A review of the types of childhood cancer associated with a medical X-ray examination of the pregnant mother

DOI:
10.1080/09553002.2021.1906463

Document Version
Accepted author manuscript

Link to publication record in Manchester Research Explorer

Citation for published version (APA):

Published in:
International Journal of Radiation Biology

Citing this paper
Please note that where the full-text provided on Manchester Research Explorer is the Author Accepted Manuscript or Proof version this may differ from the final Published version. If citing, it is advised that you check and use the publisher's definitive version.

General rights
Copyright and moral rights for the publications made accessible in the Research Explorer are retained by the authors and/or other copyright owners and it is a condition of accessing publications that users recognise and abide by the legal requirements associated with these rights.

Takedown policy
If you believe that this document breaches copyright please refer to the University of Manchester’s Takedown Procedures [http://man.ac.uk/04Y6Bo] or contact uml.scholarlycommunications@manchester.ac.uk providing relevant details, so we can investigate your claim.
A Review of the Types of Childhood Cancer Associated with a Medical X-ray Examination of the Pregnant Mother

Richard WAKEFORD¹ and John F. BITHELL²†

¹ Centre for Occupational and Environmental Health, The University of Manchester, Ellen Wilkinson Building, Oxford Road, Manchester, M13 9PL, United Kingdom.  Richard.Wakeford@manchester.ac.uk

Corresponding author.
ORCID ID: https://orcid.org/0000-0002-2934-0987

² Department of Statistics, University of Oxford, 24-29 St Giles’, Oxford, OX1 3LB, United Kingdom

Notes on contributors

Richard Wakeford, PhD, before retiring at the end of 2019 was Professor in Epidemiology in the Centre for Occupational and Environmental Health of The University of Manchester, United Kingdom. He is now an Honorary Professor in the Centre.

John Francis Bithell, DPhil, was an Emeritus Fellow of St Peter’s College, University of Oxford, United Kingdom, and a former Tutor and Fellow in Biomathematics and Statistics at the College. Sadly, he died in March 2020 (https://iopscience.iop.org/article/10.1088/1361-6498/ab85bb).

† Sadly, John Bithell died in March 2020 while this paper was being completed.
A Review of the Types of Childhood Cancer Associated with a Medical X-ray Examination of the Pregnant Mother

ABSTRACT

Purpose: For 65 years the interpretation of the statistical association between the risk of cancer in a child and a prior diagnostic X-ray examination of the abdomen of the pregnant mother has been debated. The objections to a direct cause-and-effect explanation of the association vary in their strength, but one of the most notable grounds for controversy is the finding from the first and largest case-control study reporting the association, the Oxford Survey of Childhood Cancers (OSCC), of an almost uniformly raised relative risk (RR) for nearly all of the types of cancer that are most frequent in children. Here we compare the antenatal X-ray associations found in the OSCC for different types of childhood cancer with the results of all other case-control and case-cohort studies appropriately combined in meta-analyses, and we also review the findings of the few cohort studies that have been conducted.

Conclusions: From the case-control/case-cohort studies other than the OSCC there are consistent and clear elevations of risk for all types of childhood cancer combined, all leukaemia, and all cancers except leukaemia combined. This compatibility of the findings of the OSCC with those of the combined other studies is less clear, or effectively absent, when some categories containing smaller numbers of incident cases/deaths are considered, but lack of precision of risk estimates due to sparse data presents inferential challenges, although there is a consistent absence of an association for bone tumours. Further, more recent studies almost certainly address lower intrauterine doses, with an anticipated decrease in estimated risks, which could be misleading when comparisons involve a limited number of studies that are mainly from later years, and a similar problem arises when having to employ all types of antenatal X-ray exposures for a study because data for abdominal exposures are absent. The problem of low statistical power is greater for cohort studies, and this, together with other shortcomings
identified in the studies, limits the interpretational value of results. The findings of non-medical intrauterine exposure studies are constrained by sparse data and make a limited contribution to an understanding of the association. Certain aspects of the various studies require a need for caution in interpretation, but overall, the appropriate combination of all case-control/case-cohort studies other than the OSCC lends support to the inference that low-level exposure to radiation in utero proportionally increases the risk of the typical cancers of childhood to around the same level.
1. Introduction

Ever since a positive statistical association between the risk of mortality from cancer in childhood and a previous medical diagnostic X-ray examination of the maternal abdomen during pregnancy was first tentatively reported from a case-control study 65 years ago (Stewart et al. 1956), there has been controversy surrounding its interpretation. A causal explanation of the association in terms of exposure to ionising radiation in utero would be of importance because, inter alia, it would be one of the few pieces of direct epidemiological evidence for radiation doses as low as ~10 mGy of X-rays increasing the risk of cancer. However, although the statistical association has now been accepted as real – see, for example, the US National Council for Radiation Protection and Measurements (NCRP) Report No. 174 (Brent et al. 2013) and the International Agency for Research on Cancer (IARC) Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 100D, Radiation (Armstrong et al. 2012; El Ghissassi et al. 2009) – its interpretation continues to be debated. The grounds for controversy over the interpretation have been much discussed (Bithell and Stiller 1988b; Bithell 1989; MacMahon 1989; Miller 1990; Bithell 1992; Muirhead et al. 1993; Wakeford 1995; Doll and Wakeford 1997; Wakeford, Doll, and Bithell 1997a, 1997b; Boice and Miller 1999; Wakeford and Little 2003; Streffer et al. 2003; Brent 2007; UNSCEAR 2008; Wakeford 2008; Boice 2011; Wakeford 2013; Brent et al. 2013; Brent 2014, 2015; Bithell et al. 2018), and as with other studies of medical exposure to radiation for diagnostic purposes, confounding by indication (i.e., selection for a radiographic examination is associated with some factor that predisposes to the disease under study) must be given due consideration.

A number of objections to a cause-and-effect explanation of the association have been raised (see, for example, Boice and Miller (1999) and UNSCEAR (2008)), including:

- the apparent absence of an excess of cases of childhood cancer, in particular, childhood leukaemia, in the cohort of Japanese atomic bomb survivors irradiated in utero;
• cohort studies of children exposed antenatally to X-ray examinations provide little evidence for an association, which therefore depends on the findings of case-control studies;
• these case-control studies provide estimates of the excess risk per unit dose for childhood cancers other than leukaemia that are notably greater than those derived from studies of exposure of young children;
• twins are not at greater risk of childhood cancer than are singletons, despite a higher rate of obstetric X-ray examinations of twins.

Some of these objections provide only weak evidence against a causal relationship and reasons have been advanced to address the more substantial challenges (Doll and Wakeford 1997; Wakeford, Doll, and Bithell 1997a, 1997b; Wakeford and Little 2003; Wakeford 2008), but a serious impediment to inferring causation is the apparent uniformity of the relative risk (RR) of an antenatal X-ray examination for the major types of cancer that occur during childhood (see, for example, (Boice and Miller 1999; Streffer et al. 2003; UNSCEAR 2008; Brent et al. 2013)). Such uniformity is unusual when compared with the pattern of cancer types that are observed to be in excess following exposure to radiation after birth, particularly those cancers appearing in adult life that provide the primary evidence for the estimation of radiation risks. For example, acute leukaemia and cancers of the thyroid and female breast are at a notably raised risk following postnatal irradiation whereas Hodgkin lymphoma and cancers of the uterine cervix and rectum show little if any excess risk (UNSCEAR 2008); it should be noted, however, that the spectrum of cancer types experienced in childhood differs markedly from that in adult life (Murphy et al. 2013; Stiller 2007). It is this feature of the association between childhood cancer and antenatal diagnostic X-ray exposure that we shall examine in this paper.

The largest study of intrauterine exposure to diagnostic X-rays and childhood cancer is the case-control study initiated by Alice Stewart in the 1950s (Stewart et al. 1956; Stewart, Webb, and Hewitt 1958; Stewart and Barber 1962), which eventually became a nationwide study of childhood cancer mortality in Great Britain known as the Oxford Survey of Childhood Cancers (OSCC) (see Bithell et al. (2018)). When the OSCC ended in 1981 it
included 15,276 matched case-control pairs available for analysis (Gilman et al. 1989), but the most recent report from the OSCC giving details of specific types of childhood cancer was that of Bithell and Stewart (1975). Bithell and Stewart (1975) studied childhood cancer deaths in Great Britain during 1953-1967, and their analyses were based upon 8513 case-control pairs; the RRs associated with an antenatal X-ray examination for the principal types of cancer that occur in children are summarised in Figure 1 – the three types of leukaemia considered by Bithell and Stewart (1975), “lymphatic, myeloid and other/unspecified”, have been combined in Figure 1 because the RRs are similar and “other/unspecified” leukaemias represent 30% of the 4052 leukaemia deaths.

A formal test of homogeneity of the RRs for the nine types of childhood cancer (including the three categories of leukaemia) considered by Bithell and Stewart (1975) did not reveal statistically significant heterogeneity. Although subsequent analyses of the OSCC data have not investigated cancer types in the detail of Bithell and Stewart (1975), several studies have found no significant difference in the RR for lympho-haematopoietic cancers (leukaemia and lymphoma) as a grouping and that for solid cancers (all cancers apart from leukaemia and lymphoma) as a grouping (see, for example, Bithell and Stiller (1988b) and Muirhead and Kneale (1989)).

Figure 1 illustrates the issue under consideration in this paper: with the exception of bone tumours, all the common forms of cancer in childhood have a statistically significant elevation of RR to a similar level of around 1.5. Our objective was to collect and collate the antenatal X-ray exposure and childhood cancer data from case-control and case-cohort studies other than the OSCC, and to appropriately combine these data in meta-analyses to examine whether the pattern of increased RRs by childhood cancer types as presented in Figure 1 is reproduced. Data from the limited number of cohort studies of cancer in children born to women who had experienced a medical X-ray examination during pregnancy were analysed separately.

2. Methods
Studies that have considered childhood cancer in relation to exposure in utero to medical X-rays for diagnostic purposes were identified from a number of sources. These included previous compilations of such studies (Rose 1988; Bithell 1989, 1992; Doll and Wakeford 1997; Little 1999; Streffer et al. 2003; Wakeford 2008; Schulze-Rath, Hammer, and Blettner 2008; Wakeford 2009; Brent et al. 2013) and searches on PubMed and Google Scholar using various combinations of keywords, such as, for example, one search on PubMed using “(fetal OR fetus OR pregnant OR pregnancy OR utero OR uterine OR intrauterine OR embryo OR antenatal OR prenatal OR obstetric) AND (radiation OR irradiation OR radiography OR x-ray OR pelvimetry) AND (cancer OR malignancy OR malignant OR tumor) AND (children OR childhood OR pediatric)” (last conducted on 14 September 2020).

The studies so-identified were examined in detail to select those publications from the OSCC that have provided data for individual types of childhood cancer and groupings of cancer types, and those publications from other studies of intrauterine exposure to radiation for medical diagnostic purposes that present the data required for input to meta-analyses (Blettner and Schlattmann 2005; Greenland and O’Rourke 2008; Sutton and Higgins 2008; Deeks, Higgins, and Altman 2019). The objective was to provide estimates of the relative risk associated with antenatal exposure to X-rays for cancer types and groups of cancer types from the OSCC and from appropriately combined other studies.

Analyses were performed in terms of intrauterine exposure or non-exposure to diagnostic radiation since details of an examination (such as the number of X-ray films exposed) or the numbers of separate examinations occurring during a pregnancy are only infrequently provided in publications. Data from studies of both mortality and incidence were included in the meta-analyses since the relative risk associated with exposure should be largely insensitive to survival. Antenatal exposures were identified in specific studies using either medical records or maternal interviews/questionnaires (and occasionally using more than one source); both categories of study were included in the main analyses. Abdominal exposures of the pregnant mother were used in the analyses where these were available for a study since such exposures would tend to lead to the highest doses being received in utero;
otherwise, all antenatal exposures were used. When abdominal exposures were used for a study, those mothers who received non-abdominal exposures during pregnancy were excluded from the unexposed group if these data were available. Sensitivity analyses were conducted to investigate the influence of the inclusions of these various data categories.

It would not have been possible to maintain any matching or modelling adjustments carried out in a particular case-control/case-cohort study when conducting meta-analyses. For a given study, removing the matching allows the maximum number of controls (or the full cohort sample) to be used to derive odds ratios, and by excluding adjustments any variation in results between studies produced by differing modelling strategies was eliminated. In this way, for each study, the crude (unmatched and unadjusted) odds ratio was obtained to approximate the relative risk (RR). Previous investigations of the effects of matching and adjustments for potential confounding factors in the OSCC have found that these have only a marginal impact upon estimates of the RR for an antenatal X-ray examination (Bithell and Stewart 1975; Bithell 1989, 1992).

Owing to their fundamental differences in design, case-control and case-cohort studies were treated separately from cohort studies, and this also prevents cohort study results being eclipsed in meta-analyses by case-control/case-cohort study results as the latter studies tend to include larger, often much larger, numbers of incident cases/deaths with consequent greater precision of risk estimates.

For a given cohort study, the unadjusted risk ratio was derived where a comparison unexposed cohort was available. When an unexposed cohort was not available for a study an expected number of cases/deaths for the exposed cohort was derived by applying appropriate age-adjusted national rates to the number of individuals in the exposed cohort to obtain observed to expected case/death ratios – this was required for some British studies, when the rates were obtained from Draper et al. (1982), and for some French studies, when the rates were obtained from Hill et al. (1993) (supplemented by personal communication from C. Hill to R. Doll, 1996).

In order to make an assessment of the compatibility of the OSCC findings for particular childhood cancer types with those of other studies,
meta-analyses of the case-control and case-cohort studies excluding the OSCC, and separate meta-analyses of the cohort studies, were conducted. For the case-control/case-cohort studies, the meta-analyses used weighted averaging of the log_{e}-odds ratios from the individual studies. The statistical weight for a particular study was one quarter of the harmonic mean of the numbers of exposed and unexposed cases and controls. This quantity is a general-purpose measure of the statistical information provided by a study (Bithell 1989) and is, to a good approximation, the reciprocal of the variance of the unadjusted log_{e}-relative risk for the association, regardless of the design; it is therefore directly related to the precision of the RR estimate (Bithell 1989, 1992). These meta-analyses of the case-control/case-cohort studies, therefore, use inverse-variance fixed-effect models, with statistical weighting of contributing studies as defined above.

To some degree, heterogeneity of the results from the case-control/case-cohort studies must exist given the diversity of the studies being combined – for example, studies of different populations, age groups, periods of birth and diagnosis/death, and with abdominal or all types of antenatal exposure data gathered from records or interviews/questionnaires. Therefore, the results of the meta-analyses should be viewed as providing informal indications of underlying patterns of risks rather than generating estimates of specific relative risks of intrauterine exposure for each cancer type or grouping of types. Basically, the meta-analyses were conducted to examine the comparability of the overall patterns of results produced by the OSCC and the combined case-control/case-cohort studies other than the OSCC.

Formal assessment of the homogeneity of the risk estimates input to the meta-analyses was made using the Cochrane Q test and Higgins I^2 statistic (Greenland and O’Rourke 2008; Deeks, Higgins, and Altman 2019), although the limitations of such an exercise have to be recognised (Ioannidis, Patsopoulos, and Evangelou 2007; Higgins et al. 2003; von Hippel 2015). The influence that any heterogeneity of the results of the case-control/case-cohort studies could have upon the findings of the meta-analyses was examined using the Review Manager software tool (RevMan, Version 5.3) made available by The Cochrane Collaboration (RevMan 2014), with the meta-analyses performed using the alternative Mantel-Haenszel random-
effects models and the Peto “one-step” odds ratio method (Bradburn et al. 2007; Deeks, Higgins, and Altman 2019).

Mole (1974) pointed to the importance of considering twin births in the OSCC because twins experience a higher rate of radiography than singleton births, predominantly for obstetric reasons. Consequently, twin studies are separated out from the other case-control/case-cohort studies so that the OSCC findings for twins may be compared with the results of combining other case-control/case-cohort studies of twins in meta-analyses.

For the cohort studies, the approach to the meta-analyses was somewhat different owing to the small numbers of incident cases/deaths in the limited number of studies, which is known to pose problems of bias for some of the meta-analytical methods, including inverse-variance models (Bradburn et al. 2007; Efthimiou 2019; Deeks, Higgins, and Altman 2019). Scoping meta-analysis runs using RevMan (2014) had demonstrated that inverse-variance (both fixed-effect and random-effects models) and Mantel-Haenszel random-effects models produced higher risk ratio estimates than the Mantel-Haenszel fixed-effect models, so the estimates from Mantel-Haenszel fixed-effect models, with less scope for bias, were adopted to estimate RRs (Bradburn et al. 2007; Deeks, Higgins, and Altman 2019). The Peto “one-step” odds ratio method is also reported to provide reasonable estimates when data are sparse (Bradburn et al. 2007; Deeks, Higgins, and Altman 2019), so Peto odds ratios were also generated using RevMan (2014) to check the sensitivity of the meta-analysis results to the method adopted.

3. Results

A total of 4 publications reporting results from relevant analyses of OSCC case-control study data, 67 other case-control and case-cohort studies, and 12 cohort studies were identified in the literature search; some of the studies addressed more than one type of childhood cancer while others addressed specific types. Details of the case-control and case-cohort studies are presented in Supplementary Table S1 and the cohort studies in Supplementary Table S2. In these tables, the studies are ranked by statistical
information content (Bithell 1989), and each study précis includes: whether abdominal exposures were available or if all antenatal exposures had to be used in the meta-analyses; whether exposure data were gathered from medical records or interviews/questionnaires; and whether mortality or incidence data were used – with the exception of three analyses of OSCC data (Gilman et al. 1989; Kneale and Stewart 1986; Sorahan and Stewart 1993), mortality studies were confined to deaths during the earliest periods (before 1970) when for many types of childhood cancer (including leukaemia) mortality rates were effectively equivalent to incidence rates (Stiller 2007). In addition to specific types of childhood cancer, groupings of types have been adopted where these groupings have been used in individual studies. However, if a study has examined only one particular type of childhood cancer then that study will not be included in a grouping that includes that specific type because the other types of cancer in the grouping are not included. For example, a study of just brain and central nervous system (CNS) tumours will not be included in the grouping of all solid cancers combined because the other relevant cancer types in this grouping were not the subject of the study. This needs to be borne in mind when considering the results for cancer type groupings.

The case-control/case-cohort studies identified in the literature search, for each childhood cancer type and groupings of types, are listed in Table 1, with studies ranked by statistical information content (Bithell 1989). The relative risk (RR) estimates associated with an antenatal X-ray exposure obtained from the OSCC and from the meta-analyses of the studies apart from the OSCC, using inverse-variance fixed-effect models, are presented in Table 2 and summarised in Figure 2. For all cancers combined, leukaemia and all cancers except leukaemia combined, the RR estimates from the OSCC and the combined other studies are broadly compatible and persuasive of genuine associations between the risk of these cancers and intrauterine exposure to diagnostic X-rays: the RR for leukaemia is 1.51 (95% confidence interval (CI): 1.35, 1.69) for the OSCC against 1.28 (95% CI: 1.16, 1.41) for the combined other studies, and for all cancers except leukaemia the RR is 1.46 (95% CI: 1.31, 1.62) for the OSCC against 1.31 (95% CI: 1.13, 1.53) for the combined other studies. More disparity is observed when categories
involving fewer cases/deaths are involved – the results for peripheral neural
tumours and kidney tumours are notable in this respect. The RR\textsuperscript{s} for the
OSCC tend to be higher than those for the combined other studies, but factors
such as the birth periods covered by the studies and the resulting differences
in intrauterine doses must be taken into account, as discussed below.

Formal assessments of homogeneity (Cochrane Q and Higgins I\textsuperscript{2}
statistics) of the individual case-control/case-cohort study odds ratios did not
detect heterogeneity in any of the cancer types or groups of types. The
results of using two alternative models for the meta-analyses are presented in
Supplementary Figure S1, which includes forest plots for the Mantel-Haenszel
random-effects model. Differences between the RR estimates produced by
the three meta-analytical methods are minor, being largest for bone tumours,
but even then, only amount to proportional changes of a few percent (see
Table 2 and Supplementary Figure S1). This is unsurprising given the
absence of discernible heterogeneity from the Cochrane Q tests and Higgins
I\textsuperscript{2} statistics (see Supplementary Figure S1).

Where relevant, Table 2 shows alternative findings of the meta-
analyses with the study of Robinette and Jablon (1976) omitted. The results
of this study were only presented in an Abstract, raising doubts over whether
the authors considered the results of this study to be reliable. Further, the
large Japanese leukaemia case-control study of Hirayama (1980) has not
been included in the leukaemia meta-analysis because the results of this
study, showing a notably raised RR (Supplementary Table S1), have only
been mentioned briefly in conference proceedings and details of the study are
unclear\textsuperscript{1}; the results of this large study would be especially influential in the
meta-analysis for leukaemia.

Results of case-control studies of twin births are shown in Table 3,
using inverse-variance fixed-effect models in the meta-analyses. Apart from
the OSCC, data from two case-control studies nested in twin birth cohorts
have been combined to provide RR estimates to compare with those of the
OSCC. Given that the meta-analyses are restricted to two studies with limited
numbers of cases (see Supplementary Table S1), attention needs to be paid

\textsuperscript{1} Enquiries made of colleagues in Japan have not provided clarity.
to the sensitivity of the RR to the methods adopted (see the relevant discussion on cohort studies in the Methods section). In fact, from the assessment of homogeneity and the range of results presented in Table 3, this does not appear to be a problem, with the exception of brain/CNS tumours; for brain/CNS tumours, the Mantel-Haenszel fixed-effect model and the Peto odds ratio method are likely to provide the most reliable RR estimates (see Table 3).

The cohort studies identified in the literature search are listed in Table 4 (and detailed in Supplementary Table S2), ranked by statistical information content (Bithell 1989), and the results of the meta-analyses presented. As discussed in the Methods section, most attention should be paid to the RR estimates generated by the Mantel-Haenszel fixed-effect model and the Peto odds ratio method, regarded to be the more reliable estimates when numbers of incident cases/deaths in the cohorts are small. In contrast to the findings from the combined case-control/case-cohort studies, there is little evidence from the results of the combined cohort studies for a raised risk of the types and groups of types of childhood cancers analysed being associated with an antenatal X-ray examination. However, there are a number of issues with the meta-analyses of the cohort studies that need to be considered when judging the findings; the various results set out in Table 4 take these issues into account.

First, the validity of the study of Court Brown, Doll, and Hill (1960) of leukaemia mortality in children born in eight hospitals in Edinburgh and North-west London has been questioned by one of the authors (R Doll), who became dissatisfied with the adequacy of the identification of exposed mothers when he tried to extend the study some years later, and believed that the results are unreliable (UNSCEAR 1994; Doll and Wakeford 1997; Wakeford, Doll, and Bithell 1997a, 1997b). Second, the study of Lewis (1960) was based on births during 1943-1958 in one of the London hospitals included in the study of Court Brown, Doll, and Hill (1960) of births during 1945-1956, so a substantial overlap of births between the two studies is to be expected. Further, it is unclear whether the maternal identification problems associated with the study of Court Brown, Doll, and Hill (1960) extend to the study of Lewis (1960). Third, Lejeune et al. (1960) initially studied birth
cohorts of antenatally exposed and unexposed individuals identified in medical records in a maternity hospital in Paris, but these cohorts were extended to include “germains” (siblings and first-cousins) identified at maternal interview (see Supplementary Table S2). Insufficient information on the extended cohorts is available to allow the expected number of childhood cancer deaths in the extended exposed cohort to be calculated (and there are no cancer deaths reported as occurring in childhood in either the original or extended unexposed cohorts), so the original exposed cohort is used in the meta-analyses. Fourth, there is some uncertainty over the numbers of cases of cancers other than leukaemia included in the Chicago study of Griem, Meier, and Dobben (1967) (see Supplementary Table S2), but the numbers are assumed to be as reported by Griem, Meier, and Dobben (1967). Finally, four very small cohort studies (Neumeister and Wässer 1985; Nøkkentved 1968; Mills et al. 1958; Dempster 1958), each with <200 individuals in the cohorts and with no childhood cancer cases/deaths identified (see Supplementary Table S2) were not included in the meta-analyses to avoid computational difficulties posed by zero cases in these very small cohorts.

Consequently, the main results of the leukaemia meta-analysis of cohort study data are for the exclusion of the studies of Court Brown, Doll, and Hill (1960) and Lejeune et al. (1960), although sensitivity analyses were conducted with these studies included (Table 4). When the study of Court Brown, Doll, and Hill (1960) is included in a meta-analysis, the study of Lewis (1960) is not because of the substantial proportion of the births included in the study of Lewis (1960) that must also be included in the study of Court Brown, Doll, and Hill (1960). Further, a sensitivity meta-analysis is performed with both the studies of Court Brown, Doll, and Hill (1960) and Lewis (1960) excluded (in addition to the exclusion of the study of Lejeune et al. (1960)) to address concerns that the problems of the accurate identification of mothers in the study of Court Brown, Doll, and Hill (1960) may extend to the study of Lewis (1960).

A problem apparent in the meta-analyses of the cohort study results is the evidence of notable heterogeneity in the results, as indicated by Cochrane Q tests and Higgins I² statistics generated by RevMan (2014). This heterogeneity is due to the inclusion of the Parisian study of Lejeune et al.
(1960), with its notably raised observed to expected mortality ratios for the three cancer groupings (Supplementary Table S2); details are provided in Table 4. Hence, the main results of the meta-analyses are taken to be those generated with the exclusion of the study of Lejeune et al. (1960), although sensitivity findings are also presented in Table 4 with the study of Lejeune et al. (1960) included.

4. Discussion

4.1 The epidemiological studies reviewed

4.1.2 Case-control and case-cohort studies

Data from the Oxford Survey of Childhood Cancers (OSCC) dominate the statistical information obtained from case-control and case-cohort studies of an association between the risk of all types of childhood cancer combined and medical exposure in utero to X-rays for diagnostic purposes (Table 1). However, this is not the situation for specific types of childhood cancer: for leukaemia, brain/CNS tumours and bone tumours, the aggregated information obtained from case-control/case-cohort studies other than the OSCC is greater than that available from the Oxford Survey (Table 1). This is partly due to the most recent analysis of OSCC data that distinguished between different types of cancer (Bithell and Stewart 1975) including only about 55% of the overall number of cancer case-control pairs that were included in the latest analysis of all childhood cancer deaths combined (Gilman et al. 1989), and the latter analysis including as abdominally exposed subjects those with antenatal exposures reported at maternal interview whereas the former analysis included only those subjects with exposures confirmed by medical records (Bithell 1989). Further, later relevant case-control/case-cohort studies have tended to concentrate upon particular types of childhood cancer, and leukaemia is an especially notable example of this for which the principal RR estimate for the combined studies apart from the OSCC is based upon 35 studies (Table 1).
Table 2 presents the results of analyses using the available OSCC data for specific types of childhood cancer and groups of types, and compares these with the results of meta-analyses of the findings of all other case-control/case-cohort studies combined, as illustrated in Figure 2. It is apparent that for the major types and groupings of types of childhood cancer there is broad consistency between the RRs obtained from the OSCC and those derived from the combined other case-control/case-cohort studies, such that when a RR is raised for the OSCC then it is also raised for the combined other studies. However, the marginally increased RRs from the combined other studies for peripheral neural tumours and kidney tumours are in notable contrast to the RRs obtained from the OSCC data, which are clearly raised; but the small numbers of cases of these cancer types associated with an abdominal X-ray exposure of the pregnant mother in the combined other studies, 10 and 19 cases, respectively, limits the power of the comparisons with the OSCC, which includes 99 and 87 exposed cases, respectively. Of interest is the absence of a discernibly increased risk of bone tumours found in the combined other studies, which is compatible with the equivalent result from the Oxford Survey.

A number of aspects of these comparisons must be taken into account when interpreting the findings presented in Table 2. First, if a study is of a specific type of childhood cancer alone then that study will not be included in the meta-analyses of groupings of childhood cancer types that encompass that type of childhood cancer because the other relevant types of cancer are not included (see Supplementary Table S1). This is particularly notable for brain/CNS tumours for which a number of influential case-control studies, such as that of Stålberg et al. (2007), are specific to this cancer type and are therefore not included in, for example, the grouping of all solid cancers.

Second, even with a case-control study as large as the Oxford Survey, and after combining the results of all the other relevant case-control/case-cohort studies, the statistical uncertainty associated with the RR estimates for the rarer types of childhood cancer is still considerable. For example, the marginally raised RR for peripheral neural tumours derived from studies other than the OSCC, 1.03 (95% CI: 0.52, 2.02), is still statistically compatible with the equivalent RR derived from the OSCC, 1.46 (95% CI: 1.16, 1.82).
Third, the tendency for the RR estimates derived from the combined case-control/case-cohort studies other than the OSCC to be lower than those obtained from the OSCC will be noted (see Figure 2). One of the features of the inevitable presence of inherent (but statistically undetectable) heterogeneity in the studies under consideration is the variation of the average dose received in utero by the subjects included in the various studies due to a number of factors including differences and improvements in radiographic equipment and the use of fetal shielding, with the anticipation that the intrauterine dose is correlated with the RR. Assessments of the fetal doses received from X-ray examinations over the calendar period of births covered by the OSCC have inferred that, as a general trend, average doses will have decreased with time (Doll and Wakeford 1997; Bithell and Stiller 1988a; Bithell 1992; Wakeford and Little 2003), and this pattern is likely to be repeated in other study settings. Although the presence of various biases may have had some influence on the temporal pattern of RR estimates, the main reason for the highly significant decrease in RR found in later periods of birth as the OSCC was extended (Bithell and Stiller 1988a) is most likely to be the reduction in intrauterine doses over the study period, such that the overall RR decreased as later births were included in the study (Doll and Wakeford 1997; Bithell and Stiller 1988a; Bithell 1992; Wakeford and Little 2003). In this respect, it has to be borne in mind that greater than one-third of the children included in the OSCC were born during 1939-1955 (Gilman et al. 1989) when intrauterine doses received during antenatal radiography would be expected to be comparatively high.

Since many of the studies detailed in Supplementary Table S1 included births many years after the earlier birth periods covered by the OSCC, lower RR estimates would be predicted from these studies. For example, the large nationwide case-control study of leukaemia incidence in Sweden of Naumburg et al. (2001) included births during 1973-1989, while only 5% of case-control pairs included in the OSCC were born after 1972, so lower RRs would be anticipated from the Swedish study, and similar arguments apply to the comparatively recent large leukaemia incidence case-control studies of Roman et al. (2005) and Shu et al. (2002) – together, these three studies
contribute 21% of the statistical weight in the main leukaemia meta-analysis (see Supplementary Table S1).

To examine this issue further, case-control/case-cohort studies other than the OSCC have been grouped into those with all subjects born in periods up to and including 1970 and those with all subjects born in periods after 1970; for the purposes of this exercise, studies including births in periods that straddle 1970-71 have been excluded. Table 5 presents the RR estimates obtained after separately combining in meta-analyses data from these two groups of studies for those types, or groups of types, of childhood cancer with a reasonable prospect of making meaningful comparisons between the RRs obtained from the two groups, that is, when all the studies other than the OSCC for a specific type, or group of types, of childhood cancer have a combined statistical information content greater than 50 (Table 1). Inevitably, restricting the numbers of studies included in the meta-analyses increases the statistical uncertainty of the RR estimates, but whereas in most instances the difference in the RRs for the two groups of studies is unremarkable, of note is that the greatest differences are for leukaemia and brain/CNS tumours, when the RRs for the later period of birth are lower (Table 5). Early studies concentrated on leukaemia, and it is possible to further restrict studies of leukaemia to those eight that included births in periods ending in 1960 or before (Monson and MacMahon 1984; Polhemus and Koch 1959; Kaplan 1958; Ford, Paterson, and Treuting 1959; Ager et al. 1965; Wells and Steer 1961; Kjeldsberg 1957; Murray, Heckel, and Hempelmann 1959), producing a RR of 1.41 (95% CI: 1.20, 1.66). This compares with a leukaemia RR of 1.08 (95% CI: 0.92, 1.27) derived from combining studies with birth periods after 1970, providing further evidence of a decrease of the RR for leukaemia with period of birth. It seems likely that this effect of birth period on the leukaemia RR indicates a more general tendency for RR estimates obtained from the OSCC to be greater than those obtained from the combined other case-control/case-cohort studies, particularly when a cancer category includes a comparatively large proportion of recent studies, as with brain/CNS tumours (Table 5).

A related issue is the use of antenatal exposures of all types in the meta-analyses when data for abdominal exposures are not available for a
The problem with this approach is that non-abdominal exposures of the pregnant mother are very likely to lead to lower intrauterine doses than abdominal exposures. Since the number of non-abdominal exposures in a study is usually greater, often markedly greater in more recent years, than the number of abdominal exposures, this would assign a spuriously high weight to the study in a meta-analysis that includes studies for which abdominal exposure data are available, potentially introducing bias into the resulting RR estimate. To investigate the effect of this issue on findings, the meta-analyses were repeated including just studies having abdominal exposure data. The only cancer types, or groupings of types, for which the RR estimates for the combined studies other than the OSCC were affected to any notable extent (a >10% change) were: lymphoma, decreasing from 1.75 (95% CI: 1.08, 2.84) to 1.45 (95% CI: 0.83, 2.53) due to the exclusion of the study of Shu, Jin, et al. (1994); bone tumours, increasing from 1.11 (95% CI: 0.81, 1.53) to 1.93 (95% CI: 1.00, 3.70), due to the exclusion of the studies of Winn et al. (1992) and Holly et al. (1992); rhabdomyosarcoma, increasing from 1.45 (95% CI: 0.89, 2.36) to 1.62 (95% CI: 0.97, 2.70) due to the exclusion of the study of Grufferman et al. (1982); and germ cell tumours, increasing from 0.88 (95% CI: 0.52, 1.49) to 1.33 (95% CI: 0.48, 3.62) due to the exclusion of the study of Shu et al. (1995). This sounds a note of caution in the interpretation of the findings for these cancer types, and in particular for lymphoma and bone tumours, but the sensitivity analyses are broadly reassuring as far as overall results are concerned.

The six case-control/case-cohort studies other than the OSCC that used mortality data (Table 1) were among those covering the earliest periods identified in the literature search (see Supplementary Table S1); during these early years mortality was effectively equivalent to incidence for many types of childhood cancer (Stiller 2007). In any event, the inclusion of studies of both incidence and mortality in the meta-analyses should not pose a problem when it is the relative risk under consideration because the same rates of survival over a study period will apply to both exposed and unexposed cases. All six of these mortality studies addressed childhood leukaemia (two exclusively so), and combining just these six studies produces a leukaemia RR = 1.36 (95% CI: 1.17, 1.59) (or a leukaemia RR = 1.49 (95% CI: 1.24, 1.79) if the
study of Robinette and Jablon (1976) is excluded from this group), while the
incidence studies alone produce a leukaemia RR = 1.20 (95% CI: 1.07, 1.35)
– the leukaemia RR from the incidence studies is raised but less than that
from the mortality studies, which is likely to be due, at least in part, to the
generally later birth years covered (see discussion above). A similar exercise
for other types, or groupings of types, of childhood cancer did not reveal
noteworthy differences between results for separately combined mortality and
incidence studies.

The assessment of the effect on findings of the source of information
on antenatal exposure in a study poses difficulties. Records of antenatal X-
ray examinations would be considered to be the preferred source, although
such records cannot be guaranteed to be comprehensive or free from errors.
The alternative source is maternal interviews or questionnaires, but then
potential systematic effects from, for example, participation bias and recall
bias have to be taken into account. In the OSCC it was found that maternal
recall of exposures was broadly confirmed by medical records (Hewitt,
Sanders, and Stewart 1966), but this cannot be assumed to necessarily hold
for other studies, particularly if, say, abdominal exposures had to be
distinguished from other exposures during a telephone interview. To check
the influence of different sources of exposure information, the meta-analyses
were re-run including only those studies using records to determine
exposures. The only types, or groups of types, of childhood cancer to be
affected to any notable extent were: lymphoma, with the RR decreasing from
1.75 (95% CI: 1.08, 2.84) to 1.45 (95% CI: 0.83, 2.53); brain/CNS tumours,
with the RR increasing from 1.13 (95% CI: 0.97, 1.31) to 1.24 (95% CI: 1.01,
1.51); all cancers except leukaemia and brain/CNS tumours, with the RR
decreasing from 1.24 (95% CI: 1.02, 1.52) to 1.19 (95% CI: 0.97, 1.47); and
eye tumours, with the RR decreasing from 2.14 (95% CI: 1.04, 4.39) to 1.65
(95% CI: 0.65, 4.19). These differences should be borne in mind, but overall,
the sensitivity analyses do not indicate that studies relying on
interview/questionnaire data have a particularly strong influence on the
findings for the studies other than the OSCC.

Mole (1974) drew attention to the inferential value of studies confined
to twins: compared to singleton births, twin births experience a substantially
higher frequency of antenatal X-ray examinations, predominantly for obstetric reasons, so twin studies can address the possibility in singleton studies of confounding through antenatal radiodiagnostic examinations being associated with some risk factor for childhood cancer, say potentially, maternal health.

Table 3 demonstrates the broad compatibility of the results of studying twins included in the OSCC (55% of controls exposed) (Stewart 1973; Mole 1974) with those of studying singletons in the OSCC from (nearly) the same period of birth (10% of controls exposed) (Bithell and Stewart 1975), and also with the results of combining two nested case-control studies of twins from Sweden (Rolvall et al. 1990) and Connecticut (Harvey et al. 1985). Even though twins may have a generally reduced risk of childhood cancer compared to singletons (Murphy et al. 2008), confining case-control studies to twin births effectively eliminates this difference when investigating the influence of intrauterine X-ray exposure. Further, the early periods of birth of the cases and controls included in these twin studies avoids any complications of carcinogenic risks associated with subfertility and assisted reproduction technology (Hargreave et al. 2019). A major difficulty of conducting studies of antenatal X-ray examinations and childhood cancer in twins is the size and quality of the databases required to produce meaningful results – for example, in a large dataset of 83,316 Swedish twins, Rolvall et al. (1990) identified 95 cases of childhood cancer of which 25 cases were exposed through an abdominal X-ray examination of the pregnant mother, so numbers are comparatively small. Nonetheless, within the limited power of these twin case-control studies, the compatibility of the two sets of results presented in Table 2 is noteworthy.

4.1.2 Cohort studies

The methodological superiority of cohort studies over case-control studies is contrasted by the limited ability of cohort studies to address rare diseases because of the size of the cohorts required to achieve reasonable statistical power to detect realistically raised risks. This is illustrated in Supplementary Table S2 and Table 4 – the two largest antenatally exposed cohort studies (Court Brown, Doll, and Hill 1960; Diamond, Schmerler, and
Lilienfeld 1973) have much lower statistical information contents (<10 units) than most of the case-control/case-cohort studies presented in Table 1 (and summarised in Supplementary Table S1). Nonetheless, the principal strength of the cohort study of Court Brown, Doll, and Hill (1960) is that, in considering a cohort of nearly 40,000 exposed births during 1945-1956 with an expected number of childhood leukaemia deaths of 10.5, it could meaningfully address the RR for leukaemia of 1.90 (95% CI: 1.38, 2.60) reported by Stewart, Webb, and Hewitt (1958) from their case-control study. The 9 observed deaths (Court Brown, Doll, and Hill 1960) produced a RR of 0.86 (95% CI: 0.39, 1.63), suggesting that if there was a raised leukaemia risk then its magnitude would be towards the lower end of the confidence interval derived by Stewart, Webb, and Hewitt (1958).

However, although shortcomings of the study of Court Brown, Doll, and Hill (1960) included not having a comparison unexposed cohort and that children antenatally exposed in London and Edinburgh hospitals with modern equipment might have received X-ray doses lower than those received in Great Britain as a whole, which complicates the comparison with the nationwide case-control study, the major weakness of the cohort study of Court Brown, Doll, and Hill (1960) was the inadequacy of the identification of the mothers undergoing radiography, discovered by one of the authors (R Doll) after the study’s publication (UNSCEAR 1994). The records of the radiology departments of the eight hospitals included in the study were used to identify pregnant women abdominally exposed to X-rays for diagnostic purposes during 1945-1956 and the data so-gathered, together with additional information obtained from maternity and birth registration records, were used for comparison with the personal data recorded on the death certificates of all those who had died of leukaemia in Great Britain during 1945-1958, which had been collected previously (Court Brown, Doll, and Hill 1960). Inadequate identification of exposed mothers could have led to a failure to link antenatally exposed children to leukaemia deaths and a consequent underestimation of the RR, calculated by comparing the observed number of deaths with the expected number obtained by applying mortality rates based upon the leukaemia death certificate and population data to the temporal distribution of all births to women recorded as being exposed at the hospitals during
pregnancy. Doll believed that this rendered the findings of the study unreliable (Doll and Wakeford 1997; Wakeford, Doll, and Bithell 1997a, 1997b).

In addition, Lewis (1960) studied births in one of the London hospitals included in the study of Court Brown, Doll, and Hill (1960), so many of the exposed births that were the subject of the study of Lewis (1960) can be expected to have also been included in the study of Court Brown, Doll, and Hill (1960). Whether the study of Lewis (1960) suffered from the same problems of maternal identification as that of Court Brown, Doll, and Hill (1960) is not known, although this is a possibility. There are also unresolved issues with some of the other cohort studies, such as those of Lejeune et al. (1960) and Griem, Meier, and Dobben (1967), as noted in the Results section and in Table 4 and Supplementary Table S2.

All but two of the cohort studies ((Griem, Meier, and Dobben 1967; Ray et al. 2010) are of cancer mortality. Excluding these two studies of incidence from the meta-analyses makes no material difference to the cohort study findings.

Finally, the difficulties faced by those conducting recent studies of antenatal diagnostic exposures, particularly cohort studies, are illustrated by the study of Ray et al. (2010). This cohort study included all births in Ontario over a period of 16 years, just over 1.8 million births, but the low prevalence of intrauterine exposures meant that the authors were able to identify just 4 incident cases of childhood cancer among 5590 exposed births, producing low power to detect any realistically sized effect. Further, unlike earlier studies, the radiodiagnostic procedures in this study were CT scans (73%) and radionuclide imaging (27%), and the embryo/fetal doses received during these procedures are variable and uncertain. In particular, of the CT scans, 68% were head CT scans and the doses received in utero from such procedures would be expected to be very low.

Given these issues it is perhaps not too surprising that the interpretation of the cohort study findings presented in Table 4 is problematic. Point estimates of RRs are marginally raised, but with, in general, wide confidence intervals easily including no increased risk. The cohort study findings give little support to elevated risks indicated by the case-control/case-cohort study results, but are equivocal when the limited power and various
sources of uncertainty are taken into account and cannot be inferred to refute the case-control/case-cohort study findings.

### 4.2 Other epidemiological studies

The analyses conducted in this paper are of data for antenatal exposures to medical X-rays for diagnostic purposes, but other studies relevant to the risk of childhood cancer consequent to irradiation in utero have been published. Hagstrom et al. (1969) reported the results of a cohort study of children born following an experimental study in the late-1940s in which pregnant women ingested radioactive iron to study iron absorption during pregnancy. It would appear that the fetal doses received from the radioiron are somewhat uncertain (Moeller and Merwin 2000; Stabin, Stubbs, and Russell 1997). Of the exposed children, 634 were located, and cancer mortality in this cohort was compared with that in a comparison cohort of 655 unexposed children during follow-up in 1964-1967. Four deaths from childhood cancer were reported from the exposed cohort: leukaemia, lymphoma, soft tissue tumour and liver tumour; no cancer death was found in the unexposed cohort. An increased childhood cancer risk in the exposed cohort is indicated (Peto one-step odds ratio = 7.7 (95% CI: 1.1, 54.6)), but how the fetal doses in this study relate to those received during an antenatal X-ray examination is unclear.

The cohort of 1878 Japanese people who were present in utero in Hiroshima and Nagasaki during the atomic bombings in 1945 and who survived until October 1950 are a particularly important group for study; 908 of these survivors received RBE-weighted absorbed doses (approximated by maternal DS02R1 uterine doses) of $\geq 5$ mGy during the bombings, with a mean dose of 254 mGy (Sugiyama et al. 2021). Two incident cases of childhood cancer were found among these exposed survivors on follow up: a kidney tumour and a liver tumour (Yoshimoto, Kato, and Schull 1991). Approximate childhood cancer incidence rates for Japan during the 1950s were derived by Wakeford and Little (2003), and applying these rates to the 908 survivors exposed in utero produces an estimated expected number of cases of cancer incident before the age of 15 years in this group of, at most,
0.42, of which 0.18 and 0.24 are the expected numbers of cases of leukaemia and other childhood cancers, respectively. The RR of childhood cancers other than leukaemia, 8.3 (mid-P 95% CI: 1.4, 28), is indicative of an excess risk of these cancers associated with radiation exposure during the atomic bombings, but is based upon just two observed cases. However, the absence of a case of childhood leukaemia is disconcerting, especially given the findings of the case-control studies of antenatal X-ray exposure and the marked excess of childhood leukaemia among the atomic bomb survivors irradiated as young children (Wakeford and Little 2003), although it should be noted that the mid-P upper 95% confidence limit for the RR derived from 0 observed and 0.18 expected cases is 17. There are a number of potential explanations for the absence of childhood leukaemia cases, such as missed cases in the late-1940s before systematic follow-up of survivors commenced or failure to have recognised the involvement of leukaemia in deaths from infectious diseases (of which there were many in this cohort), but the intriguing findings of Ohtaki et al. (2004) may provide a clue to the explanation.

Ohtaki et al. (2004) analysed the frequency of stable chromosome transformations in peripheral blood lymphocytes, sampled at 40 years of age, of 150 survivors who had received doses of ≥5 mGy while in utero and found a small increase at low doses (<100 mGy), but no increase at higher doses. This surprising finding contrasted with the increasing frequency with increasing dose anticipated from prior chromosome aberration studies, and as found in a small group of mothers of those irradiated in utero during the atomic bombings. This result for exposure in utero and transformations in haematopoietic cells was confirmed by an experimental study using mice (Nakano et al. 2007) (but differed from the results of experiments examining cells relevant to certain solid tumours (Hamasaki and Nakamura 2019)). The authors suggested that aberrant lymphocytes arising from cellular damage caused by doses >100mGy are replaced by the progeny of fetal stem cells largely unaffected by exposure, and this could provide an explanation for the absence of cases of childhood leukaemia in the survivors irradiated in utero.

There is accumulating evidence from the Japanese atomic bomb survivors irradiated in utero of a dose-related increased risk of solid cancer.
incidence and mortality in adult life (Preston et al. 2008; Sugiyama et al. 2021); no variation of risk with trimester of exposure was discernible. In the most recent follow-up (Sugiyama et al. 2021), an excess risk of solid cancer mortality was apparent in women (ERR/Gy = 2.10 (95% CI: 0.26, 5.61)) but not men (ERR/Gy = -0.08 (95% CI: < -0.82, 1.36)); survivors had attained an age of 67 years and only 15% of those exposed had died, so more data gathered at older ages will provide firmer inferences. In the interim, a plausible conclusion is that radiation exposure in utero during the atomic bombings has led to an increased risk of solid cancer in adulthood (at least, in women), although the magnitude of this increased risk is, at present, uncertain.

Studies have been undertaken of cancer incidence and mortality in the offspring of women who had been exposed to radiation while pregnant and working at the Mayak nuclear installation in the Southern Urals in Russia, and in the offspring of pregnant women resident near the Techa River that was heavily contaminated by radioactive discharges from Mayak. Numbers of incident cases and deaths among children <15 years of age among those exposed in utero were small: in the Mayak offspring cohort (mean dose, 35 mGy) the numbers of incident cases of leukaemia, lymphoma and solid cancers were 7, 1 and 4, respectively (Akleyev et al. 2016; Schüz et al. 2017), while in the Techa River cohort (mean red bone marrow (RBM) dose, 30 mGy; mean soft tissue dose, 4 mGy – the difference is due to the RBM dose from internal emitters, including 90Sr) the numbers of incident cases were 2, 3 and 11, respectively (Krestinina et al. 2017). These small numbers of cases lead to unremarkable risk estimates for childhood cancer – for example, the RR of childhood leukaemia plus lymphoma incidence in the combined Mayak and Techa River cohorts at an estimated RBM dose of 100 mGy received in utero was modelled to be 0.91 (95% CI: not defined, 2.74) (Schüz et al. 2017) – but other sources of uncertainty (such as dosimetry, additional radiation exposure after birth and case ascertainment in earlier years of follow-up) need to be taken into account when assessing findings.

Individuals in utero or <6 years of age at the time of the Chornobyl (aka Chernobyl) nuclear accident in northern Ukraine in 1986 were the subject of a case-control study of childhood acute leukaemia incidence in contaminated
districts around Chornobyl, the 421 cases having an estimated mean RBM dose of \(~10\text{ mGy}\) (Davis et al. 2006). A positive dose-response was reported, but published results do not distinguish between those exposed \textit{in utero} and those exposed after birth; moreover, the study appears to have suffered from various shortcomings that raise doubts over the accuracy of its findings (Moysich, McCarthy, and Hall 2011; Davis et al. 2006). Eight cases of thyroid cancer in adults were found among a cohort of those exposed \textit{in utero} to Chornobyl fallout in Ukraine (where thyroid doses were largely from radioactive iodine) and who had participated in a thyroid screening programme, with an imprecise raised risk indicated (Hatch et al. 2019). No other reliable individual-based studies of intrauterine exposure to Chornobyl radioactive contamination have been conducted. Inconsistent findings for infant leukaemia incidence in a period broadly corresponding to maternal pregnancy at the time of the Chornobyl accident have been reported from group-averaged “ecological” studies of regions affected by fallout, which are not readily interpretable (a summary of results is given by Brent et al. (2013)).

In a case-control study, the mothers of cases in the UK National Registry of Childhood Tumours and matched controls were linked to women in the National Registry for Radiation Workers (Bunch et al. 2009). For all childhood cancers, the mothers of 7 cases and 1 control were occupationally exposed to radiation while pregnant, \(\text{OR} = 7.00\) (95% CI: 0.90, 315), but only 1 case and no control had a recorded intrauterine dose >2 mSv. For leukaemia and NHL, \(\text{OR} = 2.00\) (95% CI: 0.10, 118), and for all other childhood cancers, \(\text{OR} = 6.73\) (95% CI: 0.92, \(\infty\)); the single case with a dose >2 mSv was of an other cancer. Childhood cancer in almost 106,000 offspring of a cohort of US radiographers was studied by Johnson et al. (2008). Among the offspring of female radiographers occupationally exposed while pregnant, the observed numbers of cases of leukaemia, lymphoma and solid cancers ascertained through a questionnaire were 35, 34 and 64, respectively, although expected numbers were not presented. Hazard ratios in three intrauterine dose categories, with offspring unexposed \textit{in utero} as the reference category, were unremarkable for leukaemia and solid cancers, but were raised in all three dose categories for lymphoma. However, there was little indication of a trend with dose for any of the cancer types studied, and
the highest dose estimated to have been received in utero by a case (of solid cancer) was 3.3 mGy.

It has been suggested (Boice and Miller 1999) that studies of offspring of women who received radiotherapy during pregnancy would be informative with respect to the risk of childhood cancer following intrauterine exposure to radiation. Some studies have investigated health outcomes in groups of such offspring, but the numbers of children are small and very few studies have examined cancer as an outcome (Woo et al. 1992; Kal and Struikmans 2005; Luis et al. 2009; Brent et al. 2013). Consequently, although such studies are potentially illuminating, none that impart reliable quantitative information on cancer risks has so far been carried out (Vandenbroucke et al. 2017).

4.3 Interpretation

A considerable challenge to the accurate interpretation of a statistical association that emerges from observational epidemiological studies, once chance has been confidently excluded, is the elimination of a substantial role for bias and confounding, leaving cause-and-effect as a reasonable explanation for the association (Hill 2015). Medical exposure to radiation occurs either as therapy for a known disease or as an aid to diagnosing a disease – patients are selected for exposure because they are ill or suspected of being ill. The inferential problems posed by selection for medical exposure have been highlighted by the associations reported from recent studies of cancer incidence following computed tomography (CT) scanning of young people, the interpretation of which has been complicated by potential selection effects: reverse causation (the early signs of a slowly developing and undiagnosed cancer caused the CT scan rather than the reverse) and other sources of confounding by indication (an underlying medical condition led to a higher frequency of CT scanning, but the condition also caused a raised risk of cancer) (Walsh et al. 2014; Boice 2015; Journy et al. 2016; Meulepas et al. 2016; Berrington de Gonzalez et al. 2016). Similarly, caution is required in the interpretation of studies of radiation exposure in utero for medical reasons.
A number of features of the design and conduct of the Oxford Survey of Childhood Cancers has provoked discussion of the potential for the introduction of various sources of bias (see Streffer et al. (2003)). Early concerns about the possibility of maternal recall bias were met by confining analyses to exposures confirmed by medical records (Bithell and Stewart 1975), and doubts over the quality of data collected in the later years of the study (Bithell 1989) can be addressed by restricting analyses to earlier deaths (Bithell and Stewart 1975). Even so, the OSCC covers childhood cancer mortality over a period of almost 30 years, during which time survival increased substantially – for example, when the study commenced in the 1950s childhood leukaemia was almost invariably fatal, but treatment had much improved when the study ended in the 1980s (Doll 1989). Not only did this steadily reduce the number of (fatal) cases included in the study with the passage of time, but differences in the proportions of cases of different cancer types between the beginning and end of the study period could introduce subtle biases (Wakeford and Little 2003). Whether biases could have been introduced by case ascertainment, the degree of success in tracing mothers of cases, control selection, and the participation of mothers of cases and controls willing to be interviewed has been mooted (Streffer et al. 2003), but it is not possible to confidently infer the direction and magnitude of any systematic error potentially introduced by such effects. As with any observational epidemiological study, the OSCC results needed confirmation by independent studies and this is one important aspect of the findings of the case-cohort study of MacMahon (1962), which through its design eliminated the possibility of biases due to maternal recall and control selection, and pointed to the reality of the association between the risk of childhood cancer and antenatal X-ray exposure reported by Stewart, Webb, and Hewitt (1958).

Overall, the variety of approaches to the design and conduct of the case-control and case-cohort studies presented in Supplementary Table S1 effectively rules out bias as a realistic explanation for the associations between an antenatal X-ray examination and the raised risks of childhood cancer shown in Table 2. Some common confounding factor is more difficult to exclude confidently, although the results of the nested case-control studies of twins shown in Table 3 are reassuring in this respect. As discussed above,
limited power and other problems with the cohort studies pose problems for a reliable interpretation of the results shown in Table 4.

The possibility of confounding of the association initially reported from the OSCC has been much discussed and investigated, with little to suggest that such an explanation is plausible (Bithell and Stewart 1975; Bithell 1989). Nonetheless, comprehensively addressing potential confounding is problematic when most of the major risk factors for childhood cancer remain unknown, and the recent interest in the role of high birthweight in childhood cancer risk illustrates the point. A large fetus could be more likely to be the subject of an obstetric X-ray examination because of, for example, concerns about the safety of a vaginal birth, and if high birthweight increases the risk of cancer in childhood, as now seems likely (O'Neill et al. 2015), then confounding is possible. Perhaps surprisingly, although many different sets of data were collected in the Oxford Survey, birthweight was not systematically recorded, so the potentially confounding role of birthweight in the association between an antenatal X-ray examination and childhood cancer found by the OSCC requires investigation (Wakeford and Bithell 2015). Even so, when Wakeford and Bithell (2015) examined the results of the large case-cohort study of Monson and MacMahon (1984) they found little evidence for confounding by birthweight.

The inference that the findings of this review indicate that the risk of those cancer types that are most frequently incident in children are raised to approximately the same extent by antenatal radiography has implications for the aetiology of these cancers; the exception to this pattern is bone tumours, which show little suggestion of a raised risk, but are not typical childhood cancers. Since intrauterine diagnostic exposures in medical studies are dominated by those occurring in the final weeks of pregnancy the implication is that irradiation of the late fetus increases the risk of most types of childhood cancer; there is evidence of risks from exposure in the second and, in particular, the first trimesters, but limited data and other issues preclude reliable conclusions (Mole 1990; Doll and Wakeford 1997). Boice and Miller (1999) have argued that it is implausible that radiation exposure shortly before birth could give rise to such a diverse range of cancer types – including embryonal tumours (e.g., neuroblastoma and Wilms’ tumour) that are
effectively confined to early childhood – with similar proportional increases in risk per unit fetal dose. In contrast, an excess of childhood cancers following exposure after birth is essentially confined to leukaemia (and thyroid cancer, which is not a typical cancer of childhood), apart from some evidence for increases in some childhood cancers (in particular, brain/CNS tumours (Braganza et al. 2012)) following the receipt of moderate and high therapeutic doses. On the other hand, Doll and Wakeford (1997) have argued that the cells from which the typical solid cancers of childhood arise remain sensitive throughout pregnancy, but persist and maintain the ability to divide for only a short time after birth (if at all), so it should not be surprising that the carcinogenic effects of irradiation of the fetus and young child differ. It seems likely that a consensual interpretation of the association between an antenatal X-ray examination and the risk of childhood cancer will be achieved only when the biology and pathology of childhood cancer are better understood.

5. Conclusions

The findings of meta-analyses of the results of case-control and case-cohort studies other than the OSCC offer broad support for the associations between the risk of different types, and groups of types, of childhood cancer and an antenatal X-ray examination originally reported from the Oxford Survey (Bithell and Stewart 1975). Apparent inconsistencies in the relative risks for peripheral neural tumours and kidney tumours may be explained by chance, given the small numbers of cases/deaths of these rarer cancer types included in the meta-analyses, although other explanations are possible; there is agreement on the absence of a discernibly increased risk of bone tumours. Case-control studies of twins show similar associations to those found for singleton births, reducing the likelihood of confounding being responsible for the associations. Cohort studies of diagnostic exposures add little to the understanding of how intrauterine doses of radiation may affect the risk of childhood cancer because of limited power and other problems with the studies, but continued study of the cohort of Japanese atomic bomb survivors irradiated in utero has strengthened the evidence for an increased risk of adult solid cancers, albeit at higher doses and presently confined to women.
Overall, the findings of this review strengthen the evidence for an increased risk of most types of childhood cancer consequent to the receipt *in utero* of a low dose of radiation, although a greater understanding of biological mechanisms is required for definitive conclusions to be drawn for specific types of cancer.

**Disclosure statement**


**Acknowledgements**

The work underlying this paper was partially funded by a grant, reference number 17-252, from CHILDREN with CANCER UK.

The preliminary findings of the analyses reported in this paper were presented in a poster at the CHILDREN with CANCER UK Workshop on *In Utero* Exposure and Cancer in Children, held in London during June 2014.

Thanks are due for the additional information on particular studies helpfully provided at various times by Jean Golding, Andrea Sherriff, Michael Stjernfeldt and Jill Simpson.

Many thanks to John Bithell’s close colleagues in the former Childhood Cancer Research Group (CCRG), University of Oxford, for their encouragement to complete this paper following John’s death in March 2020. Particular thanks to Gerry Kendall, Mike Murphy and Charles Stiller for their valuable comments on a draft manuscript.

Thanks to the manuscript reviewers for their insights.

Many thanks to Joy Bithell, John’s wife, for her support in the completion of this paper.
References


Voillequé, T. Chegerova, K. Falkner, S. Kulikov, E. Maslova, V. Ostapenko, N. Rivkind, V. Shevchuk, and A. F. Tsyb. 2006. 'Childhood leukaemia in Belarus, Russia, and Ukraine following the Chernobyl power station accident: results from an international collaborative population-based case-control study', *Int J Epidemiol*, 35: 386-96.


Hewitt, D., B. Sanders, and A. Stewart. 1966. 'Oxford Survey of Childhood Cancers: progress report. IV. Reliability of data reported by case and


Nekkentved, K. 1968. Effect of diagnostic radiation upon the human foetus: Follow-up study of 152 children exposed to irradiation during the first 4 months of foetal life due to X-ray examination of the maternal abdomen (Munksgaard: Copenhagen).

childhood cancer: international population-based case control studies of 40 000 cases', *Int J Epidemiol*, 44: 153-68.


Table 1. For each specific type, or group of types, of childhood cancer associated with a medical diagnostic X-ray examination of the pregnant mother, the studies contributing to the findings of the Oxford Survey of Childhood Cancers and those of all other case-control and case-cohort studies appropriately combined in a meta-analysis. (Further details of individual studies are presented in Supplementary Table S1.)

<table>
<thead>
<tr>
<th>Type, or Group of Types, of Childhood Cancer</th>
<th>Oxford Survey of Childhood Cancers</th>
<th>All Other Case-control/Case-cohort Studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Contributing Studies&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Number of Cases, Exposed/Total Units of Statistical Information&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>Gilman et al. (1989)</td>
<td>2281/15,276 852.4</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>Bithell and Stewart (1975); Stewart (1973)</td>
<td>620/4122</td>
</tr>
<tr>
<td>Diagnosis</td>
<td>Authors (Year)</td>
<td>Cases</td>
</tr>
<tr>
<td>-----------------------------------------</td>
<td>-----------------------------------------</td>
<td>-------</td>
</tr>
<tr>
<td>All cancers except leukaemia</td>
<td>Bithell and Stewart (1975); Stewart (1973)</td>
<td>672/4552</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>10:</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>246/4715</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>Bithell and Stewart (1975)</td>
<td>92/719</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>21/374</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>17/435</td>
</tr>
<tr>
<td>Leukaemia and lymphoma</td>
<td>Kneale and Stewart (1986)</td>
<td>1100/7347</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------</td>
<td>------------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All solid cancers$^f$</td>
<td></td>
<td>1018/6582</td>
</tr>
<tr>
<td></td>
<td>Kneale and Stewart (1986)</td>
<td></td>
</tr>
<tr>
<td>Brain/CNS tumours</td>
<td>Bithell and Stewart (1975)</td>
<td>179/1332</td>
</tr>
<tr>
<td>Category</td>
<td>Reference</td>
<td>Cases/Census</td>
</tr>
<tr>
<td>---------------------------------------------</td>
<td>----------------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>All cancers except leukaemia and brain/CNS tumours</td>
<td>Bithell and Stewart (1975)</td>
<td>433/3129</td>
</tr>
<tr>
<td>All solid cancers except brain/CNS tumours</td>
<td>Bithell and Stewart (1975)</td>
<td>341/2410</td>
</tr>
<tr>
<td>Peripheral neural tumours</td>
<td>Bithell and Stewart (1975)</td>
<td>99/720</td>
</tr>
<tr>
<td>Cancer Type</td>
<td>Source</td>
<td>Incidence</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------------------------</td>
<td>-----------</td>
</tr>
<tr>
<td>Kidney tumours</td>
<td>Bithell and Stewart (1975)</td>
<td>87/590</td>
</tr>
<tr>
<td></td>
<td></td>
<td>67.6</td>
</tr>
<tr>
<td>Bone tumours</td>
<td>Bithell and Stewart (1975)</td>
<td>26/244</td>
</tr>
<tr>
<td></td>
<td></td>
<td>22.5</td>
</tr>
<tr>
<td>Other solid cancers</td>
<td>Bithell and Stewart (1975)</td>
<td>129/856</td>
</tr>
<tr>
<td></td>
<td></td>
<td>95.7</td>
</tr>
<tr>
<td>Eye tumours</td>
<td>Sorahan and Stewart (1993)</td>
<td>17/86</td>
</tr>
<tr>
<td></td>
<td></td>
<td>13.5</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other soft tissue tumours (^h)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>----------------------------------</td>
<td>-----</td>
<td>-----</td>
</tr>
<tr>
<td>Germ cell tumours</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Liver tumours (^i)</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>


CNS = central nervous system
N/A = not available from published information

\(^a\) The OSCC is a study of cancer mortality. Numbers of deaths and controls included in each OSCC study can be found in Supplementary Table S1.
\(^b\) One quarter of the harmonic mean of the numbers of exposed and unexposed cases and controls (i.e., the reciprocal of the sum of the reciprocals of the number of exposed cases, the number of unexposed cases, the number of exposed controls, and the number of unexposed controls).
\(^c\) Listed in order of statistical information content. The following six studies are of cancer mortality, otherwise studies are of cancer incidence: Monson and MacMahon (1984); Robinette and Jablon (1976); Ford, Paterson, and Treuting (1959); Kaplan (1958); Ager et al. (1965); Murray, Heckel, and Hempelmann (1959). Numbers of cases/deaths and controls (or cohort sample) included in each study can be found in Supplementary Table S1.
\(^d\) Robinette and Jablon (1976) excluded from the meta-analysis (see text).
\(^e\) Hirayama (1980) is not included in the meta-analysis (see text).
\(^f\) All cancers except leukaemia and lymphoma.
\(^g\) All solid cancers except brain/CNS, peripheral neural, kidney and bone tumours (but see individual study précis in Supplementary Table S1).
\(^h\) Soft tissue tumours excluding rhabdomyosarcoma.
\(^i\) Insufficient data for quantitative analysis.
Table 2. Relative risk of specific types, and groups of types, of childhood cancer associated with a medical diagnostic X-ray examination of the pregnant mother, comparing the findings of the Oxford Survey of Childhood Cancers with those of all other case-control and case-cohort studies appropriately combined in a meta-analysis using inverse-variance fixed-effect models. Studies contributing to the calculation of the relative risks are shown in Table 1.

<table>
<thead>
<tr>
<th>Type, or Group of Types, of Childhood Cancer</th>
<th>Relative Risk (95% confidence interval)(^a)</th>
<th>All Other Case-control/Case-cohort Studies(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Oxford Survey of Childhood Cancers</td>
<td></td>
</tr>
<tr>
<td>All cancers</td>
<td>1.39 (1.30, 1.49)</td>
<td>1.30 (1.18, 1.43)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.35 (1.21, 1.50) (^c)</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>1.51 (1.35, 1.69)</td>
<td>1.28 (1.16, 1.41) (^c) (^d)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.26 (1.14, 1.38) (^d)</td>
</tr>
<tr>
<td>All cancers except leukaemia</td>
<td>1.46 (1.31, 1.62)</td>
<td>1.31 (1.13, 1.53)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>1.34 (1.06, 1.69)</td>
<td>1.75 (1.08, 2.84)</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>N/A</td>
<td>1.56 (0.92, 2.65)</td>
</tr>
<tr>
<td>Leukaemia and lymphoma</td>
<td>1.40 (1.29, 1.52)</td>
<td>1.21 (1.04, 1.41)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.28 (1.06, 1.54) (^c)</td>
</tr>
<tr>
<td>All solid cancers (^e)</td>
<td>1.46 (1.34, 1.59)</td>
<td>1.22 (1.03, 1.45)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1.25 (1.01, 1.54) (^c)</td>
</tr>
<tr>
<td>Brain/CNS tumours</td>
<td>1.42 (1.19, 1.69)</td>
<td>1.13 (0.97, 1.31)</td>
</tr>
<tr>
<td>All cancers except leukaemia and brain/CNS tumours</td>
<td>1.47 (1.30, 1.66)</td>
<td>1.24 (1.02, 1.52)</td>
</tr>
<tr>
<td>All solid cancers except brain/CNS tumours</td>
<td>1.51 (1.32, 1.72)</td>
<td>1.26 (0.90, 1.75)</td>
</tr>
<tr>
<td>Peripheral neural tumours</td>
<td>1.46 (1.16, 1.82)</td>
<td>1.03 (0.52, 2.02)</td>
</tr>
<tr>
<td>Kidney tumours</td>
<td>1.58 (1.24, 2.01)</td>
<td>1.11 (0.64, 1.91)</td>
</tr>
<tr>
<td>Bone tumours</td>
<td>1.09 (0.72, 1.65)</td>
<td>1.11 (0.81, 1.53)</td>
</tr>
<tr>
<td>Other solid cancers</td>
<td>1.62 (1.33, 1.98)</td>
<td>1.26 (0.81, 1.96)</td>
</tr>
<tr>
<td>---------------------</td>
<td>-------------------</td>
<td>-------------------</td>
</tr>
<tr>
<td>Eye tumours</td>
<td>1.95 (1.15, 3.33)</td>
<td>2.14 (1.04, 4.39)</td>
</tr>
<tr>
<td>Rhabdomyosarcoma</td>
<td>N/A</td>
<td>1.45 (0.89, 2.36)</td>
</tr>
<tr>
<td>Other soft tissue tumours</td>
<td>N/A</td>
<td>0.85 (0.20, 3.58)</td>
</tr>
<tr>
<td>Germ cell tumours</td>
<td>N/A</td>
<td>0.88 (0.52, 1.49)</td>
</tr>
<tr>
<td>Liver tumours</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

CNS = central nervous system
N/A = not available from published information

a As approximated by the unmatched and unadjusted odds ratio.
b Obtained from a meta-analysis of results from published case-control or case-cohort studies, with odds ratios and 95% confidence intervals calculated using inverse-variance fixed-effect models. (The small changes produced by using Mantel-Haenszel random-effects models to estimate odds ratios are presented in Supplementary Figure S1. Peto one-step odds ratios for the childhood cancer groupings are also presented in Supplementary Figure S1, and show only minor differences from the other two methods of estimating relative risks.)
c Robinette and Jablon (1976) excluded from the meta-analysis (see text).
d Hirayama (1980) is not included in the meta-analysis (see text).
e All cancers except leukaemia and lymphoma.
f All solid cancers except brain/CNS, peripheral neural, kidney and bone tumours (but see individual study précis in Supplementary Table S1).
g Soft tissue tumours excluding rhabdomyosarcoma.
h Insufficient data for quantitative analysis.
Table 3. Relative risks of specific types, and groups of types, of childhood cancer associated with a medical diagnostic X-ray examination of the abdomen of the pregnant mother, for case-control studies that have considered twin births only. A comparison of findings of the Oxford Survey of Childhood Cancers with the appropriately combined results of two nested case-control studies (Harvey et al. 1985; Rodvall et al. 1990) using inverse-variance fixed-effect models. (Further details of individual studies are presented in Supplementary Table S1.)

<table>
<thead>
<tr>
<th>Type, or Group of Types, of Childhood Cancer</th>
<th>Oxford Survey of Childhood Cancers a, b</th>
<th>Combined Other Case-control Studies c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Deaths, Exposed/Total</td>
<td>Units of Statistical Information d</td>
</tr>
<tr>
<td>All cancers</td>
<td>111/161</td>
<td>19.8</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>51/70</td>
<td>10.7</td>
</tr>
<tr>
<td>All cancers except leukaemia</td>
<td>60/91</td>
<td>14.2</td>
</tr>
<tr>
<td>Brain/CNS tumours</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>All cancers except leukaemia and brain/CNS tumours</td>
<td>N/A</td>
<td>N/A</td>
</tr>
</tbody>
</table>

CNS = central nervous system
N/A = not available from published information

b Comparable RR from OSCC for singleton births (Bithell and Stewart 1975): all cancers, 1.47 (95% CI: 1.34, 1.62); leukaemia, 1.49 (95% CI: 1.33, 1.67); all cancers except leukaemia, 1.45 (95% CI: 1.30, 1.62). Statistical information content: 434.0, 297.1, 311.1, respectively.
c Obtained from appropriately combining the results from the nested case-control studies of cancer incidence of Harvey et al. (1985) and Rodvall et al. (1990) (see Supplementary Table S1), with odds ratios and 95% confidence intervals calculated using inverse-variance fixed-effect models.
Numbers of controls included in the combined two twin studies: exposed/total = 67/299.

d One quarter of the harmonic mean of the numbers of exposed and unexposed cases and controls (i.e., the reciprocal of the sum of the reciprocals of the number of exposed cases, the number of unexposed cases, the number of exposed controls, and the number of unexposed controls).

e As approximated by the unmatched and unadjusted odds ratio.

f Mantel-Haenszel random-effects model: RR = 1.52 (95% CI: 0.94, 2.47)
   Peto one-step odds ratio model: RR = 1.53 (95% CI: 0.93, 2.52)

Mantel-Haenszel random-effects model: RR = 1.82 (95% CI: 0.90, 3.66)
   Peto one-step odds ratio model: RR = 1.91 (95% CI: 0.90, 4.05)

h Mantel-Haenszel random-effects model: RR = 1.36 (95% CI: 0.77, 2.43)
   Peto one-step odds ratio model: RR = 1.37 (95% CI: 0.76, 2.50)

i Mantel-Haenszel random-effects model: RR = 2.47 (95% CI: 0.43, 14.35)
   Mantel-Haenszel fixed-effect model: RR = 1.74 (95% CI: 0.78, 3.88)
   Peto one-step odds ratio model: RR = 1.83 (95% CI: 0.77, 4.35)

j Mantel-Haenszel random-effects model: RR = 1.11 (95% CI: 0.53, 2.34)
   Peto one-step odds ratio model: RR = 1.11 (95% CI: 0.52, 2.37)
Table 4. Relative risk of specific types, and groups of types, of childhood cancer associated with a medical diagnostic X-ray examination of the pregnant mother, as obtained from cohort studies appropriately combined in a meta-analysis. Relative risks are approximated by Mantel-Haenszel fixed-effect models and Peto “one-step” odds ratio models (see text). (Further details of individual studies are presented in Supplementary Table S2.)

<table>
<thead>
<tr>
<th>Type, or Group of Types, of Childhood Cancer</th>
<th>Number of Cohort Studies: Contributing Studies a</th>
<th>Units of Statistical Information b</th>
<th>Relative Risk (95% confidence interval) c d</th>
<th>Mantel-Haenszel e</th>
<th>Peto f</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancers</td>
<td>5 h [6] i: Diamond, Schmerler, and Lilienfeld (1973); Ray et al. (2010); Train (1960); Griem, Meier, and Dobben (1967); Lejeune et al. (1960); Magnin (1962) g</td>
<td>18.2 h [20.2] i</td>
<td>1.04 (0.66, 1.64) h</td>
<td>1.04 (0.65, 1.65) h</td>
<td>[1.15 (0.73, 1.83)] i</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>4 j [5] k [4] l [3] m: Court Brown, Doll, and Hill (1960); Diamond, Schmerler, and Lilienfeld (1973); Train (1960); Lejeune et al. (1960); Lewis (1960); Griem, Meier, and Dobben (1967)</td>
<td>5.8 j [6.8] k [13.9] l [4.9] m</td>
<td>1.10 (0.50, 2.44) j</td>
<td>[1.26 (0.60, 2.65)] k [1.01 (0.60, 1.71)] l [1.41 (0.58, 3.41)] m</td>
<td>[1.29 (0.58, 2.88)] k [1.01 (0.60, 1.69)] l [1.44 (0.56, 3.68)] m</td>
</tr>
</tbody>
</table>
All cancers except leukaemia

|                          | 4 \(^n\) \([5]^{o}\); Diamond, Schmerler, and Lilienfeld (1973); Train (1960); Griem, Meier, and Dobben (1967); Lejeune et al. (1960); Magnin (1962) | 9.1 \(^n\) \([10.1]^{o}\) | 1.07 (0.56, 2.05) \(^n\) \([1.18 (0.64, 2.18)]^{o}\) | 1.08 (0.54, 2.15) \(^n\) \([1.21 (0.61, 2.40)]^{o}\) |

\(^a\) Listed in order of statistical information content. Studies of cancer mortality with the exception of the cancer incidence studies of Ray et al. (2010) and Griem, Meier, and Dobben (1967). Numbers of cases/deaths and totals included in the cohorts can be found in Supplementary Table S2.

\(^b\) When an unexposed cohort is available, one quarter of the harmonic mean of the numbers of exposed and unexposed cases and non-cases (i.e., the reciprocal of the sum of the reciprocals of the number of exposed cases, the number of unexposed cases, the number of exposed non-cases, and the number of unexposed non-cases). When an unexposed cohort is not available, one half of the harmonic mean of the numbers of exposed cases and non-cases (i.e., in effect, the number of exposed cases).

\(^c\) The unadjusted risk ratio when a comparison unexposed cohort is available, otherwise the ratio of the observed number of cases/deaths in the exposed cohort, with the expected number of cases/deaths calculated by applying appropriate age-adjusted national rates for both sexes combined to the number of individuals in the exposed cohort (except for the study of Court Brown, Doll, and Hill (1960), for which an expected number of leukaemia deaths was provided by the authors).

\(^d\) If an unexposed cohort is available then the 95% confidence interval is approximated by the Woolf 95% confidence interval, and if an unexposed cohort is not available then the 95% confidence interval is approximated by the Fisher "exact" 95% confidence interval for the ratio of the observed number of cases/deaths divided by the expected number of cases/deaths (and assuming the expected number is exact).

\(^e\) Risk ratios computed using Mantel-Haenszel fixed-effect models.

\(^f\) Odds ratios computed using Peto “one-step” odds ratio method.

\(^g\) The very small studies of Mills et al. (1958), Nøkkentved (1968), Dempster (1958) and Neumeister and Wässer (1985), each including <200 individuals in an exposed cohort and with no identified incident cases/deaths (see Supplementary Table S2), have been excluded from the meta-analysis to avoid computational problems.

\(^h\) Excluding the study of Lejeune et al. (1960).

\(^i\) Including the study of Lejeune et al. (1960). However, there is then strong evidence for heterogeneity of the relative risk estimates: for the Mantel-Haenszel fixed-effect model, Cochrane Q p-value = 0.006 and Higgins \(I^2 = 70\%\).

\(^j\) Excluding the studies of Court Brown, Doll, and Hill (1960) and Lejeune et al. (1960).

\(^k\) Excluding the study of Court Brown, Doll, and Hill (1960). With the study of Lejeune et al. (1960) included there is evidence for heterogeneity of the relative risk estimates: for the Mantel-Haenszel fixed-effect model, Cochrane Q p-value = 0.10 and Higgins \(I^2 = 49\%).
Excluding the studies of Lewis (1960) and Lejeune et al. (1960).

Excluding the studies of Court Brown, Doll, and Hill (1960), Lewis (1960) and Lejeune et al. (1960).

Excluding the study of Lejeune et al. (1960).

Including the study of Lejeune et al. (1960). However, there is then evidence for heterogeneity of the relative risk estimates: for the Mantel-Haenszel fixed-effect model, Cochrane Q p-value = 0.05 and Higgins $I^2 = 57\%$. 
Table 5. Relative risks of specific types, and groups of types, of childhood cancer associated with a medical diagnostic X-ray examination of the pregnant mother, comparing the results of appropriately combining data in meta-analyses using inverse-variance fixed-effect models from case-control/case-cohort studies of children born within a calendar period finishing in 1970 or before with those from case-control/case-cohort studies of children born within a calendar period starting in 1971 or after. (Further details of individual studies are presented in Supplementary Table S1.)

<table>
<thead>
<tr>
<th>Type, or Group of Types, of Childhood Cancer</th>
<th>Case-control/Case-cohort Studies Including Births Restricted to Calendar Years Before 1971</th>
<th>Units of Statistical Information&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Relative Risk (95% confidence interval)&lt;sup&gt;b c&lt;/sup&gt;</th>
<th>Case-control/Case-cohort Studies Including Births Restricted to Calendar Years After 1970</th>
<th>Units of Statistical Information&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Relative Risk (95% confidence interval)&lt;sup&gt;b c&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancers</td>
<td>Monson and MacMahon (1984); Robinette and Jablon (1976); Ford, Paterson, and Treuting (1959); Salonen (1976); Harvey et al. (1985); Shiono, Chung, and Myrianthropoulos (1980); Golding, Paterson, and Kinlen (1990)</td>
<td>253.6 [175.7]&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.30 (1.15, 1.47) [1.38 (1.19, 1.60)]&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Rajaraman et al. (2011); McKinney et al. (1999); Shu, Jin, et al. (1994)</td>
<td>64.6</td>
<td>1.20 (0.94, 1.53)</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>Monson and MacMahon (1984); Robinette and Jablon (1976);</td>
<td>222.5 [178.9]&lt;sup&gt;d&lt;/sup&gt;</td>
<td>1.39 (1.20, 1.61)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>Naumburg et al. (2001); Roman et al. (2005); Shu et al. (2002); Infante-</td>
<td>154.3</td>
<td>1.08 (0.92, 1.27)</td>
</tr>
<tr>
<td>All cancers except leukaemia</td>
<td>Monson and MacMahon (1984); Salonen (1976); Ford, Paterson, and Treuting (1959); Harvey et al. (1985)</td>
<td>86.8</td>
<td>1.26 (1.02, 1.55)</td>
<td>Rajaraman et al. (2011); Shu, Jin, et al. (1994); McKinney et al. (1999)</td>
<td>51.7</td>
<td>1.34 (1.02, 1.77)</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>-------------------------------------------------------------------------------------------------</td>
<td>------</td>
<td>------------------</td>
<td>---------------------------------------------------------------------</td>
<td>------</td>
<td>------------------</td>
</tr>
<tr>
<td>Leukaemia and lymphoma</td>
<td>Robinette and Jablon (1976); Ford, Paterson, and Treuting (1959); Harvey et al. (1985)</td>
<td>66.5</td>
<td>1.21 (0.95, 1.53)</td>
<td>Roman et al. (2005); Shu, Jin, et al. (1994); McKinney et al. (1999); Roman et al. (1993)</td>
<td>48.8</td>
<td>1.25 (0.94, 1.65)</td>
</tr>
<tr>
<td>All solid cancers e</td>
<td>Robinette and Jablon (1976); Ford, Paterson, and</td>
<td>56.8</td>
<td>1.30 (1.00, 1.69)</td>
<td>Rajaraman et al. (2011); Shu, Jin, et al. (1994)</td>
<td>42.9</td>
<td>1.23 (0.91, 1.65)</td>
</tr>
<tr>
<td>Brain/CNS tumours</td>
<td>Monson and MacMahon (1984); Salonen (1976); Ford, Paterson, and Treuting (1959); Harvey et al. (1985)</td>
<td>40.0</td>
<td>1.33 (0.97, 1.81)</td>
<td>Stålberg et al. (2007); Rajaraman et al. (2011); Schüz et al. (2001); Bunin et al. (1994); McCredie, Maisonneuve, and Boyle (1994); Milne et al. (2014); Pasqual et al. (2020); Tettamanti et al. (2017); McKinney et al. (1999); Shu, Jin, et al. (1994); Spix et al. (2009)</td>
<td>86.2</td>
<td>1.13 (0.91, 1.39)</td>
</tr>
<tr>
<td>All cancers except leukaemia and brain/CNS tumours</td>
<td>Monson and MacMahon (1984); Salonen (1976); Ford, Paterson, and Treuting (1959); Harvey et al. (1985)</td>
<td>52.7</td>
<td>1.22 (0.93, 1.60)</td>
<td>Rajaraman et al. (2011); Shu, Jin, et al. (1994); McKinney et al. (1999)</td>
<td>37.5</td>
<td>1.30 (0.94, 1.79)</td>
</tr>
</tbody>
</table>

CNS = central nervous system

* One quarter of the harmonic mean of the numbers of exposed and unexposed cases and controls (i.e., the reciprocal of the sum of the reciprocals of the number of exposed cases, the number of unexposed cases, the number of exposed controls, and the number of unexposed controls).

* As approximated by the unmatched and unadjusted odds ratio.
Obtained from a meta-analysis of results from published case-control or case-cohort studies, with odds ratios and 95% confidence intervals calculated using inverse-variance fixed-effect models.

Robinette and Jabion (1976) excluded from the meta-analysis (see text).

All cancers except leukaemia and lymphoma.
Figure 1. The relative risk (as approximated by the unmatched and unadjusted odds ratio) of mortality for specific types, or groups of types, of childhood cancer associated with a medical diagnostic X-ray examination of the abdomen of the pregnant mother. Oxford Survey of Childhood Cancers case-control study data for deaths at age 0-15 years during 1953-1967, as presented by Bithell and Stewart (1975). Error bars and band are 95% confidence intervals. Square markers indicate particular types of childhood cancer, while circular markers indicate groupings of types of childhood cancers. “All solid cancers” are all cancers except leukaemia and lymphoma, and “other solid cancers” are solid cancers except neuroblastoma and CNS, Wilms’ and bone tumours. CNS = central nervous system.
Figure 2. The relative risk (as approximated by the unmatched and unadjusted odds ratio) of mortality/incidence for specific types, and groups of types, of childhood cancer associated with a medical diagnostic X-ray examination of the pregnant mother, from the Oxford Survey of Childhood Cancers (filled markers) and from all other case-control and case-cohort studies with results combined in meta-analyses using inverse-variance fixed-effect models (empty markers). Square markers indicate particular types of childhood cancer while circular markers indicate groupings of types of childhood cancer; studies contributing to specific cancer types may differ from those contributing to the groupings containing that cancer type (see text and Supplementary Table S1). Error bars show 95% confidence intervals. “All solid cancers” are all cancers except leukaemia and lymphoma, and “other solid cancers” are solid cancers except brain/CNS, peripheral neural, kidney and bone tumours (but see individual study précis in Supplementary Table S1); eye tumours are included in the other solid cancers grouping. CNS = central nervous system.