Cancer risks among studies of medical diagnostic radiation exposure in early life without quantitative estimates of dose

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Abstract

Background: There is accumulating evidence of excess risk of cancer in various populations exposed at acute doses below several tens of mSv or doses received over a protracted period. There is also evidence that relative risks are generally higher after radiation exposures *in utero* or in childhood.

Methods and Findings: We reviewed and summarised evidence from 89 studies of cancer following medical diagnostic exposure *in utero* or in childhood, in which no direct estimates of radiation dose are available. In all of the populations studied exposure was to sparsely ionising radiation (X-rays). Several of the early studies of *in utero* exposure exhibit modest but statistically significant excess risks of several types of childhood cancer. There is a highly significant ($p<0.0005$) negative trend of odds ratio with calendar period of study, so that more recent studies tend to exhibit reduced excess risk. There is no significant inter-study heterogeneity ($p>0.3$). In relation to postnatal exposure there are significant excess risks of leukaemia, brain and solid cancers, with indications of variations in risk by cancer type ($p=0.07$) and type of exposure ($p=0.02$), with fluoroscopy and computed tomography scans associated with the highest excess risk. However, there is highly significant inter-study heterogeneity ($p<0.01$) for all cancer endpoints and all but one type of exposure, although no significant risk trend with calendar period of study.

Conclusions: Overall, this large body of data relating to medical diagnostic radiation exposure *in utero* provides support for an associated excess risk of childhood cancer. However, the pronounced heterogeneity in studies of postnatal diagnostic exposure, the implied uncertainty as to the meaning of summary measures, and the distinct possibilities of bias, substantially reduce the strength of the

evidence from the associations we observe between radiation imaging in childhood and the subsequent risk of cancer being causally related to radiation exposure.

Keywords: radiation; childhood; in utero; cancer risk

1. Introduction

Quantitative estimates of the excess risk per unit dose of various types of cancer are the cornerstone of radiation protection (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), with risk estimates at low doses supported by mechanistic information (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), 2021). From this it might be imagined that little could be learnt from studies which lack quantified dose estimates. However, this would be to over-state the case. One has only to consider, for example, the importance and impact of the British case-control study (which came to be known as the Oxford Survey of Childhood Cancers, OSCC) of childhood cancer mortality and antenatal radiography by Alice Stewart and her colleagues (Bithell et al., 2018; Bithell and Stewart, 1975; Stewart et al., 1956; Stewart et al., 1958). When first published, this study lacked dose information, although risk estimates based on fetal dose estimates have now been made (Bithell, 1993; Bithell and Stiller, 1988; Doll and Wakeford, 1997; Mole, 1990; Muirhead and Kneale, 1989; Wakeford and Little, 2003), and point to an excess relative risk (ERR) per unit fetal dose for childhood cancer of around 50% per 10 mGy, although there remains substantial uncertainty in this risk estimate (Wakeford and Little, 2003). Perhaps surprisingly, it would also appear that the risk associated with exposure *in utero* is proportionally raised to around the same extent for most of the cancers typical of childhood, with the possible exception of bone tumours (Bithell and Stewart, 1975; Wakeford and Bithell, 2021). There are many other studies of medical diagnostic radiation *in utero*, most without quantitative individual estimates of radiation dose, which also point to an associated increased risk of childhood cancer (Wakeford and Bithell, 2021). There is also growing evidence in a number of

exposed groups (Grant et al., 2017; Little et al., 2020; United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), 2013) that radiation exposure in childhood is generally associated with higher cancer risks compared with exposure later in life. However, in contrast to exposure *in utero*, evidence that low-level exposure to radiation in childhood is associated with an increased risk of subsequent cancer has been equivocal (Linet et al., 2012; Rajaraman et al., 2011; Wakeford, 2008), although the recent large studies of cancer following computed tomography (CT) scans at a young age have provided a stronger base of evidence (Gilbert et al., 2020). Again, in contrast to childhood cancers following exposure *in utero*, exposure in childhood is associated with subsequent increases in cancer risk that show a notable variation with cancer type. Although some of these studies have individual estimates of radiation dose (and therefore risk), this is not the case for all (Linet et al., 2012).

In the present paper we review studies of early life medical diagnostic exposures, both antenatal and postnatal, in which quantitative radiation dose estimates are lacking, though general indications of the magnitude of the doses are likely to be implicit. The present study complements a parallel and contemporary review that evaluated studies in which quantitative estimates of radiation risk with respect to doses are available (Little et al., 2022b).

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; United Nations Scientific

Committee on the Effects of Atomic Radiation (UNSCEAR), 2013; United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), 2018) were scanned to assess additional literature, as well as recent review articles (Abalo et al., 2021; Han and Kim, 2018; Kendall et al., 2021; Linet et al., 2009; Linet et al., 2012; Memon et al., 2019; Wakeford and Bithell, 2021). We restricted attention to those studies of persons exposed *in utero* or postnatally at age 20 years or less to medical diagnostic radiographic procedures. There was no restriction on language or date of publication. Editorials, abstracts and reviews were excluded, except to identify potential additional studies.

A total of 3117 papers were returned. A PECO statement is given in Supplementary Table S3. The titles and abstracts of these papers were independently double scanned by MPL and GMK, and case reports, review papers and other clearly inapplicable results (e.g., relating to populations not exposed in childhood) were eliminated. Consistency was established via consensus. Additionally, recent UNSCEAR reports (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), 2008; United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), 2013; United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), 2018) were scanned to assess additional literature, as well as recent review articles (Abalo et al., 2021; Han and Kim, 2018; Kendall et al., 2021; Linet et al., 2009; Linet et al., 2012; Memon et al., 2019; Wakeford and Bithell, 2021). A total of 299 papers that were deemed applicable based on the title/abstract search, and the associated full publications were then obtained for more detailed review of these by MPL and GMK. Of the 299 consensus samples we restricted attention to those studies of persons exposed *in utero* or in childhood (age 20 years or less) to medical diagnostic radiographic procedures and in which quantitative estimates of radiation doses were not available. Again, consistency between the reviewers was established

via consensus; all studies that had been superseded by others were eliminated. This yielded a total of 89 papers, 29 of which were derived from the PubMed search.

2.2 Meta-analysis

Meta-analysis was conducted of odds ratios (OR) or relative risks (RR), combining these equivalent measures. Wherever possible the maximally adjusted OR or RR were taken directly from the relevant publication; further details of the risk estimates for each study are given in Tables 1-2 and Supplementary Tables S1-S2. Further details of data exclusions and of how the data abstraction was performed for particular studies are given in the Supplementary Methods. The type of radiological procedure used within each study of postnatal exposure was classified as catheterisation, fluoroscopy, CT scan, X-ray, mixed or unknown; associated codes (C, F, CT, X, M, U, respectively) were given for each endpoint within studies in Table 2. For the purposes of the meta-analysis, to avoid double counting of cases, we concentrated on results in relation to procedures likely to result in the largest radiation dose, specifically catheterisation, fluoroscopy or CT scan.

An aggregate estimate of meta OR (mOR) or meta RR (mRR) was computed across subsets of these studies (with non-overlapping endpoints within each study if more than one was available) using log-transformed risk estimates, random effects models and standard statistical methods (inverse variance weighted least squares) (see Supplementary Methods). Restricted maximum-likelihood fits were used by default to derive estimates of variation of risk over time; ordinary maximum likelihood fits were also used, as these facilitate comparison of nested models (in particular, to test against improvement over the null, i.e., lack of homogeneity of risk, where homogeneity of risk across categories is the assumed null hypothesis. Confidence intervals on mOR/mRR were derived using the method of Knapp and Hartung (Knapp and Hartung, 2003).

The analysis was done in two ways. In the first, only those cancer sites within each study that contributed to one of the four endpoints (a) leukaemia, (b) lymphoma, (c) brain/central nervous system (CNS) tumours and (d) any other cancer (i.e., all solid cancers except brain/CNS tumours) were used; leukaemia, brain/CNS tumours and lymphoma are the commonest forms of cancer in childhood. In the second type of analysis, as far as possible the endpoint used was "any available cancer site" from each study.

In order to assess selection or publication bias, funnel plots were employed. Funnel plots are scatterplots of the central estimate of OR or RR against estimates of standard error, and as discussed by Egger *et al* (Egger et al., 1997; Sterne and Egger, 2001) are useful qualitative means of detecting various types of selection bias, in particular publication bias. If the funnel plot has the form of an inverted symmetric funnel, then selection bias is considered to be unlikely (Egger et al., 1997; Sterne and Egger, 2001). More formal tests of selection or publication bias were also conducted using the test statistic suggested by Egger *et al* (Egger et al., 1997). We also employed the trim-and-fill method of Duval and Tweedie (Duval and Tweedie, 2000) to assess the likely magnitude of the change in OR/RR that may result from selection bias.

All statistical models, including funnel plots, were fitted using the metafor package (Viechtbauer, 2010; Viechtbauer, 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 literature review yielded 89 papers on cancer incidence/mortality following medical diagnostic radiation exposure antenatally or postnatally, principally of those diagnosed or dying while aged less than 21 years, in which quantitative dose estimates were not given. The papers

were divided by whether they dealt with results of *in utero* exposure (70 papers) (Table 1, Figure 1) or were in relation to postnatal exposure (41 papers) (Table 2, Figure 2). There were 22 papers that contributed both to Tables 1 and 2. Overall, 29 of the 89 papers were derived from the PubMed database search. While for most of the studies in Table 1 follow-up is restricted to cancer incidence or death while ≤ 20 years of age, for eight studies this is not the case, specifically those of Gunz and Atkinson (Gunz and Atkinson, 1964), Preston-Martin *et al* (Preston-Martin et al., 1982), Operskalski *et al* (Operskalski et al., 1987), Bunin *et al* (Bunin et al., 1989), Gardner *et al* (Gardner et al., 1990), Holly *et al* (Holly et al., 1992), Winn *et al* (Winn et al., 1992) and Roman *et al* (Roman et al., 1997); only for Holly *et al* (Holly et al., 1992) and Roman *et al* (Roman et al., 1997) does the upper age limit exceed 25 years (at 31 and 29 years, respectively). Likewise four of the studies listed in Table 2, those of Preston-Martin *et al* (Preston-Martin et al., 1980) (age at diagnosis 18-64 years), McLaughlin *et al* (McLaughlin et al., 1993) (age at diagnosis/death 0->30 years), Modan *et al* (Modan et al., 2000) (age at diagnosis 15-49 years) and Hong *et al* (Hong et al., 2019) (age at diagnosis <30 years) relate to cancer occurring both in childhood and beyond. For all other studies in Table 2 exposure and follow-up both occurred at age ≤ 20 years.

3.1 Risks of in utero exposure

Table 1 presents the data and risk estimates for malignant disease endpoints in a large number of studies of *in utero* exposure for medical diagnostic purposes; these are predominantly case-control studies, although there are two cohort studies of antenatal exposure (Diamond et al., 1973; Ray et al., 2010) (Table 1). The tendency for risks to be raised is apparent for the four cancer endpoints displayed in Figure 1 (any cancer, leukaemia, brain/CNS tumours, lymphoma), particularly for the earlier studies, and the large studies of Bithell and Stewart (Bithell and Stewart, 1975) and Monson

and MacMahon (Monson and MacMahon, 1984) are notable in this respect; risks tend to reduce in the later studies.

3.2 Risks of radiation exposure in childhood

Table 2 presents the data and risk estimates for malignant disease endpoints in studies of postnatal exposure for medical diagnostic purposes. Again, the tendency for risks to be raised is apparent in Figure 2 showing risks from the studies for the three main cancer endpoints (leukaemia, brain/CNS tumours, lymphoma), and raised risks are more evident in earlier studies. Among the more striking of the reported risks are those for leukaemia in the study of patients exposed to diagnostic X-rays and fluoroscopy by Polhemus *et al* (Polhemus and Koch, 1959), for brain tumours and dental X-rays in the studies of Preston-Martin *et al* (Preston-Martin et al., 1980; Preston-Martin et al., 1982) for brain tumours and skull X-rays in the Canadian study of Howe *et al* (Howe et al., 1989), non-Hodgkin lymphoma (NHL) in the Israel cardiac catheterisation study of Modan *et al* (Modan et al., 2000), and in relation to various cancer endpoints and CT scans in the studies of Hong *et al* (Hong et al., 2019) and Li *et al* (Li et al., 2020).

It is notable that a large majority of the studies in Table 2 are from the period before 2010. The relative rarity of more recent studies without quantitative dose information is probably due to the greater availability of dose estimates with more modern radiography, particularly CT scans (Little et al., 2022b).

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

3.3.1 Exposure in utero

Significantly raised OR/RR estimates for *in utero* exposure are obtained from the meta-analysis for all four separate cancer endpoints and for any available cancer type (Table 3). There was little

indication (p>0.3) of differences in mOR/mRR between different cancer endpoints, although there was perhaps a suggestion that the risk was somewhat lower (but still significantly greater than zero) for brain/CNS tumours (Table 3). There is a highly significant (p<0.0001) decreasing trend of OR/RR from studies of *in utero* exposure with calendar year (mid-point of the study period), by about 0.84% per year (Table 3, Figure 3). Little difference was made in central estimates or in width of CI by fitting using the 1-step method of DerSimonian and Laird (DerSimonian and Laird, 1986), restricted maximum likelihood (REML) or maximum likelihood random effects (results not shown). When analysis was done using, as far as possible, all cancers analysed together for each study rather than the four-endpoint analysis a slightly weaker temporal trend was found, of about 0.78% per year, although still highly significant (p=0.0002) (Table 3). The analyses do not suggest that notable heterogeneity is present, as indicated by the Q statistic (p>0.3), and values of the I^2 statistic are generally small (mostly < 15% and all <25%) (Table 3).

3.3.2 Postnatal exposure

The meta-analysis found statistically significant excess risks for leukaemia, brain/CNS tumours and the group of solid cancers other than brain/CNS tumours, but not for lymphoma; the excess risk was most pronounced for solid cancers other than brain/CNS tumours (Table 5). There were marginally significant variations in risk by the four cancer endpoints (Table 5, p=0.0663). As Table 2 shows, there are a variety of types of postnatal exposure included in studies, ranging from chest and dental X-rays to CT scans, and also in the cancer endpoints studied. The meta-analysis confirms that these types of exposure are associated with somewhat different risks (Table 5), although the precise level of statistical significance varies depending on whether analysis uses either four specific cancer endpoints (p=0.0242) or any cancer endpoint per study (p=0.0570). Risks tend to be higher for fluoroscopy (although based on a single study from 1959) and CT scans

(five studies from 2010 or later), although the four-endpoint analysis of catheterisation (four studies) also indicates a high risk. There are no significant trends with calendar year (p>0.5), whichever type of analysis is performed (Table 5, Figure 4). Of note is that all analyses by cancer endpoint in the four-endpoint analysis yield highly significant heterogeneity, as indicated by the Q statistic (p<0.0005), and values of the I^2 statistic are also uniformly high (>50%). For all types of exposure apart from fluoroscopy (for which there was only a single study) the heterogeneity was also highly significant (p<0.01) (Table 3). Analysis in which exposures due to CT scans, catheterisation or fluoroscopy were omitted yielded lower estimates of risks for all endpoints, so that only those for all cancers and leukaemia remained (marginally) statistically significant, with mOR/mRR = 1.21 (95% CI 1.04, 1.42) and mOR/mRR = 1.19 (95% CI 1.01, 1.39), respectively (results not shown), versus mOR/mRR = 1.37 (95% CI 1.23, 1.53) and mOR/mRR = 1.25 (95% CI 1.07, 1.46), respectively (Table 5), for the main analysis; the reduction was particularly pronounced in the risk for lymphoma, with a mOR/mRR = 1.10 (95% CI 0.26, 4.67) (results not shown) versus mOR/mRR = 1.30 (95% CI 0.66, 2.59) for the main analysis (Table 5).

3.3.3 Possible selection bias

The general symmetry of the funnel plots does not suggest any marked selection bias in relation to the *in utero* exposure studies (Figure 5), except, perhaps, for a few of the studies with largest standard error. However, the formal analysis of selection bias in Table 4 suggests that there are some indications of selection bias for these studies (p=0.0064), although only when analysed using the four cancer endpoints; when combining any cancer estimates per study there was little evidence of selection bias (p=0.1802). In any case, the analyses of Table 4 also demonstrate 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 estimate of mOR/mRR.

There are at best weak suggestions of asymmetry in the funnel plot in relation to postnatal exposure (Figure 6), and this is confirmed by the Egger test, whether performed on the pooled four cancer endpoint data (p=0.3991) or using any cancer endpoint (p=0.5095); adjusting for selection bias using the trim-and-fill method of Duval and Tweedie (Duval and Tweedie, 2000) does not lead to marked changes in the central estimates of mOR/mRR.

4. Discussion

Our review has highlighted that both in relation to *in utero* exposure and postnatal exposure to medical diagnostic radiation there are multiple studies that yield statistically significant excess cancer risks. For *in utero* exposure, modest but significant excess risks tend to be concentrated in the earlier studies (Table 1) while for postnatal exposure, significant excess risks are also apparent in later studies, in particular in recent CT scan studies (Table 2).

The meta-analysis of the *in utero* exposure data (Table 3) does not suggest that there are significant differences in mOR/mRR between the four cancer endpoints considered (p>0.3), although there is a highly significant decreasing trend (p<0.0005) with calendar year. This may well be due to a progressive decrease in fetal dose per X-ray examination (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), 1972), reflecting advances in radiographic technology, and possibly also to the influence on medical practice of the early studies of Stewart *et al* (Stewart et al., 1956; Stewart et al., 1958). That the risks of childhood cancer associated with an antenatal X-ray examination are elevated to approximately the same extent for all the common types of cancer in childhood (with the possible exception of bone tumours) was reported in the mid-1970s by Bithell and Stewart (Bithell and Stewart, 1975) using data from the OSCC. This finding has provoked comment, such as that by Boice and Miller (Boice

and Miller, 1999), who noted that this was “perplexing” and not the pattern of radiation-related cancer risks seen after postnatal exposure, and they suggested that this finding pointed away from a causal interpretation of the association. Nonetheless, recently Wakeford and Bithell (2021) reported that the results of all studies of antenatal radiography and childhood cancer other than the OSCC when appropriately combined in a meta-analysis produced a broadly similar pattern of raised relative risks as originally found by Bithell and Stewart (Bithell and Stewart, 1975), so the similarly increased risks for the typical cancers of childhood is not confined to the OSCC.

In contrast to the antenatal studies, a troubling feature of the meta-analysis of postnatal exposure is that for the four cancer outcomes analysed, highly significant heterogeneity ($p<0.0005$) was found, and the high values (generally >50%) of the I^2 statistic imply that a material proportion of the variance is due to inter-study heterogeneity (Table 5). This makes interpretation of summary measures of risk especially problematic. Again, in contrast to the *in utero* data, there are no significant trends by calendar year (Table 5, Figure 4). Previous narrative reviews (e.g., Linet *et al* (Linet et al., 2012)) have concluded that studies of postnatal radiography and childhood cancer have produced ambivalent results, but these reviews have not included more recent studies including those of CT scans. The substantial heterogeneity of the risk estimates from the postnatal studies found here poses considerable difficulties to a reliable interpretation of the meta-analysis results – whether these results are indicative of underlying raised risks for the cancer endpoints is questionable under these circumstances.

This paper focuses exclusively on studies of persons receiving medical diagnostic exposures for which there are no individual estimates of radiation dose, and therefore of dose-related risk. In this respect it contrasts with the paper of Little *et al* (Little et al., 2022b) which included only those studies which had radiation dose estimates. Clearly, the latter analysis is more informative about

the magnitude of risks in relation to the level of radiation exposure, but the large number of studies where quantified dose information is not available are still informative about the presence of radiation-related risk, if not its magnitude. We judge that the studies of *in utero* exposure are likely to be particularly informative in this respect because of the degree of homogeneity of the findings. However, owing to significant inter-study heterogeneity, the studies of postnatal exposure are more difficult to interpret. It is possible that some of the observed heterogeneity may result from disparities in the levels of radiation exposure in these postnatal studies. This is not implausible, as radiation doses from CT scans are likely to be considerably larger, by at least an order of magnitude, than those from many diagnostic X-ray procedures, in particular from dental X-rays (National Council on Radiation Protection and Measurements (NCRP), 2019). It is possible that other factors, such as the variety of populations under study and the types of exposure could contribute, and also methodological factors such as whether a cohort or case-control study; however, a case-control study nested within a cohort would be expected to yield the same relative risk as that in the underlying cohort (Breslow and Day, 1980), so this latter factor probably does not play a large role. There are indications that type of exposure accounts for borderline significant (p=0.02-0.06) variation in risk (Table 5), and it is therefore conceivable that uncontrolled variation in this factor could account for some of the inter-study heterogeneity.

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 the OSCC (Bithell and Stewart, 1975; Stewart et al., 1956) and Monson and MacMahon (Monson and MacMahon, 1984), and many others (Wakeford, 2008; Wakeford and Bithell, 2021) (see Table 1, Figure 1), provides persuasive epidemiological evidence that exposure *in utero* to external sources of penetrating radiation increases the risk of cancer in childhood. By definition, the exact level of

dose incurred is not known for the studies considered here, but analogy with other studies (Little et al., 2022b) suggests that they would have been from several mGy to a few tens of mGy, values that are consistent with estimates of fetal doses made by UNSCEAR (United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), 1972). This level of dose is much lower (by around an order of magnitude) than the lowest doses producing significantly increased risks of cancer in all other epidemiological studies except studies of natural background radiation (Little et al., 2022b; United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR), 2008), and indicates that cancer may be caused by low levels of exposure to radiation; it may be, however, that exposure *in utero* produces a higher risk per unit dose than postnatal exposure and that different types of cancer are affected (Doll and Wakeford, 1997).

Case-control studies have often been used in a medical setting, and can be subject to a number of biases, in particular selection, participation and recall biases. This can make them a poor choice for studies of medical exposure, but with care, large case-control studies have produced results without appreciable bias because they are entirely record-based (MacMahon, 1962). The interpretation of the associations found in studies of *in utero* exposure has long been controversial, see for example, the critical review of Boice and Miller (Boice and Miller, 1999). Some have concluded that the association is likely to have a causal explanation (Doll and Wakeford, 1997), although certain objections to this interpretation continue to prevent universal acceptance (International Commission on Radiological Protection (ICRP), 2003; National Council on Radiation Protection and Measurements (NCRP), 2013). Nonetheless, the concerns over a cause-and-effect interpretation have weakened in recent years (Armstrong et al., 2012; Wakeford and Bithell, 2021; Wakeford and Little, 2003) making this explanation more likely.

A potential problem in the analysis of the studies considered here is that there may have been an element of publication (sometimes called reporting) bias. By this we mean that studies (in particular small and underpowered studies) finding an apparent effect of radiation exposure were more likely to be published than similar studies that found no association, a bias that might affect smaller studies preferentially; large studies are more likely to be published whether positive or not (Hauptmann et al., 2020). There are indications of selection bias in the *in utero* exposure data, although only for the four cancer endpoint analysis (p=0.006); there is no significant indication of such bias when all cancers are analysed together (p>0.1) (Table 4), and nor is any bias suggested by the funnel plot (Figure 5). In any case, adjustment for such bias does not generally change the mOR/mRR estimate (Table 4). Examination of the funnel plot (Figure 6) for the studies of postnatal exposure, as well as more formal tests of selection bias (Table 6), do not suggest any such bias. It is *a priori* more plausible that selection bias may preferentially affect older studies, particularly in the period before 1970. One disconcerting aspect of our analysis is the small proportion, ~33% (29/89), of papers that were ascertained in our PubMed search. Part of the reason for this is undoubtedly that the older papers tend not to be indexed in PubMed; the percentage of papers covered by the PubMed search was markedly lower among papers published before 1970, 10% (1/10), increasing to 28% (7/25) for papers published in 1970-1989 and to ~39% (21/54) among papers published in 1990 or later.

The presence of bias resulting from confounding by indication, in other words the possibility that conditions predisposing to cancer also lead to an increase in prevalence of radiation imaging, must always be considered in studies of medical diagnostic exposure. This is particularly so in relation to the finding of large excess risk associated with catheterisation in the four-cancer endpoint analysis (Table 5). It is known that many chromosomal congenital abnormalities are

associated with heart defects and increased risk of cancer (Johnson et al., 1997; Ko, 2015; Lupo et al., 2019), and catheterisation is commonly used as part of the diagnosis and treatment of cardiac anomalies (Kumar et al., 2014b). Further, in their cohort study of cardiac catheterisations, the striking findings of Harbron *et al* (Harbron et al., 2018) for a markedly raised risk of lymphoma (in particular, NHL) in relation to organ transplantation and associated radiation exposure demonstrate the importance of confounding as a potential explanation for radiation exposures in a medical context because the excess of lymphoma disappeared completely when the transplant patients were excluded from the study, and the raised risk was very likely to be attributable to the immunosuppressive drugs used after transplantation.

There have been a variety of studies evaluating risks of cancer after a childhood CT scan, some indicating 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). However, the interpretation of these findings is not straightforward (Boice, 2015; Walsh et al., 2014). Reverse causation, that is the possibility 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, is a source of concern in these studies, and as noted above, confounding by indication is also a source of potential bias (Boice, 2015; Walsh et al., 2014). Both issues are usually dealt with in the analysis by employing lag and exclusion periods, and a simulation study suggests that this should be enough to eliminate bias from this cause (Little et al., 2022a). However, for solid cancers it is common to use larger values of lag and exclusion than the period of two years used in the studies of Tettamanti *et al* (Tettamanti et al., 2017), Hong *et al* (Hong et al., 2019) and Li *et al* (Li et al., 2020), or the period of 6 months employed in the studies of Bailey *et al* (Bailey et al., 2010) and Milne *et al* (Milne et al., 2014), that are considered here.

Tettamanti *et al* (Tettamanti et al., 2017) and Hong *et al* (Hong et al., 2019) employed a variety of different lags between 1 year and 5 years in analysis of all cancers, and both studies observed a modest diminution in RR when longer lag periods were used. Milne *et al* (Milne et al., 2014) also evaluated lag periods between 6 months and 5 years in relation to all radiological procedures, but little difference in brain tumour risk was observed. Reverse causation and confounding by indication are general problems in studies of diagnostic radiation exposure; only a few of the studies of other types of postnatal exposure assembled here deal with this by use of lag periods (Ager et al., 1965; Baaken et al., 2019; Bartley et al., 2010; Graham et al., 1966; Howe et al., 1989; Meinert et al., 1999; Preston-Martin et al., 1982; Rajaraman et al., 2011; Schuz et al., 2001; Shu et al., 2002), even to the limited extent that is attempted by Tettamanti *et al* (Tettamanti et al., 2017), Hong *et al* (Hong et al., 2019), Li *et al* (Li et al., 2020), Bailey *et al* (Bailey et al., 2010) and Milne *et al* (Milne et al., 2014) (see Table 2). Hence, one cannot discount the possibility that the relatively modest increases we have seen for postnatal exposures may largely result from such biases, and in this respect it is of interest that in the CT scan study of Hong *et al* (Hong et al., 2019), of the many different types of cancer investigated, the RR (with a lag of 2 years) was <1.0 only for lymphoid leukaemia while the RR estimates were >1.0 for all other types of cancer, some significantly so (e.g., digestive and respiratory cancers and NHL) and others not.

The meta-analysis for antenatal radiography reported here differs somewhat from that conducted by Wakeford and Bithell (Wakeford and Bithell, 2021), the principal objective of which was to compare the results of the OSCC studies for different childhood cancers with those produced by all other case-control/case-cohort studies appropriately combined in a meta-analysis. However, the broad compatibility of these findings of the two sets of studies (Wakeford and Bithell, 2021) invites the pooling of the results of all studies, including the OSCC, that has been

conducted here. We have confined attention to four main cancer endpoint groups (leukaemia, lymphoma, brain/CNS tumours, other solid cancers), which *inter alia* were also employed by Wakeford and Bithell (Wakeford and Bithell, 2021), but we also considered the composite of any type of cancer, which was not examined by Wakeford and Bithell (Wakeford and Bithell, 2021). Wakeford and Bithell (Wakeford and Bithell, 2021) also conducted a separate analysis of the (admittedly few) cohort studies, whereas in the present paper both types of study were analysed together.

There are other methodological differences, specifically the use by Wakeford and Bithell (Wakeford and Bithell, 2021) of unadjusted OR estimates derived from the exposed and unexposed totals of cases and controls in each study, as opposed to our use, wherever possible, of OR (wherever possible the maximally adjusted ones) as given in the various publications. In those cases where an OR or CI were not given in a study we employed a hypergeometric model to derive an estimate of the OR, fitted by maximum likelihood, with Fisher exact CI (see footnotes to Table 1), rather than the crude OR and asymptotic CI (Breslow and Day, 1980) employed by Wakeford and Bithell (Wakeford and Bithell, 2021) for all their individual estimates. It is to be expected that the crude OR and asymptotic CI will be nearly the same as the hypergeometric maximum likelihood estimates (and exact CI) when numbers of cases and controls are large in all four parts of the associated 2 x 2 table ([case, controls] x [exposed, unexposed]), but this will not be the case when numbers are small (< 10) in any component cell, as is the case for a few studies in our analysis (Table 1); however, these small studies would not be expected to be of much consequence in the meta-analysis. Table 7 compares results of the meta-analysis of Wakeford and Bithell (Wakeford and Bithell, 2021) with those of the present paper taken from Table 3. The Mantel-Haenszel random-effects meta-analysis of Wakeford and Bithell (Wakeford and Bithell, 2021)

yields a mOR for all cancers for the OSCC of 1.39 (95% CI 1.30, 1.49), and for all other antenatal case-control and cohort studies of 1.30 (95% CI 1.18, 1.43), both of which are comparable with both the maximum likelihood and REML mOR from our own analysis (Table 3, Table 7) of 1.33 (95% CI 1.26, 1.40) and 1.32 (95% CI 1.25, 1.40), respectively. Wakeford and Bithell (Wakeford and Bithell, 2021) do not incorporate the results of antenatal cohort studies in their meta-analysis, and the cohort studies were considered separately from the case-control studies, but as these are mostly small (Table 1) they would be expected to have little weight in the analysis.

Inevitably, meta-analysis using the results reported in published papers (as opposed to pooled analysis using individual data from each study) presents problems in that, for example, different approaches to adjustments have been employed to obtain ORs or the actual numbers of cases and controls used in deriving ORs are not presented. This leads to difficulties in interpreting results, particularly when significant heterogeneity between studies is present (see, for example, (Blettner et al., 2014; Blettner et al., 1999)). However, the consistency of the findings for studies of antenatal radiography and childhood cancer found using the approach of Bithell and Wakeford (Wakeford and Bithell, 2021) and that of the present study encourages confidence in the reliability of the results of the meta-analysis of *in utero* exposure studies reported here.

As well as the medical diagnostic exposure studies without assessed doses, there is information in a large number of studies of various exposed groups in which individual dose estimates are available, which are reviewed elsewhere (Little et al., 2022b) with the conclusion that they offer support for low doses (<0.1 Gy) received in early life increasing the subsequent risk of cancer.

5. Conclusions

We have considered the relationship between low-level exposure to radiation *in utero* and in childhood and the consequent risk of cancer, principally at a young age, in medical diagnostic studies which did not include estimates of radiation dose. A large body of data relates to children exposed *in utero*, which suggests a radiation-related cancer risk that has attenuated over time, most likely due to reductions in the doses received from antenatal radiography. Taken together with findings of studies based upon quantitative dose data in a parallel review of radiation risk (Little et al., 2022b) this strengthens the evidence for a carcinogenic effect of low doses of radiation with respect to exposure *in utero*. However, the pronounced heterogeneity of findings from studies of medical diagnostic exposure after birth, and the real possibilities of bias due to reverse causation or confounding by indication, substantially reduces the strength of a causal interpretation of the association we have found between postnatal radiation exposure and the subsequent risk of cancer.

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Table 1. Summary of case-control and cohort studies of childhood cancer and *in utero* exposure to medical diagnostic radiation that do not incorporate estimates of dose, with estimates of odds ratio (OR) or relative risk (RR)

Case-control studies						
Reference	Type of X-ray exposure, other features[a]	Description of study data	Study years	Cancer endpoint[b]	Number of cases exposed / total[c]	Odds Ratio, (95% CI)
(Kjeldsberg, 1957)	Fetal X-ray vs no X-ray	Oslo cohort, based on single hospital	1946-1956	Leukaemia	5 / 55	0.56 (0.14, 2.22)[d]
	Abdomen X-ray vs no abdomen X-ray				5 / 55	0.69 (0.16, 2.72)[d]
	Abdomen X-ray vs no X-ray				5 / 55	0.67 (0.16, 2.66)[d]
(Kaplan, 1958)	Sibling control, maternal abdominal X-rays vs no abdominal	California mortality cohort	1955-1956	Acute leukaemia mortality	40 / 150	1.91 (1.05, 3.53)[d]
	Playmate control, maternal abdominal X-rays vs no abdominal				34 / 125	1.35 (0.73, 2.53)[d]
	Sibling control, maternal abdominal X-rays vs no X-ray				40 / 128	2.08 (1.13, 3.90)[d]
	Playmate control, maternal abdominal X-rays vs no X-ray				34 / 106	1.29 (0.68, 2.47)[d]
(Ford et al., 1959)	Abdominal or pelvic X-rays vs unexposed, medical-record based	Louisiana mortality cohort	1951-1955	All malignant tumour mortality	42 / 152	1.77 (1.08, 2.87)[d]
				Leukaemia mortality	21 / 78	1.70 (0.90, 3.14)[d]
				Brain/CNS mortality	6 / 16	2.77 (0.79, 8.83)[d]
				Kidney mortality	4 / 14	1.85 (0.41, 6.71)[d]
				Neuroblastoma mortality	2 / 11	1.03 (0.11, 5.17)[d]
				Lymphoma mortality	4 / 14	1.85 (0.41, 6.71)[d]
				All solid tumour excluding brain/CNS mortality	11 / 44	1.54 (0.66, 3.37)[d]
(Murray et al., 1959)	Pelvimetry vs no pelvimetry, medical record based	Mortality cohort among patients in Monroe County, New York	1930-1956	Leukaemia mortality	3 / 65	1.24 (0.21, 5.17)[d]
	Other abdominal X-ray vs no other abdominal X-ray, medical record based				0 / 65	0.00 (0.00, 8.99)[d]
	Pelvimetry + other abdominal X-ray vs no pelvimetry or other abdominal X-ray, medical record based				3 / 65	0.92 (0.16, 3.56)[d]
(Polhemus and Koch, 1959)	Pelvimetry vs no pelvimetry	Cohort based on Children's Hospital of Los Angeles	1950-1957	Leukaemia	66 / 251	1.19 (0.77, 1.82)[d]
	Pelvimetry vs no exposure, excluding non-obstetric X-rays and maternal occupational radiation				66 / 245	1.23 (0.80, 1.88)[d]
(Wells and Steer, 1961)	X-ray pelvimetry vs unexposed (excluding dental), medical-record based	Columbia Presbyterian Medical Center, New York	<1961	Leukaemia	4 / 62	1.31 (0.27, 5.38)[d]
	X-ray pelvimetry + other abdominal vs unexposed (excluding dental), medical-record based				4 / 62	0.83 (0.19, 2.97)[d]
	X-ray pelvimetry vs unexposed (including dental), medical-record based				4 / 67	1.22 (0.25, 5.02)[d]
	X-ray pelvimetry + other abdominal vs unexposed (including dental), medical-record based				4 / 67	0.78 (0.17, 2.77)[d]
	Abdominal X-ray vs unexposed	New Zealand national cohort	1958-1961	Leukaemia	14 / 92	1.11 (0.43, 2.90)[d]

(Gunz and Atkinson, 1964)	Any X-ray vs unexposed				14 / 102	1.00 (0.48, 2.06)[d]
(Ager et al., 1965)	Sibling controls, abdominal + pelvic X-ray vs not	Minnesota childhood leukaemia study, mortality	1953-1957	Leukaemia mortality	20 / 107	1.21 (0.55, 2.67)[d]
	Neighbourhood controls, abdominal + pelvic X-ray vs not				20 / 107	1.35 (0.62, 2.98)[d]
	Sibling + neighbourhood controls, abdominal + pelvic X-ray vs not				20 / 107	1.28 (0.65, 2.46)[d]
	Sibling controls, abdominal + pelvic X-ray vs no X-ray				20 / 94	1.21 (0.55, 2.72)[d]
	Neighbourhood controls, abdominal + pelvic X-ray vs no X-ray				20 / 94	1.32 (0.60, 2.94)[d]
	Sibling + neighbourhood controls, abdominal + pelvic X-ray vs no X-ray				20 / 94	1.27 (0.64, 2.46)[d]
(Graham et al., 1966)	Intrauterine abdominal radiation exposure vs no abdominal radiation exposure, medical-record based	USA Tri-state Study	1959-1962	Leukaemia	27 / 313	1.40 (0.83, 2.31)[d]
	Intrauterine abdominal radiation exposure vs no X-ray exposure, medical-record based				27 / 244	1.54 (0.91, 2.56)[d]
(Stewart, 1973)	Maternal X-ray, cancer mortality	Oxford Survey of Childhood Cancer Twin Study, deaths within 10 years of birth	1943-1967	Leukaemia mortality	51 / 70	1.40 (0.84, 2.44)[e]
				All tumour excluding leukaemia mortality	60 / 91	1.05 (0.69, 1.64)[e]
				All cancer mortality	111 / 161	1.18 (0.85, 1.66)[e]
(Bithell and Stewart, 1975)	Maternal X-ray, cancer mortality	Oxford Survey of Childhood Cancer	1953-1967	Lymphatic leukaemia mortality	290 / 2007	1.54 (1.34, 1.78)
				Myeloid leukaemia mortality	120 / 866	1.47 (1.20, 1.81)
				Other/unspecified leukaemia mortality	159 / 1179	1.43 (1.19, 1.71)
				All leukaemia	569 / 4052	1.47 (1.28, 1.69)[d]
				Lymphoma mortality	92 / 719	1.35 (1.07, 1.69)
				All lymphatic/haemopoietic mortality	661 / 4771	1.47 (1.32, 1.64)
				Wilms' tumour	87 / 590	1.59 (1.25, 2.01)
				CNS mortality	179 / 1332	1.42 (1.20, 1.69)
				Neuroblastoma mortality	99 / 720	1.46 (1.17, 1.83)
				Bone tumour mortality	26 / 244	1.11 (0.74, 1.66)
				Other solid tumour (excluding Wilms' tumour, CNS, neuroblastoma, bone tumour) mortality	129 / 856	1.63 (1.33, 1.98)
				All solid tumour mortality	520 / 3742	1.47 (1.31, 1.66)
				All malignant tumour mortality	1181 / 8513	1.47 (1.34, 1.62)
(Salonen, 1976)	Pelvic radiography, medical-record based	Finnish national cancer registry	1959-1968	Leukaemia	15 / 300	1.10 (0.55, 2.10)[d]
				Brain	11 / 186	1.31 (0.59, 2.70)[d]

				Other tumour (excluding leukaemia, brain)	15 / 278	1.19 (0.59, 2.27)[d]
				All tumour	41 / 764	1.18 (0.72, 1.93)[d]
				All tumour excluding leukaemia	26 / 464	1.24 (0.70, 2.15)[d]
(Shiono et al., 1980)	"High" or "medium" doses of X-rays (barium enemas, pyelogram etc), medical-record based	Collaborative Perinatal Project	1959-1965	All malignant neoplasms	7 / 40	1.09 (0.47, 2.40)
				All benign neoplasms	9 / 105	0.94 (0.46, 1.82)
(Herrmann, 1980)	X-ray examination in pregnancy	German Democratic Republic leukaemia study	1957-1973	Leukaemia	32 / 75	1.41 (0.70, 2.83)[d]
	Abdominal X-ray examination in pregnancy vs unexposed				3 / 46	1.23 (0.16, 9.66)[d]
(Grufferman et al., 1982)	Radiographic examination during pregnancy	North Carolina statewide cohort	1967-1976	Rhabdomyosarcoma	2 / 33	0.5 (0.1, 2.4)
(Preston-Martin et al., 1982)	Pelvic X-ray	Cancer Surveillance Program in Los Angeles county	1972-1977	Brain tumour	38 / 209	1.28 (0.74, 2.22)[d]
(Monson and MacMahon, 1984)	Pelvimetry, flat plate of abdomen, upper or lower GI series, intravenous pyelogram or gallbladder series, medical-record based	42 hospitals in New England and mid-Atlantic US states, mortality	1947-1967	Leukaemia mortality	94 / 704	1.48 (1.17, 1.86)[d]
				All cancer excluding leukaemia mortality	68 / 638	1.15 (0.87, 1.49)[d]
				CNS mortality	32 / 298	1.16 (0.77, 1.68)[d]
				All cancer excluding leukaemia and CNS mortality	36 / 340	1.14 (0.78, 1.62)[d]
				All cancer mortality	162 / 1342	1.32 (1.11, 1.58)[d]
(van Steensel-Moll et al., 1985)	Prenatal radiation exposure	Netherlands national cohort	1973-1980	Acute lymphoblastic leukaemia	41 / 519	2.2 (1.2, 3.8)
(Harvey et al., 1985)	Abdominal X-ray during pregnancy, medical-record based	Connecticut twin birth register	1930-1969	Leukaemia	5 / 13	1.6 (0.4, 6.8)
				All cancer excluding leukaemia	7 / 18	3.2 (0.9, 10.7)
				All cancer	12 / 31	2.4 (1.0, 5.9)
				Brain	3 / 4	8.48 (0.65, 459.72)[d]
				Lymphoma	1 / 3	1.44 (0.02, 28.69)[d]
				All solid excluding brain	3 / 11	1.08 (0.17, 4.93)[d]
(Hopton et al., 1985)	One or more pelvic X-rays, medical-record based	Inter-Regional Epidemiological Study of Childhood Cancer (N England)	1980-1983	Leukaemia + lymphoma	37 / 245	1.33 (0.85, 2.08)
	One or more pelvic X-rays, medical-record based			Solid tumour	35 / 310	1.14 (0.73, 1.76)
	One or more pelvic X-rays, medical-record based			All tumour	72 / 555	1.23 (0.89, 1.70)[d]
	Other X-rays, medical-record based			Leukaemia + lymphoma	11 / 245	0.75 (0.37, 1.53)
	Other X-rays, medical-record based			Solid tumour	15 / 310	1.23 (0.63, 2.38)
	Other X-rays, medical-record based			All tumour	26 / 555	0.94 (0.56, 1.55)[d]
(Johnston et al., 1986)	X-rays during pregnancy, GP controls, medical-record based		1980-1983	Germ cell tumour	6 / 41	1.23 (0.28, 5.60)[d]

	X-rays during pregnancy, hospital controls, medical-record based	Inter-Regional Epidemiological Study of Childhood Cancer			6 / 41	3.30 (0.54, 35.47)[d]
	X-rays during pregnancy, GP+hospital controls, medical-record based				6 / 41	1.83 (0.47, 6.89)[d]
(Kneale and Stewart, 1986)	X-rays during pregnancy	Oxford Survey of Childhood Cancer	1953-1977	Reticuloendothelial neoplasms	1100 / 7347	1.39 (1.26, 1.54)[d]
				Solid tumours	1018 / 6582	1.32 (1.19, 1.46)[d]
(Bunin et al., 1987)	Abdominal or pelvic X-ray	Based on three tertiary-care hospitals in Philadelphia-area, resident in New Jersey, Pennsylvania, Delaware, Maryland	1970-1983	Wilms' tumour	≥7 / 88	1.0 (0.3, 3.7)
(Operskalski et al., 1987)	Any X-ray during pregnancy	Los Angeles county	1972-1982	Osteosarcoma	24 / 55	1.5 (0.8, 3.0)
	Pelvic X-ray during pregnancy				14 / 60	2.0 (0.9, 4.4)
	Other X-ray except dental during pregnancy				9 / 60	1.8 (0.7, 4.8)
(Shu et al., 1988)	Abdomen exposure	Shanghai Cancer Institute based cohort	1974-1986	Leukaemia	8 / 307	1.5 (0.5, 4.1)
				Acute lymphoblastic leukaemia	6 / <307	2.0 (0.7, 5.9)
				Acute non-lymphoblastic leukaemia	1 / <307	0.6 (0.1, 5.0)
(Bunin et al., 1989)	Any X-ray during pregnancy, direct fetal exposure	Children's Cancer Group (US+Canada hospitals)	1982-1985	Non-heritable retinoblastoma	8 / 115	4.0 (0.8, 38.7)
	Any X-ray during pregnancy, no direct fetal exposure				10 / 115	1.7 (0.5, 5.6)
	Any abdominal/pelvic X-ray during pregnancy				9 / 115	0.4 (0.2, 0.9)
	Any X-ray during pregnancy, direct fetal exposure			Sporadic-heritable retinoblastoma	2 / 67	1.0 (0.07, 13.8)
	Any X-ray during pregnancy, no direct fetal exposure				5 / 67	1.3 (0.3, 6.3)
	Any abdominal/pelvic X-ray during pregnancy				10 / 67	2.0 (0.6, 7.5)
(Gilman et al., 1989)	Any pregnancy X-ray, partial medical-record based	Oxford Survey of Childhood Cancer	1953-1981	All cancer mortality	2281 / 15,276	1.39 (1.30, 1.49)[d]
(Howe et al., 1989)	Abdominal X-ray	Southern Ontario cohort based on Princess Margaret Hospital, Toronto	1977-1983	Brain tumour	7 / 74	0.896 (0.334, 2.41)
(Magnani et al., 1989)	Pelvic or abdominal X-ray	Cohort based in the pediatric hospitals of the universities of Turin and Padua	1983-1984	Soft tissue sarcoma	4 / 52	1.9 (0.5, 6.5)
				Rhabdomyosarcoma	3 / 36	1.55 (0.28, 5.75)[d]
(Gardner et al., 1990)	Area controls, using medical records for maternal abdominal X-ray exposure	West Cumbria (NW England)	1950-1985	Leukaemia	3 / 20	1.15 (0.31, 4.28)
	Local controls, using medical records for maternal abdominal X-ray exposure			Leukaemia	3 / 20	1.21 (0.31, 4.66)
	Area controls, using medical records for maternal abdominal X-ray exposure			Leukaemia + NHL	5 / 28	1.19 (0.43, 3.32)

	Local controls, using medical records for maternal abdominal X-ray exposure			Leukaemia + NHL	5 / 28	1.34 (0.46, 3.88)
	Local controls, using medical records for maternal abdominal X-ray exposure			NHL	2 / 8	1.74 (0.14, 12.81)[d]
	Pooled area and local controls, using medical records for maternal abdominal X-ray exposure			NHL	2 / 8	1.52 (0.14, 9.52)[d]
(Golding et al., 1990)	Matched analysis of any X-ray exposure in pregnancy (including dental), medical-record based	UK cohort, based on 1 week of 1970 births	1970-1980	All cancer	12 / 33	2.75 (1.22, 6.21)
	Abdomen X-ray exposure vs X-ray unexposed, medical-record based				4 / 25	3.16 (0.58, 16.14)[d]
(Kuijten et al., 1990)	Abdominal or pelvic X-ray	Tumour registries of 8 hospitals in New Jersey, Pennsylvania and Delaware	1980-1986	Astrocytoma	34 / 163	0.9 (0.5, 1.5)
(Rodvall et al., 1990)	All X-ray, medical-record based	Swedish Twin Register	1936-1967	All cancer	39 / 95	1.2 (0.7, 2.1)
	Abdominal X-ray, medical-record based			All cancer	25 / 95	1.4 (0.8, 2.5)
	All X-ray, medical-record based			Leukaemia	12 / 29	1.0 (0.4, 2.6)
	Abdominal X-ray, medical-record based			Leukaemia	10 / 29	1.7 (0.7, 4.1)
	All X-ray, medical-record based			CNS	13 / 32	1.1 (0.4, 2.6)
	Abdominal X-ray, medical-record based			CNS	8 / 32	1.5 (0.5, 4.2)
	All X-ray, medical-record based			All cancer except leukaemia and CNS	14 / 34	1.7 (0.7, 4.2)
	Abdominal X-ray, medical-record based			All cancer except leukaemia and CNS	7 / 34	1.0 (0.3, 2.9)
	All X-ray, medical-record based			All cancer except leukaemia	27 / 66	1.34 (0.69, 2.56)[d]
	Abdominal X-ray, medical-record based			All cancer except leukaemia	15 / 66	1.20 (0.54, 2.59)[d]
(Magnani et al., 1990)	Pelvic + abdominal X-ray	Turin cohort	1981-1984	Acute lymphoblastic leukaemia	8 / 142	1.1 (0.4, 2.8)
	Abdominal + thoracic X-ray			Acute non-lymphoblastic leukaemia	4 / 22	2.4 (0.8, 7.3)
(Golding et al., 1992)	X-ray of abdomen or pelvis, medical-record based	South West England cohort, with updated numbers from Wakeford and Bithell (Wakeford and Bithell, 2021)	1971-1991	All cancer	37 / 185	1.78 (1.10, 2.82)[d]
				Leukaemia	14 / 63	2.03 (0.98, 3.99)[d]
				All cancer except leukaemia	23 / 122	1.65 (0.93, 2.84)[d]
(Holly et al., 1992)	Radiography during pregnancy	San Francisco 5 Bay area counties	1978-1986	Ewing's sarcoma	9 / 43	0.7 (0.3, 1.8)
(Stjernfeldt et al., 1992)	Abdomen/pelvis X-ray vs known unexposed	Swedish Child Leukaemia Group with numbers taken from Wakeford and Bithell (Wakeford and Bithell, 2021)	1976-1981	Solid tumour	8 / 42	1.45 (0.50, 3.84)[d]
(Winn et al., 1992)	Diagnostic X-rays, using regional controls	Intergroup Ewing's Sarcoma study	1983-1985	Ewing's sarcoma	44 / 204	0.8 (0.5, 1.2)
	Diagnostic X-rays, using sibling controls				41 / 191	1.5 (0.8, 3.2)
(Fajardo-Gutierrez et al., 1993)	Any X-ray during pregnancy	Mexico City	<1993	Leukaemia	16 / 80	1.89 (0.84, 4.22)

(Roman et al., 1993)	Abdominal X-rays, using obstetric records	West Berkshire & North Hampshire	1972-1989	Leukaemia + NHL	5 / 37	1.1 (0.3, 3.7)
(Sorahan and Stewart, 1993)	Maternal X-ray, cancer mortality, partially medical-record based	Oxford Survey of Childhood Cancer	<1993	Retinoblastoma mortality	17 / 86	1.95 (1.07, 3.36)[d]
(Bunin et al., 1994)	X-ray of lower abdomen	Children's Cancer Group (US+Canada hospitals)	1986-1989	Astrocytoma	6 / 155	1.1 (0.3, 3.9)
				Primitive neuroectodermal tumour	9 / 166	0.8 (0.3, 2.3)
(McCredie et al., 1994a)	Diagnostic X-rays	Australian (New South Wales) registry	1985-1989	Brain tumour	13 / 82	1.3 (0.6, 2.6)
(Shu et al., 1994b)	Any X-ray in pregnancy	Children's Cancer Group (US+Canada hospitals)	1983-1988	All infant leukaemia	59 / 302	1.12 (0.77, 1.63)
	Lower abdomen X-ray and pelvimetry			All infant leukaemia	≥7 / 302	1.26 (0.48, 3.29)
	Any X-ray in pregnancy			Acute lymphoblastic leukaemia	NA / 203	0.84 (0.52, 1.35)
	Lower abdomen X-ray and pelvimetry			Acute lymphoblastic leukaemia	5 / 203	1.12 (0.36, 3.50)
	Any X-ray in pregnancy			Acute myeloid leukaemia	NA / 88	1.58 (0.80, 3.12)
	Lower abdomen X-ray and pelvimetry			Acute myeloid leukaemia	2 / 88	1.48 (0.23, 9.52)
(Shu et al., 1994a)	Abdominal X-ray exposure	Shanghai Cancer Institute based cohort	1981-1991, 1986-1991 for leukaemia	All cancer	9 / 642	2.1 (0.7, 7.0)
	Prenatal X-ray exposure			All cancer	27 / 642	1.8 (0.9, 3.6)
				Acute leukaemia	7 / 166	2.4 (0.5, 10.6)
				Lymphoma	6 / 87	3.6 (0.6, 21.6)
				Brain tumour	3 / 107	1.3 (0.2, 9.0)
(van Duijn et al., 1994)	Prenatal X-ray exposure	Dutch Childhood Leukemia Study Group	1973-1979	Acute non-lymphoblastic leukaemia	6 / 80	1.7 (0.6, 5.3)
(Shu et al., 1995)	X-ray during pregnancy	Children's Cancer Group	1982-1989	Germ cell tumour	13 / 105	0.9 (0.5, 1.8)
(Roman et al., 1997)	Lower abdomen X-ray, medical-record based	South England study, based on three hospitals (Oxford, Cambridge, Reading)	1962-1992	Leukaemia	16 / 143	0.7 (0.4, 1.3)
	Pelvimetry, medical-record based			Leukaemia	9 / 143	1.6 (0.6, 3.9)
	Lower abdomen X-ray, medical-record based			Acute lymphoblastic leukaemia	15 / 113	0.8 (0.4, 1.6)
	Pelvimetry, medical-record based			Acute lymphoblastic leukaemia	8 / 113	1.6 (0.6, 4.3)
	Lower abdomen X-ray, medical-record based			Acute myeloid leukaemia	0 / 15	0.0 (0.0, 2.9)
	Pelvimetry, medical-record based			Acute myeloid leukaemia	0 / 15	0.0 (0.0, 2.9)
	Lower abdomen X-ray, medical-record based			NHL	6 / 34	1.0 (0.3, 3.3)
	Pelvimetry, medical-record based			NHL	3 / 34	2.0 (0.4, 9.9)
(McKinney et al., 1999)	One or more abdominal X-rays vs none, medical-record based	Scotland UKCCS study	1991-1994	Leukaemia	6 / 144	2.26 (0.69, 7.45)
				Acute lymphoblastic leukaemia	5 / 124	2.50 (0.67, 9.31)
				Lymphoma	3 / 45	0.71 (0.17, 2.97)

				CNS tumours	3 / 75	1.11 (0.24, 5.05)
				Other tumours (than leukaemia, lymphoma, CNS)	3 / 26	1.20 (0.29, 5.02)
				All cancer	15 / 290	1.80 (0.85, 3.73)[d]
(Meinert et al., 1999)	Diagnostic X-ray in pregnancy	German Childhood Cancer registry	1992-1994	Leukaemia	46 / 1184	0.94 (0.65, 1.36)
				NHL	12 / 234	1.22 (0.61, 2.44)
				Solid tumour	40 / 940	0.92 (0.63, 1.35)
	Diagnostic X-ray of abdomen, pelvis, intestinal tract in pregnancy vs completely unexposed			Acute leukaemia	3 / 1141	0.93 (0.16, 4.10)[d]
				NHL	2 / 224	3.19 (0.32, 16.87)[d]
				Solid tumour	2 / 902	0.79 (0.08, 4.14)[d]
				All cancer	7 / 2267	1.10 (0.33, 3.67)[d]
(Fear et al., 2001)	Pelvimetry, medical-record based	Cohort assembled from birth records in three hospitals (Oxford, Cambridge, Reading)	1956-1992	Brain tumour	7 / 83	0.9 (0.4, 2.4)
	Abdominal X-ray, medical-record based			Brain tumour	6 / 83	0.8 (0.3, 2.1)
(Naumburg et al., 2001)	Abdominal X-ray, adjusted for age at birth, gestational age, parity, smoking, cesarean section, birthweight, medical-record based	Sweden national cohort	1973-1989	Leukaemia	68 / 624	1.14 (0.79, 1.65)
				Lymphoblastic leukaemia	55 / 552	1.01 (0.68, 1.51)
				Myeloid leukaemia	13 / 72	1.74 (0.53, 5.74)
(Schuz et al., 2001)	Diagnostic X-ray in pregnancy	German Childhood Cancer registry	1993-1997	CNS	16 / 453	0.78 (0.44, 1.36)
(Shu et al., 2002)	Pelvimetric X-ray	Children's Cancer Group (US+Canada hospitals)	1989-1993	Acute lymphoblastic leukaemia	55 / 1842	1.2 (0.8, 1.7)
	Any X-ray in pregnancy				112 / 1842	1.0 (0.8, 1.7)
(Infante-Rivard, 2003)	Pelvimetry	Quebec two-phase paediatric study cohort	1980-1998	Acute lymphoblastic leukaemia	38 / 701	0.80 (0.50, 1.27)[d]
	Abdominal X-ray				4 / 701	2.00 (0.29, 22.20)[d]
	Pelvimetry + abdominal X-ray				42 / 701	0.85 (0.54, 1.33)[d]
(Patton et al., 2004)	Maternal gonadal X-ray exposure in pregnancy	Pediatric Oncology Group + Children's Cancer Group	1992-1994	Neuroblastoma	1 / 496	1.0 (0.1, 16.0)
	Maternal X-ray exposure in 1st trimester				7 / 496	0.7 (0.3, 1.8)
	Maternal X-ray exposure in 2nd trimester				5 / 496	1.2 (0.3, 4.6)
	Maternal X-ray exposure in 3rd trimester				6 / 496	1.2 (0.4, 3.9)
(Stålberg et al., 2007)	Exposure to abdominal X-ray during pregnancy, medical-record based, adjusted for maternal age, parity, multiple birth, mother born in a Nordic country, gestational age at birth, mode of delivery, breech position, birth weight, birth head circumference, level of hospital, hypertension during pregnancy	Sweden national cohort	1975-1984	Brain tumour	55 / 503	1.02 (0.64, 1.62)
	Exposure to non-abdominal X-ray during pregnancy, medical-record based, adjusted for maternal age, parity, multiple birth, mother born				53 / 503	0.78 (0.52, 1.17)

	in a Nordic country, gestational age at birth, mode of delivery, breech position, birth weight, birth head circumference, level of hospital, hypertension during pregnancy					
	Exposure to any abdominal X-ray during pregnancy compared with non-X-ray exposed, medical-record based				55 / 459	1.17 (0.76, 1.81)[d]
(Goel et al., 2009)	Maternal gonadal X-ray exposure in pregnancy, adjusted for income, maternal education and matched on age at diagnosis and geographic region of residence	Children's Oncology Group	1999-2002	Wilms' tumour	1 / 506	1.0 (0.1, 15.5)
	Maternal X-ray exposure in 1st trimester, adjusted for income, maternal education and matched on age at diagnosis and geographic region of residence				9 / 506	0.8 (0.3, 2.1)
	Maternal X-ray exposure in 2nd trimester, adjusted for income, maternal education and matched on age at diagnosis and geographic region of residence				8 / 506	0.7 (0.3, 1.8)
	Maternal X-ray exposure in 3rd trimester, adjusted for income, maternal education and matched on age at diagnosis and geographic region of residence				8 / 506	0.9 (0.3, 2.4)
(Grufferman et al., 2009)	Pelvis or abdomen X-ray exposure, matched on age, sex, race and adjusted for length of pregnancy, type of delivery, spotting/cramping/abnormal vaginal bleeding during pregnancy	Children's Oncology Group	1982-1988	Rhabdomyosarcoma	24 / 312	1.4 (0.7, 2.9)
(Spix et al., 2009)	Diagnostic X-ray exposure	German Childhood Cancer registry	1993-2003	Brain tumour	2 / 88	0.31 (0.06, 1.68)
(Bailey et al., 2010)	Any plain abdominal X-ray or CT	Australia Study of Causes of Acute Lymphoblastic Leukaemia in Children <15 y age at diagnosis (Aus-ALL)	2003-2006	Acute lymphoblastic leukaemia	4 / 388	0.73 (0.19, 2.84)
(Bartley et al., 2010)	Any X-ray in pregnancy	Northern California Childhood Leukemia Study	1995-2008	Acute lymphoblastic leukaemia	NA / 652	1.20 (0.71, 2.04)
				Acute myeloid leukaemia	NA / 111	0.85 (0.26, 2.78)
(Castro-Jimenez and Orozco-Vargas, 2011)	Any X-ray	Colombian 6-hospital neighbourhood-based study	2000-2005	Acute lymphoblastic leukaemia	2[f] / 85	2.00 (0.18, 22.06)
(Rajaraman et al., 2011)	Any radiation exposure *in utero*, medical-record based	UKCCS study	1976-1996	All cancer	120 / 2690	1.14 (0.90, 1.45)
				Leukaemia	48 / 1253	1.36 (0.91, 2.02)
				Acute lymphoblastic leukaemia	36 / NA	1.20 (0.76, 1.88)
				Acute myeloid leukaemia	11 / NA	2.44 (0.95, 6.33)
				Lymphoma	16 / 231	1.06 (0.55, 2.06)
				NHL	13 / NA	1.48 (0.66, 3.32)
				Brain/CNS	25 / 482	1.06 (0.64, 1.77)
				Sarcoma	10 / NA	1.13 (0.49, 2.61)
				Peripheral neural tumours	7 / NA	1.00 (0.37, 2.67)
				Renal	5 / NA	1.64 (0.48, 5.59)
	Abdominal radiation exposure *in utero*, medical-record based			All cancer	90 / 2690	1.12 (0.85, 1.48)

				Leukaemia	37 / 1253	1.21 (0.78, 1.88)
				Acute myeloid leukaemia	8 / NA	1.76 (0.63, 4.90)
(Hassanzadeh et al., 2011)	History of mother's radiography	Southern Iran leukaemia cohort	2005-2009	Leukaemia	6 / 163	3.00 (0.61, 14.86)
(Milne et al., 2014)	Any fetal X-ray exposure	Australian cohort via 10 paediatric oncology centres	2005-2010	Brain tumour	8 / 293	1.71 (0.69, 4.23)
(Kumar et al., 2014a)	History of mother's radiography	Sharma Institute, India cohort	2008-2012	Leukaemia	32 / 132	0.79 (0.44, 1.42)[d]
(Tettamanti et al., 2017)	X-ray or other scan during pregnancy	CEFALO International multicentre study, diagnosed at age 7-19 y	2004-2008	Brain tumour	31 / 337	0.96 (0.54, 1.68)
	X-ray or other scan to the abdomen during pregnancy				5 / 337	0.72 (0.17, 2.97)
Cohort studies						
Reference	Type of X-ray exposure, other features[a]	Description of study data	Study years	Cancer endpoint[b]	Number of cases exposed / total	Relative risk, (95% CI)
(Diamond et al., 1973)	Abdominal X-rays, medical-record based	Cohort of mortality after births at nine hospitals in Baltimore	1947-1959	Leukaemia mortality	6 / 13	1.62 (0.52,4.89)[g]
				Lymphoma mortality	2 / 5	1.30 (0.17, 7.88)[g]
				Brain/CNS mortality	3 / 11	0.68 (0.15, 2.35)[g]
				All other malignant neoplasm mortality	2 / 7	0.72 (0.10, 3.35)[g]
(Ray et al., 2010)	Any diagnostic radiation exposure *in utero*, hazard ratio computed via Cox model, medical-record based	Ontario radiodiagnostic imaging infant birth cohort	1992-2008	All childhood malignancies	4 / 2543	0.69 (0.26,1.82)

[a]questionnaire based, unless otherwise stated
[b]incidence unless otherwise stated
[c]the comparison "unexposed" group is generally given by the negation of the indicated exposed criteria, and so the total number of cases is therefore the combination of "exposed" + "unexposed", unless otherwise stated.
[d]based on odds ratio estimated via maximum likelihood from hypergeometric model conditional on marginal totals, with exact CI, estimated by fisher.test routine in R (R Project version 3.6.1, 2019).
[e]via Poisson regression, using expected deaths as offset, with likelihood-based CI.
[f]numbers of exposed cases (2) and controls (1) estimated via reverse engineering based on the OR and CI in (Castro-Jimenez and Orozco-Vargas, 2011).
[g]via Poisson regression of sex-averaged data, with likelihood-based CI.

Table 2. Summary of case-control and cohort studies of postnatal exposure to medical diagnostic radiation in childhood that do not incorporate estimates of dose, with estimates of odds ratio (OR) or relative risk (RR)

Reference	Type of X-ray exposure, other features[a]	Description of study data[b]	Study years	Cancer endpoint[c]	Number of cases exposed / total	Odds ratio/relative risk (95% CI)
(Stewart et al., 1958)	Diagnostic X-rays (X)	Oxford Survey of Childhood Cancers, with deaths before age 10 in 1953-1955 and birth-register controls, excluding therapeutically exposed	1953-1955	Leukaemia mortality	90 / 614	1.15 (0.82, 1.62)[d]
				Other cancer mortality	88 / 677	0.89 (0.65, 1.24)[d]
				All cancer mortality	178 / 1291	1.01 (0.80, 1.27)[d]
(Polhemus and Koch, 1959)	Diagnostic X-rays (X)	Cohort based on Children's Hospital of Los Angeles, excluding therapeutically exposed	1950-1957	Leukaemia	135 / 214	2.13 (1.44, 3.18)[d]
	Fluoroscopy (F)				17 / 96	3.48 (1.35, 9.77)[d]
(Ager et al., 1965)	Postnatal X-ray vs not, sibling controls; exposures within 1 y of death excluded (X)	Minnesota childhood leukaemia study, mortality, age < 5 y	1953-1957	Leukaemia mortality	22 / 109	1.26 (0.59, 2.73)[d]
	Postnatal X-ray vs not, neighbourhood controls; exposures within 1 y of death excluded (X)				22 / 109	1.14 (0.55, 2.37)[d]
(Graham et al., 1966)	Any postnatal radiation exposure vs none, excluding exposures 6 months before diagnosis, medical-record based (U)	USA Tri-state Study, diagnosed 0-14 y of age	1959-1962	Leukaemia	93 / 319	0.73 (0.55, 0.97)[d]
	Any postnatal radiation exposure vs none, excluding exposures 12 months before diagnosis, medical-record based (U)				81 / 319	0.71 (0.53, 0.96)[d]
(Preston-Martin et al., 1980)	First diagnostic medical X-ray exposure at age <20 y (X)	Cancer Surveillance Program in Los Angeles county study, women <65 y age at diagnosis	1972-1975	Intracranial meningiomas	53 / 185	1.60 (0.97, 2.68)[d]
	First diagnostic X-ray exposure (medical or dental) at age <20 y (X)				99 / 185	1.51 (0.98, 2.32)[d]
	First full-mouth dental X-ray series at age <20 y (X)				41 / 101	4.04 (2.07, 8.12)[d]
(Preston-Martin et al., 1982)	Five or more full-mouth dental X-rays, starting at least 10 y before diagnosis (X)	Cancer Surveillance Program in Los Angeles county, aged 15-24 y at diagnosis	1972-1977	Brain tumour	17 / 68	2.48 (0.92, 7.23)[d]
(Greenberg, 1983)	Chest radiograph, hospital non-cancer controls (X)	North Carolina paediatric (age < 15 y at diagnosis) neuroblastoma case-control study	1972-1981	Neuroblastoma or ganglioneuroblastoma	16 / 104	0.29 (0.14, 0.61)
	Chest radiograph, hospital Wilms' tumour controls (X)				16 / 104	1.95 (0.73, 5.19)
	Cranial radiograph, hospital non-cancer controls (X)				2 / 104	0.30 (0.07, 1.36)
	Cranial radiograph, hospital Wilms' tumour controls (X)				2 / 104	1.57 (0.13, 19.13)
	Abdominal radiograph, hospital non-cancer controls (X)				3 / 104	0.41 (0.12, 1.45)
	Abdominal radiograph, hospital Wilms' tumour controls (X)				3 / 104	0.81 (0.15, 4.34)
(Spengler et al., 1983)	Mortality after cardiac catheterisation. Observed cases and expected, relative risk assessed via exact Poisson model (Garwood, 1936) (C)	Toronto Hospital for Sick Children cardiac catheterisation cohort study, medical record based; catheterisation at age <30 y (99.8% < age 20y), follow-up 1946-1975, age at death, 0-45 y.	1946-1968	All cancer mortality, male	1 / 3.09[e]	0.32 (0.01, 1.80)[f]
				Leukaemia mortality, male	1 / 1.22[e]	0.82 (0.02, 4.57)[f]
				All cancer mortality, female	4 / 1.78[e]	2.25 (0.61, 5.75)[f]
				Leukaemia mortality, female	2 / 0.66[e]	3.03 (0.37, 10.95)[f]

				Kidney mortality, female	1 / 0.09[e]	11.11 (0.28, 61.91)[f]
				All cancer mortality	5 / 4.87[e]	1.03 (0.33, 2.40)[f]
				Leukaemia mortality	3 / 1.88[e]	1.60 (0.33, 4.66)[f]
(Operskalski et al., 1987)	Any radiation exposure except dental X-ray (U)	Los Angeles county, diagnosed age <25 y	1972-1982	Osteosarcoma	41 / 62	0.9 (0.4, 1.8)
(Hartley et al., 1988)	Neonatal X-ray (X)	Inter-Regional Epidemiological Study of Childhood Cancer, medical record based, diagnosed age <15 y	1980-1983	Any cancer incidence	5 / 465	1.11 (0.32, 3.63)
(Shu et al., 1988)	Any X-ray exposure (X)	Shanghai Cancer Institute cancer registry, diagnosed age <15 y	1974-1986	Leukaemia	79 / 309	0.91 (0.66, 1.26)[d]
	1-5 X-ray exposure vs none (X)				71 / 301	0.8 (0.6, 1.1)
	6+ X-ray exposure vs none (X)				8 / 238	2.4 (0.6, 9.2)
	Any X-ray exposure (X)			Acute lymphoblastic leukaemia	42 / 172	0.86 (0.57, 1.28)[d]
	1-5 X-ray exposure vs none (X)				38 / 168	0.8 (0.5, 1.2)
	6+ X-ray exposure vs none (X)				4 / 134	3.3 (0.7, 15.9)
	Any X-ray exposure (X)			Acute non-lymphoblastic leukaemia	26 / 94	1.02 (0.60, 1.68)[d]
	1-5 X-ray exposure vs none (X)				25 / 93	0.9 (0.5, 1.5)
	6+ X-ray exposure vs none (X)				1 / 69	1.2 (0.1, 12.5)
(Howe et al., 1989)	Chest X-rays, ever vs never (X)	Southern Ontario study, based on Princess Margaret Hospital, Toronto, diagnosed age <20 y, X-ray exposures within 5 y of diagnosis excluded	1977-1983	Brain tumour	9 / 74	3.32 (1.17, 9.43)
	Chest X-rays, per film (X)				9 / 74	3.54 (1.61, 7.77)
	Skull X-rays, ever vs never (X)				11 / 74	8.35 (2.13, 32.8)
	Skull X-rays, per film (X)				11 / 74	2.67 (1.37, 5.19)
	Chest X-rays, ever vs never, adjusted for skull X-rays (X)				9 / 74	2.07 (0.62, 6.95)
	Skull X-rays, ever vs never, adjusted for chest X-rays (X)				11 / 74	6.71 (1.65, 27.3)
(Magnani et al., 1989)	Any diagnostic X-ray exposure (X)	Paediatric hospital study of the universities of Turin and Padua, diagnosed in children	1983-1984	Rhabdomyosarcoma	16 / 36	1.0 (0.5, 2.1)
				Soft tissue sarcoma	20 / 52	0.8 (0.4, 1.5)
(Nishi and Miyake, 1989)	Dental X-ray film (X)	Hokkaido Prefecture study, diagnosed aged 0-14 y	1981-1987	Non T-cell acute lymphoblastic leukaemia	NA / 63	1.4 (1.0, 2.0)
	Hip joint X-ray (X)				49 / 63	1.1 (0.9, 1.3)
(Kuijten et al., 1990)	Head or neck X-ray (X)	Tumour registries of 8 hospitals in New Jersey, Pennsylvania and Delaware, diagnosed aged <15 y	1980-1986	Astrocytoma	18 / 163	1.0 (0.5, 2.1)
	Dental X-ray (X)				18 / 163	0.9 (0.4, 1.8)
(Magnani et al., 1990)	Any diagnostic X-ray (X)	Turin study, diagnosed in childhood	1974-1984	Acute lymphoblastic leukaemia	48 / 142	0.7 (0.5, 1.2)
				Acute non-lymphoblastic leukaemia	10 / 22	0.98 (0.37, 2.56)[d]
				NHL	6 / 19	0.54 (0.17, 1.58)[d]

(Fajardo-Gutierrez et al., 1993)	Any postnatal X-ray, hospital + community controls (X)	Mexico City study, diagnosed in childhood	<1993	Leukaemia	23 / 79	1.11 (0.57, 2.13)
	Any postnatal X-ray, community controls (X)				23 / 79	2.32 (0.97, 5.73)
(McLaughlin et al., 1993)	Any catheterisation. Observed cases and expected, relative risk assessed via exact Poisson model (Garwood, 1936) (C)	Cohort study of cardiac catheterisation among Ontario residents at a major Toronto hospital, catheterised at age <19 y and followed to 1985 for incidence and mortality, medical record based	1950-1965	All cancer mortality	7 / 5.70[e]	1.23 (0.49, 2.53)[f]
				All cancer incidence	13 / 17.27[e]	0.75 (0.40, 1.29)[f]
				Leukaemia incidence	3 / 1.87[e]	1.60 (0.33, 4.69)[f]
(Bunin et al., 1994)	Dental X-ray (X)	Children's Cancer Group (US+Canada hospitals), diagnosed at age 0-5 y	1986-1989	Astrocytoma	14 / 155	1.0 (0.4, 2.7)
	Dental X-ray (X)			Primitive neuroectodermal tumour (PNET)	8 / 166	0.5 (0.1, 1.6)
	Other head or neck X-ray (X)			Astrocytoma	12 / 155	1.6 (0.6, 4.3)
	Other head or neck X-ray (X)			Primitive neuroectodermal tumour (PNET)	10 / 166	3.3 (0.7, 22.1)
	Any head, neck, dental X-ray (X)			Astrocytoma	24 / 155	1.2 (0.6, 2.4)
	Any head, neck, dental X-ray (X)			Primitive neuroectodermal tumour (PNET)	22 / 166	1.1 (0.5, 2.4)
(McCredie et al., 1994b)	X-rays of teeth (X)	Australian (New South Wales) registry, diagnosed at age 0-14 y	1985-1989	Brain tumour	3 / 82	0.4 (0.1, 1.4)
	X-rays of head (X)				4 / 82	2.3 (0.5, 10.8)
(Shu et al., 1994a)	Postnatal X-ray exposure (X)	Shanghai Cancer Institute based, diagnosed at age 0-14 y	1981-1991	All cancer	223 / 642	1.3 (1.0, 1.7)
				Acute leukaemia	64 / 166	1.6 (1.0, 2.6)
				Lymphoma	29 / 87	1.3 (0.6, 2.7)
				Brain tumour	41 / 107	1.5 (0.8, 3.0)
(Meinert et al., 1999)	Any diagnostic X-rays up to 1 year before diagnosis vs none (X)	German Childhood Cancer registry diagnosed at age <15 y, born after June 1975	1992-1994 (solid tumours) 1980-1994 (acute leukaemia+NHL)	Acute leukaemia	328 / 1145	0.80 (0.68, 0.93)[d]
	1-4 diagnostic X-rays up to 1 year before diagnosis vs none (X)			Acute leukaemia	289 / 1145	0.78 (0.65, 0.93)
	4+ diagnostic X-rays up to 1 year before diagnosis vs none (X)			Acute leukaemia	39 / 1145	1.00 (0.65, 1.55)
	Any diagnostic X-rays up to 1 year before diagnosis vs none (X)			NHL	85 / 224	1.22 (0.91, 1.63)[d]
	1-4 diagnostic X-rays up to 1 year before diagnosis vs none (X)			NHL	77 / 224	0.71 (0.51, 1.00)
	4+ diagnostic X-rays up to 1 year before diagnosis vs none (X)			NHL	8 / 224	0.60 (0.27, 1.34)
	Any diagnostic X-rays up to 1 year before diagnosis vs none (X)			Solid tumour	261 / 922	0.79 (0.66, 0.93)[d]
	1-4 diagnostic X-rays up to 1 year before diagnosis vs none (X)			Solid tumour	235 / 922	0.80 (0.55, 0.98)
	4+ diagnostic X-rays up to 1 year before diagnosis vs none (X)			Solid tumour	26 / 922	0.78 (0.48, 1.27)
(Modan et al., 2000)			1950-1970	NHL, males	3 / 0.45[e]	6.7 (1.3, 19.5)

	Cardiac catheterisationof children; observed cases and expected numbers based on Israeli national cancer incidence rates, follow-up starts 5 y after first catheterisation, relative risk assessed via exact Poisson model (Garwood, 1936) (C)	Israel national cardiac catheterisation due to congenital anomaly cohort, medical record based, follow-up to end-1996		Hodgkin's disease, males	1 / 0.25[e]	4.0 (0.05, 22.2)
				All lymphomas, males	4 / 0.70[e]	5.7 (1.5, 14.6)
				Melanoma, males	3 / 0.62[e]	4.87 (1.0, 14.2)
				Bladder, males	1 / 1.86[e]	0.54 (0.01, 3.0)
				Stomach, males	1 / 0.13[e]	7.8 (0.1, 43.6)
				Testis, males	1 / 0.34[e]	2.9 (0.04, 16.2)
				Prostate, males	1 / 0.93[e]	1.1 (0.01, 6.0)
				All sites, males	11 / 4.75[e]	2.3 (1.2, 4.1)
				All sites, females	0 / 6.80[e]	0.00 (0.00, 0.54)[f]
				All sites, males+females	11 / 11.55[e]	0.95 (0.48, 1.70)[f]
(Schuz et al., 2001)	Any X-ray examination up to 1 y before diagnosis (X)	German national childhood cancer study diagnosed at age <15 y	1993-1997	All CNS	142 / 458	0.73 (0.57, 0.94)
				Astrocytoma	42 / 118	0.78 (0.50, 1.23)
				Ependymoma	10 / 49	0.57 (0.25, 1.31)
				Medulloblastoma	32 / 110	0.78 (0.49, 1.23)
(Shu et al., 2002)	Ever X-ray exposure, excluding dental X-rays (X)	Children's Cancer Group (US+Canada hospitals) study	1989-1993	Acute lymphoblastic leukaemia	939 / 1842	1.6 (1.4, 1.9)
	Ever X-ray exposure, excluding exposures within 2 y of diagnosis (X)			Acute lymphoblastic leukaemia	NA / 1842	1.1 (0.9, 1.2)
				T-cell acute lymphoblastic leukaemia	NA / 183	1.1 (0.7, 1.7)
				Early pre-B cell acute lymphoblastic leukaemia	NA / 893	1.1 (0.8, 1.3)
				Pre-B cell acute lymphoblastic leukaemia	NA / 233	1.7 (1.1, 2.7)
(Infante-Rivard, 2003)	Single X-ray vs none (excluding dental) (X)	Quebec two-phase paediatric study, diagnosed at ages 0-14 y, males	1980-1998	Acute lymphoblastic leukaemia	157 / 589	1.17 (0.79, 1.73)
	≥ 2 X-rays vs none (excluding dental) (X)				196 / 628	1.41 (0.99, 2.01)
	Single X-ray vs none (excluding dental) (X)	Quebec two-phase paediatric study, diagnosed at ages 0-14 y, females			106 / 483	1.11 (0.78, 1.78)
	≥ 2 X-rays vs none (excluding dental) (X)				104 / 481	1.67 (1.01, 2.74)
(Mellemkjaer et al., 2006)	Diagnostic X-rays, adjusted for gestational age (X)	Danish National Hospital Discharge Registry study, medical record based, diagnosed at ages 0-19 y	1977-1989	CNS tumours (excluding pituitary)	11 / 25	2.20 (0.60, 8.80)
(Bailey et al., 2010)	Any diagnostic X-ray exposure more than 6 months before diagnosis (CT)	Australia Study of Causes of Acute Lymphoblastic Leukaemia in Children <15 y age at diagnosis (Aus-ALL)	2003-2006	Acute lymphoblastic leukaemia	156 / 359	1.15 (0.88,1.51)
	Any plain X-ray exposure more than 6 months before diagnosis (X)				150 / 359	1.15 (0.88,1.52)
	Any CT exposure more than 6 months before diagnosis (CT)				6 / 359	0.87 (0.32,2.34)
(Bartley et al., 2010)			1995-2008	Acute lymphoblastic leukaemia	NA / 711	1.21 (0.96, 1.51)

	Any postnatal X-ray excluding dental X-rays and X-rays received within 1 y of diagnosis (X)	Northern California Childhood Leukemia Study		B-cell acute lymphoblastic leukaemia	NA / 472	1.40 (1.06, 1.86)
				T-cell acute lymphoblastic leukaemia	NA / 52	0.54 (0.21, 1.35)
				Acute myeloid leukaemia	NA / 116	0.78 (0.38, 1.61)
(Khan et al., 2010)	Head X-ray due to head injury (X)	Children's Oncology Group Study, age <6 y at diagnosis	1991-1997	Medulloblastoma/primitive neuroectodermal tumours	8 / 299	0.62 (0.21,1.9)
	Head X-ray not due to head injury, with possibly tumour-related X-rays deemed unexposed (X)				15 / 299	1.3 (0.49,3.7)
	Head X-ray any reason, with possibly tumour-related X-rays deemed unexposed (X)				23 / 299	1.2 (0.54,2.5)
	Dental X-ray any reason (X)				16 / 299	0.85 (0.37,1.90)
(Rajaraman et al., 2011)	Any radiation exposure in early infancy (0-100 days), medical-record based, 2 y lag (U)	UK Childhood Cancer Study (UKCCS), diagnosed at ages 0-14 y	1992-1996	All cancer	50 / 2690	1.19 (0.82, 1.74)
				Leukaemia	27 / 1253	1.35 (0.81, 2.27)
				Acute lymphoblastic leukaemia	26 / NA	1.55 (0.90, 2.67)
				Lymphoma	7 / 231	5.14 (1.27, 20.80)
				NHL	6 / NA	6.85 (1.31, 35.70)
				Brain/CNS	6 / 482	0.94 (0.31, 2.92)
(Claus et al., 2012)	Bitewing X-ray at age < 10 y (X)	Five state (Connecticut, Massachusetts, North Carolina, California, Texas) meningioma case-control study	2006-2011	Meningioma	239 / 1433	1.3 (1.0,1.7)
	Bitewing X-ray at age 10-19 y (X)				682 / 1433	1.4 (1.1,1.7)
	Full mouth X-ray at age < 10 y (X)				100 / 1433	1.2 (0.8,1.7)
	Full mouth X-ray at age 10-19 y (X)				371 / 1433	1.1 (0.9,1.4)
(Huang et al., 2014)	Any CT examination, males, lag 2 y (CT)	Taiwan National Health Insurance research database (NHIRD), age < 18 y undergoing CT exams	1996-2008	Brain tumour overall	11 / 28	2.62 (1.23,5.59)
	Any CT examination, females, lag 2 y (CT)			Brain tumour overall	8 / 21	2.48 (1.03,5.99)
	Any CT examination, males, lag 2 y (CT)			Malignant brain tumour	4 / 11	2.32 (0.68,7.92)
	Any CT examination, females, lag 2 y (CT)			Malignant brain tumour	1 / 5	1.00 (0.11,8.97)
	Any CT examination, males, lag 2 y (CT)			Benign brain tumour	7 / 17	2.82 (1.08,7.42)
	Any CT examination, females, lag 2 y (CT)			Benign brain tumour	7 / 16	3.15 (1.17,8.45)
	Any CT examination, males, lag 2 y (CT)			Leukaemia	6 / 18	2.02 (0.76,5.38)
	Any CT examination, females, lag 2 y (CT)			Leukaemia	2 / 7	1.62 (0.31,8.33)
	Any CT examination, males, lag 2 y (CT)			Other cancers (than leukaemia, brain)	7 / 52	0.62 (0.28,1.36)
	Any CT examination, females, lag 2 y (CT)			Other cancers (than leukaemia, brain)	5 / 34	0.69 (0.27,1.79)
(Liao et al., 2014)	Cystourethrography (X)		1997-2008	All cancer	52 / 151	1.92 (1.34,2.74)

		Taiwan National Health Insurance research database (NHIRD) case-control study, matched for sex, age (within 5 y), geographic region, parents occupation, aged 1-18, adjusted for age		Abdominal cancers excluding genitourinary cancers	5 / 10	2.98 (0.77,11.60)
				Neuroendocrine cancers	11 / 39	1.21 (0.57,2.59)
				Non-abdominal cancers	1 / 11	0.49 (0.06,3.86)
				Genital cancers	4 / 7	6.19 (1.37,28.00)
				Urinary system cancers	7 / 11	5.80 (1.54,21.90)
				Hematologic cancers	22 / 66	1.82 (1.05,3.13)
				All other cancers	2 / 7	1.93 (0.37,9.97)
(Milne et al., 2014)	Any diagnostic radiological procedure, lag 6 m (CT)	Australian cohort via 10 paediatric oncology centres	2005-2010	Brain tumour	102 / 281	0.66 (0.48,0.90)
	Any plain X-ray, lag 6 m (X)				97 / 281	0.68 (0.49,0.93)
	Any CT scan, lag 6 m (CT)				13 / 281	0.78 (0.38,1.59)
	Any diagnostic radiological procedure to the head (including dental), lag 6 m (CT)				37 / 281	0.68 (0.42,1.08)
	Any plain X-ray to the head, lag 6 m (X)				27 / 281	0.61 (0.36,1.03)
	Any CT scan to the head, lag 6 m (CT)				12 / 281	0.83 (0.40,1.75)
(Shih et al., 2014)	Any X-ray (X)	Taiwan National Health Insurance research database (NHIRD) based case-control study, ages 6-18, matched by age, sex, level of urbanisation, parental occupation, index year	1998-2010	Leukaemia	34 / 58	2.14 (1.18,3.87)
(Tettamanti et al., 2017)	Exposure to any X-ray or scan (excluding dental X-rays) more than 2 y before diagnosis (CT)	CEFALO International multicentre study, diagnosed at age 7-19 y	2004-2008	Brain tumour	159 / 350	0.76 (0.58,1.01)
	Exposure to any X-ray or scan to head or body+head (excluding dental X-rays) more than 2 y before diagnosis (CT)				41 / 350	1.09 (0.71,1.67)
	Exposure to CT scan to head or body+head vs no X-ray or scan to the head, more than 2 y before diagnosis (CT)				10 / 350	1.86 (0.82,4.22)
(Harbron et al., 2018)	X-ray guided cardiac catheterisation, including transplant recipients (C)	UK cardiac catheterisation study, exposed while ≤ 22 years of age (>90% aged <20 years at first exposure)	<1980-2014	All malignancies	36 / NA	3.01 (2.09,4.19)
				Leukaemia	4 / NA	1.73 (0.43,4.53)
				Lymphoma	22 / NA	9.15 (5.66,13.97)
				Hodgkin lymphoma	4 / NA	2.70 (0.68,7.07)
				NHL	18 / NA	19.49 (11.39,31.10)
				Central nervous system	3 / NA	1.57 (0.28,4.70)
	X-ray guided cardiac catheterisation, excluding post-transplant patients (C)			All malignancies	11 / NA	0.98 (0.48,1.77)
				Leukaemia	4 / NA	1.80 (0.45,4.71)
				Central nervous system	2 / NA	1.10 (0.09,4.11)

				Lymphoma	0 / NA	0.00 (0.00, 1.64)[f]
				Other tumours (than leukaemia, lymphoma, brain/CNS)	5 / NA	1.01 (0.33, 2.35)[f]
(Baaken et al., 2019)	Any diagnostic X-ray procedure during 1976-2003, exposure lag of 2 y (M)	Dr von Hauner Children's Hospital cohort, age <14.5 y at first examination, without cancer at first examination, SIR analysis	1980-2016	All cancers	71 / NA	0.98 (0.76,1.23)
				Leukaemia	24 / NA	0.99 (0.63,1.47)
				Lymphoblastic leukaemia	16 / NA	0.83 (0.48,1.36)
				Acute myeloid leukaemia	4 / NA	1.15 (0.31,2.94)
				Lymphomas	7 / NA	0.61 (0.25,1.26)
				Hodgkin lymphoma	1 / NA	0.21 (0.01,1.16)
				NHL	5 / NA	1.35 (0.44,3.16)
				CNS tumours	8 / NA	0.51 (0.22,1.00)
				Blastomas	10 / NA	1.89 (0.91,3.47)
				Sarcomas	13 / NA	1.54 (0.82,2.64)
				Other solid tumours	9 /NA	3.32 (1.52,6.31)
(Hong et al., 2019)	Any diagnostic radiation exposure. exposure lag 1 y (U)	South Korean National Health Insurance System study, ages 0-19 y at exposure, 0-29 y at diagnosis	2006-2015	All cancer	1921 / 21,912	1.72 (1.64, 1.80)
	Any diagnostic radiation exposure. exposure lag 2 y (U)			All cancer	1444 / 21,912	1.64 (1.56, 1.73)
	Any diagnostic radiation exposure. exposure lag 5 y (U)			All cancer	434 / 21,912	1.48 (1.35, 1.63)
	Any diagnostic radiation exposure, exposure lag 2 y (U)			All solid	987 / 15314	1.70 (1.59, 1.81)
				Mouth/pharynx	30 / 380	2.01 (1.38, 2.92)
				Digestive	76 / 974	1.83 (1.22, 2.74)
				Respiratory	35 / 431	1.95 (1.38, 2.75)
				Bone	53 / 1123	1.05 (0.79, 1.38)
				Melanoma	14 / 262	1.32 (0.77, 2.26)
				Soft tissue	43 / 821	1.20 (0.88, 1.63)
				Breast	14 / 239	2.32 (1.35, 3.99)
				Female genital	76 / 1385	1.77 (1.41, 2.24)
				Male genital	23 / 377	1.28 (0.84, 1.95)
				Urinary	20 / 386	1.16 (0.74, 1.82)
				Brain	183 / 2872	1.57 (1.38, 1.78)
				Thyroid	363 / 5225	2.19 (1.97, 2.44)

				Unspecified solid	57 / 839	1.68 (1.29, 2.20)
				Lymphoid & haemopoietic malignant neoplasms	457 / 6598	1.53 (1.39, 1.69)
				Hodgkin lymphoma	21 / 385	1.32 (0.85, 2.05)
				Other lymphoma	47 / 599	1.73 (1.28, 2.32)
				Other lymphoid	57 / 1024	1.27 (0.97, 1.66)
				Leukaemia & myeloid	332 / 4590	1.58 (1.42, 1.77)
				Leukaemia	294 / 4218	1.51 (1.34,1.71)
				Lymphoid leukaemia	74 / 1879	0.81 (0.64,1.02)
				Other myeloid	220 / 2339	2.14 (1.86,2.46)
				Myelodysplasia	38 / 372	2.48 (1.77,2.47)
	Any computed tomography exposure, exposure lag 2 y (CT)			All solid	840 / 15314	1.62 (1.51, 1.74)
				Mouth/pharynx	29 / 380	2.19 (1.50, 3.20)
				Digestive	65 / 974	1.97 (1.53, 2.53)
				Respiratory	34 / 431	2.01 (1.46, 2.78)
				Bone	47 / 1123	1.03 (0.77, 1.38)
				Melanoma	13 / 262	1.38 (0.79, 2.41)
				Soft tissue	40 / 821	1.24 (0.90, 1.71)
				Breast	13 / 239	2.53 (1.44, 4.43)
				Female genital	71 / 1385	1.92 (1.51, 2.43)
				Male genital	22 / 377	1.36 (0.88, 2.09)
				Urinary	18 / 386	1.15 (0.72, 1.85)
				Brain	166 / 2872	1.55 (1.36, 1.77)
				Thyroid	273 / 5225	1.87 (1.65, 2.11)
				Unspecified solid	49 / 839	1.61 (1.21, 2.15)
				Lymphoid & haemopoietic malignant neoplasms	376 / 6598	1.38 (1.25, 1.54)
				Hodgkin lymphoma	20 / 385	1.42 (0.90, 2.23)
				Other lymphoma	41 / 599	1.66 (1.20, 2.27)
				Other lymphoid	49 / 1024	1.22 (0.91, 1.62)
				Leukaemia & myeloid	266 / 4590	1.38 (1.22, 1.57)

				Leukaemia	233 / 4218	1.31 (1.15,1.49)
				Lymphoid leukaemia	68 / 1879	0.82 (0.64,1.04)
				Other myeloid	165 / 2339	1.73 (1.48,2.03)
				Myelodysplasia	33 / 372	2.38 (1.66,3.40)
(Li et al., 2020)	Computed tomography, 1 y exclusion (CT)	Taiwan National Health Insurance research database (NHIRD), age < 16 y at exposure and diagnosis	1997-2013	Leukaemia	NA / 1423	1.04 (0.72, 1.48)
				Intracranial malignancy	NA / 838	1.95 (1.40, 2.71)
				Lymphoma	NA / 272	1.69 (1.34, 2.13)
	Computed tomography, 2 y exclusion (CT)			Leukaemia	NA / 1423	0.85 (0.54, 1.34)
				Intracranial malignancy	NA / 838	1.56 (1.04, 2.33)
				Lymphoma	NA / 272	0.93 (0.42, 2.05)

[a]questionnaire based, unless otherwise stated. The coding of types of exposure is as follows: X=X-ray, F=fluoroscopy, C=catheterization, U=mixed diagnostic radiation/unknown, CT=computed tomography
[b]case-control studies, unless otherwise mentioned
[c]incidence unless otherwise stated
[d]based on odds ratio estimated via maximum likelihood from hypergeometric model conditional on marginal totals, with exact CI, estimated by fisher.test routine in R (R Project version 3.6.1, 2019).
[e]expected cases/deaths.
[f]relative risk CI assessed via exact Poisson model (Garwood, 1936)

Table 3. Univariate meta-regression maximum likelihood fit and restricted maximum likelihood fits of random effects models to childhood cancer outcome data from studies of *in utero* exposure to medical diagnostic radiation (odds ratio (OR) and relative risk (RR) as in Table 1)

Cancer endpoint (number of studies)	Meta odds ratio (mOR) / meta relative risk (mRR) (+95% CI)[a]	*p*-value improvement over null [model with constant risk][b]	Residual heterogeneity *p*-value[c]	I^2 (%) (95% CI)[d]	Heterogeneity *p*-value
Analysis by cancer endpoint (fitted via restricted maximum likelihood (REML))					
Leukaemia (38)	1.35 (1.25,1.46)	<0.0001	0.6344	9.94 (0.00,34.86)	0.3097
Lymphoma (10)	1.31 (1.15,1.49)	0.0010	0.9674	0.00 (0.00,10.42)	
Brain/CNS (21)	1.16 (1.02,1.32)	0.0222	0.7094	10.56 (0.00,39.29)	
Other (19)	1.34 (1.16,1.55)	0.0004	0.3307	23.21 (0.00,62.30)	
All cancers [four cancer endpoints] (62)	1.32 (1.25,1.40)	<0.0001	0.7629	10.19 (0.00,16.17)	
All cancers [any cancer] (66)	1.21 (1.13,1.30)	<0.0001	0.4982	12.98 (0.00,28.16)	
Calendar year trend for any childhood cancer combined – four separate cancer endpoints analysis (fitted via REML)					
Trend in OR/RR, % per year	-0.84 (-1.16, -0.52)	<0.0001	0.9875	0.00 (NA)	-
Calendar year trend for any childhood cancer combined – any cancer analysis (fitted via REML)					
Trend in OR/RR, % per year	-0.78 (-1.17, -0.39)	0.0002	0.8859	2.06 (0.00, 14.97)	-
Analysis by cancer endpoint (fitted via maximum likelihood)					
Leukaemia (38)	1.36 (1.26,1.47)	<0.0001	0.6344	6.37 (0.00,34.86)	0.3097
Lymphoma (10)	1.31 (1.15,1.49)	0.0010	0.9674	0.00 (0.00,10.42)	
Brain/CNS (21)	1.17 (1.04,1.33)	0.0146	0.7094	7.96 (0.00,39.29)	
Other (19)	1.38 (1.21,1.58)	<0.0001	0.3307	11.49 (0.00,62.30)	
All cancers [four cancer endpoints] (62)	1.33 (1.26,1.40)	<0.0001	0.7629	8.73 (0.00,16.17)	
All cancers [any cancer] (66)	1.21 (1.13,1.30)	<0.0001	0.7919	5.20 (0.00,13.95)	

[a]estimates and CI via restricted maximum likelihood.
[b]significance evaluated via maximum likelihood fits.
[c]significance of residual heterogeneity, assessed via Cochran's *Q* statistic based on maximum likelihood fits.
[d]contribution of inter-study heterogeneity to intra-study variance, via Higgins and Thompson (Higgins and Thompson, 2002) I^2 statistic based on maximum likelihood fits.
[e]estimates and CI via maximum likelihood.

Table 4. Egger test (Egger et al., 1997) for selection bias for studies of *in utero* exposure risk, and magnitude of correction in raw meta odds ratio (mOR) or meta relative risk (mRR) suggested by trim-and-fill method of Duval and Tweedie (Duval and Tweedie, 2000)

Egger test for selection bias, *p*-value	Meta odds ratio (mOR) / meta relative risk (mRR) (95% CI) (REML estimate)	Bias corrected meta odds ratio (mOR) / meta relative risk (mRR) (95% CI) (Duval & Tweedie trim-and-fill corrected REML estimate)
	Four cancer endpoint analysis	
0.0064	1.32 (1.25,1.40)	1.38 (1.30,1.47)
	Any cancer analysis	
0.1802	1.21 (1.13,1.30)	1.26 (1.17,1.35)

Table 5. Univariate meta-regression maximum likelihood fit and restricted maximum likelihood fits of random effects models to childhood cancer outcome data from studies of postnatal exposure to medical diagnostic radiation (odds ratio (OR) and relative risk (RR) as in Table 2)

Cancer Endpoint / Type of Exposure (number of studies)	Meta odds ratio (mOR) / meta relative risk (mRR) (+95% CI)[a]	*p*-value improvement over null [model with constant risk][b]	Residual heterogeneity *p*-value[c]	I^2 (%) (95% CI)[d]	Heterogeneity *p*-value
Fits with four specific types of cancer considered separately					
Analysis by cancer endpoint					
Leukaemia (21)	1.25 (1.07,1.46)	0.0055	<0.0001	71.53 (44.18,87.70)	
Lymphoma (8)	1.30 (0.66,2.59)	0.4065	<0.0001	64.39 (<64.39,>99.91)	0.0663
Brain/CNS (18)	1.26 (1.02,1.56)	0.0339	0.0003	54.36 (14.88,85.36)	
Other (9)	1.65 (1.37,1.97)	<0.0001	0.0004	56.51 (28.81,90.14)	
Any cancer (39)	1.37 (1.23,1.53)	<0.0001	<0.0001	68.45 (65.88,90.16)	
Analysis by type of exposure					
X-ray (26)	1.25 (1.08,1.45)	0.0046	0.0002	53.04 (30.32,86.32)	
Fluoroscopy (1)	3.48 (1.29,9.37)	0.0136	NA	NA	
Computed tomography (5)	1.52 (1.34,1.72)	<0.0001	<0.0001	69.23 (42.42,88.20)	0.0242
Catheterisation (4)	2.14 (0.85,5.37)	0.0962	0.0060	19.75 (<19.75,>99.26)	
Unknown/mixed (4)	1.18 (0.77,1.80)	0.4177	0.0003	71.19 (38.40,93.34)	
Calendar year trend for any cancer combined – unadjusted for type of exposure					
Trend in OR/RR, % per year	0.15 (-0.51, 0.81)	0.6596	<0.0001	67.57 (65.83, 90.18)	-
Calendar year trend for any cancer combined – adjusted for type of exposure					
Trend in OR/RR, % per year	-0.14 (-0.86, 0.59)	0.7090	<0.0001	62.89 (60.64, 88.84)	-
Fits using any type of cancer for each study					
Analysis by type of exposure					
X-ray (27)	1.19 (1.03,1.37)	0.0167	0.0001	59.79 (33.07, 85.36)	
Fluoroscopy (1)	3.48 (1.29,9.37)	0.0136	NA	NA	
Computed tomography (5)	1.32 (1.04,1.67)	0.0272	0.0112	74.18 (5.78, 96.75)	0.0570
Catheterisation (3)	0.88 (0.61,1.27)	0.2709	0.8030	0.00 (0.00, 87.84)	
Unknown/mixed (4)	0.92 (0.65,1.32)	0.5315	0.1805	44.27 (0.00, 94.96)	
Calendar year trend for any cancer combined – unadjusted for type of exposure					

Trend in OR/RR, % per year	0.17 (-0.47, 0.81)	0.5921	<0.0001	67.47 (47.23, 86.14)	-
Calendar year trend for any cancer combined – adjusted for type of exposure					
Trend in OR/RR, % per year	0.07 (-0.69, 0.83)	0.8563	<0.0001	62.84 (36.70, 83.87)	-

[a]estimates and CI via restricted maximum likelihood.
[b]significance evaluated via maximum likelihood fits.
[c]significance of residual heterogeneity, assessed via Cochran's *Q* statistic based on maximum likelihood fits.
[d]contribution of inter-study heterogeneity to intra-study variance, via Higgins and Thompson (Higgins and Thompson, 2002) I^2 statistic based on maximum likelihood fits.

Table 6. Egger test (Egger et al., 1997) for selection bias for studies of postnatal exposure risk, and magnitude of correction in raw meta odds ratio (mOR) or meta relative risk (mRR) suggested by trim-and-fill method of Duval and Tweedie (Duval and Tweedie, 2000)

Egger test for selection bias, *p*-value	Meta odds ratio (mOR) / meta relative risk (mRR) (95% CI) (REML estimate)	Bias corrected meta odds ratio (mOR) / meta relative risk (mRR) (95% CI) (Duval & Tweedie trim-and-fill corrected REML estimate)
	Four cancer endpoint analysis	
0.3991	1.37 (1.23, 1.53)	1.34 (1.22, 1.48)
	Any cancer combined analysis	
0.5095	1.17 (1.05, 1.30)	1.16 (1.04, 1.28)

Table 7. Comparison of meta odds ratios (mOR)/meta relative risks (mRR) obtained by Wakeford and Bithell (Wakeford and Bithell, 2021) from the data of the Oxford Survey of Childhood Cancers (OSCC) and a meta-analysis of results from all other case-control/case-cohort studies (using a Mantel-Haenszel random-effects model) with those obtained from the meta-analysis of antenatal exposure in the present study (taken from Table 3).

Endpoint	Wakeford and Bithell (Wakeford and Bithell, 2021) OSCC mOR (+95% CI)	Wakeford and Bithell (Wakeford and Bithell, 2021) non-OSCC case-control and case-cohort studies mOR (+95% CI)	Present analysis (maximum likelihood) mOR/mRR (+95% CI)	Present analysis (restricted maximum likelihood) mOR/mRR (+95% CI)
Leukaemia	1.51 (1.35, 1.69)	1.28 (1.16, 1.41)	1.36 (1.26,1.47)	1.35 (1.25,1.46)
Lymphoma	1.34 (1.06, 1.69)	1.75 (1.08, 2.84)	1.31 (1.15,1.49)	1.31 (1.15,1.49)
Brain/CNS tumours	1.42 (1.19, 1.69)	1.13 (0.97, 1.31)	1.17 (1.04,1.33)	1.16 (1.02,1.32)
All solid cancer except brain/CNS tumours	1.51 (1.32, 1.72)	1.28 (0.89, 1.85)	1.38 (1.21,1.58)	1.34 (1.16,1.55)
All cancers	1.39 (1.30, 1.49)	1.30 (1.18, 1.43)	1.33 (1.26,1.40)[a]	1.32 (1.25,1.40)[a]

[a]four separate cancers

Figure 1. *In utero* exposure, odds ratio/relative risk (+95% CI) by midpoint year of study data ascertainment for (a) any cancer, (b) leukaemia, (c) brain/CNS tumour and (d) lymphoma. Each point corresponds to a single cancer endpoint (generally one per study), using all studies and endpoints in Table 1 (see Supplementary Table S1). Dashed red line is odds ratio/relative risk = 1

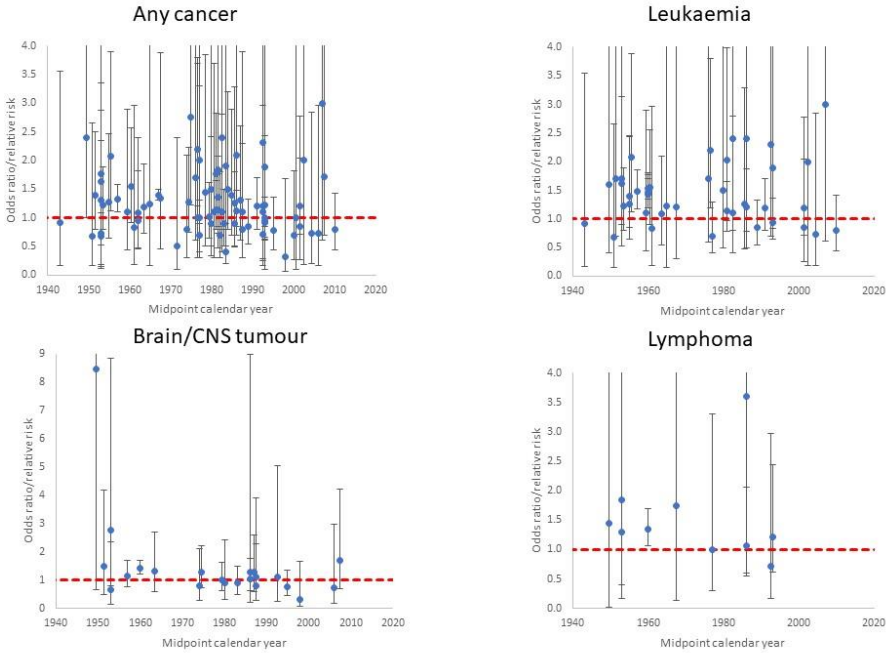


Figure 2. Postnatal exposure odds ratio/relative risk (+95% CI) for (a) leukaemia, (b) brain/CNS tumour and (c) lymphoma by midpoint year of study data ascertainment. Each point corresponds to a single study and relevant endpoint in Table 2 (see Supplementary Table S2). Dashed red line is odds ratio/relative risk = 1

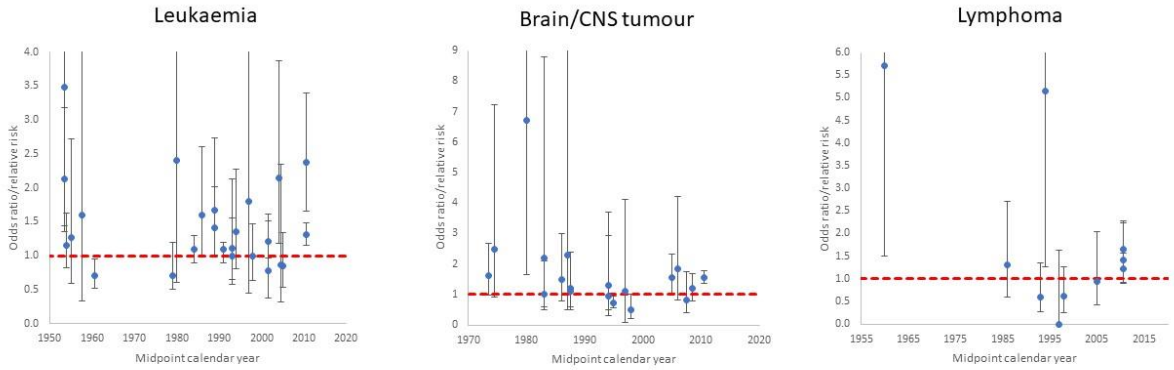


Figure 3. Meta-regression for studies of *in utero* exposure. Restricted maximum likelihood (REML) fits to odds ratio or relative risk by calendar year midpoint of study data ascertainment range (for <1950, 1950-1959, 1960-1969, 1970-1979, 1980-1989, 1990+). Plots are shown for (a) the four cancer endpoints analysis (leukaemia, lymphoma, brain/CNS cancer, other cancer) and (b) the any cancer endpoint analysis, for each *in utero* exposure study in Table 1 (see Supplementary Table S1). Dashed red line is odds ratio/relative risk = 1.

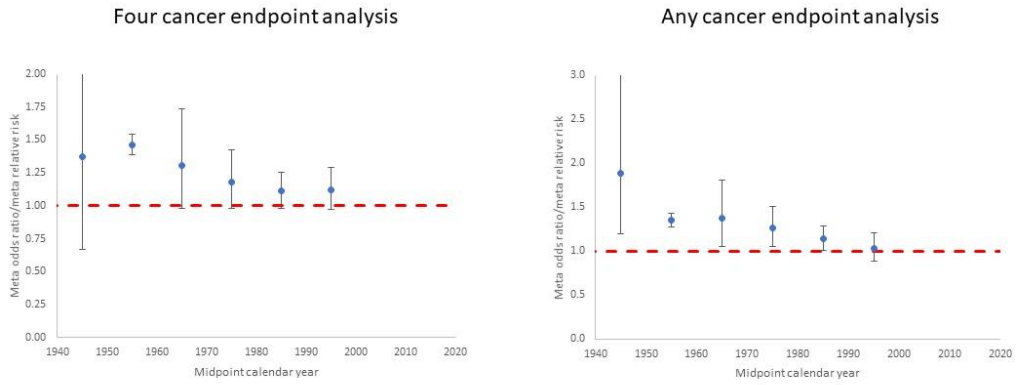


Figure 4. Meta-regression for studies of postnatal exposure. Restricted maximum likelihood (REML) fits to odds ratio or relative risk by calendar year midpoint of study data ascertainment range (for <1960, 1960-1969, 1970-1979, 1980-1989, 1990-1999, 2000+). Plots are shown for (a) the four cancer endpoints analysis (leukaemia, lymphoma, brain/CNS cancer, other cancer) and (b) the any cancer endpoint analysis, for each postnatal exposure study in Table 2 (see Supplementary Table S2). Dashed red line is odds ratio/relative risk = 1.

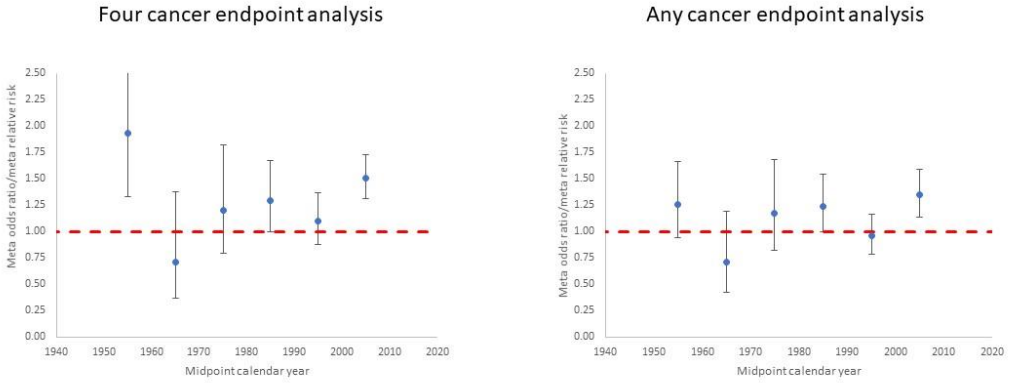


Figure 5. Funnel plot of *in utero* exposure study odds ratios/relative risks, using any cancer endpoints within all studies, as in Table 1.

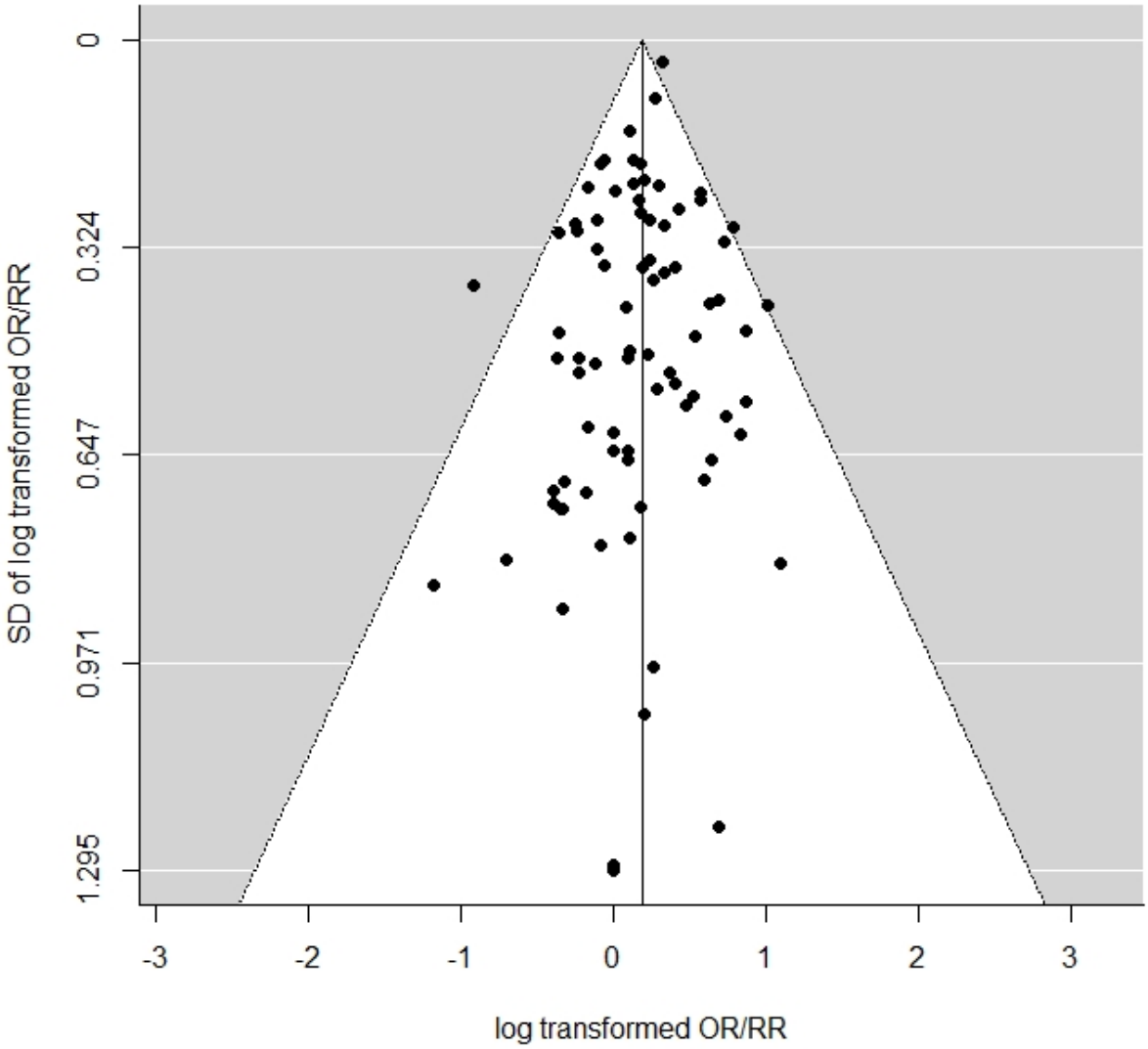
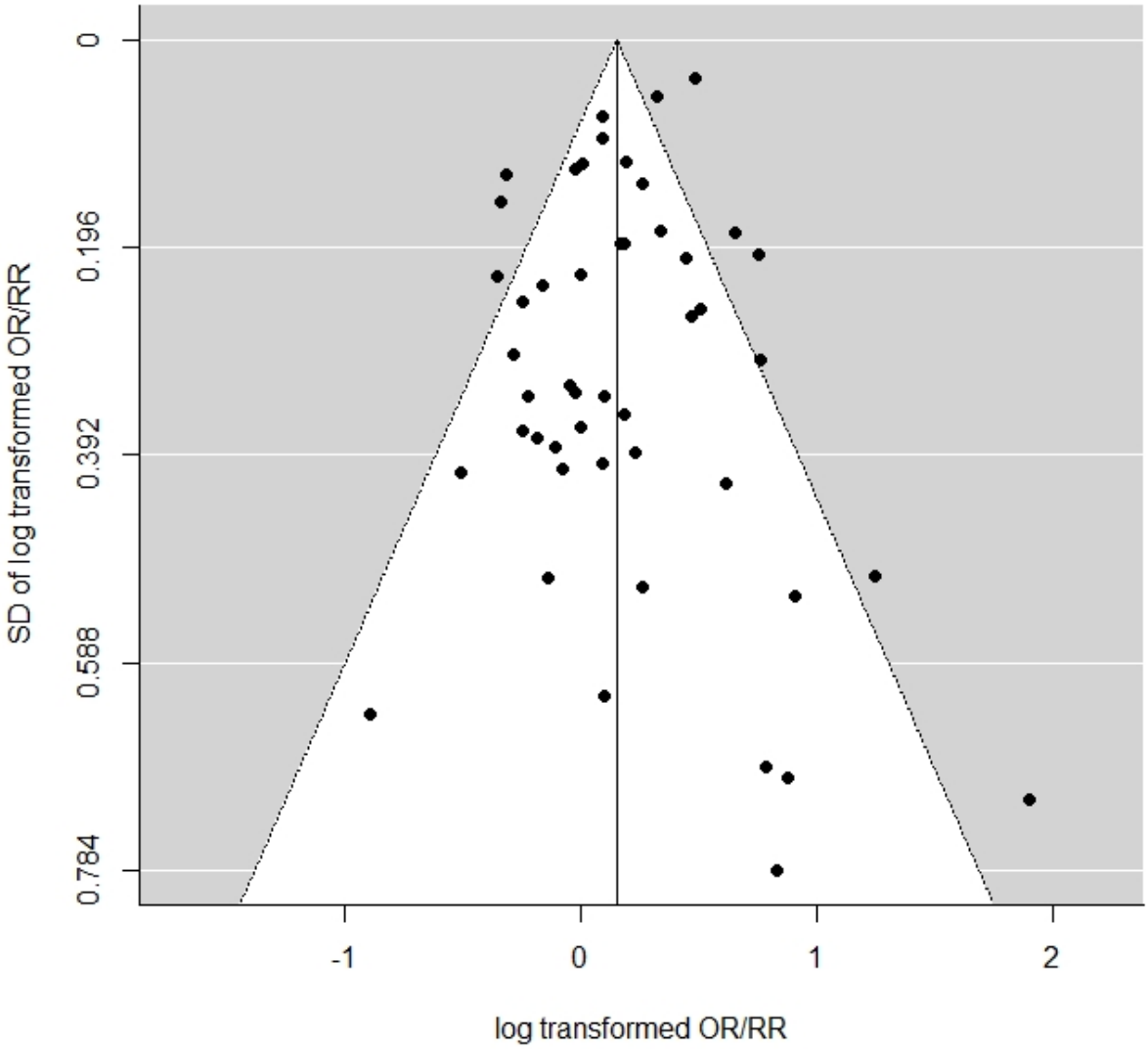


Figure 6. Funnel plot of postnatal exposure study odds ratios/relative risks, using any cancer endpoints within all studies, as in Table 2.



Supplement

Supplementary Methods

S.1 Literature review

A literature search of PubMed was performed on 16th May 2021 using the search terms:

(cancer*[tiab] OR malignan*[tiab] OR tumour*[tiab] OR tumor*[tiab])

AND ("X ray"[tiab] OR "X-ray"[tiab] OR "x-ray"[tiab] OR radiation*[tiab] OR radionuclide*[tiab] OR radioisotope*[tiab] OR "radioactive nuclide*"[tiab] OR "radioactive isotope*"[tiab] OR "CT scan*"[tiab] OR “CT-scan*”[tiab] OR "computed tomograph*"[tiab] OR "computerized tomograph*"[tiab] OR "computerised tomograph*"[tiab] OR fluoroscop*[tiab] OR radiograph*[tiab] OR angiograph*[tiab] OR cardiograph*[tiab] OR “cardiac catheter*”[tiab] OR “interventional cardiol*”[tiab] OR “interventional radiograph*”[tiab] OR radiol*[tiab] OR "atomic bomb"[tiab] OR Hiroshima[tiab] OR Nagasaki[tiab] OR Chernobyl[tiab] OR Chornobyl[tiab] OR Fukushima[tiab] OR "nuclear accident*"[tiab] OR "nuclear reactor*"[tiab])

AND (childhood*[tiab] OR "in utero"[tiab] OR obstetric[tiab] OR pregnancy[tiab])

NOT radiotherapy[tiab] NOT "radiation therapy"[tiab] NOT "chemotherapy"[tiab] NOT "roentgen therapy"[tiab] NOT "roentgen treatment"[tiab] NOT letter[ptyp] NOT editorial[ptyp] NOT comment[ptyp] NOT news[ptyp] NOT "Congress"[Publication Type] NOT "Consensus Development Conference"[Publication Type] NOT editorial[tiab] NOT commentary[tiab] NOT “conference abstract*”[tiab] NOT “conference proceeding*”[tiab] NOT “systematic review*”[ti] NOT “meta-analysis”[ptyp] NOT “meta-analysis”[ti] NOT “meta-analyses”[ti] NOT "Review"[Publication Type] NOT "Systematic Review"[Publication Type] NOT “retracted publication”[ptyp] NOT “retraction of publication”[ptyp] NOT

583 “retraction of publication”[tiab] NOT “retraction notice”[ti] NOT “retracted publication”[tiab]
584 NOT "Published Erratum"[Publication Type] NOT Corrigenda[tiab] NOT corrigendum[tiab] NOT
585 errata[tiab] NOT erratum[tiab] NOT protocol[ti] NOT protocols[ti]
586 NOT animals[tiab] NOT animal*[tiab] NOT mice[tiab] NOT mouse[tiab] NOT rat[tiab] NOT
587 rats[tiab] NOT dog[tiab] NOT dogs[tiab] NOT pig[tiab] NOT pigs[tiab] NOT swine[tiab] NOT
588 porcine*[tiab] NOT rodent*[tiab]
589 There was no restriction on language or date of publication. Editorials, abstracts and reviews were
590 excluded. A total of 3117 papers were returned. A PECO statement is given in Supplementary
591 Table S3. The titles and abstracts of these were independently double scanned by MPL and GMK,
592 and case reports, review papers and other clearly inapplicable results (e.g., relating to populations
593 not exposed in childhood) were eliminated. Consistency was established via consensus.
594 Additionally, recent UNSCEAR reports (United Nations Scientific Committee on the Effects of
595 Atomic Radiation (UNSCEAR), 2008; United Nations Scientific Committee on the Effects of
596 Atomic Radiation (UNSCEAR), 2013; United Nations Scientific Committee on the Effects of
597 Atomic Radiation (UNSCEAR), 2018) were scanned to assess additional literature, as well as
598 recent review articles (Abalo et al., 2021; Han and Kim, 2018; Kendall et al., 2021; Linet et al.,
599 2009; Linet et al., 2012; Memon et al., 2019; Wakeford and Bithell, 2021). A total of 299 papers
600 that were deemed applicable based on the title/abstract search, and the associated full publications
601 were then obtained for more detailed review of these by MPL and GMK.
602 Of the 299 consensus samples, and following reading of the full publications, we restricted
603 attention to those studies of persons exposed *in utero* or in childhood (age 20 years or less) to
604 medical diagnostic radiographic procedures and in which quantitative estimates of radiation doses
605 were not available. Again, consistency between the reviewers was established via consensus; all

studies that had been superseded by others were eliminated. This yielded a total of 29 papers. Although the catheterisation study of Spengler *et al* (Spengler et al., 1983) has been largely superseded by the later study of McLaughlin *et al* (McLaughlin et al., 1993), the later study did not report cancer incidence or mortality endpoints other than in aggregate (for all cancers and leukaemia). So for analysis of kidney cancer mortality we still employed the data of Spengler *et al* (Spengler et al., 1983), although for the all cancer and leukaemia analysis we employed the findings for cancer incidence of McLaughlin *et al* (McLaughlin et al., 1993). The CT scan study of Huang *et al* (Huang et al., 2014) has been largely superseded, with a slightly larger age range, and only a single year of coverage outside that included in the later study of Li *et al* (Li et al., 2020); both studies are listed in Table 2, but only the later study was used in the meta-analysis.

An additional 60 papers were found by screening recent review papers and other material as indicated above. A few studies were omitted because of known methodological problems or because the data presented was of a preliminary nature. Specifically, one of the authors [Richard Doll] of the study of Court Brown *et al* (Court Brown et al., 1960) "became dissatisfied with the adequacy of the identification of the irradiated women ... and believes the results are unreliable." (Doll and Wakeford, 1997). The study of Hirayama (Hirayama, 1979) is a conference proceeding, and thus represents only preliminary findings, which was never followed by a peer-refereed publication in the literature.

The type of radiological exposure used within each study of postnatal exposure was classified as catheterisation, fluoroscopy, CT scan, X-ray, mixed or unknown; associated codes (C, F, CT, X, M, U respectively) were given for each endpoint within studies in Table 2. Some studies (e.g., Polhemus and Koch (Polhemus and Koch, 1959), Bailey *et al* (Bailey et al., 2010), Milne *et al* (Milne et al., 2014), Hong *et al* (Hong et al., 2019)), gave results for multiple types of

exposure. For the purposes of the meta-analysis, to avoid double counting of cases, we concentrated on results in relation to procedures likely to result in the largest radiation dose, specifically catheterisation, fluoroscopy or CT scan. However, for the study of Polhemus and Koch (Polhemus and Koch, 1959), the cases and controls receiving each type of exposure (fluoroscopy, X-ray) were disjoint, so that results for both exposure types were employed. Similarly, where OR/RR estimates were presented in terms of the number of exposures, the estimate for the largest number of exposures was used.

S.2 Meta-analysis

Meta-analysis was conducted of odds ratios (OR) or relative risks (RR) in the *in utero* exposure studies without radiation dose information, listed in Table 1, and of postnatal exposure without estimates of dose in Table 2. OR and RR were regarded as equivalent for the purposes of the meta-analysis. Data abstraction from the published papers was performed independently by MPL, GMK and NH.

Wherever possible the maximally adjusted OR/RR estimates given in each paper were employed in the meta-analysis. In some papers the OR/RR and CI are not given explicitly and so we estimated the OR/RR via maximum likelihood from the hypergeometric model conditional on marginal totals, with Fisher exact CI, estimated by fisher.test routine in R (R Project version 3.6.1, 2019). In a few instances (e.g., the studies of Shu *et al* (Shu et al., 1988) and Meinert *et al* (Meinert et al., 1999)) additional illustrative calculations were done in this way, and presented in Tables 1-2, although only the published OR/RR estimates were generally used in the meta-analysis.

The analysis was done in two ways. In the first, only those cancer sites within each study that contributed to one of the four endpoints (a) leukaemia, (b) lymphoma, (c) brain/CNS tumours and (d) cancers other than leukaemia, lymphoma and brain/CNS cancers (i.e., all solid cancers

except brain/CNS tumours) were used; leukaemia, brain/CNS tumours and lymphoma are the commonest forms of cancer in childhood. In the second type of analysis, as far as possible the endpoint used was "any available cancer site" from each study.

Because many of the CI for individual studies were markedly asymmetric, while much more nearly symmetric on a logarithmic scale, a log-transformation was applied; this has the additional desirable feature that after transformation back to the original scale the resulting meta-analytic OR/RR must be positive. An aggregate estimate of RR or OR was computed across subsets of these studies using random effects models, using standard statistical methods, that is to say inverse-variance weighted least squares (Viechtbauer, 2010). Restricted maximum-likelihood fits were used by default, but maximum-likelihood fits were also employed, as these facilitate comparison of nested models, in particular tests of improvement in fit relative to the null, i.e., lack of homogeneity of risk. [Homogeneity of risk across categories, for example of all cancer endpoints or of all types of radiological exposure, is the assumed null hypothesis.] Residual heterogeneity was assessed using Cochran's *Q*-statistic, the significance of which was assessed by comparing it against centiles of the χ^2 distribution with the relevant number of degrees of freedom ($=N-1$). Confidence intervals were derived using the method of Knapp and Hartung (Knapp and Hartung, 2003), which yields intervals with improved coverage probability (IntHout et al., 2014). The 2-sided *p*-values in Tables 3-6 were calculated in the standard way. Statistical significance was defined by $p<0.05$. In order to assess the contribution of the heterogeneity to the aggregate data the I^2 statistic of Higgins and Thompson (Higgins and Thompson, 2002) was computed. This is expressed as a percentage, so that a value near 0% implies little estimated inter-study heterogeneity relative to the intra-study variance, and values near 100% that the inter-study heterogeneity dominates the intra-study variance (Higgins and Thompson, 2002). Values of meta RR (mRR) or

meta OR (mOR) derived from the meta-analysis are given in Table 3 and 5 for major cancer subtypes (leukaemia, lymphoma, brain/CNS tumours and other cancers) and for any available cancer site.

In order to assess publication bias, funnel plots were employed. Funnel plots are scatterplots of the central estimate of risk against estimates of standard error, and as discussed by Egger *et al* (Egger et al., 1997; Sterne and Egger, 2001) are useful qualitative means of detecting various types of selection bias, in particular publication bias. If the funnel plot has the form of an inverted symmetric funnel then publication bias is thought to be unlikely (Egger et al., 1997; Sterne and Egger, 2001). More formal tests of selection or publication bias were also conducted using the test statistic suggested by Egger *et al* (Egger et al., 1997). We also employed the trim-and-fill method of Duval and Tweedie (Duval and Tweedie, 2000) to assess the likely magnitude of the change in mOR/mRR that may result from selection bias. All statistical models, including funnel plots, were fitted using the metafor package (Viechtbauer, 2010; Viechtbauer, 2020) in R (R Project version 3.6.1, 2019).

Supplementary Table S1. Studies of *in utero* exposure to medical diagnostic radiation without dose estimates (as given in Table 1) used in meta-analysis in relation to the particular cancer endpoint (Table 3)

Reference	Type of X-ray exposure, other features [questionnaire based, unless otherwise stated]	Endpoint [incidence unless otherwise stated]	Mapped endpoint in Table 3
	Four cancer endpoint analysis		
(Kjeldsberg, 1957)	Abdomen X-ray vs no X-ray	Leukaemia	Leukaemia
(Kaplan, 1958)	Sibling control, maternal abdominal X-rays vs no X-rays	Acute leukaemia mortality	Leukaemia
(Ford et al., 1959)	Abdominal or pelvic X-rays vs unexposed, medical-record based	Leukaemia mortality	Leukaemia
	Abdominal or pelvic X-rays vs unexposed, medical-record based	Brain/CNS mortality	Brain/CNS
	Abdominal or pelvic X-rays vs unexposed, medical-record based	All solid tumour excluding brain/CNS mortality	Other
	Abdominal or pelvic X-rays vs unexposed, medical-record based	Lymph node mortality	Lymphoma
(Murray et al., 1959)	Pelvimetry + other abdominal X-ray, medical record based	Leukaemia mortality	Leukaemia
(Polhemus and Koch, 1959)	Pelvimetry vs no exposure, excluding non-obstetric X-rays and maternal occupational radiation	Leukaemia	Leukaemia
(Wells and Steer, 1961)	X-ray pelvimetry+abdominal vs unexposed (excluding dental), medical-record based	Leukaemia	Leukaemia
(Gunz and Atkinson, 1964)	Abdominal X-ray vs unexposed	Leukaemia	Leukaemia
(Ager et al., 1965)	Any abdominal or pelvic X-ray vs no X-ray, sibling+neighbourhood controls	Leukaemia mortality	Leukaemia
(Graham et al., 1966)	Intrauterine abdominal radiation exposure vs no X-ray, medical-record based	Leukaemia	Leukaemia
(Stewart, 1973)	Maternal X-ray, cancer mortality	Leukaemia mortality	Leukaemia
(Bithell and Stewart, 1975)	Maternal X-ray, cancer mortality	Lymphatic leukaemia mortality	Leukaemia
	Maternal X-ray, cancer mortality	Myeloid leukaemia mortality	Leukaemia
	Maternal X-ray, cancer mortality	Other/unspecified leukaemia mortality	Leukaemia
	Maternal X-ray, cancer mortality	Lymphoma mortality	Lymphoma
	Maternal X-ray, cancer mortality	Wilms' tumour mortality	Other
	Maternal X-ray, cancer mortality	CNS mortality	Brain/CNS
	Maternal X-ray, cancer mortality	Neuroblastoma mortality	Other
	Maternal X-ray, cancer mortality	Bone tumour mortality	Other
	Maternal X-ray, cancer mortality	Other solid tumour (excluding Wilms', CNS, neuroblastoma, bone tumour) mortality	Other
(Salonen, 1976)	Pelvic radiography, medical-record based	Leukaemia	Leukaemia

	Pelvic radiography, medical-record based	Brain	Brain/CNS
(Herrmann, 1980)	Abdominal X-ray examination in pregnancy vs unexposed	Leukaemia	Leukaemia
(Grufferman et al., 1982)	Radiographic examination during pregnancy	Rhabdomyosarcoma	Other
(Preston-Martin et al., 1982)	Pelvic X-ray	Brain tumour	Brain/CNS
(Monson and MacMahon, 1984)	Pelvimetry, flat plate of abdomen, upper or lower GI series, intravenous pyelogram or gallbladder series, medical-record based	Leukaemia mortality	Leukaemia
	Pelvimetry, flat plate of abdomen, upper or lower GI series, intravenous pyelogram or gallbladder series, medical-record based	CNS tumour mortality	Brain/CNS
(van Steensel-Moll et al., 1985)	Prenatal radiation exposure	Acute lymphoblastic leukaemia	Leukaemia
(Harvey et al., 1985)	Abdominal X-ray during pregnancy, medical-record based	Leukaemia	Leukaemia
	Abdominal X-ray during pregnancy, medical-record based	Brain	Brain/CNS
	Abdominal X-ray during pregnancy, medical-record based	Lymphoma	Lymphoma
	Abdominal X-ray during pregnancy, medical-record based	All solid cancer excluding brain	Other
(Johnston et al., 1986)	X-rays during pregnancy, general practitioner (GP)+hospital controls, medical-record based	Germ cell tumour	Other
(Bunin et al., 1987)	Abdominal or pelvic X-ray	Wilms' tumour	Other
(Operskalski et al., 1987)	Pelvic X-ray during pregnancy	Osteosarcoma	Other
(Shu et al., 1988)	Abdomen exposure	Leukaemia	Leukaemia
(Bunin et al., 1989)	Any abdominal/pelvic X-ray during pregnancy	Non-heritable retinoblastoma	Other
(Howe et al., 1989)	Abdominal X-ray	Brain tumour	Brain/CNS
(Magnani et al., 1989)	Pelvic or abdominal X-ray	Soft tissue sarcoma	Other
(Gardner et al., 1990)	Local controls, using medical records for maternal abdominal X-ray exposure	Leukaemia	Leukaemia
	Local controls, using medical records for maternal abdominal X-ray exposure	NHL	Lymphoma
(Kuijten et al., 1990)	Abdominal or pelvic X-ray	Astrocytoma	Brain/CNS
(Rodvall et al., 1990)	Abdominal X-ray, medical-record based	Leukaemia	Leukaemia
	Abdominal X-ray, medical-record based	CNS	Brain/CNS
(Magnani et al., 1990)	Pelvic + abdominal X-ray	Acute lymphoblastic leukaemia	Leukaemia
	Pelvic + abdominal X-ray	Acute non-lymphoblastic leukaemia	Leukaemia
(Golding et al., 1992)	X-ray of abdomen or pelvis, medical-record based	Leukaemia	Leukaemia
(Holly et al., 1992)	Radiography during pregnancy	Ewing's sarcoma	Other
(Winn et al., 1992)	Diagnostic X-rays, using sibling controls	Ewing's sarcoma	Other
(Fajardo-Gutierrez et al., 1993)	Any X-ray during pregnancy	Leukaemia	Leukaemia
(Sorahan and Stewart, 1993)	Maternal X-ray, cancer mortality, partially medical-record based	Retinoblastoma mortality	Other

(Bunin et al., 1994)	X-ray of lower abdomen	Astrocytoma	Brain/CNS
	X-ray of lower abdomen	Primitive neuroectodermal tumour (PNET)	Brain/CNS
(McCredie et al., 1994a)	Diagnostic X-rays	Brain tumour	Brain/CNS
(Shu et al., 1994b)	Lower abdomen X-ray and pelvimetry	All infant leukaemia	Leukaemia
(Shu et al., 1994a)	Prenatal X-ray exposure	Acute leukaemia	Leukaemia
	Prenatal X-ray exposure	Lymphoma	Lymphoma
	Prenatal X-ray exposure	Brain tumour	Brain/CNS
(van Duijn et al., 1994)	Prenatal X-ray exposure	Acute non-lymphoblastic leukaemia	Leukaemia
(Shu et al., 1995)	X-ray during pregnancy	Germ cell tumour	Other
(Roman et al., 1997)	Lower abdomen X-ray, medical-record based	Leukaemia	Leukaemia
	Lower abdomen X-ray, medical-record based	NHL	Lymphoma
(McKinney et al., 1999)	One or more abdominal X-rays vs none, medical-record based	Leukaemia	Leukaemia
	One or more abdominal X-rays vs none, medical-record based	Lymphoma	Lymphoma
	One or more abdominal X-rays vs none, medical-record based	CNS tumours	Brain/CNS
	One or more abdominal X-rays vs none, medical-record based	Other tumours (than leukaemia, lymphoma, CNS)	Other
(Meinert et al., 1999)	Diagnostic X-ray of abdomen, pelvis, intestinal tract in pregnancy vs completely unexposed	Leukaemia	Leukaemia
	Diagnostic X-ray of abdomen, pelvis, intestinal tract in pregnancy vs completely unexposed	NHL	Lymphoma
(Fear et al., 2001)	Abdominal X-ray, medical-record based	Brain tumour	Brain/CNS
(Naumburg et al., 2001)	Abdominal X-ray, adjusted for age at birth, gestational age, parity, smoking, cesarean section, birthweight, medical-record based	Leukaemia	Leukaemia
(Schuz et al., 2001)	Diagnostic X-ray in pregnancy	CNS	Brain/CNS
(Shu et al., 2002)	Pelvimetric X-ray	Acute lymphoblastic leukaemia	Leukaemia
(Infante-Rivard, 2003)	Pelvimetry + abdominal X-ray	Acute lymphoblastic leukaemia	Leukaemia
(Patton et al., 2004)	Maternal gonadal X-ray exposure in pregnancy	Neuroblastoma	Other
(Stålberg et al., 2007)	Exposure to abdominal X-ray during pregnancy, medical-record based, adjusted for maternal age, parity, multiple birth, mother born in a Nordic country, gestational age at birth, mode of delivery, breech position, birth weight, birth head circumference, level of hospital, hypertension during pregnancy	Brain tumour	Brain/CNS
(Goel et al., 2009)	Maternal gonadal X-ray exposure in pregnancy, adjusted for income, maternal education and matched on age at diagnosis and geographic region of residence	Wilms' tumour	Other
(Grufferman et al., 2009)	Pelvis or abdomen X-ray exposure, matched on age, sex, race and adjusted for length of pregnancy, type of delivery, spotting/cramping/abnormal vaginal bleeding during pregnancy	Rhabdomyosarcoma	Other
(Spix et al., 2009)	Diagnostic X-ray exposure	Brain tumour	Brain/CNS
(Bailey et al., 2010)	Any plain abdominal X-ray or CT	Acute lymphoblastic leukaemia	Leukaemia

(Bartley et al., 2010)	Any X-ray in pregnancy	Acute lymphoblastic leukaemia	Leukaemia
	Any X-ray in pregnancy	Acute myeloid leukaemia	Leukaemia
(Castro-Jimenez and Orozco-Vargas, 2011)	Any X-ray	Acute lymphoblastic leukaemia	Leukaemia
(Rajaraman et al., 2011)	Any radiation exposure in utero, medical-record based	Lymphoma	Lymphoma
	Any radiation exposure in utero, medical-record based	Brain/CNS	Brain/CNS
	Any radiation exposure in utero, medical-record based	Sarcoma	Other
	Any radiation exposure in utero, medical-record based	Peripheral neural tumours	Other
	Any radiation exposure in utero, medical-record based	Renal	Other
(Hassanzadeh et al., 2011)	Abdominal radiation exposure in utero, medical-record based	Leukaemia	Leukaemia
	History of mother's radiography	Leukaemia	Leukaemia
(Kumar et al., 2014a)	History of mother's radiography	Leukaemia	Leukaemia
(Milne et al., 2014)	Any fetal X-ray exposure	Brain tumour	Brain/CNS
(Tettamanti et al., 2017)	X-ray or other scan to the abdomen during pregnancy	Brain tumour	Brain/CNS
(Diamond et al., 1973)	Abdominal X-rays, medical-record based	Leukaemia mortality	Leukaemia
	Abdominal X-rays, medical-record based	Lymphoma mortality	Lymphoma
	Abdominal X-rays, medical-record based	Brain/CNS mortality	Brain/CNS
	Abdominal X-rays, medical-record based	All other malignant neoplasm mortality	Other
	Any cancer site analysis		
(Kjeldsberg, 1957)	Abdomen X-ray vs no X-ray	Leukaemia	
(Kaplan, 1958)	Sibling control, maternal abdominal X-rays vs no X-rays	Acute leukaemia mortality	
(Ford et al., 1959)	Abdominal or pelvic X-rays vs unexposed, medical-record based	All malignant tumour mortality	
(Murray et al., 1959)	Pelvimetry + other abdominal X-ray vs no pelvimetry or other abdominal, medical record based	Leukaemia mortality	
(Polhemus and Koch, 1959)	Pelvimetry vs no exposure, excluding non-obstetric X-rays and maternal occupational radiation	Leukaemia	
(Wells and Steer, 1961)	X-ray pelvimetry+abdominal vs unexposed (excluding dental), medical-record based	Leukaemia	
(Gunz and Atkinson, 1964)	Abdominal X-ray vs unexposed	Leukaemia	
(Ager et al., 1965)	Any abdominal or pelvic X-ray vs no X-ray, sibling+neighbourhood controls	Leukaemia mortality	
(Graham et al., 1966)	Intrauterine abdominal radiation exposure vs no X-ray, medical-record based	Leukaemia	
(Salonen, 1976)	Pelvic radiography, medical-record based	All tumour	
(Herrmann, 1980)	Abdominal X-ray examination in pregnancy vs unexposed	Leukaemia	
(Shiono et al., 1980)	"High" or "medium" doses of X-rays (barium enemas, pyelogram etc), medical-record based	All malignant neoplasms	
	"High" or "medium" doses of X-rays (barium enemas, pyelogram etc), medical-record based	All benign neoplasms	

(Grufferman et al., 1982)	Radiographic examination during pregnancy	Rhabdomyosarcoma
(Preston-Martin et al., 1982)	Pelvic X-ray	Brain tumour
(Monson and MacMahon, 1984)	Pelvimetry, flat plate of abdomen, upper or lower GI series, intravenous pyelogram or gallbladder series, medical-record based	All tumour mortality
(van Steensel-Moll et al., 1985)	Prenatal radiation exposure	Acute lymphoblastic leukaemia
(Harvey et al., 1985)	Abdominal X-ray during pregnancy, medical-record based	All cancer
Hopton et al 1985	One or more pelvic X-rays vs no pelvic X-rays, medical-record based	Leukaemia + lymphoma
	One or more pelvic X-rays vs no pelvic X-rays, medical-record based	Solid tumour
(Johnston et al., 1986)	X-rays during pregnancy, GP+hospital controls, medical-record based	Germ cell tumour
(Bunin et al., 1987)	Abdominal or pelvic X-ray	Wilms' tumour
(Operskalski et al., 1987)	Pelvic X-ray during pregnancy	Osteosarcoma
(Shu et al., 1988)	Abdomen exposure	Leukaemia
(Bunin et al., 1989)	Any abdominal/pelvic X-ray during pregnancy	Non-heritable retinoblastoma
Gilman et al 1989	Any pregnancy X-ray, partial medical-record based	All cancer mortality
(Howe et al., 1989)	Abdominal X-ray	Brain tumour
(Magnani et al., 1989)	Pelvic or abdominal X-ray	Soft tissue sarcoma
(Gardner et al., 1990)	Local controls, using medical records for maternal abdominal X-ray exposure	Leukaemia + NHL
(Golding et al., 1990)	Any X-ray exposure in pregnancy (including dental), medical-record based	All cancer
(Kuijten et al., 1990)	Abdominal or pelvic X-ray	Astrocytoma
(Rodvall et al., 1990)	Abdominal X-ray, medical-record based	All cancer
(Magnani et al., 1990)	Pelvic + abdominal X-ray	Acute lymphoblastic leukaemia
	Abdominal + thoracic X-ray	Acute non-lymphoblastic leukaemia
(Golding et al., 1992)	X-ray of abdomen or pelvis, medical-record based	All cancer
(Holly et al., 1992)	Radiography during pregnancy	Ewing's sarcoma
(Stjernfeldt et al., 1992)	Abdomen/pelvis X-ray vs known unexposed	Solid tumour
(Winn et al., 1992)	Diagnostic X-rays, using sibling controls	Ewing's sarcoma
(Fajardo-Gutierrez et al., 1993)	Any X-ray during pregnancy	Leukaemia
(Roman et al., 1993)	Abdominal X-rays, using obstetric records	Leukaemia + NHL
(Bunin et al., 1994)	X-ray of lower abdomen	Astrocytoma
	X-ray of lower abdomen	Primitive neuroectodermal tumour (PNET)
(McCredie et al., 1994a)	Diagnostic X-rays	Brain tumour

(Shu et al., 1994b)	Lower abdomen X-ray and pelvimetry	All infant leukaemia
(Shu et al., 1994a)	Abdominal X-ray exposure	All cancer
(van Duijn et al., 1994)	Prenatal X-ray exposure	Acute non-lymphoblastic leukaemia
(Shu et al., 1995)	X-ray during pregnancy	Germ cell tumour
(Roman et al., 1997)	Lower abdomen X-ray, medical-record based	Leukaemia
	Lower abdomen X-ray, medical-record based	NHL
(McKinney et al., 1999)	One or more abdominal X-rays vs none, medical-record based	Leukaemia
	One or more abdominal X-rays vs none, medical-record based	Lymphoma
	One or more abdominal X-rays vs none, medical-record based	CNS Tumours
	One or more abdominal X-rays vs none, medical-record based	Other tumours (than leukaemia, lymphoma, CNS)
(Meinert et al., 1999)	Diagnostic X-ray in pregnancy	Leukaemia
	Diagnostic X-ray in pregnancy	NHL
	Diagnostic X-ray in pregnancy	Solid tumour
(Fear et al., 2001)	Abdominal X-ray, medical-record based	Brain tumour
(Naumburg et al., 2001)	Abdominal X-ray, adjusted for age at birth, gestational age, parity, smoking, cesarean section, birthweight, medical-record based	Leukaemia
(Schuz et al., 2001)	Diagnostic X-ray in pregnancy	CNS
(Shu et al., 2002)	Pelvimetric X-ray	Acute lymphoblastic leukaemia
(Infante-Rivard, 2003)	Pelvimetry + abdominal X-ray	Acute lymphoblastic leukaemia
(Patton et al., 2004)	Maternal gonadal X-ray exposure in pregnancy	Neuroblastoma
(Stålberg et al., 2007)	Exposure to abdominal X-ray during pregnancy, medical-record based, adjusted for maternal age, parity, multiple birth, mother born in a Nordic country, gestational age at birth, mode of delivery, breech position, birth weight, birth head circumference, level of hospital, hypertension during pregnancy	Brain tumour
(Goel et al., 2009)	Maternal gonadal X-ray exposure in pregnancy, adjusted for income, maternal education and matched on age at diagnosis and geographic region of residence	Wilms' tumour
(Grufferman et al., 2009)	Pelvis or abdomen X-ray exposure, matched on age, sex, race and adjusted for length of pregnancy, type of delivery, spotting/cramping/abnormal vaginal bleeding during pregnancy	Rhabdomyosarcoma
(Spix et al., 2009)	Diagnostic X-ray exposure	Brain tumour
(Bailey et al., 2010)	Any plain abdominal X-ray or CT	Acute lymphoblastic leukaemia
(Bartley et al., 2010)	Any X-ray in pregnancy	Acute lymphoblastic leukaemia
	Any X-ray in pregnancy	Acute myeloid leukaemia
(Castro-Jimenez and Orozco-Vargas, 2011)	Any X-ray	Acute lymphoblastic leukaemia

(Rajaraman et al., 2011)	Abdominal radiation exposure in utero, medical-record based	All cancer
(Hassanzadeh et al., 2011)	History of mother's radiography	Leukaemia
(Milne et al., 2014)	Any fetal X-ray exposure	Brain tumour
(Kumar et al., 2014a)	History of radiography during pregnancy	Leukaemia
(Tettamanti et al., 2017)	X-ray or other scan to the abdomen during pregnancy	Brain tumour
(Diamond et al., 1973)	Abdominal X-rays, medical-record based	Leukaemia mortality
	Abdominal X-rays, medical-record based	Lymphoma mortality
	Abdominal X-rays, medical-record based	Brain/CNS mortality
	Abdominal X-rays, medical-record based	All other malignant neoplasm (than leukaemia, lymphoma, brain/CNS) mortality
(Ray et al., 2010)	Any diagnostic radiation exposure in utero, hazard ratio computed via Cox model, medical-record based	All childhood malignancies

691

692 **Supplementary Table S2. Studies of postnatal exposure to medical diagnostic radiation without dose estimates (as given in**
693 **Table 2) used in meta-analysis in relation to the particular cancer endpoint (Table 5)**
694

Reference	Type of X-ray exposure, other features [questionnaire based, unless otherwise stated]	Endpoint [incidence unless otherwise stated]	Coding for purposes of analysis
Four cancer endpoint analysis			
(Stewart et al., 1958)	Diagnostic X-rays	Leukaemia mortality	Leukaemia
(Polhemus and Koch, 1959)	Diagnostic X-rays	Leukaemia	Leukaemia
	Fluoroscopy	Leukaemia	Leukaemia
(Ager et al., 1965)	Postnatal X-ray vs not, sibling controls; exposures within 1 y of death excluded	Leukaemia mortality	Leukaemia
(Graham et al., 1966)	Any postnatal radiation exposure vs none, excluding exposures 12 months before diagnosis, medical-record based	Leukaemia	Leukaemia
(Preston-Martin et al., 1980)	First diagnostic medical X-ray exposure at age <20 y	Intracranial meningiomas	Brain/CNS
(Preston-Martin et al., 1982)	Five or more full-mouth dental X-rays, starting at least 10 y before diagnosis	Brain tumour	Brain/CNS
(Greenberg, 1983)	Abdominal radiograph, hospital non-cancer controls	Neuroblastoma or ganglioneuroblastoma	Other
(Spengler et al., 1983)	Mortality after cardiac catheterisation. Observed cases and expected, relative risk assessed via exact Poisson model (Garwood 1936)	Kidney mortality, female	Other
(Operskalski et al., 1987)	Any radiation exposure except dental X-ray	Osteosarcoma	Other
(Shu et al., 1988)	6+ X-ray exposure vs none	Leukaemia	Leukaemia
(Howe et al., 1989)	Skull X-rays, ever vs never, adjusted for chest X-rays	Brain tumour	Brain/CNS
(Magnani et al., 1989)	Any diagnostic X-ray exposure	Soft tissue sarcoma	Other
(Nishi and Miyake, 1989)	Hip joint X-ray	Non T-cell acute lymphoblastic leukaemia	Leukaemia
(Kuijten et al., 1990)	Head or neck X-ray	Astrocytoma	Brain/CNS
(Magnani et al., 1990)	Any diagnostic X-ray	Acute lymphoblastic leukaemia	Leukaemia
(Fajardo-Gutierrez et al., 1993)	Any postnatal X-ray, hospital + community controls	Leukaemia	Leukaemia
(McLaughlin et al., 1993)	Any catheterisation. Observed cases and expected, relative risk assessed via exact Poisson model (Garwood, 1936)	Leukaemia incidence	Leukaemia
(Bunin et al., 1994)	Any head, neck, dental X-ray	Astrocytoma	Brain/CNS
	Any head, neck, dental X-ray	Primitive neuroectodermal tumour (PNET)	Brain/CNS
(McCredie et al., 1994b)	X-rays of head	Brain tumour	Brain/CNS
(Shu et al., 1994a)	Postnatal X-ray exposure	Acute leukaemia	Leukaemia
	Postnatal X-ray exposure	Lymphoma	Lymphoma
	Postnatal X-ray exposure	Brain tumour	Brain/CNS

(Meinert et al., 1999)	4+ diagnostic X-rays up to 1 year before diagnosis vs none	Acute leukaemia	Leukaemia
	4+ diagnostic X-rays up to 1 year before diagnosis vs none	NHL	Lymphoma
(Modan et al., 2000)	Cardiac catheterisationof children; observed cases and expected numbers based on Israeli national cancer incidence rates, follow-up starts 5 y after first catheterisation, relative risk assessed via exact Poisson model (Garwood, 1936)	All lymphomas, males	Lymphoma
	Cardiac catheterisationof children; observed cases and expected numbers based on Israeli national cancer incidence rates, follow-up starts 5 y after first catheterisation, relative risk assessed via exact Poisson model (Garwood, 1936)	Melanoma, males	Other
	Cardiac catheterisationof children; observed cases and expected numbers based on Israeli national cancer incidence rates, follow-up starts 5 y after first catheterisation relative risk assessed via exact Poisson model (Garwood, 1936)	Bladder, males	Other
	Cardiac catheterisationof children; observed cases and expected numbers based on Israeli national cancer incidence rates, follow-up starts 5 y after first catheterisation, relative risk assessed via exact Poisson model (Garwood 1936)	Stomach, males	Other
	Cardiac catheterisationof children; observed cases and expected numbers based on Israeli national cancer incidence rates, follow-up starts 5 y after first catheterisation, relative risk assessed via exact Poisson model (Garwood, 1936)	Testis, males	Other
	Cardiac catheterisationof children; observed cases and expected numbers based on Israeli national cancer incidence rates, follow-up starts 5 y after first catheterisation, relative risk assessed via exact Poisson model (Garwood, 1936)	Prostate, males	Other
(Schuz et al., 2001)	Any X-ray examination up to 1 y before diagnosis	All CNS	Brain/CNS
(Shu et al., 2002)	Ever X-ray exposure, excluding exposures within 2 y of diagnosis	Acute lymphoblastic leukaemia	Leukaemia
(Infante-Rivard, 2003)	≥ 2 X-rays vs none (excluding dental) – males	Acute lymphoblastic leukaemia	Leukaemia
	≥ 2 X-rays vs none (excluding dental) - females	Acute lymphoblastic leukaemia	Leukaemia
(Mellemkjaer et al., 2006)	Diagnostic X-rays, adjusted for gestational age	CNS tumours (excluding pituitary)	Brain/CNS
(Bailey et al., 2010)	Any CT exposure more than 6 months before diagnosis	Acute lymphoblastic leukaemia	Leukaemia
(Bartley et al., 2010)	Any postnatal X-ray excluding dental X-rays and X-rays received within 1 y of diagnosis	Acute lymphoblastic leukaemia	Leukaemia
	Any postnatal X-ray excluding dental X-rays and X-rays received within 1 y of diagnosis	Acute myeloid leukaemia	Leukaemia
(Khan et al., 2010)	Head X-ray not due to head injury, with possibly tumour-related X-rays deemed unexposed	Medulloblastoma/primitive neuroectodermal tumours	Brain/CNS
(Rajaraman et al., 2011)	Any radiation exposure in early infancy (0-100 days), medical-record based, 2 y lag	Leukaemia	Leukaemia
	Any radiation exposure in early infancy (0-100 days), medical-record based, 2 y lag	Lymphoma	Lymphoma
	Any radiation exposure in early infancy (0-100 days), medical-record based, 2 y lag	Brain/CNS	Brain/CNS
(Claus et al., 2012)	Full mouth X-ray at age < 10 y	Meningioma	Brain/CNS
(Liao et al., 2014)	Cystourethrography	Abdominal cancers excluding genitourinary cancers	Other
	Cystourethrography	Non-abdominal cancers	Other
	Cystourethrography	Genital cancers	Other
	Cystourethrography	Urinary system cancers	Other

	Cystourethrography	All other cancers	Other
(Milne et al., 2014)	Any CT scan to the head, lag 6 m	Brain tumour	Brain/CNS
(Shih et al., 2014)	Any X-ray	Leukaemia	Leukaemia
(Tettamanti et al., 2017)	Exposure to CT scan to head or body+head vs no X-ray or scan to the head, more than 2 y before diagnosis	Brain tumour	Brain/CNS
(Harbron et al., 2018)	X-ray guided cardiac catheterisation, excluding post-transplant patients	Leukaemia	Leukaemia
	X-ray guided cardiac catheterisation, excluding post-transplant patients	Central nervous system	Brain/CNS
	X-ray guided cardiac catheterisation, excluding post-transplant patients	Lymphoma	Lymphoma
	X-ray guided cardiac catheterisation, excluding post-transplant patients	Other tumours (than leukaemia, lymphoma, brain/CNS)	Other
(Baaken et al., 2019)	Any diagnostic X-ray procedure during 1976-2003, exposure lag of 2 y	Leukaemia	Leukaemia
	Any diagnostic X-ray procedure during 1976-2003, exposure lag of 2 y	Lymphomas	Lymphoma
	Any diagnostic X-ray procedure during 1976-2003, exposure lag of 2 y	CNS tumours	Brain/CNS
	Any diagnostic X-ray procedure during 1976-2003, exposure lag of 2 y	Blastomas	Other
	Any diagnostic X-ray procedure during 1976-2003, exposure lag of 2 y	Sarcomas	Other
	Any diagnostic X-ray procedure during 1976-2003, exposure lag of 2 y	Other solid tumours	Other
(Hong et al., 2019)	Any computed tomography exposure, exposure lag 2 y	Mouth/pharynx	Other
	Any computed tomography exposure, exposure lag 2 y	Digestive	Other
	Any computed tomography exposure, exposure lag 2 y	Respiratory	Other
	Any computed tomography exposure, exposure lag 2 y	Bone	Other
	Any computed tomography exposure, exposure lag 2 y	Melanoma	Other
	Any computed tomography exposure, exposure lag 2 y	Soft tissue	Other
	Any computed tomography exposure, exposure lag 2 y	Breast	Other
	Any computed tomography exposure, exposure lag 2 y	Female genital	Other
	Any computed tomography exposure, exposure lag 2 y	Male genital	Other
	Any computed tomography exposure, exposure lag 2 y	Urinary	Other
	Any computed tomography exposure, exposure lag 2 y	Brain	Brain/CNS
	Any computed tomography exposure, exposure lag 2 y	Thyroid	Other
	Any computed tomography exposure, exposure lag 2 y	Hodgkin lymphoma	Lymphoma
	Any computed tomography exposure, exposure lag 2 y	Other lymphoma	Lymphoma
	Any computed tomography exposure, exposure lag 2 y	Leukaemia	Leukaemia

	Any computed tomography exposure, exposure lag 2 y	Myelodysplasia	Leukaemia
(Li et al., 2020)	Computed tomography, 2 y exclusion	Leukaemia	Leukaemia
	Computed tomography, 2 y exclusion	Intracranial malignancy	Brain/CNS
	Computed tomography, 2 y exclusion	Lymphoma	Lymphoma
Any cancer site analysis			
(Stewart et al., 1958)	Diagnostic X-rays	All cancer mortality	
(Polhemus and Koch, 1959)	Diagnostic X-rays	Leukaemia	
	Fluoroscopy	Leukaemia	
(Ager et al., 1965)	Postnatal X-ray vs not, sibling controls; exposures within 1 y of death excluded	Leukaemia mortality	
(Graham et al., 1966)	Any postnatal radiation exposure vs none, excluding exposures 12 months before diagnosis, medical-record based	Leukaemia	
(Preston-Martin et al., 1980)	First diagnostic medical X-ray exposure at age <20 y	Intracranial meningiomas	
(Preston-Martin et al., 1982)	Five or more full-mouth dental X-rays, starting at least 10 y before diagnosis	Brain tumour	
(Greenberg, 1983)	Abdominal radiograph, hospital non-cancer controls	Neuroblastoma or ganglioneuroblastoma	
(Operskalski et al., 1987)	Any radiation exposure except dental X-ray	Osteosarcoma	
(Hartley et al., 1988)	Neonatal X-ray	Any cancer incidence	
(Shu et al., 1988)	6+ X-ray exposure vs none	Leukaemia	
(Howe et al., 1989)	Skull X-rays, ever vs never, adjusted for chest X-rays	Brain tumour	
(Magnani et al., 1989)	Any diagnostic X-ray exposure	Soft tissue sarcoma	
(Nishi and Miyake, 1989)	Hip joint X-ray	Non T-cell acute lymphoblastic leukaemia	
(Kuijten et al., 1990)	Head or neck X-ray	Astrocytoma	
(Magnani et al., 1990)	Any diagnostic X-ray	Acute lymphoblastic leukaemia	
(Fajardo-Gutierrez et al., 1993)	Any postnatal X-ray, hospital + community controls	Leukaemia	
(McLaughlin et al., 1993)	Any catheterisation. Observed cases and expected, relative risk assessed via exact Poisson model (Garwood, 1936)	All cancer incidence	
(Bunin et al., 1994)	Any head, neck, dental X-ray	Astrocytoma	
	Any head, neck, dental X-ray	Primitive neuroectodermal tumour (PNET)	
(McCredie et al., 1994b)	X-rays of head	Brain tumour	
(Shu et al., 1994a)	Postnatal X-ray exposure	All cancer	
(Meinert et al., 1999)	4+ diagnostic X-rays up to 1 year before diagnosis vs none	Acute leukaemia	
	4+ diagnostic X-rays up to 1 year before diagnosis vs none	NHL	

	4+ diagnostic X-rays up to 1 year before diagnosis vs none	Solid tumour	
(Modan et al., 2000)	Cardiac catheterisationof children; observed cases and expected numbers based on Israeli national cancer incidence rates, follow-up starts 5 y after first catheterisation, relative risk assessed via exact Poisson model (Garwood, 1936)	All sites, males+females	
(Schuz et al., 2001)	Any X-ray examination up to 1 y before diagnosis	All CNS	
(Shu et al., 2002)	Ever X-ray exposure, excluding exposures within 2 y of diagnosis	Acute lymphoblastic leukaemia	
(Infante-Rivard, 2003)	≥ 2 X-rays vs none (excluding dental) - males	Acute lymphoblastic leukaemia	
	≥ 2 X-rays vs none (excluding dental) - females	Acute lymphoblastic leukaemia	
(Mellemkjaer et al., 2006)	Diagnostic X-rays, adjusted for gestational age	CNS tumours (excluding pituitary)	
(Bailey et al., 2010)	Any CT exposure more than 6 months before diagnosis	Acute lymphoblastic leukaemia	
(Bartley et al., 2010)	Any postnatal X-ray excluding dental X-rays and X-rays received within 1 y of diagnosis	Acute lymphoblastic leukaemia	
	Any postnatal X-ray excluding dental X-rays and X-rays received within 1 y of diagnosis	Acute myeloid leukaemia	
(Khan et al., 2010)	Head X-ray not due to head injury, with possibly tumour-related X-rays deemed unexposed	Medulloblastoma/primitive neuroectodermal tumours	
(Rajaraman et al., 2011)	Any radiation exposure in early infancy (0-100 days), medical-record based, 2 y lag	All cancer	
(Claus et al., 2012)	Full mouth X-ray at age < 10 y	Meningioma	
(Liao et al., 2014)	Cystourethrography	All cancer	
(Milne et al., 2014)	Any CT scan to the head, lag 6 m	Brain tumour	
(Shih et al., 2014)	Any X-ray	Leukaemia	
(Tettamanti et al., 2017)	Exposure to CT scan to head or body+head vs no X-ray or scan to the head, more than 2 y before diagnosis	Brain tumour	
(Harbron et al., 2018)	X-ray guided cardiac catheterisation, excluding post-transplant patients	All malignancies	
(Baaken et al., 2019)	Any diagnostic procedure	All cancers	
(Hong et al., 2019)	Any computed tomography exposure, exposure lag 2 y	All solid	
	Any computed tomography exposure, exposure lag 2 y	Lymphoid & haemopoietic malignant neoplasms	
(Li et al., 2020)	Computed tomography, 2 y exclusion	Leukaemia	
	Computed tomography, 2 y exclusion	Intracranial malignancy	
	Computed tomography, 2 y exclusion	Lymphoma	

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Supplementary Table S3. PECO statement[a]

PECO element	Evidence stream	Articles or features included	Articles or features excluded
Population	Human	Any population Exposure *in utero* or in childhood (age at exposure ≤ 20 y) Diagnostic exposure Study designs (a) Cohort (b) Case-cohort (c) Case-control (d) Nested case-control (e) Cross sectional	Predominant exposure is from radon or other high linear energy transfer (LET) radiation Therapeutic exposure Natural background exposure Environmental exposure Case series Ecologic studies Mechanistic studies Information on risks in relation to exposure age ≤ 20 y not given
Exposure	Human	Ionizing radiation exposure (a) Gamma rays (b) X-rays (c) Beta rays (d) Other low LET	Quantitative dose response
Comparator	Human	A comparison population, exposed to lower level of radiation exposure, or presumed largely unexposed (e.g. national population)	No comparison group
Outcome	Human	Cancer endpoints (deaths, incidence) Benign tumours (deaths, incidence)	Cancer endpoints not described Benign tumour endpoints not described
General considerations		Reports primary source Full text available	Reports secondary source (e.g. review articles) Editorials Only abstracts Correspondence

[a]PECO = Population, Exposure, Comparator and Outcome

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