Research Article

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Exposure to Diagnostic Radiological Procedures and the Risk of Childhood Acute Lymphoblastic Leukemia

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Abstract

Background: Diagnostic irradiation of the mother during pregnancy increases the risk of childhood acute lymphoblastic leukemia (ALL). There is inconsistent evidence on associations between ALL and other parental or childhood diagnostic irradiation. The aim of this analysis is to investigate whether diagnostic X-rays of the mother before birth, of the father before conception, or of the child increased the risk of childhood ALL.

Methods: Data from 389 cases and 876 frequency-matched controls were analyzed using unconditional logistic regression, adjusting for study matching factors and potential confounders. A meta-analysis of our findings in relation to paternal X-rays before conception with the published findings of previous studies was also conducted.

Results: There was no evidence of an increased risk with maternal abdominal X-rays before the birth of the index child or with the child having any X-rays more than 6 months before the censoring date. The odds ratio (OR) for any paternal abdominal X-ray before conception was 1.17 [95% confidence interval (95% CI), 0.88-1.55], and 1.47 (95% CI, 0.98-2.21) for more than one X-ray. The OR for any paternal intravenous pyelogram before conception was 3.56 (95% CI, 1.59-7.98). The pooled OR for this study with previous studies of any paternal abdominal X-rays before conception was 1.17 (95% CI, 0.92-1.48).

Conclusions: There was some evidence of an increased risk of ALL in the offspring if the father had more than one abdominal X-ray before conception or had ever had an intravenous pyelogram.

Impact: We plan to repeat this analysis by using pooled data to improve precision. *Cancer Epidemiol Biomarkers Prev; 19(11); 2897–909. ©2010 AACR.*

Introduction

Acute lymphoblastic leukemia (ALL) is the most common type of childhood cancer in developed countries. In Western countries, the age-standardized incidence rates are approximately 30 to 40 per million (1). It is more common in boys, and the majority of cases are diagnosed before the age of 5 years (2). Little is known with any certainty about the causes of ALL, although it is likely that both environmental and genetic factors play a role (3). Because of the early age at onset of ALL, parental exposure before conception, maternal exposure during pregnancy, and exposure of the child to environmental factors could all play a role.

Risk of childhood ALL has previously been associated with exposure to diagnostic X-rays. The most studied exposure has been maternal X-rays during pregnancy. In 1956, it was reported that children whose mothers

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The Australian Study of Causes of Acute Lymphoblastic Leukaemia in Children Consortium conducted the study, and the Telethon Institute for Child Health Research (TICHR), University of Western Australia, was the coordinating center. Bruce K. Armstrong (Sydney School of Public Health), Elizabeth Milne (TICHR), Frank M. van Bockxmeer (Royal Perth Hospital), Michelle Haber (Children's Cancer Institute Australia), Rodney J. Scott (University of Newcastle), John Attia (University of Newcastle), Murray D. Norris (Children's Cancer Institute Australia), Carol Bower (TICHR), Nicholas H. de Klerk (TICHR), Lin Fritschi (WA Institute for Medical Research), Ursula R. Kees (TICHR), Margaret Miller (Edith Cowan University), and Judith R. Thompson (WA Cancer Registry) were the research investigators. Helen D. Bailey (TICHR) was the project coordinator. The clinical investigators were as follows: Frank Alvaro (John Hunter Hospital, Newcastle), Catherine Cole (Princess Margaret Hospital for Children, Perth), Luciano Dalla Pozza (Children's Hospital at Westmead, Sydney), John Daubenton (Royal Hobart Hospital, Hobart), Peter Downie (Monash Medical Centre, Melbourne), Liane Lockwood (Royal Children's Hospital, Brisbane), Maria Kirby (Women's and Children's Hospital, Adelaide), Glenn Marshall (Sydney Children's Hospital, Sydney), Elizabeth Smibert (Royal Children's Hospital, Melbourne), and Ram Suppiah (previously Mater Children's Hospital, Brisbane).

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recalled having an abdominal X-ray during pregnancy were twice as likely to die of leukemia as children whose mothers did not recall having an X-ray (4). These findings were supported by those of a continuation of that study (5) and others that used medical records to assess exposure during pregnancy (6, 7). Since the 1950s and 1960s, both the radiation dose delivered in obstetric X-rays and the reported risk of childhood cancer associated with maternal X-rays during pregnancy have decreased (8). However, a recent review of case-control studies published since 1990 concluded that there remains an excess risk, albeit small, of childhood leukemia from maternal X-rays during pregnancy (9).

There is little evidence of any association of childhood ALL with maternal abdominal or pelvic X-rays before conception (10-12). Findings on the risk of paternal exposure before conception are inconsistent, with two reports suggesting an association with abdominal X-rays (12, 13) and two reports finding no association (10, 11). There is some evidence in animal models, however, that paternal exposure to high-dose radiation close to conception is associated with leukemia in the offspring (14, 15).

The association between diagnostic X-rays in children and the risk of later ALL has also been investigated with conflicting results. Since 1990, three case-control studies (16-18) have reported an increasing risk with increasing number of X-rays, whereas four case-control studies (10, 11, 13, 19) and one cohort study (20) have found no association with ever having an X-ray.

No previous study of childhood ALL has investigated the use of computerized tomography (CT) scans specifically. Because CT scans involve exposure to much higher levels of radiation than plain X-rays, concerns have been raised about the possible carcinogenic effects of their use (21, 22). Since the 1980s, the use of CT scans has increased exponentially in the United Kingdom and the United States (21), which probably reflects practice in most other developed countries; thus, further research into the risk of exposure to diagnostic radiation is warranted.

The Australian Study of Causes of Acute Lymphoblastic Leukaemia in Children (Aus-ALL) was a national study that began in 2003 and investigated genetic, dietary, and environmental causes of childhood ALL. The aim of this current analysis is to investigate whether diagnostic X-rays, including CT scans, of the parents or child in key periods increased the risk of childhood ALL. Specifically, we investigated whether maternal abdominal or pelvic region X-rays before or during the pregnancy, paternal abdominal or pelvic region X-rays before conception of the child, or any X-rays of the child increased the risk of ALL, and whether the relationship varied by the type of procedure or the part of the body X-rayed. For parents, we limited our analyses to abdominal or pelvic region X-rays as we thought these were the exposures most likely to affect the reproductive organs or developing fetus.

Materials and Methods

Study population

Aus-ALL was a national, population-based, case-control study of childhood ALL conducted in Australia between 2003 and 2007, which recruited 416 cases and 1,361 controls with ages younger than 15 years (23, 24). For a child to be eligible, the biological mother needed to be available and have sufficient English skills to complete the questionnaires. Case families were identified and recruited through all 10 pediatric oncology centers in Australia. Cases were eligible if they had been diagnosed between July 1, 2003, and December 31, 2006, and had reached remission. The study had Human Research Ethics Committee approval from participating hospitals. Controls were recruited by random digit dialing between 2003 and 2006 and were frequency matched to cases by age, sex, and state of residence in an approximate ratio of 3:1. Full details of the study population, including control recruitment methods, have been previously published (23, 24).

Data collection

Both parents were mailed questionnaires that included questions about a range of potentially leukemogenic exposures. The parents were asked whether they had had any X-rays of the abdomen (including stomach), pelvis, hips, lower back, or kidney before the birth of the child. Fathers were asked about exposures up until the birth of the child as it was thought that they would recall them more accurately than exposures in the time before conception. If they had had any X-rays, they were asked about their age at the time of each X-ray and the type of procedure [plain X-rays, CT scans, intravenous pyelograms (IVP), or barium studies]. In addition, mothers were asked if any X-ray was done before or during the pregnancy and, if the latter, the trimester of each X-ray. Mothers were also asked whether their child had any X-rays of any part of their body. For each X-ray, they were asked to choose the part of the body from the following list: head (including dental), chest, abdomen (including stomach or hips), arm(s), leg(s), or whole body. They were also asked the type of procedure and the child's age at the time of the procedure. Both parents were also asked for details of any radiotherapy to treat cancer.

Exposure metrics

For each X-ray reported by the parents, we identified the type of X-ray, parts of the body examined, and the frequency of exposure in the time period of interest.

To determine whether the father had an X-ray done before conception, the approximate conception date was calculated by subtracting the child's gestational age at birth from his or her date of birth. The father's age in years at the conception date was calculated. If the X-ray was done at that age or earlier, it was classed as being done before conception. X-rays done after this age were not included in the analyses. The association of ALL with paternal X-rays done in the year of conception was also investigated.

In analyses of the child's exposures, we included all X-rays done before diagnosis for cases and all X-rays done before the date of return of the written questionnaires for controls. There were several reasons for this approach: The control questionnaire asked about exposures "since your child was born." As controls were frequency matched, there was no corresponding case whose date of diagnosis could have been used. The analyses were then repeated including only X-rays done more than 6 months before the above censoring dates to exclude procedures done when cases were showing signs of illness but had yet to be diagnosed with ALL.

Immunophenotype and cytogenetic classification

We obtained information about immunophenotype and cytogenetic subtypes of participating cases from the medical record details provided by clinicians. The latter was determined using metaphase cytogenetics and fluorescence *in situ* hybridization screening.

Statistical analysis

Odds ratios (OR) and 95% confidence intervals (95% CI) were estimated using unconditional logistic regression in SPSS for Windows version 15 (SPSS, Inc.). Separate models were fitted to assess the associations between maternal, paternal, and filial X-rays and ALL. All models were adjusted for the study matching factors: age at diagnosis, sex, and state of residence. Variables considered a priori to be potential confounders of the association between X-rays and risk of ALL were assessed individually for inclusion in the models. Different variables were considered for analyses of maternal exposures (maternal education, family income, ethnicity, birth order, birth weight, maternal age at birth, maternal height, maternal body mass index, maternal smoking in the year before birth), paternal exposures (paternal education, family income, ethnicity, paternal age at birth, paternal smoking in the 2 years before birth), and filial exposures (maternal education, family income, ethnicity, maternal age at birth, birth order, birth weight, gestation, plurality, birth defect, maternal smoking in the year before birth, and paternal smoking in the 2 years before birth). Variables that met the empirical criteria for confounding (independently associated with both the exposure and the outcome) were included in the final models, as follows: for maternal exposures, maternal age at the child's birth, birth order, maternal education, and family income; for paternal exposures, paternal age at the child's birth, paternal education, and family income; and for filial exposures, maternal age at birth, birth defect, and family income.

We also analyzed the data by immunophenotype and cytogenetic subtypes.

Meta-analysis

We conducted a meta-analysis of our findings on paternal abdominal or pelvic region X-rays before conception with the published findings of previous studies. We did not perform meta-analyses of either maternal or filial X-ray exposures as they have been reviewed recently (9, 25, 26). To be included in the meta-analysis, each study was required to (*a*) be a cohort or case-control study that presented ORs and the corresponding 95% CIs for the association between paternal abdominal or pelvic region X-ray before conception and risk of childhood ALL (or provide data that allowed them to be calculated) and (*b*) be population based. We searched PubMed on May 13, 2010, for original studies of X-rays before conception and risk of childhood ALL published from 1970 to 2010. The following search terms were used: "leukemia," "(X-ray or radiation)" and "(child, child preschool, or infant)," and "preconception." All journal articles were read to identify studies that specifically investigated paternal abdominal or pelvic region X-rays. Four case-control studies were identified. Two of these studies restricted their investigations to subpopulations of children with ALL; one was restricted to children with Down syndrome (10); and the other was restricted to infants (17). The study by Meinert and colleagues (13) was included despite using a case definition of "acute childhood leukemia" as ALL accounts for 75% to 80% of this group (2). We extracted the most appropriate OR from each study and used fixed-effects, precision-based weighting (27) to calculate summary ORs with the most appropriate result from Aus-ALL. Statistical heterogeneity among studies was assessed using the Cochrane Q test and expressed using I^2. A forest plot was produced using STATA version 10 (StataCorp).

Results

We were notified of 568 incident cases of ALL, of whom 49 were ineligible to participate: 30 from non-English-speaking backgrounds, 12 overseas visitors, 3 whose biological mother was unavailable, and 4 who did not reach remission. Of 519 eligible cases, parents of 416 (80.2%) cases consented to participate in the study and 388 mothers (74.8% of eligible) and 328 fathers (63.2% of eligible) returned the questionnaire.

Of the 2,947 eligible control families identified through random digit dialing, 2,071 (70.3%) agreed to take part. Because of age and sex frequency-matching quotas, we only recruited 1,361 of these families to the study. Of the recruited families, 870 mothers (63.9%) and 750 fathers (55.1%) returned the written questionnaires.

The demographic characteristics of cases and controls who returned the written questionnaire were generally similar (Table 1). Case children were more likely to be a first born (47.8%) and to have a birth defect (5.7%) than were controls (41.7% and 3.1%, respectively). Control parents were more likely than case parents to be tertiary educated, have a higher income, and to have been 35 years old or older when the child was born.

Maternal X-rays before or during pregnancy

There was no evidence of an increased risk of childhood ALL with maternal abdominal or pelvic region

Table 1. Demographic characteristics of cases and controls

	Cases, *n* (%)	Controls, *n* (%)
Total available (any written questionnaire completed)	389	876
Mother questionnaire returned	388 (99.7)	870 (99.3)
Father questionnaire returned	328 (84.3)	750 (85.6)
Sex		
Boys	214 (55.0)	462 (52.7)
Girls	175 (45.0)	414 (47.3)
Age (y)		
0-1	34 (8.7)	62 (7.1)
2-4	177 (45.5)	392 (44.7)
5-9	111 (28.5)	291 (33.2)
10-14	67 (17.2)	131 (15.0)
State of residence		
NSW/ACT	120 (30.8)	270 (30.8)
QLD	69 (17.7)	183 (20.9)
SA/NT	43 (11.1)	84 (9.6)
VIC/TAS	117 (30.1)	246 (28.1)
WA	40 (10.3)	93 (10.6)
Birth order		
1	186 (47.8)	365 (41.7)
2	118 (30.3)	295 (33.7)
3+	85 (21.9)	216 (24.7)
Birth defect		
No	366 (94.3)	841 (96.9)
Yes	22 (5.7)	27 (3.1)
Child's birth year		
1988-1993	53 (13.6)	98 (11.2)
1994-1999	127 (32.6)	317 (36.2)
2000-2006	209 (53.7)	461 (52.6)
Highest education of either parent		
Nontertiary	223 (57.3)	409 (46.7)
Tertiary	166 (42.7)	467 (53.3)
Ethnicity*		
European	279 (71.7)	650 (74.2)
At least 50% European	79 (20.3)	166 (18.9)
At least 50% non-European and unknown if 50% European	14 (3.6)	23 (2.6)
Indeterminate	17 (4.4)	37 (4.2)
Household income (pa)		
<$20,000	28 (7.3)	51 (5.9)
$20,001-40,000	67 (17.4)	141 (16.2)
$40,001-70,000	113 (29.3)	287 (33.0)
$70,001-100,000	93 (24.1)	194 (22.3)
>$100,000	85 (22.0)	198 (22.6)
Mother's age at child's birth (y)		
<25	60 (15.4)	99 (11.3)
25-34	263 (67.6)	580 (66.2)
35+	66 (17.0)	197 (22.5)
Father's age at child's birth (y)		
<25	23 (6.4)	32 (4.3)
25-34	221 (61.9)	448 (59.6)
35+	113 (31.7)	272 (36.2)

Abbreviations: ACT, Australian Capital Territory; NSW, New South Wales; NT, Northern Territory; QLD, Queensland; SA, South Australia; TAS, Tasmania; VIC, Victoria; WA, Western Australia; pa, per annum.

*European = at least three European grandparents; 50% European = two European grandparents; at least 50% non-European and not known if 50% European = two non-European grandparents and the ethnicity of the other two grandparents is unknown; indeterminate = no two grandparents with the same ethnicity (i.e., European or non-European) and more than two grandparents of unknown ethnicity.

Table 2. ORs and 95% CIs for risk of ALL with parental diagnostic X-rays of the abdominal or pelvic region at any time before or during the index pregnancy

	Maternal exposures						Paternal exposures		
	Any exposure before pregnancy			Any exposure during pregnancy			Any exposure before conception		
	Cases (n = 388) %	Controls (n = 869)* %	OR‡ § (95% CI)	Cases (n = 388) %	Controls (n = 869)* %	OR‡ § (95% CI)	Cases (n = 326)† %	Controls (n = 749)† %	OR‖ ¶ (95% CI)
No diagnostic X-rays**	73.7	67.0					66.0	68.5	1.00
Any diagnostic X-rays**	26.3	33.0	0.73 (0.55-0.95)	1.0	1.8	0.46 (0.15-1.40)	34.0	31.5	1.17 (0.88-1.55)
No. of X-rays									
1	16.2	20.8	0.71 (0.51-0.98)	1.0	1.5	Not estimated	19.9	21.1	1.03 (0.73-1.44)
>1	10.0	12.2	0.76 (0.51-1.13)	0	0.3	Not estimated	14.1	10.4	1.47 (0.98-2.21)
			P for trend = 0.04						P for trend = 0.11
Type of X-ray									
Any plain X-ray	23.7	27.6	0.78 (0.59-1.04)	1.0	1.5	0.58 (0.18-1.81)	27.9	28.0	1.08 (0.80-1.46)
Any CT	1.8	4.6	0.37 (0.16-0.85)	0	0.2	Not estimated	4.3	4.3	1.11 (0.57-2.16)
Site of body and type of X-ray									
Any abdominal X-ray	9.5	11.2	0.77 (0.51-1.16)	0.8	0.9	0.73 (0.19-2.84)	9.8	9.7	1.13 (0.72-1.79)
Any plain abdominal X-ray or CT	7.2	7.7	0.83 (0.52-1.34)	0.8	0.9	0.73 (0.19-2.84)	6.1	6.5	1.06 (0.60-1.86)
Any barium study	2.8	4.6	0.60 (0.30-1.20)	0	0	Not estimated	4.6	3.3	1.59 (0.81-3.13)
Any X-ray or CT of the lower back, pelvis, or hips	17.5	23.4	0.69 (0.50-0.94)	0.3	0.8	0.25 (0.03-2.05)	23.3	23.9	1.00 (0.72-1.40)
Any kidney X-ray	3.9	4.5	0.74 (0.40-1.39)	0	0.1	Not estimated	6.7	3.3	2.13 (1.15-3.94)
Any plain kidney X-ray or CT	1.8	1.5	0.98 (0.38-2.52)	0	0	Not estimated	2.5	2.3	1.16 (0.48-2.82)
Any IVP	3.1	3.0	0.92 (0.45-1.89)	0	0.1	Not estimated	4.9	1.5	3.56 (1.59-7.98)

NOTE: The abdominal or pelvic region is defined as the abdomen (including stomach), lower back, pelvis, hips, or kidneys.

*There is one missing value as one mother did not know how the timing of the X-ray was related to the index pregnancy.

†There are two missing values for cases and one for controls because the fathers did not know either if they had had a relevant X-ray or their age at the time of the X-ray.

‡Adjusted for matching variables (age group, sex, and state), birth order, maternal education, and maternal age at birth.

§The reference groups are those who did not have diagnostic radiological X-ray of the abdomen, lower back, pelvis, hips, or kidneys before or during pregnancy (286 cases and 582 controls).

‖Adjusted for matching variables (age group, sex, and state), paternal education, and paternal age at birth.

¶The reference groups are those who did not have diagnostic radiological X-ray of the abdomen, lower back, pelvis, hips, or kidneys before the conception of the index child.

**Diagnostic X-rays are defined as any plain X-ray, CT scan, IVP or barium study.

Table 3. ORs and 95% CIs for risk of ALL with exposure of child to diagnostic X-rays

	Any exposure before the censoring date			Any exposure >6 mo before the censoring date		
	Cases (n = 386)* %	Controls (n = 870) %	OR‡ §(95% CI)	Cases (n = 360)*† %	Controls (n = 834)† %	OR‡ § (95% CI)
No diagnostic X-ray‖ (reference group)	52.8	58.4	1.00	56.7	60.9	1.00
Any diagnostic X-ray‖	47.2	41.6	1.21 (0.93-1.57)	43.3	39.1	1.15 (0.88-1.51)
No. of X-rays						
1	28.0	26.4	1.15 (0.86-1.53)	28.1	24.6	1.20 (0.89-1.61)
>1	19.2	15.2	1.34 (0.93-1.92)	15.3	14.5	1.05 (0.71-1.57)
			P for trend = 0.10			P for trend = 0.53
Type of X-ray						
Any plain X-ray	45.6	39.2	1.22 (0.94-1.59)	41.7	36.7	1.15 (0.88-1.52)
Any CT	1.8	2.1	0.90 (0.36- 2.27)	1.7	1.9	0.87 (0.32- 2.34)
Site of body and type of X-ray						
Any abdominal X-ray (including stomach or hips)	10.4	10.3	1.03 (0.67- 1.61)	9.4	10.3	0.90 (0.56- 1.44)
Any barium study	1.6	1.8	0.99 (0.36- 2.72)	1.7	1.9	0.99 (0.36- 2.72)
Any abdominal plain	8.0	7.8	0.98 (0.60- 1.60)	6.9	7.7	0.81 (0.47-1.38)
X-ray or CT scan						
Any IVP	1.0	1.4	0.77 (0.22- 2.68)	1.1	1.4	0.77 (0.22-2.68)
Any X-ray to the head (including dental X-rays)	10.1	9.5	1.00 (0.62- 1.62)	10.0	8.3	1.15 (0.70- 1.88)
Any plain head X-ray	9.1	8.4	1.06 (0.64- 1.75)	8.9	7.2	1.22 (0.72- 2.05)
Any head CT	1.3	1.7	0.77 (0.26- 2.26)	1.4	1.7	0.80 (0.27- 2.37)
Any plain chest X-ray	19.2	16.1	1.26 (0.89- 1.77)	18.3	15.3	1.24 (0.86- 1.78)
Any plain arm X-ray	16.6	11.7	1.49 (1.00- 2.22)	13.1	10.2	1.21 (0.77-1.91)
Any plain leg X-ray	8.3	7.7	1.20 (0.74-1.96)	5.3	7.2	0.76 (0.42-1.36)

*There is one missing value as the child's age when the X-ray was done was not known.
†Children who only had an X-ray within 6 months of the censoring date were excluded from this analysis.
‡Adjusted for matching variables (age group, sex, and state), birth order, maternal education, maternal age at birth, and child has birth defect.
§The reference group is children who did not have any diagnostic radiological X-rays at any time before the censoring date (date of diagnosis for cases and date of questionnaire return for controls).
‖Diagnostic X-rays are defined as any plain X-ray, CT scan, IVP, or barium study.

X-rays at any time before the pregnancy (Table 2). There was also no increased risk with any specific type of X-ray, including CT scans, or having more than one X-ray (Table 2). Relatively few women (4 cases and 16 controls) reported having an abdominal or pelvic region X-ray during pregnancy, and there was no evidence of an increased OR associated with any body site being X-rayed (Table 2). There were insufficient numbers of exposed mothers to analyze the data by trimester of exposure (results not shown).

Paternal X-rays before conception

There was little evidence of an increased risk of childhood ALL with paternal abdominal or pelvic region X-rays at any time before the conception of the child (OR, 1.17; 95% CI, 0.88-1.55; Table 2) or with any such X-rays done when the father was the same age as he was at conception (OR, 1.64; 95% CI, 0.79-3.42), although relatively few men (13 cases and 20 controls) reported such an X-ray (results not tabulated). The OR for having one abdominal or pelvic region X-ray at any time before conception was 1.03 (95% CI, 0.73-1.44) and the OR for more than one was 1.47 (95% CI, 0.98-2.21; P for trend = 0.11; Table 2). The OR for having an IVP was 3.56 (95% CI, 1.59-7.98; Table 2). A smaller increase was seen for any barium study (OR, 1.59; 95% CI, 0.81-3.13; Table 2). Among the 27 fathers who had an IVP before conception, two case fathers and one control father had more than one IVP. The median time between conception and the IVP closest to conception was 8.5 years for cases

(range 1-32 years) and 12 years for controls (range 1-16 years). There was little evidence of an increased risk of childhood ALL with paternal CT scans of the abdominal or pelvic region at any time before the conception of the child (Table 2).

X-rays in childhood

There was little evidence of an increased risk of ALL with any childhood X-rays before the censoring date (OR, 1.21, 95% 0.93-1.57; Table 3) or when the analyses were restricted to X-rays done more than 6 months before the censoring date (OR, 1.15; 95% CI, 0.88-1.51). There was some evidence of an increased risk with having more than one X-ray (OR, 1.34; 95% CI, 0.93-1.92) or an X-ray of the arm (OR, 1.49; 95% CI, 1.00-2.22) at any time before the censoring date, but no such increase when the analyses were restricted to X-rays done more than 6 months before the censoring date (Table 3). There was no evidence of an increased risk associated with X-rays of any other part of the body or other type of X-rays, including CT scans (Table 3).

Immunophenotype and cytogenetic subtypes

There was some evidence of an association between paternal X-rays before conception and risk of t(12;21) (*ETV6-Runx-1*) subtype of ALL (OR, 1.68; 95% CI, 0.92-3.06; Table 4), and X-rays of the child before the censoring date and ALL involving translocations other than t(12;21)

Table 4. ORs for any parental diagnostic radiological X-ray to the abdominal or pelvic region before the index pregnancy by immunophenotype and cytogenetic subtype

	Any time before conception					
	Maternal exposure			Paternal exposure		
	Case, *n*	Exposed cases/controls	OR* † (95% CI)	Case, *n*	Exposed cases/controls	OR‡ § (95% CI)
All cases	388	102/287	0.73 (0.55-0.95)	326	111/236	1.17 (0.88-1.55)
Pre-B cell	342	91/287	0.73 (0.55-0.97)	292	99/236	1.16 (0.87-1.56)
T cell	37	11/287	0.91 (0.43-1.89)	28	10/236	1.27 (0.57-2.85)
Normal karyotype	131	35/287	0.80 (0.53-1.22)	110	40/236	1.30 (0.85-2.00)
Any genetic feature	249	65/287	0.71 (0.52-0.99)	208	67/236	1.08 (0.77-1.50)
Chromosomal deletions	62	18/287	0.81 (0.45-1.44)	48	15/236	1.07 (0.56-2.04)
ETV6-Runx-1 t(12;21)	60	14/287	0.59 (0.31-1.13)	52	21/236	1.68 (0.92-3.06)
MLL rearrangements	17	7/287	1.74 (0.60-5.06)	15	6/236	1.38 (0.46-4.11)
Other translocations‖	47	12/287	0.72 (0.36-1.45)	43	13/236	1.03 (0.52-2.05)
Other structural changes¶ **	17	4/232	0.61 (0.19-1.92)	11	6/184	2.62 (0.78-8.84)
Hyperdiploidy	113	32/287	0.79 (0.51-1.24)	94	27/236	0.92 (0.57-1.49)
Hypodiploidy	16	8/287	2.17 (0.79-5.97)	14	3/236	0.66 (0.18-2.43)
Trisomy (or greater) of chromosome 21††	66	17/287	0.67 (0.37-1.20)	51	16/236	1.11 (0.59-2.08)
Other numerical changes	39	15/287	1.27 (0.64-2.49)	29	8/236	0.85 (0.37-1.98)

NOTE: Eight cases with no information on genetic subtype and seven cases with unknown/other lineage were excluded. Subgroups are not mutually exclusive.

*Adjusted for matching variables (age group, sex, and state), birth order, maternal education, and maternal age at birth.

†The reference category is mothers who did not have an abdominal or pelvic X-ray at any time before or during the index pregnancy.

‡Adjusted for matching variables (age group, sex, and state), paternal education, and paternal age at birth.

§The reference category is fathers who did not have an abdominal or pelvic X-ray at any time before the conception of the index child.

‖For the analyses of maternal exposure, the numbers of cases are as follows: *TCF3/PBX1* t(1;19), *n* = 7; *BCR-ABL* t(9;22), *n* = 6; other translocations, *n* = 35; for the analyses of paternal exposure: *TCF3/PBX1* t(1;19), *n* = 7; *BCR-ABL* t(9;22), *n* = 6; other translocations, *n* = 31.

¶"Other structural change" is defined as any structural change that is neither a translocation nor a deletion, such as isochromosomes or abnormal derivative chromosomes.

**There were less controls (maternal analyses 680; paternal analyses 601) included in these analyses because one state had no cases of ALL in this subcategory; therefore, controls from that state were excluded from the analyses (maternal analyses 179; paternal analyses 148).

††Refers mainly to somatic (not constitutive) changes in tumor cells. Only one of these cases had Down syndrome.

Table 5. ORs for any diagnostic radiological X-ray of the child by immunophenotype and cytogenetic subtype

		Any exposure before diagnosis		Any exposure >6 mo before diagnosis	
	Case, *n*	Exposed cases/controls	OR* † (95% CI)	Exposed cases/controls	OR* † (95% CI)
All cases	386	182/362	1.21 (0.93-1.57)	156/326	1.15 (0.88-1.51)
Pre-B cell	342	160/362	1.21 (0.92-1.59)	136/326	1.14 (0.86-1.51)
T cell	37	19/362	1.07 (0.53-2.18)	18/326	1.16 (0.56-2.38)
Normal karyotype	130	60/362	1.09 (0.74-1.63)	55/326	1.11 (0.73-1.66)
Any genetic feature	248	117/362	1.25 (0.92-1.70)	97/326	1.15 (0.83-1.60)
Chromosomal deletions	62	33/362	1.48 (0.85-2.59)	27/326	1.38 (0.77-2.49)
ETV6-Runx-1 t(12;21)	60	25/362	1.22 (0.69-2.15)	20/326	1.09 (0.59-2.01)
MLL rearrangements	17	6/362	0.67 (0.21-2.13)	6/326	0.73 (0.22-2.40)
Other translocations‡	46	32/362	2.59 (1.30-5.16)	28/326	2.64 (1.30-5.37)
Other structural changes§ ‖	17	10/292	1.79 (0.63-5.12)	8/264	1.70 (0.56-5.20)
Hyperdiploidy	113	52/362	1.14 (0.74-1.75)	41/326	0.98 (0.62-1.55)
Hypodiploidy	15	9/362	2.19 (0.71-6.75)	8/326	2.42 (0.75-7.83)
Trisomy (or greater) of chromosome 21¶	66	35/362	1.62 (0.94-2.79)	27/326	1.28 (0.71-2.30)
Other numerical changes	38	20/362	1.32 (0.64-2.68)	17/326	1.35 (0.64-2.85)

NOTE: Eight cases with no information on genetic subtype and seven cases with unknown/other lineage were excluded. Subgroups are not mutually exclusive.

*Adjusted for matching variables (age group, sex, and state), birth order, maternal education, maternal age at birth, and child has birth defect.

†The reference group is children who did not have any diagnostic radiological X-ray at any time before the censoring date (date of diagnosis for cases and date of questionnaire return for controls).

‡*TCF3/PBX1* t(1;19), *n* = 7; *BCR-ABL* t(9;22), *n* = 6; and other translocations, *n* = 33.

§Other structural change is defined as any structural change that is neither a translocation nor a deletion, such as isochromosomes or abnormal derivative chromosomes.

‖There were 687 controls included in these analyses because one state had no cases of ALL in this subcategory; therefore, 183 controls from that state were excluded from the analyses.

¶Refers mainly to somatic (not constitutive) changes in tumor cells. Only one of these cases had Down syndrome.

and *MLL* rearrangements (OR, 2.59; 95% CI, 1.30-5.16; Table 5). In the "other translocations" group, there were 7 cases with *TCF3/PBX1* t(1;19), 6 with *BCR-ABL* t(9;22), and 33 with mostly individual translocations. The OR for any X-ray of the child before the censoring date for these small numbers were 2.88 (95% CI, 0.51-16.39), 4.95 (95% CI, 0.54-45.14), and 2.27 (95% CI, 1.03-5.00), respectively.

Parental radiotherapy

One case father reported receiving radiotherapy before conception of the index child, as did three control fathers. One case mother and three control mothers reported having radiotherapy before conception. No statistical analyses were done because of the small numbers of these exposures.

Meta-analyses

Details of previous studies considered for inclusion in the meta-analyses of paternal abdominal or pelvic X-rays are summarized in Supplementary Table S1. There were two studies that investigated the risk of paternal X-rays close to conception (11, 13). The larger of these, by Shu and colleagues (11), studied the 2 years before conception, whereas the other, by Meinert and colleagues (13), studied the 2 years before the child's birth. The ORs from these two studies and ours were all above unity, and the pooled OR was 1.17 (95% CI, 0.92-1.48; Fig. 1). For this meta-analysis, we used our OR for any paternal X-rays done when the father's age at the time of the X-ray was either the same as at conception or 1 year younger, but the pooled estimates were similar when we used our OR for X-rays done when the father's age at the time of the X-ray was the same as at conception, or the OR for ever having an X-ray before conception. Another study (10) investigated the risk of paternal X-rays for a longer period of exposure (5 years before conception) in children with Down syndrome. The pooled OR for that study and Aus-ALL for any paternal X-rays within 5 years of conception from was 1.22 (95% CI, 0.85-1.74). The meta-analyses of the most appropriate ORs from our study with the study of infant ALL (12) showed heterogeneity;

thus, the results are not presented. There was no study comparable with ours that presented results on the frequency of X-rays at any time before conception; thus, we were unable to do a meta-analysis of dose response.

Discussion

There was little evidence of any increased risk of childhood ALL associated with maternal X-rays before or during the pregnancy or with X-rays of the child.

Previous studies have also reported no evidence of an increased risk of childhood ALL with maternal abdominal or pelvic region X-rays before pregnancy (10-12). The risks associated with maternal exposure during pregnancy have been well studied over the last 50 years. Although at least six studies published before 1990 suggested an increased risk of ALL (5, 28) or leukemia (7, 29-31) associated with abdominal or pelvic X-rays during pregnancy, it is probably more appropriate to compare our findings with more recent studies because of both the reduction in the radiation doses incurred from procedures (8) and the decreasing prevalence of exposure. A meta-analysis of studies published since 1990 reported that the pooled relative risk of leukemia was 1.16 (95% CI, 1.00-1.36; ref. 9). However, none of the three most recently published studies of ALL (10, 16, 32) found an association. Like us, their estimates lacked precision because of the low prevalence of exposure; for example, in Aus-ALL, less than 2% of control mothers reported having an abdominal X-ray during pregnancy, whereas in some early studies about 15% to 20% of control mothers reported exposure during pregnancy (30, 33).

Findings from case-control studies investigating the risks associated with X-ray exposures after birth have been more inconsistent. Like ours, four studies found no association between having any X-ray during childhood and risk of either leukemia (13, 29) or specifically ALL (10, 19). Three other studies found little or no increased risk of ALL with having a low number of X-rays but an increased risk with having a "higher" number,

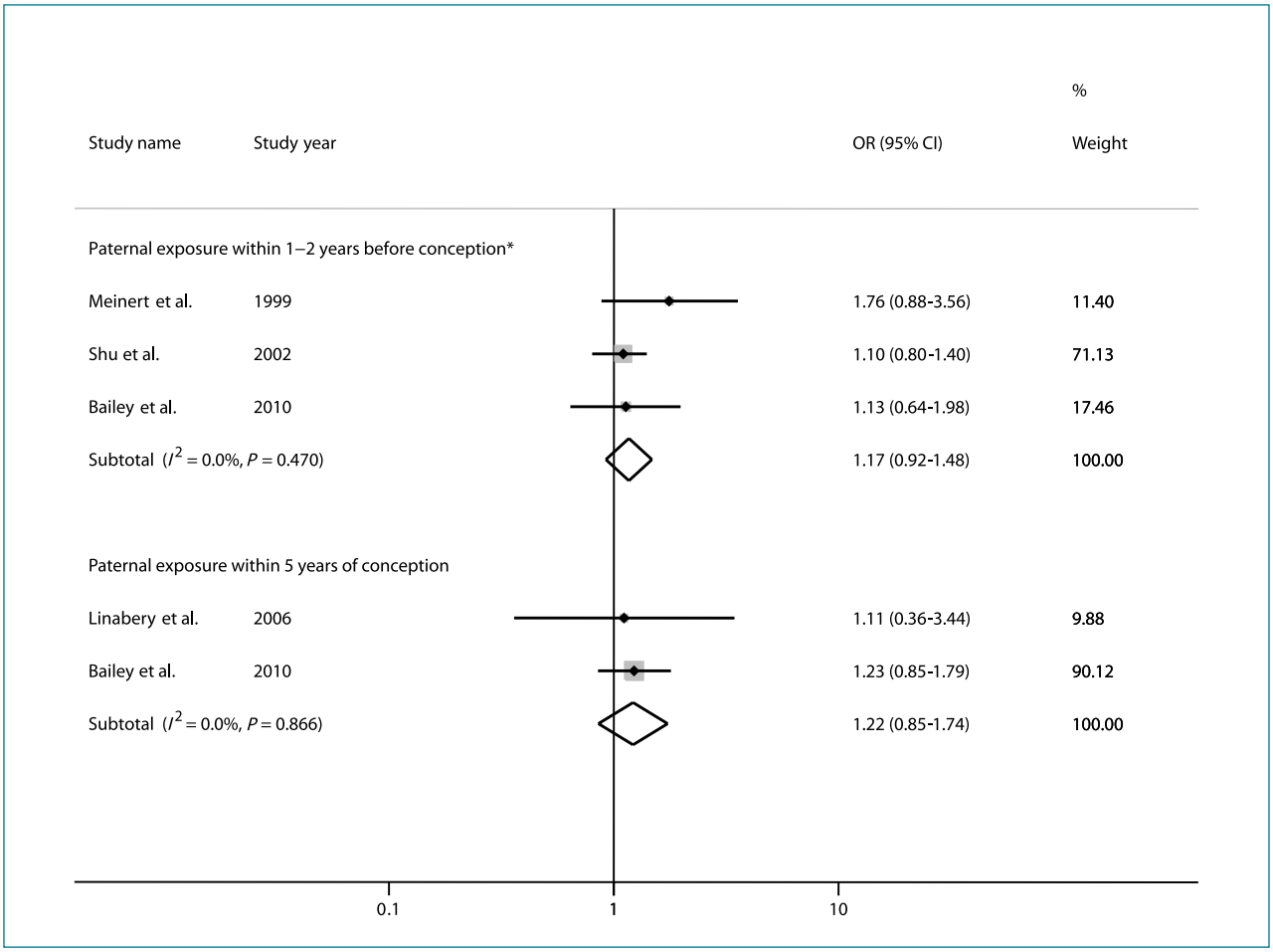

Figure 1. Forest plot showing study-specific and summary ORs for paternal abdominal or pelvic X-rays before conception. *The time period before conception varied by study: Meinert et al., within 2 years of birth; Shu et al., within 2 years of conception; Bailey et al., father's age at the time of the X-ray was the same or 1 year younger than his age at conception.

although the definition of higher varied from "more than one" to "more than five" (11, 16, 28). A Chinese study of leukemia cases diagnosed in the mid-1980s and a more recent large U.S. study of ALL both found an increased risk of disease with X-rays before diagnosis, with a dose response (17, 18). Results within studies have also been inconsistent, which makes them difficult to interpret. In Canada, Infante-Rivard and colleagues analyzed risk by genotype and found an increased risk of ALL with X-ray exposure in boys with polymorphisms of one of the DNA repair genes (*APE ex 5*) but a decreased risk among girls with the same polymorphism (16). Similarly, one small Japanese study, which used hospital-based controls, found an association between dental X-rays and non–T-cell ALL, but not with X-rays of other parts of the body involving higher doses of radiation (34).

Overall, there was little evidence in our case-control study of an increased risk of childhood ALL associated with paternal X-rays before conception, which was consistent with the results of our meta-analyses. However, there was some evidence that the father having had more than one abdominal or pelvic region X-ray at any time before conception was associated with an increased risk. There was also evidence of increased risk with the father having an IVP or barium study before conception. Only four other studies have specifically investigated paternal exposure to abdominal or pelvic region X-rays before conception, and these have had inconsistent results (10-13). In the first study, which was restricted to children diagnosed with leukemia by 18 months of age, there was evidence of increased risk, including a dose response, with both paternal lower and upper abdominal X-rays at any time before conception (12). The ORs were highest for abdominal X-rays done in the year before conception. In Aus-ALL, there were only 18 cases diagnosed by 18 months of age; thus, we did not have adequate power to do similar analyses. However, excluding those diagnosed by 18 months made little difference to our findings. The second study, conducted in Germany, also found an increased risk of acute leukemia associated with paternal X-rays of the abdomen or gastrointestinal tract in the 2 years leading up to the child's birth (13). When the analyses were restricted to children diagnosed by 18 months, no association was found. A limitation of this study was the inclusion of irrelevant paternal exposures between conception and birth. The two most recent studies, both conducted in the United States, found no association with paternal abdominal X-rays and ALL (10, 11). The first of these (11) was the study with the most cases and investigated the risk of any lower abdominal X-rays in the 2 years before conception, whereas the final study investigated the risk of paternal abdominal X-rays within the 5 years leading up to conception in a population of children with Down syndrome (10).

Studies of any paternal X-rays before conception, regardless of the site of the X-ray, have reported conflicting results, with two suggesting an association (28, 35) and two finding no association (12, 19). The risk of ALL in the offspring of male radiation workers has also been investigated using estimated dose of radiation in the 6 months before conception (36-40). The initial report of an increased risk of ALL and evidence of a dose response among children of men employed at Sellafield nuclear plant (36) has not been replicated in subsequent, larger studies (37-40).

Paternal exposure to radiation damages sperm, resulting in DNA double-strand breaks (41). Therefore, it is conceivable that exposure close to conception damages germ cell DNA and thus increases the risk of ALL in the offspring. There is evidence from animal models that paternal exposure to radiation in the spermatozoa or spermatid stages of germ cell development increases the risk of leukemia in the offspring (14). In humans, this would be equivalent to exposure about 30 to 47 days before conception (42). In addition, in the later stages of development, male germ cells lose the ability to repair DNA damage (43) and the risk of chromosomal aberrations in the offspring may depend on the efficiency of subsequent maternal repair of the DNA of the zygote (44). Therefore, to investigate if paternal X-rays are associated with the risk of ALL in the child, it may be necessary to identify exposures in the few months before conception and, perhaps, to include maternal genotype in the analyses. We found weak evidence that paternal X-rays before conception increased the risk of the *ETV6-Runx-1* t(12;21) ALL. *ETV6-Runx-1* genomic fusion sequences have been identified in dried newborn blood spots of children later diagnosed with ALL, suggesting that this subtype of ALL is initiated prenatally (45). Thus, it is plausible that these aberrations result from unrepaired paternal germ cell DNA damage.

No previous study has reported the risk of ALL associated with the father having specific types of procedures before conception, such as the increased risk we observed with the father having an IVP. If having an IVP is carcinogenic, it would be plausible that it could cause cancer in pelvic tissues as well as cancer in the offspring through damage to germ cells. A recent study reported an OR for prostate cancer of 1.67 (95% CI, 0.92-3.03) with having an IVP at least 5 years before diagnosis, suggestive of an increased risk (46). Any association may be due to some factor related to the underlying condition—that is, a condition of the kidney or urinary tract, or its subsequent treatment—rather than to the IVP itself. To our knowledge, no one has investigated whether paternal renal or urinary tract conditions are related to ALL in the offspring, and it is difficult to think of a plausible reason why they should be. In one of the few studies of the effects of paternal medication in the year before conception and the risk of childhood ALL, no association was seen with any medications, such as antibiotics, that may have been used to treat renal or urinary tract disease (47). In Aus-ALL, we did not collect any information on why the X-rays were needed, or the subsequent diagnosis or treatment. The observed association could also be due to recall bias; however, there is no reason why case fathers should selectively

report having this procedure and not other types of procedures. However, our findings were based on small numbers of exposed subjects. In addition, the lack of any clear temporal relationship between the timing of the IVP and conception is at odds with the evidence from animal models of a critical window for paternal exposure to radiation (14); thus, our findings may be due to chance.

We found evidence of an association between the child having any X-ray and ALL involving translocations other than t(12;21) and *MLL* rearrangements. The ORs for the small subgroups of *TCF3/PBX1* t(1;19), BCR-ABL t (9;22), and other rare translocations were all elevated. It is plausible that these translocations are caused by childhood X-rays. *TCF3/PBX1* t(1;19) translocations are thought to occur postnatally (48) and the frequency of t (9;22) translocations may increase with age as they are more common in adult ALL (49), which is consistent with our results. This evidence of an increased risk of ALL with translocations associated with X-ray exposure is a potentially important finding and should be examined further in larger studies.

To our knowledge, this is the first study to specifically investigate the risks associated with having CT scans. CTs were of particular interest, as the radiation dose from having a CT scan is many times larger than that received from having a plain X-ray; for example, the radiation dose from a routine CT of the abdomen or pelvis is approximately equivalent to that received from having 220 plain chest X-rays (50). In addition, the dose for similar procedures may vary significantly across institutions in both adult (50) and pediatric populations (51). It has been suggested that a large number of future cancers will be specifically related to abdominal and pelvis CT scans (52). Nonetheless, in Aus-ALL, we found no evidence of an increased risk with maternal or paternal CTs of the abdomen or pelvis before conception, or with the child ever having a CT. However, these results should be interpreted in light of the small number of exposed subjects; less than 5% of case and control parents and 2% or less of case and control children in this study had a relevant CT scan; thus, the estimates lacked precision. We were not able to investigate the risk of ALL associated with maternal CTs during pregnancy as there were only two exposed controls and no exposed cases. Such low prevalence may not be found in other populations, or indeed in Australia, if we were to repeat the study now. For example, a U.S. study found that between 1993 and 2006, the number of CTs done annually increased by more than 10% a year, whereas the population increased by less than 1% a year (53). In addition, they also estimated that ~20% of abdominal and pelvic CT scans are done on individuals ages 18 to 44 years (approximately the childbearing years; ref. 53).

Aus-ALL had strengths and limitations. Cases were ascertained from oncology centers that treat almost all children with ALL in Australia and 75% of parents of eligible cases consented to participate in Aus-ALL; 70% of eligible controls recruited by random digit dialing also agreed to participate. However, 64% of participating control parents returned the questionnaires compared with 93% of participating case parents, raising the possibility of selection bias. We had information on parental education for all Aus-ALL participants. Control parents were more likely than case parents to have a tertiary education and, using area-based measures, we have shown that control parents were of higher socio-economic status than the general Australian population (23). Furthermore, having an X-ray was positively associated with parental education level among the controls. SES was considered a priori to be a potential confounder of this association, and either maternal or paternal education level was included in our analytic models. It is therefore unlikely that selection bias related to SES had a major impact on our findings.

A limitation of Aus-ALL was that information on X-rays was collected from the parents rather than from medical records. However, apart from during pregnancy, it would be very difficult to collect evidence from medical records as it is likely that over the lifetime of an individual, X-rays would have been taken at multiple locations, and these locations could only be identified by the parents themselves. Because we collected information from parents, as with most case-control studies, there was the potential for both exposure misclassification and recall bias. We attempted to minimize this using standardized written questionnaires. Nonetheless, using these methods would not remove the potential for case parents to think more deeply about past exposures and thus to report them more frequently. However, our results suggest that this was not the case as there were comparatively few ORs above unity and, if anything, in our study, case mothers may have underreported having an X-ray before or during pregnancy. A possible reason for this is that they were so overwhelmed with details of their child's current treatment to recall their own medical history; however, there is no way that we can verify this. This theory is not supported by a previous study of ALL and maternal prenatal X-rays, which reported that case and population control parents underestimated exposure to a similar extent (54). Our method of asking about X-rays before conception meant that we were unable to restrict the period investigated to the likely critical times, such as the final few months before conception for fathers.

In conclusion, there was little evidence of any increased risk with maternal abdominal or pelvic region X-rays before or during the pregnancy or with the child having any X-rays. There was some evidence of an increased risk of ALL in the offspring if the father had more than one abdominal or pelvic region X-ray at any time before conception. There was no evidence of any increased risk with maternal or paternal abdominal or pelvic CTs before pregnancy or with the child ever having a CT. Given the high dose of radiation delivered in a CT, it is important to repeat these analyses in other populations for which the prevalence is higher or in a larger sample to improve the precision. Pooled analyses

are planned in the Childhood Leukemia International Consortium (55).

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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