fitted to data of Gilman et al. (Gilman et al. 1988) by year for 1959, using dose estimate of 6.1 mGy per obstetric radiograph of Mole (Mole 1990) for that year | All cancer mortality | 14,759 | 51 (28, 76) |
| (Pasqual et al. 2020) | 0.00005 | 0.0127 (L) | NA (M) | MOBI-Kids multinational case-control study of medical diagnostic radiation exposures among persons aged 10–24 y, OR of >5 mGy vs <5 mGy | Dose lag 0 y, ERR derived by dividing ERR for >5 mGy vs 0–5 mGy by 0.005 (the mean dose difference between >5 mGy and <5 mGy groups must be between 0.00427 and 0.0127 Gy, and assumed to be ~0.005 Gy given the skewed nature of the dose distribution) | Brain/CNS | 844 | 70 (~96,502) |

CNS, central nervous system.

\(^a\) (L) = maximum dose consistent with low dose, (M) = maximum dose consistent with moderate dose but not with low dose, (H) = maximum dose consistent with high dose but not with moderate or low dose.

\(^b\) (L) = maximum dose rate consistent with low dose rate, (M) = maximum dose rate consistent with moderate dose rate but not with low dose rate, (H) = maximum dose rate consistent with high dose rate but not with moderate or low dose rate.
### Table 3

Risks resulting from *in utero* man-made environmental and maternal occupational exposure.

| Reference                  | Mean dose (Gy) | Max dose (Gy) | Mean dose rate (Gy/h) | Max dose rate (Gy/h) | Description of study data                      | Notes                                      | Endpoint (incidence unless otherwise stated) | Number of cases / deaths | ERR / Gy (95% CI) |
|----------------------------|----------------|---------------|-----------------------|---------------------|------------------------------------------------|--------------------------------------------|---------------------------------------------|--------------------------|-------------------|
| (Akleyev et al. 2016)      | 0.0141         | 0.9449        | NA                    | NA (L)              | Techa River and Mayak Worker cohorts 1950–2009 | Solid cancer (at an attained age up to 60 years) | 369                          | −2 (−4,1)                |                   |
| (Schüz et al. 2017)        | 0.001          | 1.053         | NA                    | NA (L)              | Techa River and Mayak workers exposed/followed up 1953–2009 (TR incidence), 1950–2009 (TR mortality), 1948–2009 (MW) | Median (among those without malignancy) rather than mean dose | Solid cancer mortality (at an attained age of up to 60 years) | 196                      | −2 (−6,1)              |
| (Hatch et al. 2019)        | 0.0726         | 2.268 (H)     | 0.0002602 (M)         | 0.0001955 (L)       | Ukraine *in utero*°131I exposed cohort | Risk as given | Risk as given | Refitted using binomial odds model using data from paper < 0.799 Gy | Thyroid cancer (attained age 25–30 years) | 8               | 3.91 (−1.49, 65.66) |
|                            | 0.08456        | 0.799 (M)     | 0.0002602 (M)         | 0.0001955 (L)       | Ukraine *in utero*°131I exposed cohort | Risk as given | Risk as given | Refitted using inverse-variance reweighted least squares model using data from paper < 0.799 Gy | Thyroid nodule (benign or neoplastic or suspicious) (attained age 25–30 years) | 241             | 1.53 (0.22, 3.59)  |
|                            |                |               | 0.008127 (M)          | 0.008127 (M)        | Ukraine *in utero*°131I exposed cohort | Risk as given | Risk as given | Refitted using inverse-variance reweighted least squares model using data from paper < 0.799 Gy | Thyroid cancer (attained age 25–30 years) | 237             | 2.55 (0.66, 3.36)  |
|                            |                |               | 0.002863 (L)          |                     | Ukraine *in utero*°131I exposed cohort | Risk as given | Risk as given | Refitted using inverse-variance reweighted least squares model using data from paper < 0.799 Gy | Thyroid cancer (attained age 25–30 years) | 237             | 2.75 (1.92, 3.58)  |
| (Johnson et al. 2008)      | 0.0002         | 0.0126 (L)    | NA                    | NA (L)              | US Radiologic Technologists offspring born 1921–1984 | Refitted from published data via Poisson linear model | Leukaemia | Lymphoma | All cancer (childhood cancer < 20 years of age) | 63           | 25.52 (−105.3, 327.7) |
|                            |                |               |                       |                     | US Radiologic Technologists offspring born 1921–1984 | Refitted from published data via Poisson linear model | Leukaemia | Lymphoma | All cancer (childhood cancer < 20 years of age) | 48           | 229.1 (−36.17, 823.9) |
|                            |                |               |                       |                     | US Radiologic Technologists offspring born 1921–1984 | Refitted from published data via Poisson linear model | Leukaemia | Lymphoma | All cancer (childhood cancer < 20 years of age) | 115          | 14.17 (90.45, 213.2) |
| (Bunch et al. 2009)        | <0.0007        | >0.002 (L)    | NA                    | NA (L)              | Offspring of female members of UK National Registry for Radiation Workers | Refitted from published data via linear binomial odds model | Leukaemia and NHL | Leukaemia and NHL | All cancer (childhood cancer < 20 years of age) | 5             | 56.29 (−40.26, 203.9) |
|                            |                |               |                       |                     | Offspring of female members of UK National Registry for Radiation Workers | Refitted from published data via linear binomial odds model | Leukaemia and NHL | Leukaemia and NHL | All cancer (childhood cancer < 20 years of age) | 2             | 0.00 (41.320, 1087 v) |

CNS, central nervous system.

*L* = maximum dose consistent with low dose, *M* = maximum dose consistent with moderate dose but not with low dose, *H* = maximum dose consistent with high dose but not with moderate or low dose.

(L) = maximum dose rate consistent with low dose rate, *M* = maximum dose rate consistent with moderate dose rate but not with low dose rate, *H* = maximum dose rate consistent with high dose rate but not with moderate or low dose rate.
Table 4

Risks from postnatal and *in utero* exposure in the Japanese atomic bomb survivors.

| Reference | Mean dose (Gy) | Max dose (Gy)* | Mean dose rate (Gy/h) | Max dose rate (Gy/h) | Description of study data | Notes | Endpoint [incidence unless otherwise stated] | Number of cases / deaths | ERR / Gy (95% CI) |
|-----------|---------------|---------------|-----------------------|----------------------|----------------------------|-------|---------------------------------------------|--------------------------|------------------|
| Postnatal exposure | | | | | | | | | |
| (Preston et al. 2007) | 0.05637 | 1 (M) | 0.05637 | 1 (M) | LSS brain/CNS cancer incidence 1958–1998, DS02 brain dose | Refitted to downloadable data < 1 Gy brain dose, age < 20 y at exposure, via Poisson linear model, stratified by age at exposure, age, sex, city, distance category | Brain/CNS | 103 | 0.85 (−0.54,3.69) |
| 0.01809 | 0.2 (M) | 0.01809 | 0.2 (M) | | Refitted to downloadable data < 0.2 Gy brain dose, age < 20 y at exposure, via Poisson linear model, stratified by age at exposure, age, sex, city, distance category | | | | −0.76 (−4.21,7.80) |
| 0.01026 | 0.1 (L) | 0.01026 | 0.1 (L) | | Refitted to downloadable data < 0.1 Gy brain dose, age < 20 y at exposure, via Poisson linear model, stratified by age at exposure, age, sex, city, distance category | | | | −3.56 (−9.21,12.33) |
| 0.05543 | 1 (M) | 0.05543 | 1 (M) | | LSS breast cancer incidence 1958–1998, DS02 breast dose | Refitted to downloadable data < 1 Gy breast dose, age < 20 y at exposure, via Poisson linear model, stratified by age at exposure, age, sex, city, distance category | Breast | 425 | −1.94 (0.87,3.42) |
| 0.01787 | 0.2 (M) | 0.01787 | 0.2 (M) | | Refitted to downloadable data < 0.2 Gy breast dose, age < 20 y at exposure, via Poisson linear model, stratified by age at exposure, age, sex, city, distance category | | | | −1.81 (−1.27,6.38) |
| 0.009793 | 0.1 (L) | 0.009793 | 0.1 (L) | | Refitted to downloadable data < 0.1 Gy breast dose, age < 20 y at exposure, via Poisson linear model, stratified by age at exposure, age, sex, city, distance category | | | | −2.39 (−6.91,4.82) |
| (Cahoon et al. 2017b) | 0.05569 | 1 (M) | 0.05569 | 1 (M) | LSS incidence 1958–2009, DS02R1 dose | Refitted to downloadable data < 1 Gy lung dose, age < 20 y at exposure, via Poisson linear model, stratified by age at exposure, age, sex, city, distance category | Lung | 833 | 0.44 (−0.12,1.18) |
| 0.01782 | 0.2 (M) | 0.01782 | 0.2 (M) | | Refitted to downloadable data < 0.2 Gy lung dose, age < 20 y at exposure, via Poisson linear model, stratified by age at exposure, age, sex, city, distance category | | | | 3.74 (0.69,7.88) |

*ERR = excess relative risk.*
| Reference       | Mean dose (Gy) | Max dose (Gy) | Mean dose rate (Gy/h) | Max dose rate (Gy/h) | Description of study data                                                                 | Notes                                                                 | Endpoint [incidence unless otherwise stated] | Number of cases / deaths | ERR / Gy (95% CI) |
|-----------------|----------------|---------------|-----------------------|----------------------|-------------------------------------------------------------------------------------------|----------------------------------------------------------------------|----------------------------------------------------------------|--------------------------|------------------|
| 0.01028         | 0.1 (L)        | 0.01028       | 0.1 (L)               | Refitted to downloadable data < 0.1 Gy lung dose, age < 20 y at exposure, via Poisson linear model, stratified by age at exposure, age, sex, city, distance category |                                                                      | 711                                                               | 6.57 (0.84,14.63)  |
| 0.05569         | 1 (M)          | 0.05569       | 1 (M)                 | Refitted to downloadable data < 1 Gy lung dose, age < 20 y at exposure, via Poisson linear model, stratified by age at exposure, age, sex, city, distance category, adjusted for cigarette smoking status, cigarettes per day smoked |                                                                      | 833                                                               | 0.67 (0.30,1.15)   |
| 0.01782         | 0.2 (M)        | 0.01782       | 0.2 (M)               | Refitted to downloadable data < 0.2 Gy lung dose, age < 20 y at exposure, via Poisson linear model, stratified by age at exposure, age, sex, city, distance category, adjusted for cigarette smoking status, cigarettes per day smoked |                                                                      | 759                                                               | 0.41 (−0.15,1.13) |
| 0.01028         | 0.1 (L)        | 0.01028       | 0.1 (L)               | Refitted to downloadable data < 0.1 Gy lung dose, age < 20 y at exposure, via Poisson linear model, stratified by age at exposure, age, sex, city, distance category, adjusted for cigarette smoking status, cigarettes per day smoked |                                                                      | 711                                                               | 1.64 (0.55,3.49)   |
| 0.06851         | 1 (M)          | 0.05569       | 1 (M)                 | Refitted to downloadable data < 1 Gy lung dose, lifelong nonsmokers, age < 20 y at exposure, via Poisson linear model, stratified by age at exposure, age, sex, city, distance category |                                                                      | 160                                                               | 1.77 (0.29,4.36)   |
| 0.01962         | 0.2 (M)        | 0.01782       | 0.2 (M)               | Refitted to downloadable data < 0.2 Gy lung dose, lifelong nonsmokers, age < 20 y at exposure, via Poisson linear model, stratified by age at exposure, age, sex, city, distance category |                                                                      | 140                                                               | 5.94 (−1.06,20.73) |
| 0.01107         | 0.1 (L)        | 0.01028       | 0.1 (L)               | Refitted to downloadable data < 0.1 Gy lung dose, lifelong nonsmokers, age < 20 y at exposure, via Poisson linear model, stratified by age at exposure, age, sex, city, distance category |                                                                      | 131                                                               |                                        |
| (Grant et al. 2017) | 0.05415       | 1 (M)         | 0.05415               | LSS incidence 1958'2009, DS02R1 dose | Solid cancer Refitted to downloadable data < 1 Gy colon dose, age < 20 y at exposure, via Poisson linear model, stratified by age at exposure, age, sex, city, distance category |                                                                      | 8308                                                              | 0.90 (0.69,1.13)   |
| 0.01767         | 0.2 (M)        | 0.01767       | 0.2 (M)               | Refitted to downloadable data < 0.2 Gy colon dose, age < 20 y at exposure, via Poisson |                                                                      | 7429                                                              | 1.21 (0.40,2.09)   |
| Reference | Mean dose (Gy) | Mean dose rate (Gy/h) | Max dose (Gy) | Max dose rate (Gy/h) | Description of study data | Notes | Endpoint [incidence unless otherwise stated] | Number of cases / deaths | ERR / Gy (95% CI) |
|-----------|---------------|----------------------|--------------|---------------------|-----------------------------|-------|---------------------------------|--------------------------|------------------|
|           | 0.01008       | 0.1 (L)              | 0.01008      | 0.1 (L)             | Linear model, stratified by age at exposure, age, sex, city, distance category | Refitted to downloadable data < 0.1 Gy colon dose, age < 20 y at exposure, via Poisson linear model, stratified by age at exposure, age, sex, city, distance category | **Leukaemia mortality** | 6994 | 2.08 (0.49,3.85) |
| **In utero exposure** | | | | | | | |
| (Delongchamp et al. 1997) | 0.01461 | 1 (M) | 0.01461 | 1 (M) | LSS *in utero* mortality with DS86 doses, followed up to age 47 or 1997 | Restricted to maternal uterine dose < 1 Gy, refitted via Poisson linear model stratified by sex, using published data. Upper profile bound uses Self and Liang (Self and Liang 1987) adjustment as MLE is on boundary | **Leukaemia mortality** | 6 | −1.33 (−1.33,87.33) |
| (Preston et al. 2008) | 0.07329 | 1 (M) | 0.07329 | 1 (M) | LSS *in utero* cohort, DS02 doses, followed to 1999 or age 55 | Restricted to maternal uterine dose < 1 Gy, refitted via Poisson linear model stratified by sex, using published data | **Solid cancer mortality** | 60 | 0.25 (−1.24,5.35) |
| (Sugiyama et al. 2021) | 0.07565 | 1 (M) | 0.07565 | 1 (M) | LSS *in utero* mortality with DS02R1 doses, followed up 1950–2012, maternal uterine dose | Refitted to published data maternal uterine dose < 1 Gy via Poisson linear model | **Solid cancer mortality** | 91 | 1.45 (−0.04,3.88) |

**Endpoints**

- **Esophageal cancer mortality** 8 1.21 (−2.23,16.09)
- **Stomach cancer mortality** 26 0.01 (−1.87,4.28)
- **Colon cancer mortality** 10 0.13 (−2.40,7.95)
- **Rectal cancer mortality** 7 1.40 (−2.20,17.12)
- **Liver cancer mortality** 18 −2.10 (−2.76,0.65)
- **Pancreas cancer mortality** 7 1.40 (−2.20,16.78)
- **Lung cancer mortality** 21 −1.40 (−2.58,2.26)
| Reference | Mean dose (Gy) | Max dose (Gy)\(^a\) | Mean dose rate (Gy/h) | Max dose rate (Gy/h) | Description of study data | Notes | Endpoint [incidence unless otherwise stated] | Number of cases / deaths | ERR / Gy (95% CI) |
|-----------|----------------|---------------------|----------------------|---------------------|--------------------------|-------|---------------------------------------------|------------------------|------------------|
|           |                |                     |                      |                     |                          |       | Lymphohaematopoietic mortality             | 8                      | 4.45 (−1.90, 60.14) |
|           |                |                     |                      |                     | Leukaemia mortality      | 5     | − 2.80 (−2.84, 14.22)                  |

CNS, central nervous system.

\(^a\)(L) = maximum dose consistent with low dose, (M) = maximum dose consistent with moderate dose but not with low dose, (H) = maximum dose consistent with high dose but not with moderate or low dose.

\(^b\)(L) = maximum dose rate consistent with low dose rate, (M) = maximum dose rate consistent with moderate dose rate but not with low dose rate, (H) = maximum dose rate consistent with high dose rate but not with moderate or low dose rate.
## Table 5

Risks resulting from postnatal man-made environmental exposure.

| Reference | Mean dose (Gy) | Max dose (Gy) | Mean dose rate (Gy/h) | Max dose rate (Gy/h) | Description of study data | Notes | Number of cases / deaths | ERR / Gy (95% CI) |
|-----------|----------------|--------------|-----------------------|---------------------|---------------------------|-------|--------------------------|-----------------|
| (Stevens et al. 1990) | 0.0032 | 0.026 (L) | NA | NA (L) | Utah fallout and leukaemia case-control study 1952–1981 | Linear binomial odds model fitted to data from paper. Median dose for all cases and controls used as mean | All leukaemia Chronic lymphocytic leukaemia (CLL) Leukaemia excluding CLL | 1177 238 939 | 29.47 (−1.33, 72.21) 48.55 (−16.47, 187.70) 24.54 (−7.88, 71.26) |
| (Parkin et al. 1996) | ~7.8 × 10⁻⁵ | >0.0003 (L) | NA | NA (L) | Ecologic analysis of childhood leukaemia in 23 European countries after Chernobyl nuclear accident 1980–1991 | Inverse-variance weighted linear model fitted to data from paper. Median dose for all cases and controls used as mean | All leukaemia Chronic lymphocytic leukaemia Leukaemia excluding CLL | 1177 238 939 | 184.13 (−718, 1086.35) 187.52 (−662, 1037.14) 187.80 (−693, 1069.51) |
| (Davis et al. 2004) | 0.174 | 2.823 (H) | NA | NA (L) | Hanford cohort study of sampled births 1940–1946 in eastern Washington State, followed to 1997 | Linear model <1 Gy, OR at 1 Gy Log-linear model <1 Gy, OR at 1 Gy | Thyroid cancer Benign thyroid nodules | 19 249 | 0.00 (<−0.001, 0.02) 0.01 (<−0.022, 0.04) |
| (Cardis et al. 2005) | 0.2720 | 1 (M) | 0.000975 | 0.000358 (L) | Belarus & Russia thyroid cancer case-control study, 1992–1998 after 131I exposure from Chernobyl, persons aged <15 y at time of accident | Linear model <1 Gy, OR at 1 Gy | Thyroid cancer | 218 | 6.6 (2.0, 11.1) 8.4 (4.1, 17.3) |
| (Davis et al. 2006) | 0.01174 | 0.18619 (M) | NA | NA (L) | Belarus part of three country (Belarus, Russia and Ukraine) case-control study 1986–2000, children aged <6 y or in utero at time of Chernobyl accident | Mean dose among controls | Leukaemia | 114 | 4.09 (NA, 37.7) |
| Reference | Mean dose (Gy) | Max dose (Gy) | Mean dose rate (Gy/h) | Max dose rate (Gy/h) | Description of study data | Notes | Endpoint [incidence unless otherwise stated] | Number of cases / deaths | ERR / Gy (95% CI) |
|-----------|---------------|--------------|-----------------------|----------------------|--------------------------|-------|------------------------------------------|--------------------------|-----------------|
| (Kopecky et al. 2006) | 0.016 | 2.73 (H) | 0.000057 | 0.009782 | Russian part of three country (Belarus, Russia and Ukraine) case-control study 1986–2000, children aged <6 yr or in utero at time of Chernobyl accident | Mean dose among controls, using log-linear model | Thyroid cancer | 39 | 0.01049 (0.016, 0.0089) |
| (Lyon et al. 2006) | 0.12 | >0.41 (M) | NA | NA | Utah, Nevada, Arizona fallout cohort study 1965–1998 among persons aged 12–18 y in 1965–1966, Phase IIIR analysis | Mean dose in controls, linear part of dose response used for regression coefficient | Thyroid cancer | 8 | 0.8 (0.0,14.9) |
| (Noshchenko et al. 2010) | 0.0365 | 0.3136 (M) | NA | NA | Study cases among children (age 0-5 years at the time of accident) of four most highly Chernobyl-contaminated regions (oblasts) of Ukraine diagnosed 1987–1997 | Mean dose in controls, linear part of dose response used for regression coefficient | Leukaemia | 246 | 1.3 (1.0,1.7) |
| (Akleyev et al. 2016) | 0.0112 | 0.552 (M) | NA | NA | Techa River and Mayak Worker in utero + postnatal cohorts 1950–2009 [postnatal exposure] | Stomach dose used | Solid cancer | 369 | 2 (0, 4) |
| (Schüz et al. 2017) | >0.221 (M) | NA | NA | NA | Techa River & Mayak Worker in utero + postnatal cohort study, 1953–2009 (TR) + 1948–2009 (MW) [postnatal exposure] | Person year weighted mean dose | Solid cancer mortality | 58 | 2 (1, 5) |
| (Ohira et al. 2020) | 0.02549 | 0.058 (L) | NA | NA | Fukushima cohort study 2011–2017, ages 6–14, aged < 18 y at time of Fukushima accident | Inverse-variance weighted linear model refitted to RR data, adjusted for age, sex, examination year, by dose group from paper. | Thyroid cancer | 45 | 9.94 (2.73,22.60) |
| Reference | Mean dose (Gy) | Max dose (Gy) | Mean dose rate (Gy/h) | Max dose rate (Gy/h) | Description of study data | Notes | Endpoint [incidence unless otherwise stated] | Number of cases / deaths | ERR / Gy (95% CI) |
|-----------|---------------|---------------|-----------------------|---------------------|--------------------------|-------|-------------------------------------------|------------------------|----------------|
|           |               | a             |                       |                     |                          |       | Mean dose estimated via midpoint of each dose group weighted by persons |           |               |

CNS, central nervous system.

a (L) = maximum dose consistent with low dose, (M) = maximum dose consistent with moderate dose but not with low dose, (H) = maximum dose consistent with high dose but not with moderate or low dose.

b (L) = maximum dose rate consistent with low dose rate, (M) = maximum dose rate consistent with moderate dose rate but not with low dose rate, (H) = maximum dose rate consistent with high dose rate but not with moderate or low dose rate.
Table 6

Restricted maximum likelihood (REML) and DerSimonian and Laird 1-step random effects model fits to various subsets (as given by Supplementary Table S2). $^a$

| Endpoint | Excess relative risk (ERR) / Gy (95% CI) | $p$-value | Residual heterogeneity $p$-value | $I^2$ (%) |
|----------|------------------------------------------|-----------|-------------------------------|-----------|
| **Analysis using lower dose risk estimates** $^b$ | | | | |
| Postnatal exposure | | | | |
| Leukaemia | 5.20 (−1.13,11.53) | $0.108^c$ | $0.027^c$ | 44.13$^c$ |
| Lymphoma (including CLL) | 1.21 (−11.96,14.38) | 0.857 | 0.899 | 0.00 |
| Brain/CNS | 6.81 (0.58,13.04) | 0.032 | <0.001 | 78.57 |
| Lung | 2.23 (−5.55,10.02) | 0.574 | 0.069 | 69.87 |
| Thyroid (including nodules) | 0.00 (−0.07,0.08) | $0.928^e$ | <0.001$^e$ | 65.64$^e$ |
| All solid except brain/CNS, lung, thyroid | 0.00 (−0.41,0.42) | 0.983 | 0.189 | 0.00 |
| All six endpoints only $^d$ | 0.23 (0.07,0.39) | $0.006^e$ | <0.001$^e$ | 72.61$^e$ |
| All endpoints $^d$ | 0.26 (0.10,0.43) | $0.001^e$ | <0.001$^e$ | 73.90$^e$ |
| In utero exposure | | | | |
| Leukaemia | −2.70 (−11.07,5.67) | 0.527 | 0.966 | 0.00 |
| Lymphoma (including CLL) | 229.10 (−200.94,69.14) | 0.296 | 1.000 | 0.00 |
| Brain/CNS | 70.00 (−229.00,369.00) | 0.646 | 1.000 | 0.00 |
| Lung | −1.40 (−3.82,1.03) | 0.258 | 1.000 | 0.00 |
| Thyroid (including nodules) | 2.55 (0.20,4.90) | 0.033 | 0.937 | 0.00 |
| All solid except brain/CNS, lung, thyroid | −1.09 (−2.75,0.56) | 0.196 | 0.754 | 9.23 |
| All six endpoints only $^d$ | −0.26 (−1.92,1.39) | 0.757 | 0.478 | 29.53 |
| All endpoints $^d$ | 0.96 (−1.12,3.04) | $0.365^e$ | 0.004$^e$ | 58.84$^e$ |

| Analysis using higher dose risk estimates $^e$ | | | | |
| Postnatal exposure | | | | |
| Leukaemia | 5.20 (−1.13,11.53) | $0.108^c$ | $0.027^c$ | 44.13$^c$ |
| Lymphoma (including CLL) | 1.21 (−11.96,14.38) | 0.857 | 0.899 | 0.00 |
| Brain/CNS | 6.87 (1.02,12.72) | 0.021 | <0.001 | 85.15 |
| Endpoint                                      | Excess relative risk (ERR) / Gy (95% CI) | p-value | Residual heterogeneity p-value | $I^2$ (%) |
|-----------------------------------------------|-----------------------------------------|---------|--------------------------------|-----------|
| Lung                                          | 0.41 (−0.23,1.06)                      | 0.209   | 0.483                          | 0.00      |
| Thyroid (including nodules)                   | 0.01 (−0.08,0.09)$^c$                   | 0.874$^c$| < 0.001$^c$                    | 73.37$^c$ |
| All solid except brain/CNS, lung, thyroid     | 0.77 (−0.61,2.14)                      | 0.274   | 0.007                          | 83.57     |
| All six endpoints only$^d$                    | 0.28 (0.12,0.44)$^c$                    | < 0.001$^c$ | < 0.001$^c$                   | 74.85$^c$ |
| All endpoints$^d$                             | 0.41 (0.24,0.58)$^c$                    | < 0.001$^c$ | < 0.001$^c$                   | 80.79$^c$ |
| **In utero exposure**                         |                                         |         |                                |           |
| Leukaemia                                     | − 2.70 (−11.07,5.67)                   | 0.527   | 0.966                          | 0.00      |
| Lymphoma (including CLL)                     | 229.10 (−200.94,659.14)                | 0.296   | 1.000                          | 0.00      |
| Brain/CNS                                     | 70.00 (−229.00,369.00)                 | 0.646   | 1.000                          | 0.00      |
| Lung                                          | −1.40 (−3.82,1.03)                     | 0.258   | 1.000                          | 0.00      |
| Thyroid (including nodules)                   | 1.54 (−0.15,3.22)                      | 0.074   | 0.890                          | 0.00      |
| All solid except brain/CNS, lung, thyroid     | −1.09 (−2.75,0.56)                     | 0.196   | 0.754                          | 9.23      |
| All six endpoints only$^d$                    | −0.38 (−1.87,1.10)                     | 0.613   | 0.550                          | 26.44     |
| All endpoints$^d$                             | 0.70 (−1.17,2.57)$^c$                  | 0.463$^c$| 0.006$^c$                     | 56.70$^c$ |

$^a$ using binomial odds model to refit thyroid nodule data < 0.799 Gy of Hatch et al (Hatch et al. 2019) and leukaemia data of Stevens et al (Stevens et al. 1990), and inverse-variance weighted linear model to refit thyroid cancer data < 0.284 Gy of Kopecky et al (Kopecky et al. 2006).

$^b$ using refitted thyroid nodule data < 0.799 Gy of Hatch et al (Hatch et al. 2019), thyroid cancer data < 0.284 Gy of Kopecky et al (Kopecky et al. 2006), Cardis et al (Cardis et al. 2005) thyroid cancer data using a linear model restricted to < 1 Gy, Lubin et al (Lubin et al. 2017) data restricted to < 0.1 Gy, Preston et al (Preston et al. 2007) brain/CNS and breast cancer data restricted to < 0.1 Gy, Cahoon et al (Cahoon et al. 2017b) lung cancer data restricted to < 0.1 Gy.

$^c$ indications of non-convergence for REML model so that 1-step random effects model of DerSimonian and Laird (DerSimonian and Laird 1986) was employed instead.

$^d$ for “all endpoints” all endpoints were considered, whereas for “all six endpoints” the endpoint considered within a particular study had to lie within one of the six specified endpoints shown.

$^e$ using full range thyroid nodule data of Hatch et al (Hatch et al. 2019), thyroid cancer data of Kopecky et al (Kopecky et al. 2006), Cardis et al (Cardis et al. 2005) thyroid cancer data using a linear model restricted to < 2 Gy, Lubin et al (Lubin et al. 2017) data restricted to < 0.2 Gy, Preston et al (Preston et al. 2007) brain/CNS and breast cancer data restricted to < 1 Gy, Cahoon et al (Cahoon et al. 2017b) lung cancer data restricted to < 1 Gy.
Table 7

Maximum likelihood fits to assess significance of improvement in fit of various explanatory variables (to data as specified by Supplementary Table S2).a

| Endpoint | ERR / Gy (95% CI) (in utero dose) | ERR / Gy (95% CI) (postnatal dose) | p-value (improvement in fit over null = no difference) | Residual heterogeneity p-value | I² |
|----------|----------------------------------|------------------------------------|--------------------------------------------------------|-------------------------------|----|
| Leukaemia | −2.70 (−11.07,5.67) | 1.31 (0.96,1.66) | 0.348 | 0.052 | 0.00 |
| Lymphoma (including CLL) | 229.10 (−200.94,659.14) | 1.21 (−11.96,14.38) | 0.299 | 0.899 | 0.00 |
| Brain/CNS | 70.00 (−229.37,369.37) | 6.65 (0.80,12.49) | 0.678 | <0.001 | 75.53 |
| Lung | −1.40 (−3.82,1.03) | 1.42 (−2.68,5.52) | 0.247 | 0.069 | 0.00 |
| Thyroid (including nodules) | 2.55 (0.50,4.60) | 0.00 (−0.01,0.01) | 0.033 | 0.001 | 0.00 |
| All solid except brain/CNS, lung, thyroid | −1.31 (−2.70,0.07) | 0.00 (−0.41,0.42) | 0.074 | 0.492 | 0.00 |
| Leukaemia | 1.74 (−3.64,7.11) | 1.30 (0.95,1.65) | 0.874 | 0.042 | 0.00 |
| Lymphoma (including CLL) | 14.31 (−21.63,50.25) | −0.57 (−14.73,13.58) | 0.450 | 0.813 | 0.00 |
| Brain/CNS | 6.49 (−6.62,19.60) | 0.01 (0.19,13.23) | 0.977 | <0.001 | 74.26 |
| Lung | 6.57 (−0.32,13.46) | 1.40 (−3.58,0.79) | 0.031 | 0.999 | 0.00 |
| Thyroid (including nodules) | 9.67 (3.79,15.50) | 0.00 (−0.01,0.01) | 0.001 | 0.010 | 0.00 |

a Analysis of in utero vs postnatal exposure

b Lower dose risk estimates

c Higher dose risk estimates

d Analysis of low dose studies vs moderate + high dose studies (using L/M/H coding of maximum dose in column 3 of Tables 1–5)
### Higher dose risk estimates

| Endpoint                          | ERR / Gy (95% CI) (low dose) | ERR / Gy (95% CI) (moderate + high dose) | p-value (improvement in fit over null = no difference) | Residual heterogeneity p-value |
|-----------------------------------|-----------------------------|----------------------------------------|--------------------------------------------------------|-------------------------------|
| Leukaemia                         | 1.74 (−3.64,7.11)           | 1.30 (0.95,1.65)                       | 0.874                                                  | 0.042                         |
| Lymphoma (including CLL)          | 14.31 (−21.63,50.25)        | −0.57 (−14.73,13.58)                   | 0.450                                                  | 0.813                         |
| Brain/CNS                         | 16.63 (−1.55,34.81)         | 5.67 (0.08,11.26)                      | 0.260                                                  | 0.005                         |
| Lung                              | NA                          | NA                                     | NA                                                     | NA                            |
| Thyroid (including nodules)       | 9.94 (−2.73,22.60)          | 0.00 (−0.01,0.01)                      | 0.124                                                  | <0.001                        |
| All solid except brain/CNS, lung, thyroid | −2.39 (−8.25,3.48) | −0.09 (−0.49,0.30) | 0.444                                                  | 0.264                         |

### Lower dose risk estimates

| Endpoint                          | ERR / Gy (95% CI) (low dose rate) | ERR / Gy (95% CI) (moderate + high dose rate) | p-value (improvement in fit over null = no difference) | Residual heterogeneity p-value |
|-----------------------------------|-----------------------------------|-----------------------------------------------|--------------------------------------------------------|-------------------------------|
| Leukaemia                         | 1.30 (0.95,1.65)                 | 1.03 (−3.99,6.06)                            | 0.917                                                  | 0.042                         |
| Lymphoma (including CLL)          | 14.31 (−21.63,50.25)             | −0.57 (−14.73,13.58)                         | 0.450                                                  | 0.813                         |
| Brain/CNS                         | 6.36 (−6.75,19.48)               | 6.74 (0.23,13.25)                            | 0.960                                                  | <0.001                        |
| Lung                              | 6.57 (−0.32,13.46)               | −1.40 (−3.58,0.79)                           | 0.031                                                  | 0.999                         |
| Thyroid (including nodules)       | 0.00 (−0.01,0.01)                | 7.97 (4.06,11.88)                            | <0.001                                                 | 0.057                         |
| All solid except brain/CNS, lung, thyroid | −2.39 (−8.25,3.48) | −0.09 (−0.49,0.30) | 0.444                                                  | 0.264                         |

### Analysis of low dose rate studies vs moderate + high dose rate studies (using L/M/H coding of maximum dose rate in column 5 of Tables 1–5)

| Endpoint                          | ERR / Gy (95% CI) (low dose rate) | ERR / Gy (95% CI) (moderate + high dose rate) | p-value (improvement in fit over null = no difference) | Residual heterogeneity p-value |
|-----------------------------------|-----------------------------------|-----------------------------------------------|--------------------------------------------------------|-------------------------------|
| Leukaemia                         | 1.30 (0.95,1.65)                 | 1.03 (−3.99,6.06)                            | 0.917                                                  | 0.042                         |
| Lymphoma (including CLL)          | 14.31 (−21.63,50.25)             | −0.57 (−14.73,13.58)                         | 0.450                                                  | 0.813                         |
| Brain/CNS                         | 16.63 (−1.55,34.81)              | 5.67 (0.08,11.26)                            | 0.260                                                  | 0.005                         |
| Lung                              | NA                                | NA                                            | NA                                                     | NA                            |
| Thyroid (including nodules)       | 0.00 (−0.01,0.01)                | 3.15 (1.75,4.55)                             | <0.001                                                 | 0.030                         |
| All solid except brain/CNS, lung, thyroid | −2.39 (−8.25,3.48) | −0.09 (−0.49,0.30) | 0.444                                                  | 0.264                         |
using binomial odds model to refit thyroid nodule data < 0.799 Gy of Hatch et al. (Hatch et al. 2019) and leukaemia data of Stevens et al. (Stevens et al. 1990), and inverse-variance weighted linear model to refit thyroid cancer data < 0.284 Gy of Kopecky et al. (Kopecky et al. 2006)

b using refitted thyroid nodule data < 0.799 Gy of Hatch et al. (Hatch et al. 2019), thyroid cancer data < 0.284 Gy of Kopecky et al. (Kopecky et al. 2006), Cardis et al. (Cardis et al. 2005) thyroid cancer data using a linear model restricted to < 1 Gy, Lubin et al. (Lubin et al. 2017) data restricted to < 0.1 Gy, Preston et al. (Preston et al. 2007) brain/CNS and breast cancer data restricted to < 0.1 Gy, Cahoon et al. (Cahoon et al. 2017b) lung cancer data restricted to < 0.1 Gy.

c Indications of non-convergence for maximum likelihood fitted model.

d using full range thyroid nodule data of Hatch et al. (Hatch et al. 2019), thyroid cancer data of Kopecky et al. (Kopecky et al. 2006), Cardis et al. (Cardis et al. 2005) thyroid cancer data using a linear model restricted to < 2 Gy, Lubin et al. (Lubin et al. 2017) data restricted to < 0.2 Gy, Preston et al. (Preston et al. 2007) brain/CNS and breast cancer data restricted to < 1 Gy, Cahoon et al. (Cahoon et al. 2017b) lung cancer data restricted to < 1 Gy.