Early life ionizing radiation exposure and cancer risks: systematic review and meta-analysis

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Abstract:	Background: Ionizing radiation use for medical diagnostic purposes has substantially increased over the last three decades. Moderate to high doses of radiation are well established causes of cancer, especially for exposure at young ages. However, cancer risk from low-dose medical imaging is debated. Objective: We aim to review the literature on cancer risks associated with prenatal and postnatal medical diagnostic ionizing radiation exposure among children and to assess this risk through a meta-analysis. Methods: A literature search of five electronic databases supplemented by hand search was performed to retrieve relevant epidemiological studies published from 2000 to 2019, including patients aged < 22 years exposed to medical imaging ionizing radiation. Pooled Odds Ratio (OR pooled) and pooled Excess Relative Risk (ERR pooled) representing the excess of risk per unit of organ dose were estimated with a random-effect model. Results: Twenty-four studies were included. For prenatal exposure (X-ray or computed tomography (CT)), no significant increased risk for all-cancer, leukemia and brain tumors were reported. For postnatal exposure, increased risks were observed only for CTs, mostly for leukemia: ERR pooled =26.9 Gy -1 (95% confidence interval: 2.7, 57.1) and brain tumors: ERR pooled =9.1 Gy -1 (95% confidence interval: 5.2, 13.1). Conclusion: CT exposure in childhood appears to be associated with increased risks of cancer while no significant association was observed with diagnostic X-rays. Methodological limitations of the studies considered would be handled in upcoming large international studies. Results support optimization efforts to minimize doses to pediatric patients. Keywords: prenatal, postnatal, low-dose ionizing radiation, cancer, CT
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Original article

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Abstract

Background The cancer risk from low-dose medical imaging is debated.

Objective To review the literature on cancer risks associated with prenatal and postnatal medical diagnostic ionizing radiation exposure among children and to assess this risk through a meta-analysis.

Materials and methods A literature search of five electronic databases supplemented by a hand search was performed to retrieve relevant epidemiological studies published from 2000 to 2019, including patients younger than 22 years of age exposed to medical imaging ionizing radiation. Pooled Odds Ratio (OR_{pooled}) and pooled Excess Relative Risk (ERR_{pooled}) representing the excess of risk per unit of organ dose were estimated with a random effect model.

Results Twenty-four studies were included. For prenatal exposure (radiographs or computed tomography [CT]), no significant increased risk was reported for all cancers, leukemia and brain tumors. For postnatal exposure, increased risks were observed only for CTs, mostly for leukemia: ERR_{pooled}=26.9 Gy^{-1} (95% confidence interval [CI]: 2.7, 57.1) and brain tumors: ERR_{pooled}=9.1 Gy^{-1} (95% CI: 5.2, 13.1).

Conclusion CT exposure in childhood appears to be associated with increased risks of cancer while no significant association was observed with diagnostic radiographs.

Keywords Cancer, Children, Computed tomography, Ionizing radiation, Postnatal, Prenatal, Radiography, Risk

Introduction

Medical diagnostic imaging using ionizing radiation is a very important tool in patients' care and substantial benefits arise from its use. Recent decades have been marked by an increased use of medical radiation imaging [1] representing an annual growth of about 5% to 8% per capita [2], mostly in developed countries.

Although single doses delivered per examination have decreased over the years, thanks to advances in technologies, protocols improvements, awareness and the reactivity of radiologists to improve their daily practice in accordance with scientific and medical recommendations, overall collective doses continue to increase [3–5], resulting from the growing number of tests performed and the use of procedures, such as computed tomography (CT), that are known to deliver much higher doses than conventional radiology procedures.

Several epidemiological studies of populations exposed to high to moderate doses of ionizing radiation have shown an increased risk of cancer [6–9]. Increased risk of cancer with decreasing age at exposure has been described [2, 10], hence foetuses and children are more radiosensitive [2].

Studies in the 1950s and 1960s linked prenatal and postnatal diagnostic X-ray exposure to an increased risk of childhood cancer [11–15]. However, with the decrease of doses observed over the years, the association became weak, especially for postnatal exposure [16].

Since former reviews of literature on children exposed to medical diagnostic radiation [9, 16–19] did not include recent cohorts on CT and interventional procedures, or quantitative

summaries, we aimed to assess cancer risk subsequent to prenatal and postnatal medical diagnostic radiation exposure through a systematic review, and to provide a quantitative summary on the overall risk estimate.

Materials and methods

We followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyze guidelines (PRISMA) [20] adapted to observational studies.

Online searches

An online-based literature search was conducted in July 2019 in PubMed, Scopus, Web of Science, Global Health and EMBASE. Specific keywords: ((neoplasms OR cancer) AND risk AND medical AND (diagnosis OR diagnostic) AND ("radiation exposure" OR (radiation AND exposure)) AND (child OR children)) were used. An additional search was carried out by hand through references from relevant publications and international reports such as BEIR VII [21] and UNSCEAR 2006 & 2013 [2, 22].

All relevant articles fulfilling the selection criteria based (see below) on their title and abstract were selected and reviewed by two different authors (E.R. and K.D.A.), with a review by a third author (M.-O.B.) in case of discrepancy. Duplicate studies from the different databases

were removed and studies providing completed quantitative information and risk estimate were then included in the meta-analysis.

Selection criteria

Eligible studies were cohort and case-control studies, published in English from Jan. 1, 2000, to July 31, 2019, involving children younger than 22 years at exposure. The exposure period was restricted to 1970 onward to ensure comparability with more recent practices since doses tend to decrease over time. Abstracts of congresses, meta-analyses, letters and authors' comments were ineligible but were checked to find any relevant reference. In case of publications on overlapping populations or updated publications [23–30], only data from the most complete study were considered [25, 27, 28, 30].

Methodological quality assessment of individual studies

To assess the risk of bias for individual studies, the Newcastle-Ottawa Scale (NOS) for quality assessment of non-randomized studies [31] and Agency for Healthcare Research and Quality (AHRQ) standards [32] for observational study were applied by two investigators (E.R. and K.D.A.). NOS quality tools uses eight items, grouped into three domains of potential bias such as selection (representation of the sample, sample size, non-respondents, ascertainment of the exposure), comparability (the subjects in different outcome groups are comparable, based on the

study design or analysis, and confounding factors are controlled) and outcome/exposure (assessment of outcome or exposure and statistical test). A maximum of one star can be given for each item within the selection and outcome categories and a maximum of two stars can be given for comparability. To convert the NOS into AHRQ standards (good, fair and poor quality) thresholds are as follows:

- Good quality: 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain.
- Fair quality: 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain.
- Poor quality: 0 or 1 star in selection domain OR 0 star in comparability domain OR 0 or 1 star in outcome/exposure domain.

Statistical analysis

Studies providing a comprehensive risk estimate were set together to generate a summarized risk of cancer following medical diagnostic radiation exposure. In radiation epidemiology, however, the association between cancer risk and exposure is most often described by a risk difference or excess risk rather than a risk ratio or relative risk. In the case of an Excess Relative Risk (ERR) model, a linear multiplicative relationship between risk and exposure is assumed rather than an exponential relationship [21]. The ERR is the proportional increase in risk over the background rate of cancer (in the absence of exposure) per unit of dose, as follows: $RR = 1 + \beta D$, where

RR is the relative risk, β is the ERR and D is the dose received. For example, a RR of 1.2 equals to an ERR of 0.2, per unit of dose which corresponds to an increase in risk of 20% per unit of dose.

We estimated a pooled ERR to assess the strength of the association when provided from the individual studies otherwise a pooled relative risk (RR) or odds ratio (OR) is computed.

Analysis has been performed by period of exposure (pre- or postnatal) and type of cancer. The DerSimonian and Laird random-effect model was used to estimate the overall effect size [33] to account for within and between study heterogeneities. Confidence Intervals (CIs) bounds of ERRs commonly reported from epidemiological studies may be non-symmetric when estimated under different hypothesis with different methods (Wald test, maximum likelihood, profile likelihood). Inference of standard deviation from the ERR's CIs in such circumstance could lead to biased results. An alternative DerSimonian and Laird-based model proposed by Richardson et al. [34] was used to estimate the pooled effect of ERRs.

We assessed a study's small size effect and quantified the contribution of heterogeneity to the summarized estimate with the I^2 statistic, calculated as follows:

$$I^2 = 1 - \frac{df}{Q}$$

where Q is the Cochran's statistic of heterogeneity, which follows a standard χ^2 distribution with $df = k - 1$ degree of freedom (k is the number of individual studies).

I^2 is interpreted as the proportion of the total variation of the estimated effect due to heterogeneity between studies [33]. Publication and selection bias were assessed and tested using the Egger test [35, 36]. Statistical significance was defined by $P<0.05$.

All statistical analyses were conducted using Stata statistical software, STATA/MP 15.1 (Stata Corp, College Station, Texas, USA) and R 3.5.1 software.

Results

The systematic search yielded 1,674 articles. Figure 1 displays the flow diagram of selection of the relevant studies. After excluding duplicated studies (n=181), 1,493 articles have been screened and 254 eligible articles have been reviewed, with 24 included in the review according to prenatal (Table 1) [37–44] and postnatal radiation exposure (Tables 2 and 3) [25, 26, 29, 30, 37, 38, 41, 43–55]. There were 13 case-control studies [26, 37–41, 43, 44, 52–56] and 11 cohort studies [25, 29, 30, 42, 45–51] (Fig. 1).

Prenatal diagnostic radiation exposure

Cancer risks related to prenatal radiation exposure have been investigated in seven case-control studies [37–41, 43, 44] and in one cohort study [42] (Table 1). Medical examinations investigated were X-ray in five out of eight studies [37–40, 43], and X-ray coupled with CT in two studies [41, 44]. Intravenous pyelograms and radionuclide tests were evaluated in one study [41].

In the case-control studies, cancer cases were identified from cancer registries while controls were randomly selected from population registries and matched to cases on gender and

age at cancer diagnosis. Additional matching criteria such as geographic region and residence were applied in several studies [37, 39–41, 44]. Age at cancer diagnosis ranged from 0 to 16 years except in one study in which the diagnosis age ranged from 7 to 19 years [44]. Maternal exposure to radiation was ascertained by questionnaires or interviews reporting the type of examination, the trimester of pregnancy at the time of the examination and the body part examined. In three out of seven studies, questionnaires were completed by obstetrical records [39, 42, 43].

No statistically significant increased risk of all cancer, leukemia or brain tumors, neither for X-ray nor CT exposure were reported in the eight studies considered. Since doses to the fetus were not estimated, no study was able to derive dose-response analyses.

Risk summaries were estimated for leukemia and brain tumors based on four [38, 39, 41, 43] and three studies [37, 43, 44], respectively. The pooled analyses included, respectively, 6,274 cases and 12,426 controls for the leukemia subgroup and 3,461 cases and 7,924 controls for the brain tumors subgroup. Methodological quality scores of included studies were all satisfied, with NOS scores ranging from 6 to 9 (good quality according to AHRQ scores).

No increased risk for leukemia following prenatal exposure (any exposure versus no exposure) could be observed OR_{pooled}=1.08; 95% confidence interval (CI): 0.90, 1.28 (Fig. 2), with no reported heterogeneity between studies I^2=23.2%, P=0.27.

No increased risk of brain tumors was reported OR_{pooled}=0.93; 95% CI: 0.68, 1.28 (Fig. 3) and no heterogeneity between studies was observed I^2=0.0, P=0.72.

No publication bias was idenitified by the Egger tests for leukemia (P=0.52) and brain tumors (P=0.49).

Postnatal diagnostic radiation exposures

There were 21 studies [25, 26, 29, 30, 37, 38, 41, 43–56] on childhood radiation medical exposure (Tables 2 and 3). Beside X-ray and CT, which were the most frequently studied types of procedures, some specific examinations such as cardiac catheterization or cystography were also considered. CT exposure was mainly investigated in cohort studies whereas case-control studies predominantly explored X-ray exposure.

Subjects' exposures were identified from hospital records or from health insurance databases while cancer cases were retrieved from cancer registries [25, 27, 30, 41, 44–47, 49, 56]. In some CT studies with medical information available, children with cancer-predisposing factors [25, 28, 46] and children subjected to CT because of suspected cancer [30, 56] were excluded from the analyses. To deal with reverse causality (cancers that were caused by the underlying medical conditions prompting the CT rather than by the dose delivered during the examination), various latency periods were applied, ranging from 3 to 24 months for lymphohematopoietic malignancies, and from 12 to 60 months for solid cancers. Age at inclusion, i.e. at first exposure, varied from 0 to 22 years, with some studies focusing only on children first exposed before the age of 10 years [28] or 15 years [25, 49]. Mean follow-up extended from 4 years [49] to 8.5 years [50].

Organ doses were estimated only for CT studies, based on patient characteristics (age, gender), type of examination and machine-specific settings retrieved from radiology protocols [28], published radiologic survey data [30, 45, 49], or from the Picture Archiving and

Communication System (PACS) [57]. The cumulative estimated doses ranged from 5.9 mGy to 10.1 mGy to the red bone marrow and from 18.3 mGy to 49 mGy to the brain (Table 2). X-ray exposure was not associated with increased risks of all cancers [45, 49, 50], lymphohematopoietic malignancies or brain tumors [37, 43, 44, 52, 54].

Exposure to cystourethrography procedures was statistically associated with increased risks of genital and urinary system cancers as well as hematological system malignancies [47]. Standardized incidence ratio (SIR) of all cancers (SIR 3.01, 95% CI 2.09-4.19) and lymphoma (SIR 9.15, 95% CI 5.66-13.97) were increased and significantly associated with childhood cardiac catheterization procedures [51] but were no more increased after censoring transplant recipients (SIR 0.90, 95% CI 0.49, 1.49 for all cancers with 0 case for lymphoma).

CT studies reported significant increased risks for lymphohematopoeitic malignancies [30, 45, 50] and for leukemia [56] when others found nonsignificant increased risks for leukemia [41, 49] by comparing children undergoing one or more CTs versus none. An almost twofold increase of risks of brain tumor have been reported [45, 46, 50] (one or more CT versus none) while some studies have not shown any increased risk [44, 54] regardless of the region exposed.

Among the six CT studies providing organ doses [28, 30, 45, 49, 50, 56], pooled ERRs per Gy were calculated for leukemia and brain tumors. Overall, the pooled analysis included 11,398,728 and 11,393,070 subjects for leukemia and brain tumor risks analyses, respectively. Among them, 437 leukemias and 478 brain tumor cases were observed. The studies were comparable, and the methodological quality of the included studies wasgood, according to AHRQ, with NOS scores ranging from 7 to 9. We observed a significant increased risk for leukemia ERR_{pooled}=26.9 Gy^{-1} 95% CI: 2.7, 57.1 based on 6 studies [28, 30, 45, 49, 50, 56] (Fig. 4), which represents an increase of 2.69% per mGy of dose over the background risk of leukemia.

There was moderate heterogeneity between studies I^2=60.3% (P=0.03). Sensitivity analyses in which the pooled ERR was calculated excluding each study one at a time revealed no substantial alteration of the aggregate ERR except when excluding the Dutch study [50], which accounted for a large weight of the pooled analysis, leading to a higher pooled ERR after the exclusion of this study. Publication bias was suspected (P=0.03) suggesting that small studies with negative results were less often published.

The pooled ERR for brain tumors was significantly increased ERR_{pooled}=9.1 Gy^{-1} 95% CI: 5.2, 13.1 based on 5 studies [28, 30, 45, 49, 50] (Fig. 5), which represents an increase of 0.91% per mGy of dose over the background risk of brain tumors. Small heterogeneity between study was found I^2=32% and no publication or selection bias was suspected (P=0.16).

Discussion

Cancer risks after prenatal or postnatal medical diagnostic radiation exposure were analyzed based on 24 studies. Our review did not find any statistically increased risks of all cancers, leukemia and brain tumors after prenatal X-ray or CT exposures. For postnatal exposure, increased risks were observed for leukemia as well as brain tumors after CT exposure while no evidence of an increased risk of all cancers was observed after X-ray exposure.

Early published data in the 1950s, mainly the Oxford Survey of Childhood Cancers studies [11, 13, 58] and other epidemiological studies [59, 60], reported an increased cancer risk related to prenatal X-ray exposure [11, 13]. However, the following studies carried out a few

years later did not show such a statistically significant association [16, 61, 62]. Nevertheless, the positive association, albeit non-statistically significant, between prenatal X-ray and leukemia (OR_{pooled} 1.08; 95% CI: 0.90, 1.28) is consistent with earlier much more statistically informative analyses that found results rejecting the null [13, 60].

A possible explanation for the difference between the cancer risk associated with prenatal irradiation estimated in this meta-analysis and estimated from previous studies may be linked to the decline in X-ray frequency during pregnancy by shifting to nonionizing procedures such as sonography or magnetic resonance imaging [15, 63] and the decrease in X-ray doses due to the setting and improvement of radiation protection rules for patients. Current x-ray systems delivere fetal radiation doses of about 1.7 µGy for spine measurement and 2.7 µGy for femur measurement during the first trimester [65].

Little is known about the potential harm of CT exposure to the fetus. Because of higher doses delivered by CT compared to conventional radiology [63, 64], the increased use of CT during pregnancy [65, 66] for non-obstetrical conditions might be an issue. Only one study [42] focused specifically on the link between maternal CTs and a subsequent malignancy in the child and didn't observed any cancer risk in children (hazard ratio [HR] 0.68; 95% CI: 0.25, 1.80) [42]. But a limit of this study is the lack of dosimetry assessment of the fetus exposure [42].

Postnatal diagnostic X-ray exposure has been the focus of numerous studies in the last half century. Early studies [11, 67, 68] reported increased risks of leukemia in patients exposed to diagnostic X-ray compared to controls while more recent studies [69–71] did not report increased risks.

Because of the large increase in CT use over the years, several recent epidemiological studies have assessed the risk of cancer following CT exposure in childhood [28, 30, 45]. Among

these studies, most reported increased risks of leukemia [28, 30, 45] and brain tumors [30, 45, 46], some of them without reaching significance [48]. In the present analysis, we reported a summarized excess relative risk of ERR_{pooled}=26.9 Gy^{-1} (95% CI: 2.7- 57.1) for leukemia and ERR_{pooled}=9.1 Gy^{-1} (95% CI: 5.2- 13.1) for brain tumors, indicating an increase in the risks of leukemia and brain tumors over the background risks of 2.69% and 0.91%, respectively, per unit of mGy due to postnatal CT exposure based on linear dose-response models. That means, for a given CT delivering 10 mGy to the red bone marrow (or to the brain), the leukemia (or brain tumor) risk increases by about 27% (or 9% for brain tumor risk) over the respective background risks, holding all other factors constant. The major limits encountered in the CT studies are indication and reverse causation bias, uncertainties in dose reconstruction and insufficient statistical power. Indication and reverse causation bias can be suspected respectively when cancer-predisposing factors or early symptoms of undetected cancer are the indication of the CT [72]. Thus, the apparent excess incidence of cancer is not linked to the CTs performed but to the underlying conditions or undetected cancer that motivate the indication of the CT. In most of studies on CT [30, 45, 46], no information on the indication of the CT examination was available. Then, the association between CT and cancer risk might likely be overestimated in case of bias. Authors challenged reverse causation bias by applying several increasing lag periods (minimal latent time between the exposure and the cancer diagnosis) to exclude as much as possible CTs that could be performed after the cancer initiation but before the diagnosis of cancer. Because leukemia genesis is rather short and diagnosis is not assessed by CT examination, reverse causation bias is unlikely to obscure the leukemia dose response analysis. The similar values of ERR for leukemia (ERR=0.045 per mGy, 95% CI 0.016, 0.188) reported in the Life Span Study supports this hypothesis [6, 30, 45]. It is much more difficult to exclude such a bias for brain

tumors as their development might take years, when several exams, especially CTs, could be performed to investigate the undetected condition.

Confounding bias linked to underlying conditions predisposing to cancer has been scarcely investigated [23, 28]. Reanalysis of the previous published data [30] according to medical information available for 40% of the UK CT cohort showed a decrease of previously estimated ERRs of 15% for leukemia and 30% for brain tumors, albeit still significantly increased. In the French cohort [28], analysis restricted to the patients without predisposing factors to cancer (97% of the studied population) reported risk estimates in the same range as those obtained in the whole cohort, ruling out a potential bias linked to predisposing conditions to cancer. However, the rather small number of cases and the short duration of follow-up prevent from definitive conclusions.

Aside from CT, studies of other procedures such as fluoroscopy and cardiac catheterization were scarce. A study of adults with congenital heart defects reported significantly higher cancer risks associated with increasing numbers of diagnostic and treatment cardiac procedures [73]. Cancer risk associated with cardiac catheterization during childhood has been analyzed in three studies with divergent results [51, 74, 75]. The most recent study from the UK with individual dose reconstruction [51] reported no increase in all cancers after disregarding transplant patiens, whose condition might predispose to cancer. The study had relatively low statistical power to detect an association as only 11,270 children were included.

One of the major limits in the reviewed studies is the lack of precise dose assessment, especially in earlier studies. Although the doses might be quite easily estimated based on machine-specific parameters, this information was scarcely documented until recently. The

assessment of X-ray exposure based on interviews or questionnaires in case-control studies may lead to a recall bias, unless confirmed by a review of medical records [39, 42, 43].

One strength of our study is the ability to estimate pooled ERR thanks to the alternative random-effect method of Richardson et al. [34], which allows the derivation of estimates of variance of published ERRs in case of nonsymmetrical confidence intervals.

Assessing the quality of individual studies included in a systematic review is fundamental to interpreting the review. Quality assessment is challenging due to the methodological intricacies and its subjective nature. We used two recognized tools, NOS for quality assessment of non-randomized studies [31] and AHRQ standards [32]) to assess quality and methodological limits of included studies in a standardized manner, and we applied the Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) recommendations [20] for the reporting of the study's results. However, we did not weigh the pooled estimates on quality criteria, as quality scores were in the same range of values (NOS scores 6 to 9, and good quality for AHRQ scores) for the studies considered in each analysis. We used a random effect model to calculate the pooled estimates, which allows for potential between- and within-study heterogeneities, even if the hypothesis of heterogeneity was rejected in most of our analyses. Publication bias linked to the absence of studies of small size with negative results seems not to be a major limitation of our analysis as demonstrated by statistical tests. Restricting the study period to published articles from 2000 to 2019 ruled out studies with exposure before the 1970s, for the purpose of insuring a certain homogeneity in the exposure scenario since a downturn in doses per X-ray exam have been reported and CT machines had been introduced after that period [15]. This prevented the inclusion of old studies with outdated exposure conditions and medical practices.

An important common limitation is the lack of statistical power linked to the small expected risk, the rather low frequency of these procedures during pregnancy and childhood, and the short follow-up of recent studies. Hopefully, ongoing international studies will be able to assess, with greater statistical power, the risks associated with radiation-induced malignancies in medical exposures and to address some limits of previous published data.

In that way, the ongoing European collaborative project EPI-CT (Epidemiological study to quantify risks for pediatric computerized tomography and to optimize doses) pools nine national cohorts of children exposed to CT and provides individual organ doses taking into account uncertainties in dose assessment. With the inclusion of about 1 million patients, EPI-CT will provide statistically powerful estimates of cancer risk associated with CT exposure [76]. An extension of the follow-up of the main cohorts of EPI-CT is also planned in the international MEDIRAD project (Implications of Medical Low Dose Radiation Exposure) [77], which aims to enhance the scientific bases and clinical practice of radiation protection in the medical field. Another ongoing study, HARMONIC (Health effects of cardiac fluoroscopy and modern radiotherapy in paediatrics) [78] is partly devoted to assess the risk of radiation-related malignancies in children undergoing cardiac catheterizations.

Conclusion

Although prenatal medical radiation during the last 50 years appeared unlikely related to a subsequent later life risk of cancer, pooled results from studies on CT exposure during childhood showed greater risks for leukemia and brain tumors. Published studies present some

methodological limitations. Although the benefits of prenatal and postnatal diagnostic radiation examinations outweigh the risks associated with the doses delivered by these procedures, the results of this analysis justify continued efforts to optimize doses to patients.

Compliance with ethical standards

Conflicts of interest None

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Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of search, selection and inclusion of relevant studies

Fig. 2 Odds ratio (OR) of leukemia risk following prenatal medical diagnostic X-ray exposure

ORpooled pooled odds ratio

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Fig. 3 Odds ratio (OR) of brain tumors risk following prenatal medical diagnostic X-ray exposure

ORpooled pooled odds ratio

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Fig. 4 Excess relative risk (ERR) of leukemia following postnatal medical diagnostic exposure to computed tomography scan

ERRpooled pooled excess relative risk

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Fig. 5: Excess relative risk (ERR) of brain tumors following postnatal medical diagnostic exposure to computed tomography scan

ERRpooled pooled excess relative risk

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Table 1 Studies on prenatal medical ionizing radiation exposure and cancer risk

Study	Country	Type	Enrolled subject/Exposed[$]	Procedures	Outcom
Schuz J et al, 2001 [37]	Germany	Case-control	Cases: 453/16 Controls: 2,424/105	X-ray	- Brain tur
Shu XO et al, 2002 [38]	USA	Case-control	Cases: 1,809/112 Controls: 1,950/127	X-ray	- Acute lymphobla leukemi
Roman E et al, 2005 [39]	UK	Case-control	Cases: 1,421/62 Controls: 4,753/182	X-ray	- Leuken - Lympho
Goel R et al, 2009 [40]	USA & Canada	Case-control	Cases: 512/13 Controls: 509/18	X-ray	- Wilms tu
Bailey HD et al, 2010 [41]	Australia	Case-control	Cases: 388/4 Controls: 869/16	X-ray, CT, intravenous pyelograms and barium study	- Acute lymphobla leukemi
Ray JG et al, 2010 [42]	Canada	Retrospective Cohort	Exposed: 5,590/4 cases Unexposed: 1,829,927 / 2,539 cases	CT and radionuclide tests	- All canc
Rajaraman P et al, 2011 [43]	England, Scotland and Wales	Case-control	Cases: 2,656/120 Controls: 4,854/185	X-ray	- All canc - Leuken - Lympho - Brain tur
Tettamanti G et al, 2017 [44]	Denmark, Norway, Sweden and Switzerland	Case-control (Multicenter)	Cases: 352/31 Controls: 646/57	X-ray and CT	- Brain tur

$ Value reported in the “Enrolled subject/Exposed” column is that for all cancer combined or that for the given cancer reported; § adjus
adjusted on at least age, gender and geographic area); * first trimester of pregnancy, ** second trimester of pregnancy, ***: third trimes
tomography, *HR* hazard ratio, *OR* odds ratio. Ray JG et al. 2010 [42]: 4 cases among 5.590 exposed subjects and 2.539 cases among 1.8

Table 2 Cohort studies on postnatal medical ionizing radiation exposure and cancer risk

Study	Enrolled subject/cases	Period of inclusion	Age at inclusion (years)	Procedures	Outcomes	I ((
Hammer GP et al, 2011 [25], Germany	78,527/68	1976-2003	<14.5	X-ray	- All cancer - Leukemia and lymphoma	—
Pearce MS et al, 2012 [30], UK	178,604/74 176,587/135	1985–2002 1986-2002	0–22 0-22	CT	- Leukemia - Brain tumors	RBM: 2.32 Brain: 0.25
Mathews JD et al, 2013 [45], Australia	Exposed: 680,211/3,150 Unexposed: 10,261,420/57,524	1985-2005	0-19	CT	- All cancer* - Lymphoma and hematopoietic - Brain tumors	RBM: 5.9[m] Brain: 49[m]
Huang WY et al, 2014 [46], Taiwan	Exposed: 24,418/39 Unexposed: 97,668/122	1998-2006	<18	CT	- All-cancer - Leukemia - Brain tumors	—
Liao YH et al, 2014 [47], Taiwan	Exposed: 31,908/52 Unexposed: 127,632/99	1997-2008	1-18	Cystourethrography	- Genital cancer - Urinary system cancer - Hematologic system	—
White IK et al, 2014 [48], USA	104/0	1991-2001	0-6 years	CT	- All cancer - Leukemia - Brain tumors	—
Krille L et al, 2015 [49] Germany	39,184/38	1980-2010	<15	CT	- All-cancer - Leukemia - Brain tumors	RBM: 11.7 Brain: 34.4
Journy N et al, 2016 [28], France	67,274/106	2000-2010	<10	CT	- Leukemia - Lymphoma - Brain tumors	RBM: 8.9 Brain: 23.1
Meulepas JM et al, 2018 [50] The Netherlands	168,394/454	1979-2012	<18	CT	- Leukemia - Brain tumors	RBM: 9.5 Brain: 38.5 49.4)[m(IQR)]
Harbron RW, 2018 [51] UK	11,270/41	—	<22	Cardiac catheterization and CT	- Lymphohaematopoietic neoplasia	RBM: 8.8

Exclusion period: * 1 year, ** 2 years,*** 5 years. † per 100mSv, § ERR for the whole population, $ ERR after exclusion of patients with transplant, *95% CI* 95% confidence interval, *CT* computed tomography, *h* hazard ratio, *IQR* interquartile range, *m* mean, *RBM* red bone marrow; *s* standardized incidence ratio,

sd standard deviation **Table 3** Case control studies on postnatal medical ionizing radiation exposure and cancer risk

Study	Enrolled subject/exposed	Period of diagnosis	Age at diagnosis (years)	Procedures	Outcomes	Risk estimate (adjusted) (95% CI)	
Schuz J et al, 2001 [37], Germany	Cases: 458/142 Controls: 2,425/818	1988-1993	<15	X-ray	- Brain tumors	OR	0.73 (0.57-0.94)
Shu XO et al, 2002 [38], USA	Cases: 1,842/939 Controls: 1,986/775	1989-1993	<15	X-ray	- Acute lymphoblastic leukemia	OR	1.1 (0.9-1.2)
Infante-Rivard C, 2003 [26], Canada	Cases: 682/301 Controls: 690/262	1980-1993	<14	X-ray[$] **1** **>= 2**	- Acute lymphoblastic leukemia	OR	1.16 (0.87–1.55) 1.48 (1.11–1.97)
Mellemkjaer L et al, 2006 [52], Denmark	Cases: 25/11 Controls: 50/15	1977-1989	Newborns	X-ray	- Brain tumors	OR	2.2 (0.6-8.8)
Bailey HD et al, 2010 [41], Australia	Cases: 360/156 Controls: 834/326	2003-2006	<14	- X-ray - CT	- Acute lymphoblastic leukemia	OR	1.15 (0.881.52) 0.87 (0.32-2.34)
Khan S et al, 2010 [53], USA	Cases: 299/15 Controls: 299/12	1991-1997	<6	Head X-ray[§]	Medulloblastoma and primitive neuroectodermal tumor (PNET)	OR	1.3 (0.49-3.7)
Rajaraman P et al, 2011 [43], England, Scotland and Wales	Cases: 2,656/50 Controls: 4,854 /75	1992-1996	1-5	X-ray	- All cancers - Leukemia - Lymphoma - Brain tumors	OR	1.19 (0.82-1.74) 1.35 (0.81-2.27) 5.14 (1.27-20.8) 0.94 (0.31-2.92)
Milne E et al, 2014 [54], Australia	Cases: 306/102 Controls: 950/375	2005-2010	<14	- All procedures[£] - X-ray - CT	- Brain tumors	OR	0.66 (0.48-0.90) 0.68 (0.49-0.93) 0.78 (0.38-1.59)
Shih T-Y et al, 2014 [55], Taiwan	Cases: 58/34 Controls: 232/95	1998-2010	6-18	X-ray	- Leukemia	OR	2.14 (1.18-3.87)
Tettamanti G et al, 2017 [44], Denmark, Norway, Sweden and Switzerland	Cases: 352/159 Controls: 646/333	2004-2008	7-9	X-ray and CT	- Brain tumors	OR *	0.76 (0.58-1.01)
Nikkila A et al, 2018 [56], Finland	Cases: 911/8 Controls: 2,730/9	1990-2011	<15	CT	Leukemia	OR EOR	2.82 (1.05-7.56) 13 (2-26)[α]

All estimated risks taking into account the latency period presented in the table.

95% CI 95% confidence interval, * non-adjusted OR, § only head X-ray not due to head injury, $ *X-ray excluding dental procedures*, £ all procedures, including dental procedures
CT computed tomography, EOR excess odds ratio per 100mGy, *IQR* interquartile range, OR odds Rratio; *RBM* red bone marrowα : Nikkila A et al, 2018 [56] : leukemia excess odds ratio (EOR) 13 (95% CI 2–26) per 100mGy, RBM (median+IQR): 10.1 (4.79-13.6) in the exposed group and RBM (median+IQR): 6.29 (5.69-7.14) in controls.

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of search, selection and inclusion of

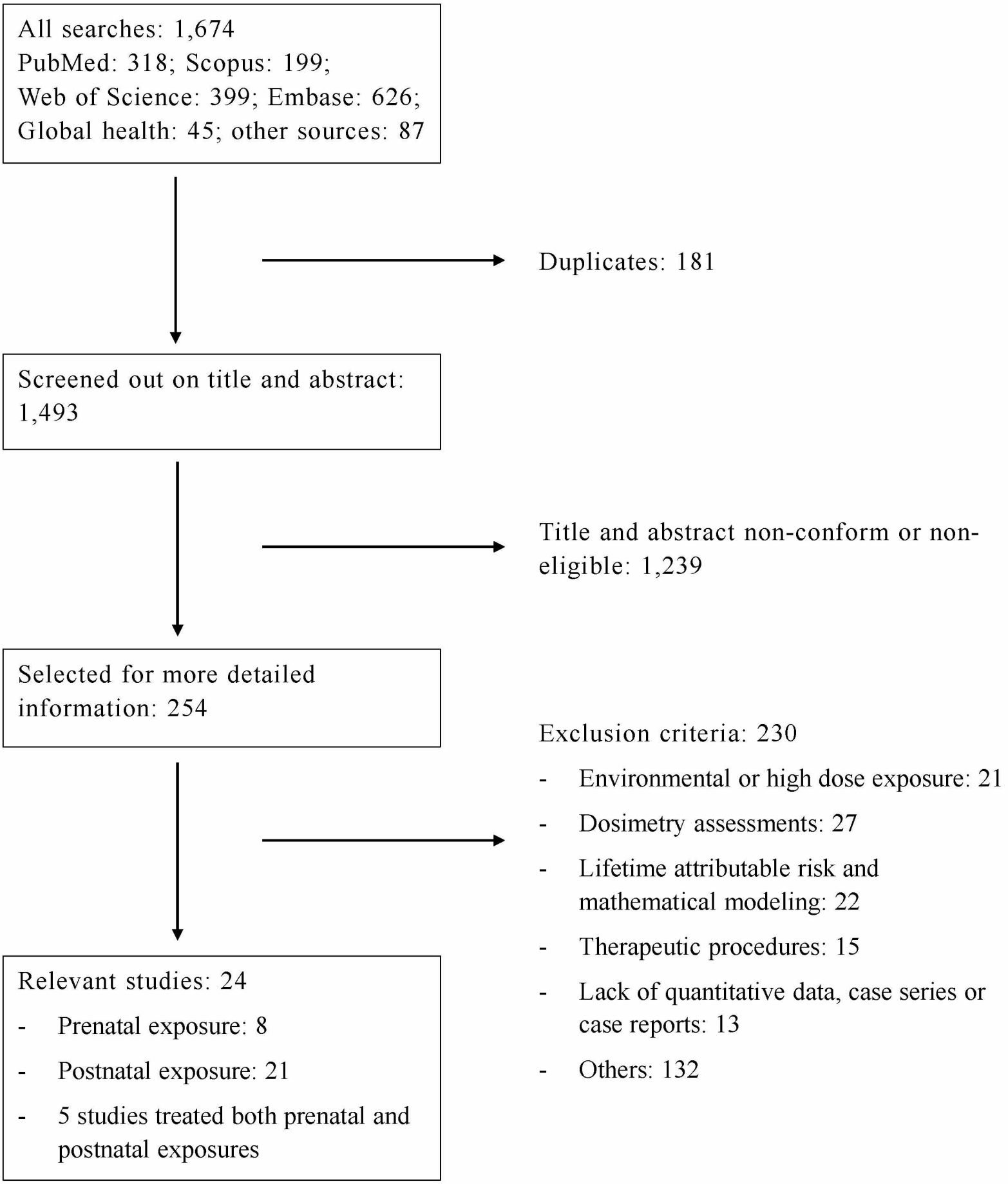


Figure 2: Odds ratio (OR) of leukemia risk following prenatal medical diagnostic X-ray exposure

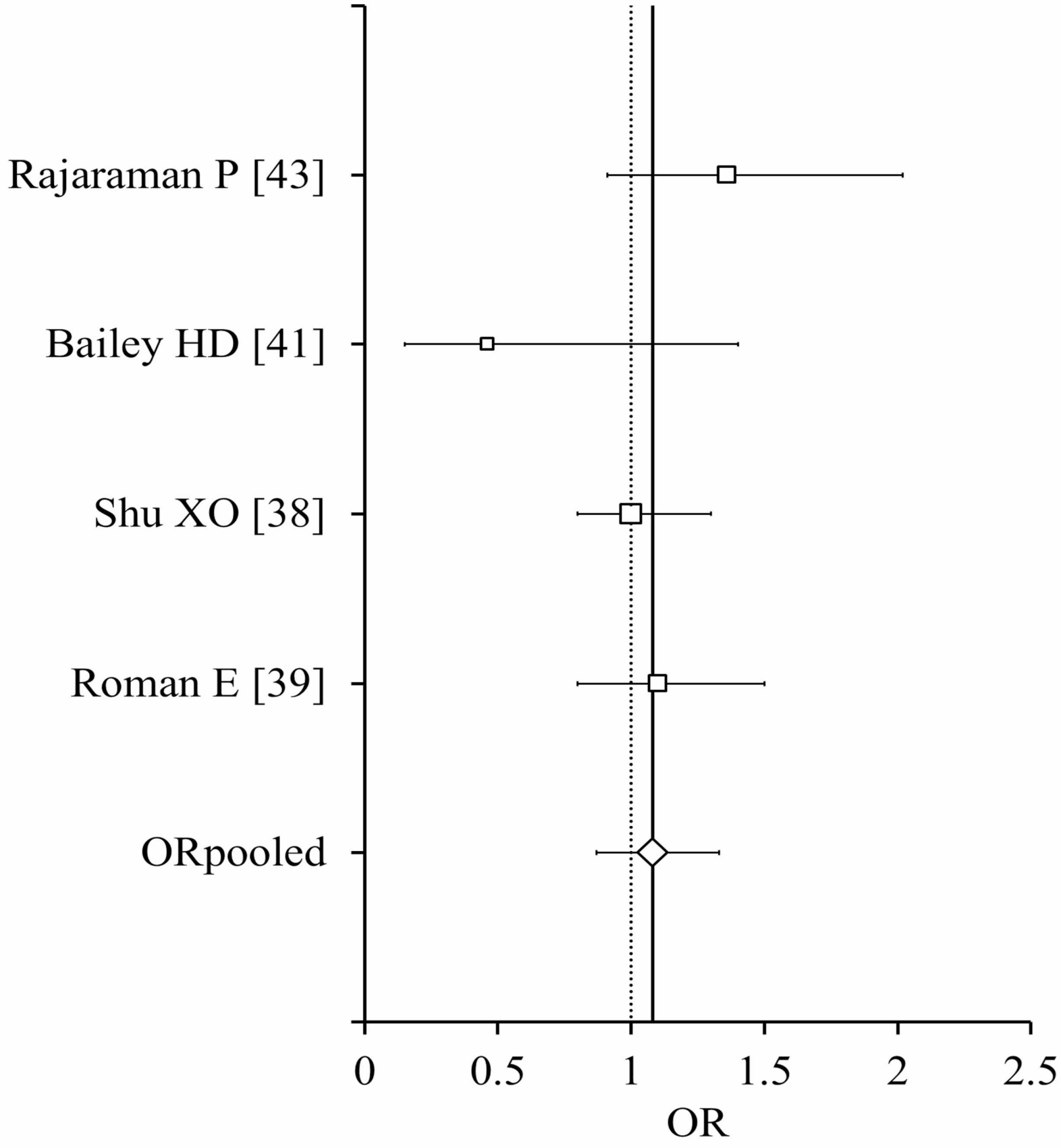


Figure 3: Odds ratio (OR) of brain tumors risk following prenatal medical diagnostic X-ray exposure

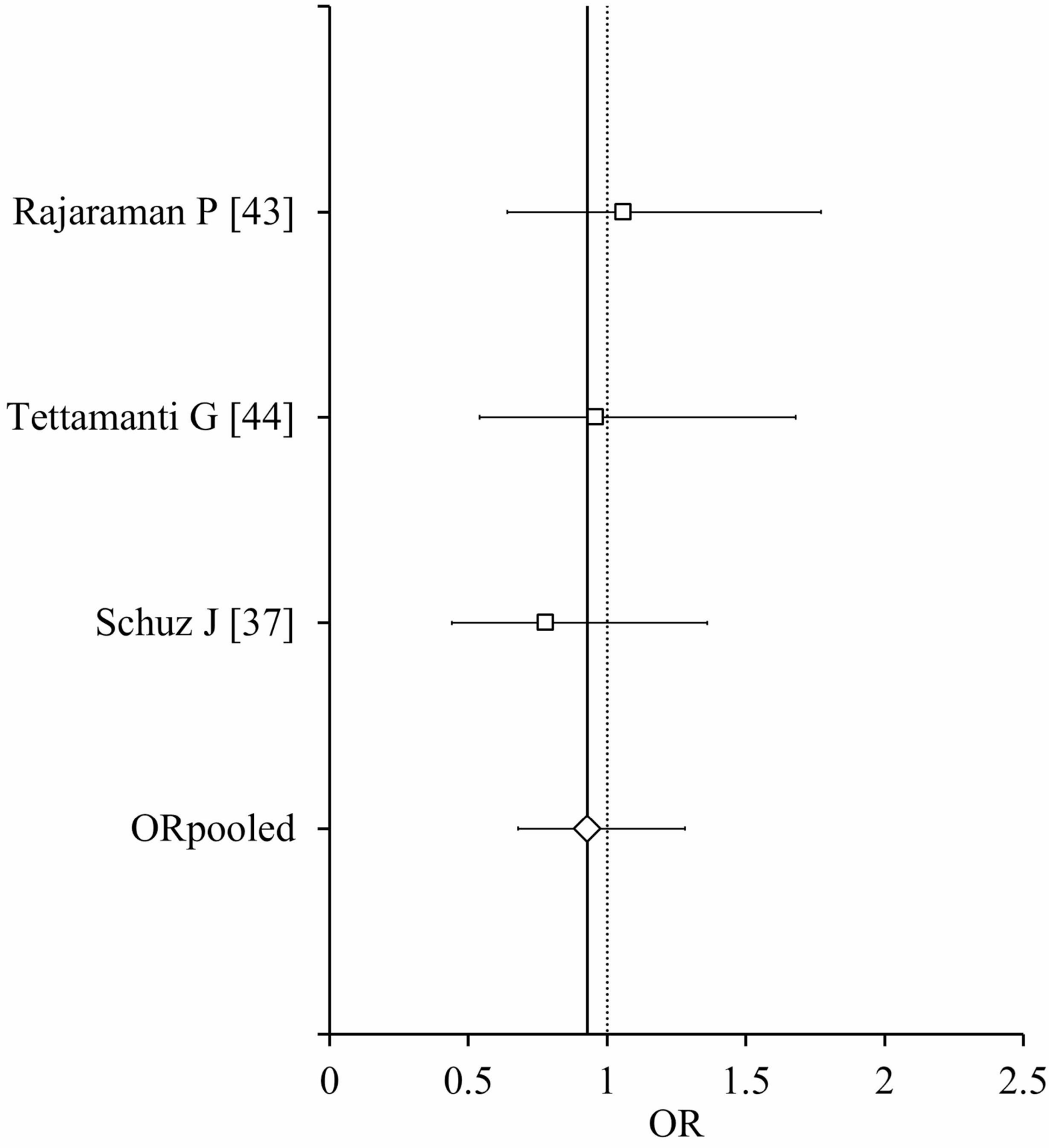


Figure 4: Excess relative risk (ERR) of leukemia risk following postnatal medical diagnostic exposure to computed tomography

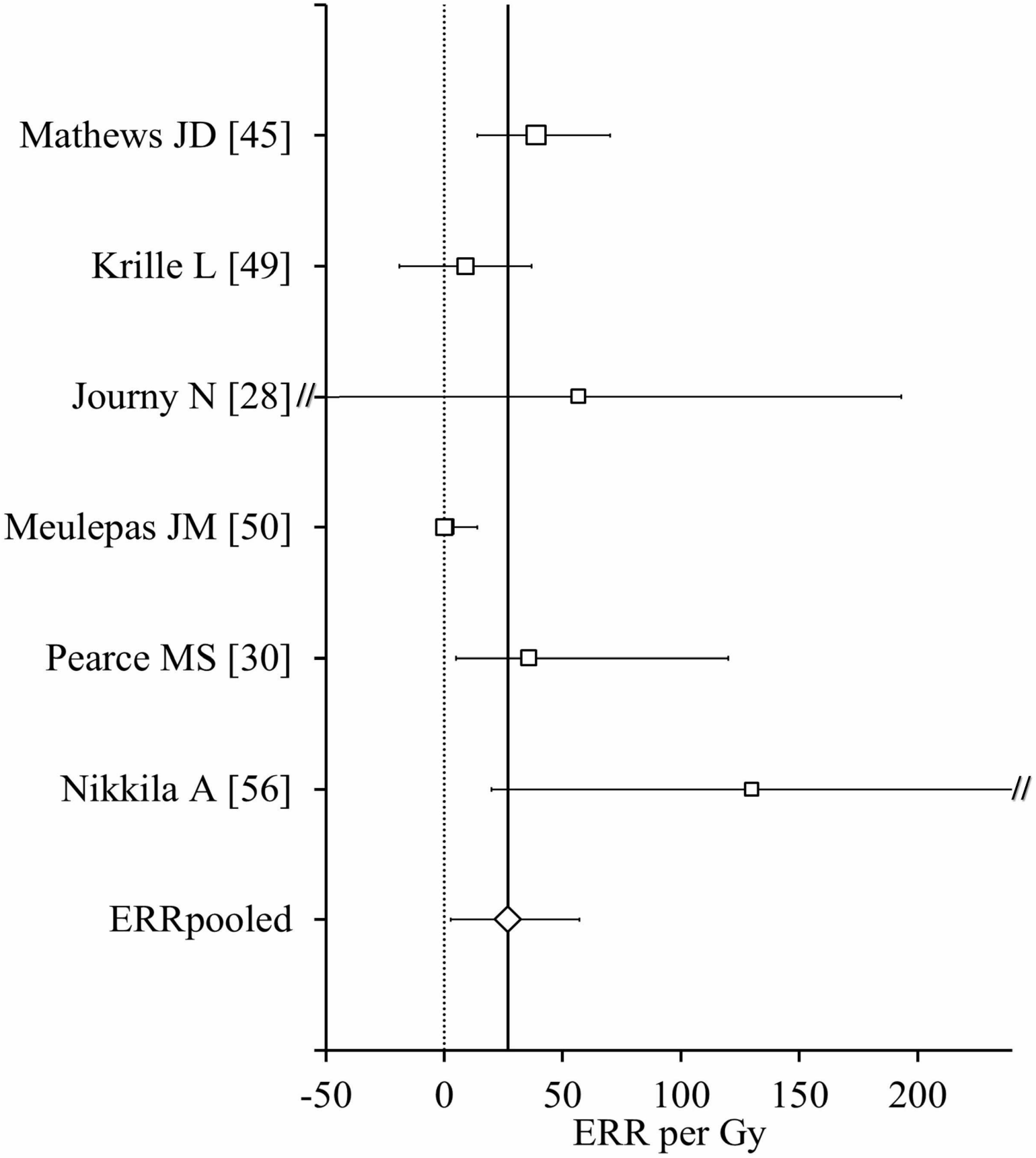
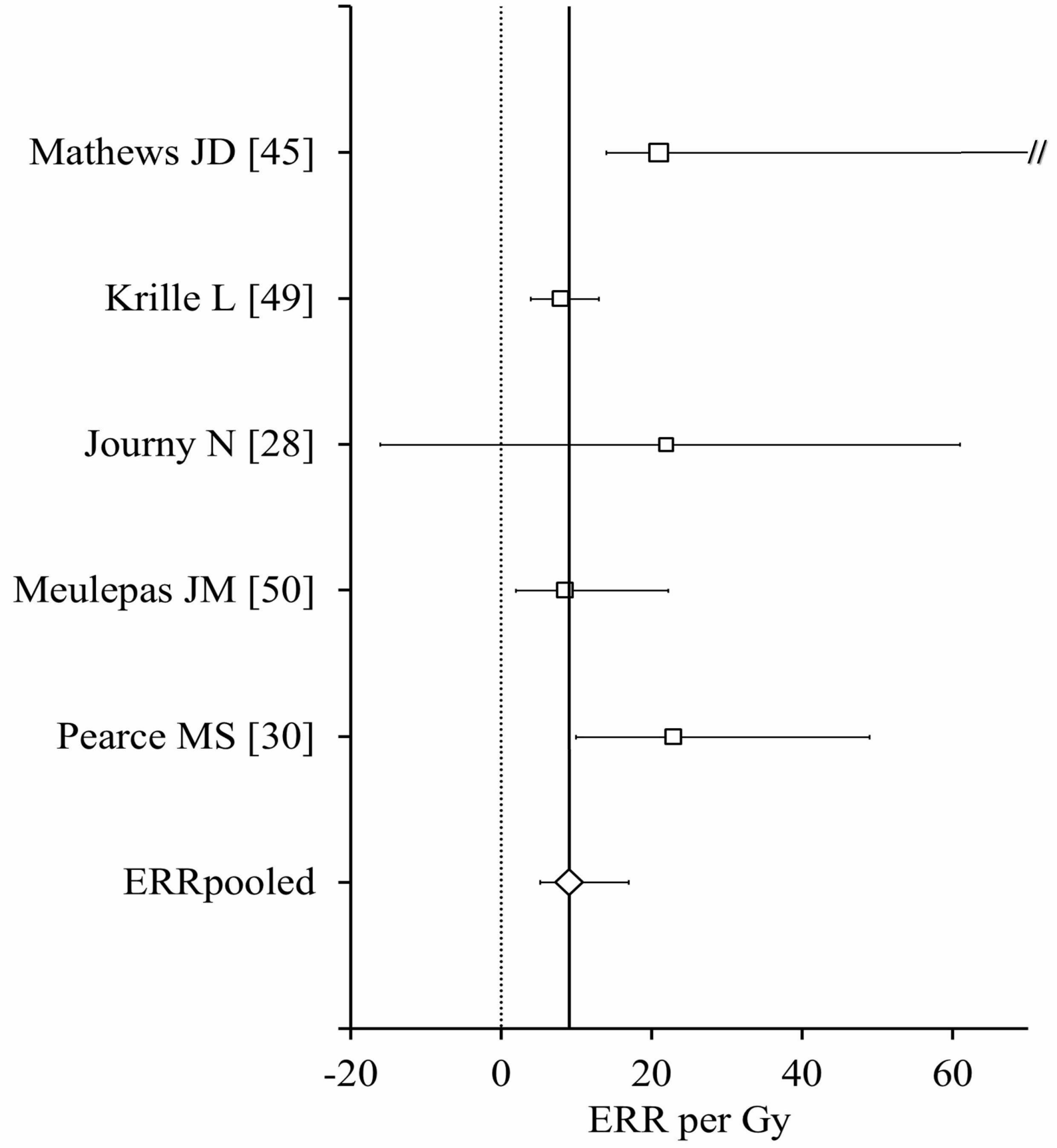


Figure 5: Excess relative risk (ERR) of brain tumors risk following postnatal medical diagnostic exposure to computed tomography



Prisma checklist revised

(Figure as TIFF object) Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of search,

(Figure as TIFF object) Figure 2: Odds ratio (OR) of leukemia risk following prenatal medical diagnostic X-ray exposure

(Figure as TIFF object) Figure 3: Odds ratio (OR) of brain tumors risk following prenatal medical diagnostic X-ray exposure

(Figure as TIFF object) Figure 4: Excess relative risk (ERR) of leukemia risk following postnatal medical diagnostic exposure to

(Figure as TIFF object) Figure 5: Excess relative risk (ERR) of brain tumors risk following postnatal medical diagnostic exposure

Answers to the comments of the Editor:

Thanks to the editor for the interest on our paper and for the comments. Below is a point-by-point response to the comments provided

1. I thank you for a very well executed revision. I think the article now is excellently readable and interesting. Only some minor comments as follows.

2. The figure are pixelated. They should be re-exported from source, either as loss-less vector graphics (e.g. pdf) or else as tiff with at least 8,000 pixels' width.

Figures have been formatted accordingly

3. The lines remain too thin and fonts too small. Before submitting, please check how the figures would look at final size. Keep in mind they will appear smaller in the article.

Figures' lines have been modified

4. Fig 1: 'Exclusion criterion' should be 'Exclusion criteria'

Figure 1 has been modified

5. Figs 2, 3: Decimal point should be '.' not ','

Figures 2 and 3 have been modified

6. It may be helpful to the reader if you expand the figure legends slightly to explain what the figures demonstrate?

Figures' legends have been changed:

Figure 1: Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of search, selection and inclusion of relevant studies

Figure 2: Odds ratio (OR) of leukemia risk following prenatal medical diagnostic X-ray exposure

Figure 3: Odds ratio (OR) of brain tumors risk following prenatal medical diagnostic X-ray exposure

Figure 4: Excess relative risk (ERR) of leukemia risk following postnatal medical diagnostic exposure to computed tomography scan

Figure 5: Excess relative risk (ERR) of brain tumors risk following postnatal medical diagnostic exposure to computed tomography scan

7. The enrolled/exposed columns do not seem to lead to the number in the OR columns of the tables. I

suppose because some studies looked at several different outcomes? Please can you add an explanation? Thank

As noted by the editor, the "Enrolled subject/Exposed" column in table 1 did not seem to lead readily to the OR reported because some studies considered various outcomes e.g. All cancer, leukemia, lymphoma, brain tumors etc., in that case the size reported in the "enrolled subject/Exposed" column is that for all cancer combined. In addition, since these studies are case controls, they accounted for major confounding factors and matched at least on factors such as age, sex, and geographic area. And the OR presented are yet the adjusted values on these variables, which are slightly different from the crude value. We modified the legend of the table accordingly.

"$ Value reported in the "Enrolled subject/Exposed" column is that for all cancer combined or that for the given cancer reported"

"§ Adjusted Odds Ratio or Hazard Ratio (value adjusted on at least age, sex and geographic area)"