Diagnostic X-Rays and Ultrasound Exposure and Risk of Childhood Acute Lymphoblastic Leukemia by Immunophenotype[1]

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Abstract

The objective of this study was to evaluate the association between *in utero* diagnostic X-rays and childhood acute lymphoblastic leukemia (ALL) and the less well-studied relationship of this malignancy to preconception and postnatal diagnostic X-rays or fetal ultrasound exposures. The Children's Cancer Group conducted a case-control study including interviews with parents of 1842 ALL cases diagnosed under the age of 15 years and 1986 individually matched controls. Associations of self-reported parental preconception, *in utero*, and postnatal X-ray exposure with risk of childhood ALL were examined using odds ratios (ORs) and corresponding 95% confidence intervals (CIs) obtained from logistic regression models among the overall group of ALL cases as well as immunophenotypic and age-specific subgroups. Overall, *in utero* pelvimetric diagnostic X-rays were not associated with the risk of pediatric ALL (OR, 1.2; 95% CI, 0.8–1.7). Childhood ALL, all types combined (OR, 1.1; 95% CI, 0.9–1.2) and specific types were also not linked with postnatal diagnostic X-ray exposures. Neither maternal (OR, 0.9; 95% CI, 0.8–1.2) nor paternal (OR, 1.1; 95% CI, 0.8–1.4) lower abdominal preconception diagnostic X-rays were associated with risk of childhood ALL. Among the multiple comparisons for age-, sex-, and subtype-specific subgroups, we observed an elevated risk of total ALL among children ages 11–14 at diagnosis (OR, 2.4; 95% CI, 1.1–5.0) in relation to *in utero* pelvimetric diagnostic X-ray exposures and a small increase in pre-B ALL for all ages combined (OR, 1.7; 95% CI, 1.1–2.7) in relation to postnatal diagnostic X-rays. *In utero* diagnostic ultrasound tests were not linked with risk of childhood ALL. We found little consistent evidence that *in utero* diagnostic ultrasound tests or X-rays were linked with an increased risk of childhood ALL. Small increases in total or pre-B ALL risks for children in selected age groups to very low ionizing radiation exposures from postnatal or preconception diagnostic X-ray exposures may represent chance findings or biases. Future studies of diagnostic X-rays and childhood leukemia in the United States will require extensive additional efforts and resources to quantify risk because of declining *in utero* exposures in the general population (thus necessitating large numbers of subjects, particularly cases) and the difficulty in validating reported exposures.

Introduction

ALL[4] is the most common malignancy in children <15 years of age in the United States and many other western countries (1). The age-adjusted incidence rate for ALL among children <15 years of age is 29.2 per million, and the peak incidence occurs at 2–3 years of age (2). Approximately 4900 United States children are diagnosed with ALL annually in the United States (2). The etiology of childhood ALL is poorly understood (3–5).

The association of *in utero* diagnostic X-ray exposure with subsequent occurrence of childhood leukemia has been the subject of great controversy over the last 40 years (6, 7). Although most earlier studies (8–10) and meta-analyses (6, 11–13) reported that *in utero* X-ray exposure was associated with a 40% elevated risk of childhood ALL, the biological plausibility of such an association has been much debated (7, 14). Those arguing against a true association have cited the absence of increased childhood leukemia risks among the Japanese atomic bomb survivors exposed *in utero* (15, 16) or cohorts of children exposed *in utero* in the United Kingdom (17) and the United States (18). Experimental data do not support a relationship between fetal irradiation and increased occurrence of leukemia (19).

In contrast to the numerous epidemiological investigations evaluating the relationship between diagnostic X-ray exposures during pregnancy and risk of childhood leukemia in singletons (9, 10, 20–31) and in twins (32, 33), the effects of parental preconception (10, 29, 30, 34–36) and children's postnatal (10, 20, 22, 25, 29, 30, 35, 37) exposure to diagnostic X-rays on the risk of childhood leukemia have been evaluated less extensively. Experimental studies, primarily evaluating the effect of preconception external or internal irradiation and the risk of leukemia in offspring, have shown elevated risks of leukemia in offspring in some studies (38–40), but most of these studies have exposed animals to considerably higher external radiation

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[4] The abbreviations used are: ALL, acute lymphoblastic leukemia; CCG, Children's Cancer Group; OR, odds ratio; CI, confidence interval.

doses than those likely with diagnostic X-ray exposure. Risks also varied with the timing of the X-ray exposure.

A growing body of studies suggest that childhood ALL is not a homogeneous entity but instead consists of heterogeneous subgroups, defined by immunophenotyping, that differ biologically in host characteristics and in response to therapies (41, 42). Childhood ALL subtypes also may represent a diverse group of diseases with distinct etiologies, but this hypothesis has not been systematically evaluated. To investigate whether biologically and prognostically distinct subgroups of childhood ALL have different etiologies, the CCG conducted a large case-control study that evaluated a broad range of postulated risk factors.

Materials and Methods

Selection of Cases. Cases were institutionally based and identified through the member institutions of the CCG, one of two large cooperative pediatric clinical trials groups in the United States that treat >93% of childhood cancer in the United States (3). Institutional Review Board approval for the study was obtained from all participating CCG institutions before case accrual. Case eligibility depended upon four criteria. Participants had to be newly diagnosed between January 1, 1989 and June 15, 1993 and be <15 years of age at diagnosis. They had to live in a home with a telephone, and an English-speaking biological mother had to be available for interview. A total of 2081 eligible cases were identified during the study period. Informed consent was obtained from the physician and the parents of all eligible study subjects. One case was later determined ineligible for this study. A total of 1914 cases (92%) were successfully enrolled (*e.g.*, a telephone interview was completed with the mother). Among the 167 nonrespondents, there were 41 (2%) physician refusals, 70 (3.4%) parental refusals, 18 (0.9%) lost to follow-up after first contact, and 38 (1.8%) not participating for other reasons.

Assignment of B- or T-Lineage. The assignment of B- or T-lineage of ALL cases was made at the treating institution at diagnosis. The protocol also required that a pretreatment bone marrow specimen be sent to a designated CCG Reference Laboratory for immunophenotyping. A standard panel of monoclonal antibodies applied to all specimens included CD2, CD5, and CD7 as T-lineage markers and CD19, CD10, and CD24 as B-lineage markers. During the initial phase of the study, those cases diagnosed as B-lineage leukemias were further classified by the determination of cytoplasmic immunoglobulin. Cases were classified into one of the following mutually exclusive groups: T-cell, early pre-B ALL (B-lineage markers and cytoplasmic immunoglobulin negative), pre-B ALL (B-lineage markers and cytoplasmic immunoglobulin positive), B-lineage ALL not otherwise specified (NOS; B-lineage markers but cytoplasmic immunoglobulin not performed), or unclassifiable. A computer algorithm was developed to classify cases based on the percentage of positivity of the bone marrow specimens to each of the monoclonal antibodies. In instances where the treating institution and reference laboratory assignment of lineage disagreed, the case was reviewed independently by the two reference laboratory directors, and an assignment was made.

Selection of Controls. Controls were randomly selected, using a previously described random-digit dialing procedure (43), and individually matched to cases for age (within 25% of the case's age at diagnosis, with a maximum difference of ±2 years of age), race, (white, black, or other), and telephone area code and exchange. When an exact match could not be achieved after 300 random numbers had been telephoned, relaxation of the age- and race-matching was implemented. As with the cases, there had to be a telephone in the control's residence and the biological English-speaking mother had to be available for interview. A total of 2597 eligible controls were identified, and data were successfully collected for 1987 subjects (76.5%). One control was excluded because the matched case was later found to be ineligible for the study. Reasons for nonparticipation of controls were: parental refusal (n = 457; 17.6%), loss to follow-up (n = 17; 0.7%), and other reasons (n = 136; 5.2%). Matched controls could not be found for 72 (3.8%) enrolled cases. After exclusion of these nonmatched cases, a total of 1842 case-control pairs (1,704 sets of 1:1 match, 132 sets of 1:2 match, and 6 sets of 1:3 match) remained for statistical analyses. During control selection, there were situations where the first eligible control was not successfully enrolled, necessitating identification of the next eligible control. Some of the "first controls" were subsequently successfully enrolled, thus resulting in multiple controls/case.

Data Collection Procedures. Most data were collected during telephone interviews with mothers of cases and controls using a structured questionnaire. Extensive efforts were also made to interview independently all fathers of cases and controls to obtain information about each father's medical and occupational history, also using structured questionnaires. The averaged time interval between case diagnosis and interview was 8.4 months. Questionnaires administered to mothers ascertained information about demographic factors, socioeconomic status, medication use, and X-ray exposures before and during the index pregnancy and birth; ultrasound examinations during the index pregnancy; the mother's history of selected medical conditions, reproductive history and contraceptive use, personal habits (including tobacco and alcohol use), household exposures, occupational history; family medical history; the index child's medical history (including history of diagnostic X-rays, medical conditions, and medication use); and history of pesticide and insecticide exposures. Questionnaires were completed by mothers of 1914 (92%) of the 2081 eligible cases and of 1987 (76.5%) of the 2597 eligible controls, resulting, as noted above, in 1842 matched sets. Medical and occupational data about fathers' exposures were ideally to be obtained directly from fathers, but if the father was not available, the mother was asked about the father's history of medically related information and of jobs that were held. The fathers' questionnaires were completed for a total of 1801 (86.5%) of the 2081 eligible cases and of 1813 (69.8%) of the 2597 eligible controls, resulting in 1618 matched sets. Of these matched sets, interview data were obtained directly from fathers for 83.4% of the cases and 67.7% of the controls. Thus, mothers provided data about the fathers' exposures for 16.6% of cases and 32.3% of controls. The major reasons for nonresponse by case fathers were: respondent not available (4.1%), refusal (4.3%), physician refusal (2.0%), and other reasons (2.2%). Nonresponse among fathers of controls was because of: refusal (19.1%), the respondent not available (4.6%), and other reasons (6.4%).

Data Collection for All Exposure Histories. Detailed information was collected on *in utero*, postnatal, and preconception (within 2 years of estimated date of conception) through telephone interviews with parents. The questionnaire admin-

istered to mothers asked about history of maternal X-rays during the 2-year period before conception and during the index pregnancy, as well as the history of the child's postnatal diagnostic X-ray exposures. For prenatal X-ray exposure, mothers were asked "Did you have any of the following X-rays during your pregnancy with (index child)?" Questions were asked about X-rays of specific anatomical sites (*e.g.,* "X-rays of the lower abdomen or back—pelvimetry or of the fetus," "X-rays of the lower abdomen or back—not pregnancy related," "X-rays of the head and neck (excluding dental X-rays)," "X-rays of the limbs," "X-rays of the chest," "X-rays of the upper abdomen or back," "X-rays of the back—exact region not specified," and "Other X-rays—specify"). Fathers were asked questions only about their diagnostic X-ray exposures within 2 years of the estimated date of conception of the index child. For the period within 2 years of conception, the mother and the father were asked first if they had had any diagnostic X-rays taken within 1 month, 1 year, or 2 years before the index pregnancy. If either parent reported a history of X-ray exposure, information was collected on the specific anatomical site of the X-rays, the main clinical reason for the X-ray, and the cumulative number of X-rays taken at each site. The timing of the X-ray examination was determined for the postnatal period up to 6 months before diagnosis for the cases and the reference date for the controls (the reference date was defined as the date of diagnosis of the individually matched case). Unfortunately, we were unable to validate any reported X-ray exposure information by reviewing medical records because of financial constraints.

Data on history of ultrasound examinations during pregnancy were collected during the telephone interview of the mother. Information on socioeconomic, demographic, and other potential confounding variables was also obtained from the mother during the telephone interview.

Data Analysis. Specific hypotheses to be tested in the study were: "Were *in utero* prenatal diagnostic X-rays, postnatal diagnostic X-rays at all anatomical sites, and preconception maternal and paternal diagnostic X-rays to the lower abdominal area associated with risk of childhood ALL?" Data were analyzed for all types of ALL combined among children of all ages and by 5-year age group, given that an age-specific association with paternal preconception X-ray exposure has been reported previously (30, 36). Although there are no epidemiological or experimental data linking low-level ionizing radiation exposure with specific immunophenotypes of ALL, we nevertheless conducted an exploratory analysis evaluating risks according to immunophenotype of ALL. Patients with B-cell (not otherwise specified) leukemias were not separately evaluated because of the heterogeneous nature of patients in this group. ORs were used to measure the association between X-ray exposure in each of the three periods (preconception, prenatal, and postnatal) and risk of ALL and between prenatal exposure to ultrasound tests and risk of ALL. Because it is generally believed that infant leukemia (defined as leukemia diagnosed during the first 12 months after birth) arises *in utero* and that postnatal exposure is irrelevant to its etiology (44), we excluded cases diagnosed at <12 months of age and their matched controls from the analyses of postnatal diagnostic X-ray exposures. Because mothers may not have known about the fathers' diagnostic X-ray exposures before conception of the child, analyses of paternal preconception exposure excluded all data from interviews of surrogate respondents. Conditional logistic regression was used in data analyses to estimate ORs and 95% CIs, adjusting for potential confounders (45). In the final model, we adjusted for maternal education, family income, and race. Paternal occupation was not adjusted for because it was not available for all study subjects and had little impact on the ORs. To maximize the number of cases and controls included in analyses focusing on paternal preconception diagnostic X-ray exposures, unconditional logistic regression analyses were conducted in which adjustment was performed for two matching variables, *i.e.,* child's age and sex, in addition to the adjustment of paternal education, family income, and race. Tests for trend were performed by treating levels of categorical variables as continuous variables in the logistic model (45). All statistical tests were two-sided.

Results

Demographic Characteristics. The distribution of ALL immunophenotypes as well as characteristics of cases and controls are shown in Table 1. Cases and controls included in the study were born during 1972–1992 and interviewed during 1989–1995, with the average interval between birth and interview being 6.2 and 7.2 years for cases and controls, respectively. Compared with controls, cases were less likely to be white and more likely to be Hispanic and to come from families characterized by lower socioeconomic status as defined by parental education, family income, and paternal occupation. Of these variables, race, parental education, and family income were associated with both X-ray exposure and ALL. Thus, we adjusted for these variables in the logistical regression analyses.

There were 28 cases and 5 controls with Down's syndrome. Children with Down's syndrome have been found to be at substantially higher risk of developing leukemia, with estimated risks ranging from a 10- to 40-fold increase (3, 46). Therefore, we excluded from this analysis all matched pairs (n = 33) in which either a case or a control had Down's syndrome.

***In Utero* Exposure to Diagnostic X-rays or Ultrasound.** Overall, a similar proportion of case mothers (6.6%) and control mothers (7.0%) reported a history of one or more diagnostic X-ray exposures to any anatomical site during the index pregnancy (OR, 1.0; 95% CI, 0.8–1.3; Table 2). Similarly, approximately the same proportions of case mothers (3.0%) and control mothers (2.6%) described undergoing "X-rays to the lower abdomen or back—pelvimetry or of the fetus" (hereafter abbreviated as "pelvimetry") during the index pregnancy (OR, 1.2; 95% CI, 0.8–1.7). For mothers of both cases and controls, the proportion undergoing pelvimetry during the index pregnancy declined with increasing recency of the calendar year period of birth (10.2, 2.4, and 1.3%, respectively, for cases born in 1980 or before, those born during 1981–1986, and those born after 1986, compared with 6.0, 2.3, and 1.8%, respectively, for controls born in the same time periods). There was an excess of maternal pelvimetric diagnostic X-ray exposure among children diagnosed with ALL at ages 11–14 years compared with controls (OR, 2.4; 95% CI, 1.2–5.0; 24 exposed cases *versus* 13 exposed controls). Among younger children, however, the risk of ALL was not affected by the number or anatomical site of X-rays reported during the index pregnancy (for pelvimetric X-rays among children <6 years of age: OR, 1.0; 95% CI, 0.5–2.0; and for pelvimetric X-rays among children ages 6–10 years: OR, 0.7; 95% CI, 0.3–1.5). There

Table 1 Demographic characteristics of cases and controls

	Cases $n = 1842$	Controls $n = 1986$	P
Immunophenotype			
T-cell	183 (9.9%)		
Early Pre-B cell	893 (48.5%)		
Pre-B cell	233 (12.6%)		
B not specified	231 (12.5%)		
Unknown	302 (16.4%)		
Calendar year of birth	1972–1992	1972–1992	
Calendar year of interview	1989–1995	1989–1995	
Interval between date of birth and interview	6.2	7.2	
Sex			
Male	1018 (55.3%)	1076 (54.2%)	0.50
Female	824 (44.7%)	910 (45.8%)	
Age			
<12 mo	64 (3.5%)	81 (4.1%)	0.07
12–23 mo	138 (7.5%)	189 (9.5%)	
2–5 yr	1020 (55.4%)	1038 (52.3%)	
6–10 yr	408 (22.2%)	466 (23.5%)	
11+ yr	212 (11.5%)	212 (10.7%)	
Race			
White	1492 (81.0%)	1720 (86.6%)	<0.01
Black	109 (5.9%)	94 (4.7%)	
Hispanic	153 (8.3%)	121 (6.1%)	
Native American Indian/ Alaska Native	19 (1.0%)	13 (0.7%)	
Asian/Pacific Islander	56 (3.0%)	32 (1.6%)	
Other or Unknown	13 (0.7%)	6 (0.3%)	
Index child			
Single birth	1803 (97.9%)	1952 (98.3%)	0.42
Twin birth	39 (2.1%)	34 (1.7%)	
Maternal education			
≤ High school	797 (43.3%)	762 (38.4%)	
Some post high school	592 (32.1%)	701 (35.3%)	<0.01
≥ College	453 (24.6%)	523 (26.3%)	
Paternal education[a]			
≤ High school	676 (41.8%)	638 (37.1%)	
Some post high school	480 (29.7%)	510 (29.6%)	<0.01
≥ College	462 (28.6%)	574 (33.4%)	
Income ($)			
<10,000	217 (11.8%)	176 (8.9%)	<0.01
10,000–19,999	390 (21.2%)	370 (18.6%)	
20,000–29,999	433 (23.5%)	475 (23.9%)	
30,000–39,999	334 (18.1%)	369 (18.6%)	
40,000–49,999	204 (11.1%)	221 (11.1%)	
50,000+	250 (13.6%)	357 (18.0%)	
Unknown	14 (0.8%)	18 (0.9%)	
Paternal occupation[a]			
Prof/Tech/Manager	498 (30.8%)	580 (33.7%)	<0.01
Clerical/Sales	200 (12.4%)	214 (12.4%)	
Service	95 (5.9%)	108 (6.3%)	
Agriculture/Fish/Forest	63 (3.9%)	65 (3.8%)	
Processing	45 (2.8%)	43 (2.5%)	
Machine trades	149 (9.2%)	144 (8.4%)	
Benchwork	27 (1.7%)	38 (2.2%)	
Structural work	252 (15.6%)	225 (13.1%)	
Miscellaneous	151 (9.3%)	125 (7.3%)	
Unknown	138 (8.5%)	180 (10.5%)	

[a] Based on 1618 cases and 1722 matched controls who responded to paternal interview.

Table 2 ORs for ALL associated with maternal ultrasound and X-ray exposure during pregnancy

	Category	Cases	Controls	OR[a] (95% CI)
Total ALL				
Ever had ultrasound	No	628	663	1.0
	Yes	1161	1273	0.9 (0.8–1.1)
No. of ultrasound examinations	1	574	618	0.9 (0.8–1.1)
	2	329	373	0.9 (0.6–1.1)
	3+	251	276	0.9 (0.7–1.1)
Trend test				$P = 0.36$
Ever had X-ray	No	1697	1823	1.0
	Yes	112	127	1.0 (0.8–1.3)
Pelvimetric X-ray	No	1749	1891	1.0
	Yes	55	51	1.2 (0.8–1.7)
T-cell ALL				
Ever had ultrasound	No	71	88	1.0
	Yes	108	108	1.2 (0.7–1.9)
No. of ultrasound examinations	1	52	56	1.0 (0.6–1.8)
	2	34	27	1.5 (0.8–2.8)
	3+	21	24	1.0 (0.4–2.2)
Trend test				$P = 0.59$
Ever had X-ray	No	168	184	1.0
	Yes	13	13	1.0 (0.5–2.3)
Pelvimetric X-ray	No	172	193	1.0
	Yes	8	4	2.2 (0.6–7.6)
Early Pre-B Cell ALL				
Ever had ultrasound	No	302	306	1.0
	Yes	568	641	0.9 (0.7–1.1)
No. of ultrasound examinations	1	281	312	0.9 (0.7–1.1)
	2	159	193	0.9 (0.6–1.1)
	3+	127	134	0.9 (0.7–1.3)
Trend test				$P = 0.52$
Ever had X-ray	No	829	889	1.0
	Yes	51	66	0.9 (0.6–1.3)
Pelvimetric X-ray	No	849	923	1.0
	Yes	28	26	1.2 (0.7–2.2)
Pre-B cell ALL				
Ever had ultrasound	No	73	88	1.0
	Yes	153	152	1.2 (0.8–2.0)
No. of ultrasound examinations	1	83	66	1.5 (0.9–2.5)
	2	42	49	1.0 (0.6–1.8)
	3+	27	36	0.9 (0.5–1.8)
Trend test				$P = 0.61$
Ever had X-ray	No	211	225	1.0
	Yes	17	16	1.1 (0.5–2.4)
Pelvimetric X-ray	No	221	233	1.0
	Yes	6	8	0.7 (0.2–2.3)

[a] Adjusted for maternal education, family income, and race. Subjects with missing values in exposure variables or confounders were excluded.

was very little variation in the risk for ALL associated with *in utero* diagnostic X-ray exposure or pelvimetry among subgroups defined by immunophenotype (data not shown). No appreciable differences were found between cases and controls according to the reported history of any ultrasound test during the index pregnancy or in the number of ultrasound tests during the pregnancy.

Postnatal Diagnostic X-Ray Exposures. Mothers of 51% of cases and 39% of controls reported that the index child had been exposed to one or more diagnostic X-rays, excluding dental X-rays (OR, 1.6; 95% CI, 1.4–1.9; Table 3). The elevated ALL risk was more evident for X-ray exposures reported close to the reference date, whereas X-ray exposures >2 years before the reference date were not related to a significantly increased risk of ALL (data not shown). Because many of the early signs and symptoms of ALL could lead physicians to order diagnostic X-rays, we conducted analyses excluding X-ray exposures occurring within 2 years of the reference date. After exclusion of the more recent exposures, diagnostic X-rays were not generally associated with an increased risk of childhood ALL, except for an increase in risk for pre-B cell ALL (OR, 1.7; 95% CI, 1.1–2.7; trend test $P < 0.01$) for children of

Table 3 ORs for ALL associated with postnatal X-ray exposure[a] by immunophenotype and age at diagnosis

Variable	Category	Total OR[b] (95% CI)	1–5 yr OR[b] (95% CI)	6+ yr OR[b] (95% CI)
Total ALL				
Ever X-rayed	Yes	1.1 (0.9–1.2)	1.0 (0.8–1.3)	1.0 (0.8–1.3)
Total no. of X-rays	1–2	0.9 (0.8–1.1)	0.8 (0.6–1.1)	0.9 (0.7–1.3)
	3+	1.2 (1.0–1.6)	1.3 (0.9–1.8)	1.2 (0.9–1.6)
Trend test		$P = 0.19$	$P = 0.57$	$P = 0.36$
Years since last X-ray	2–3yr	1.2 (1.0–1.4)	1.2 (0.9–1.6)	1.1 (0.8–1.5)
	4+yr	1.1 (0.9–1.4)	1.0 (0.6–1.8)	1.0 (0.8–1.3)
T-cell ALL				
Ever X-rayed	Yes	1.1 (0.7–1.7)	1.3 (0.5–3.4)	0.9 (0.5–1.6)
Total no. of X-rays	1–2	1.0 (0.6–1.9)	1.0 (0.3–3.2)	0.8 (0.3–2.0)
	3+	1.0 (0.5–1.9)	3.2 (0.5–19.2)	0.7 (0.3–1.6)
Trend test		$P = 0.94$	$P = 0.38$	$P = 0.48$
Years since last X-ray	2–3yr	1.2 (0.7–2.3)	1.4 (0.5–4.6)	1.0 (0.4–2.3)
	4+yr	1.1 (0.6–1.9)	2.1 (0.4–10.1)	0.9 (0.5–1.6)
Early Pre-B cell ALL				
Ever X-rayed	Yes	1.1 (0.8–1.3)	1.2 (0.9–1.7)	0.8 (0.5–1.1)
Total no. of X-rays	1–2	0.9 (0.7–1.3)	0.9 (0.6–1.4)	0.7 (0.4–1.1)
	3+	1.2 (0.9–1.7)	1.6 (1.0–2.7)	0.9 (0.5–1.4)
Trend test		$P = 0.55$	$P = 0.21$	$P = 0.40$
Years since last X-ray	2–3yr	1.2 (0.9–1.5)	1.4 (1.0–2.1)	0.8 (0.5–1.3)
	4+yr	1.0 (0.7–1.5)	1.8 (0.7–4.4)	0.7 (0.4–1.1)
Pre-B cell ALL				
Ever X-rayed	Yes	1.7 (1.1–2.7)	1.4 (0.7–2.9)	2.1 (1.0–4.2)
Total no. of X-rays	1–2	1.5 (0.8–2.6)	1.2 (0.5–2.9)	1.7 (0.7–4.2)
	3+	3.2 (1.5–7.2)	2.8 (0.8–9.7)	3.8 (1.1–13.3)
Trend test		$P < 0.01$	$P = 0.08$	$P = 0.01$
Years since last X-ray	2–3yr	2.1 (1.1–4.0)	2.0 (0.8–4.5)	4.5 (1.2–16.4)
	4+yr	1.5 (0.8–2.9)	0.5 (0.1–3.0)	1.5 (0.7–3.3)

[a] Excludes X-rays taken during 2 years before diagnosis (cases) or reference date (controls), children <1 year of age, and subjects with missing values in exposure variables or confounders.
[b] Adjusted for maternal education, family income, and race.

Table 4 ORs for ALL associated with maternal lower abdominal X-ray exposure before conception[a]

	Category	Case	Control	OR[b] (95% CI)
Total ALL				
Ever X-rayed, lower abdomen	No	1689	1815	1.0
	Yes	122	151	0.9 (0.8–1.2)
Total no. of X-rays	1–2	74	89	0.8 (0.6–1.1)
	3+	47	62	0.8 (0.5–1.2)
Trend test				$P = 0.10$
T-cell ALL				
Ever X-rayed, lower abdomen	No	168	187	1.0
	Yes	13	11	1.2 (0.7–2.1)
Total no. of X-rays	1–2	2	4	0.4 (0.1–2.5)
	3+	11	7	1.8 (0.7–4.9)
Trend test				$P = 0.40$
Early Pre-B cell ALL				
Ever X-rayed, lower abdomen	No	826	878	1.0
	Yes	55	81	0.8 (0.6–1.1)
Total no. of X-rays	1–2	36	45	0.7 (0.5–1.2)
	3+	19	36	0.5 (0.3–1.0)
Trend test				$P = 0.02$
Pre-B cell ALL				
Ever X-rayed, lower abdomen	No	215	232	1.0
	Yes	12	13	1.0 (0.6–1.8)
Total no. of X-rays	1–2	8	6	1.2 (0.4–3.5)
	3+	4	7	0.7 (0.2–2.3)
Trend test				$P = 0.68$

[a] Refers to 2-year period before the index pregnancy.
[b] Adjusted for maternal education, family income, and race. Subjects with missing values in exposure variables or confounders were excluded.

all age groups combined. This finding primarily reflected an elevated risk among those diagnosed at ages 6–14 years (OR, 2.1; 95% CI, 1.0–4.2). Among children in this age group, risks were higher among those children who received more diagnostic X-ray tests and for those whose exposures occurred earlier in calendar year time.

Parental Preconception X-ray Exposures. Neither maternal nor paternal preconception diagnostic X-ray exposure to the lower abdomen were associated with risk of childhood ALL, all types combined, or specific subtypes (Tables 4 and 5). There was also no evidence of increasing risk of total or subtypes of childhood ALL in relation to increasing number of diagnostic X-rays to the lower abdomen.

Discussion

Overall, the results for *in utero* prenatal, lower abdominal preconception, and all anatomical site postnatal diagnostic X-ray exposures in relation to risk childhood ALL (including all types combined and immunophenotypically defined subtypes) were generally reassuring. We also found no association between ultrasound tests during pregnancy and risk of ALL among children <15 years of age, consistent with the lack of relationship seen in earlier studies (36, 47–49).

In utero X-ray exposures have been linked previously with small increases in risk (estimated relative risks ranging from 1.1 to 2.0, with most of the risk ratios equal to or lower than 1.6) in most case-control studies (9, 10, 20–22, 25–27, 29–33, 35, 36). However, cohort investigations in the United Kingdom (17) and the United States (18) reported no increase in risk of childhood leukemia linked with maternal pelvimetry during pregnancy. In addition, risks of leukemia were not increased among offspring of Japanese atomic bomb survivors who were pregnant at the time of the bombings (16).

In contrast with the findings from the present investigation, two large earlier studies described small excesses of leukemia diagnosed in younger children linked with *in utero* diagnostic X-rays but reported no increase in risk of leukemia among older children (14, 20). Alternative explanations for the elevated risk of leukemia among children diagnosed at ages 11–14 in our study (and the other subgroup- or subtype-specific associations) include a true causal association, chance, and bias. We observed a decline in the proportion of mothers undergoing pelvimetry with increasing recency of calendar year of birth of study subjects. Risks of childhood leukemia also declined between earlier and later birth cohorts in several other countries and/or time periods [*e.g.*, between 1936–1959 and 1960–1967 in Sweden (33), between 1940–1956 and 1957–1969 in the United Kingdom (13), and between 1947–1957 and 1958–1960 in the northeast United States (14)]. Nevertheless, in contrast with the decline in risk seen after 1980 in the present study, risks decreased beginning in the late 1950s in the three earlier studies (13, 14, 33).

We found small increases in risk of pre-B cell ALL linked with postnatal exposures. Because our study is one of the first to evaluate risks of childhood ALL according to immunophenotype, direct comparisons with earlier investigations are difficult, particularly because earlier United States studies did not report risks separately for ALL *versus* acute myelogenous leukemia or for subtypes of ALL. Similar to our findings for pre-B ALL, childhood leukemia subse-

Table 5 ORs for ALL associated with paternal lower abdominal X-ray exposure before conception[a]

	Category	Case	Control	OR[b] (95% CI)
Total ALL				
Ever X-rayed, lower abdomen	No	1507	1606	1.0
	Yes	139	137	1.1 (0.8–1.4)
Total no. of X-rays	1–2	73	68	1.2 (0.8–1.6)
	3+	66	69	1.0 (0.7–1.4)
Trend test				$P = 0.69$
T-cell ALL				
Ever X-rayed, lower abdomen	No	148	157	1.0
	Yes	14	12	1.3 (0.5–3.0)
Total no. of X-rays	1–2	7	5	1.5 (0.4–5.1)
	3+	7	7	1.1 (0.4–3.4)
Trend test				$P = 0.69$
Early Pre-B cell ALL				
Ever X-rayed, lower abdomen	No	743	776	1.0
	Yes	67	62	1.2 (0.8–1.7)
Total no. of X-rays	1–2	36	26	1.5 (0.9–2.5)
	3+	31	36	0.9 (0.6–1.5)
Trend test				$P = 0.77$
Pre-B cell ALL				
Ever X-rayed, lower abdomen	No	185	196	1.0
	Yes	20	21	0.9 (0.5–1.8)
Total no. of X-rays	1–2	11	11	1.0 (0.4–2.4)
	3+	9	10	0.9 (0.3–2.3)
Trend test				$P = 0.80$

[a] Refers to 2-year period before the index pregnancy.
[b] Obtained from unconditional logistic regression analysis adjusted for paternal education, family income, race, age, and sex of index child. Subjects with a surrogate interview or missing values in exposure variable or confounders were excluded.

quent to postnatal diagnostic X-ray exposures of children in the United States and United Kingdom were elevated, ranging from 1.1 to 2.1 (10, 20), although the recent interview-based study in Germany found no association between postnatal diagnostic X-ray exposures and risk of childhood leukemia (50).

During the past two decades, the relationship of paternal preconception ionizing radiation exposures with risk of childhood leukemia has been much debated. A report linking the notably elevated risks for leukemia and lymphoma among young people residing in close proximity to the Sellafield nuclear plant with paternal preconception occupational exposures from employment in the nuclear industry (51) was not confirmed in subsequent investigations (52, 53). Studies of children of atomic bomb survivors and of childhood cancer survivors also failed to find an excess of childhood leukemia (54, 55). Previous studies of parental preconception diagnostic X-ray exposure, although limited in number, however, appeared to suggest a small increased risk of leukemia in young children associated with paternal exposure (10, 29, 30, 36). However, a large case-control study conducted in England failed to find an association between paternal preconception X-ray exposure and childhood leukemia, although analysis stratified by age was not conducted (34). In the current study, we found a slightly elevated, but statistically significant, risk of ALL among children diagnosed at <6 years of age in relation to any paternal preconception diagnostic X-ray exposure (data not shown). However, no association was found when exposure was restricted to the lower abdominal X-ray exposure, the more relevant (*e.g.*, gonad) exposure. This suggests that the small and positive association between paternal ever-exposure to preconception X-ray and leukemia risk among young children found in current and previous studies may be caused by factors other than X-ray exposure. Recall bias and underlying medical conditions that were associated with the X-ray exposure are among the possible explanations.

Our study also has other limitations. Perhaps the greatest problem is the absence of validation of the interview data. Differences in the level of participation between case (92%) and control (76.5%) mothers, in the further loss of participation among fathers of subjects (83.4% of the eligible fathers of cases *versus* 67.7% of the eligible fathers of controls), and in socioeconomic status between families of cases *versus* controls suggest the possible effect of selection bias affecting the results. As with many other case-control studies, the effect of potential recall bias is a concern, because all information evaluated in the present analysis was derived from telephone interview. Biases resulted from nondifferential recall based on health status of the index child would further increase with recall interval. This may explain the few positive associations (*in utero* and postnatal X-ray exposure) found in older children because the recall interval for controls and older children was longer than that of cases and young children. The possible effect of nondifferential misclassification of exposure attributable to errors in recall also cannot be excluded. Although such misclassification may lead to an underestimate in risk, it is also possible that this type of misclassification may cause an overestimate (56). The lack of specific radiation dose information, particularly regarding gonad dose for the parental exposure, also introduced exposure misclassification. Finally, the lack of *a priori* hypotheses or data linking a specific immunophenotype of ALL with diagnostic X-ray exposure also suggests that the findings could be attributable to chance as a result of the multiple comparisons.

In summary, the results of this large case-control investigation suggest that ALL is not linked with exposure to ultrasound tests during pregnancy, regardless of the number of such tests. ALL risks do not appear to be linked with diagnostic X-ray exposures among children <11 years of age, and it is unclear if the elevated risks among older children are real or attributable to chance or bias. Although *in utero* diagnostic X-ray exposure has previously been one of the few consistently reported factors linked with 40% elevated risks in earlier studies (11–13), the risks of childhood leukemia associated with this exposure are believed to have declined subsequently, attributable to declining exposures to ionizing radiation related to improvements in radiological techniques and to decreasing use of diagnostic X-rays during pregnancy (6, 21, 57, 58). The latter is most likely related to expanding use of diagnostic ultrasound tests (59). Given the substantial resources that would be required to validate interview data on diagnostic X-ray exposures in the United States for a condition as rare as childhood ALL, it may not be efficient to initiate further United States epidemiological studies to evaluate these exposures. Forthcoming results based on medical records from a large nationwide United Kingdom investigation may shed additional light on the results of the present study. In the absence of biological evidence linking specific immunophenotypes of childhood leukemia with low-level ionizing radiation exposures, further progress in understanding these relationships may require *in vitro* and *in vivo* studies.

APPENDIX

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