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Birth characteristics, maternal reproductive history, hormone use during pregnancy, and risk of childhood acute lymphocytic leukemia by immunophenotype (United States)

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Abstract

Objective: To investigate the associations of birth characteristics and maternal reproductive factors with risk of childhood acute lymphoblastic leukemia (ALL) by immunophenotypic subtypes.

Methods: Data collected from a case–control study including 1842 ALL cases (age <15 years) and 1986 individually matched controls were analyzed. Exposure information was obtained through telephone interviews of parents.

Results: Factors associated with risk of ALL from all subgroups combined included high birth weight (OR = 1.4, 95% CI = 1.1–1.8), high birth order (OR = 2.0, 95% CI = 1.3–3.0 for fourth-born child compared to first-born child), young maternal age (<20 compared to 25–29, OR = 1.4, 95% CI = 1.1–1.9), advanced paternal age (> 39 compared to 25–29, OR = 1.4, 95% CI = 1.0–1.9), induced abortion prior to the index pregnancy (OR = 1.2, 95% CI = 1.0–1.4), and oral contraceptive use during the index pregnancy (OR = 1.5, 95% CI = 1.0–2.2) with children under the age of 2 (OR = 5.1, 95% CI = 1.0–24.7) being the predominantly affected group. Risk of early pre-B-cell ALL increased with advanced paternal age (OR = 1.7, 95% CI = 1.1–2.7) and high birth order (OR = 2.0, 95% CI = 1.1–3.6), while risk of pre-B-cell ALL increased with both younger (OR = 3.4, 95% CI = 1.4–8.4) and advanced maternal age (OR = 2.6, 95% CI = 1.1–5.9). T-cell ALL was associated with high birth weight (OR = 2.4, 95% CI = 1.1–5.5) and history of induced abortion (OR = 2.4, 95% CI = 1.3–4.5).

Conclusion: This study suggests that the association of ALL with birth characteristics and maternal reproductive factors varies with the immunophenotype of the ALL. Future studies are needed to better understand the effect of maternal hormone in the development of subtype of childhood ALL.

Introduction

Acute lymphocytic leukemia (ALL) is the most common childhood malignancy. Increased risk of childhood ALL has been previously linked to birth characteristics and reproductive factors, including high birth weight [1–12], advanced maternal and/or paternal age [7], and history of adverse pregnancy outcomes [3, 7, 8], although the evidence is not entirely consistent [13–17]. First-born children have been found to be at a higher risk of ALL in some studies [2, 11], while other studies have suggested that the risk is greater for later-born children [1, 5, 7]. Recently it has been recognized that childhood ALL is a heterogeneous group of malignancies. Classified by immunophenotype the subtypes of ALL differ markedly in biological features, host characteristics, and response to therapy [18, 19]. It is conceivable that the subtypes may

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also have distinct etiologies. Investigations within subtypes of ALL, however, have generally not been feasible due to the relatively low incidence of the disease. Failure to take into consideration the heterogeneity of ALL might account for some inconsistent findings from early epidemiological studies and, moreover, could hinder the identification of risk factors that may be subtype-specific.

The Children's Cancer Group (CCG) has completed a case–control study including 1842 childhood ALL patients and 1986 matched controls. We present here the results of analyses of birth characteristics and maternal reproductive factors within immunophenotypic subgroups.

Materials and methods

Cases were identified from participating institutions of the CCG [20], one of the two cooperative clinical trials groups that care for about 93% of pediatric cancer patients in the US (about 50% of childhood leukemia cases in the US are cared for by CCG institutes) [21]. Eligible cases had to be newly diagnosed between 1 January, 1989 and 15 June, 1993, and be 14 years of age or younger. There were 120 CCG institutes during the study period and 108 of them participated in the current study. Additional eligibility criteria were a telephone in the patient's residence and availability of the biological mother for a telephone interview. A total of 2081 eligible cases were identified during the study period and telephone interviews with mothers were completed for 1914 cases (92%). Among the 167 non-respondents there were 41 (2.0%) physician refusals, 70 (3.4%) parental refusals, and 18 (0.9%) lost to follow-up after first contact; 38 (1.8%) fell into the miscellaneous category.

The initial diagnosis and assignment of B- or T-lineage was made at the treating CCG institution. A pretreatment bone marrow specimen was required to 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-cell markers and CD19, CD10, and CD24 as B-lineage markers. A computer algorithm was developed to classify cases based on the percent positivity of the bone marrow specimens to each of the monoclonal antibodies. Cases were classified as either T-cell or B-lineage, or as unclassifiable (immunophenotype unavailable). B-lineage leukemias were further characterized as follows: early pre-B ALL (B-lineage markers and cytoplasmic immunoglobulin negative), pre-B ALL (B-lineage markers and cytoplasmic immunoglobulin positive), and B-lineage ALL not otherwise specified (NOS) (B-lineage markers but cytoplasmic immunoglobulin not performed).

Control subjects were randomly selected, using a previously described random-digit dialing procedure [22], and individually matched to cases on 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. Controls for T-cell ALL were also matched to cases on gender because of its higher frequency among males. The first eight digits of a case's telephone number, the area code, the exchange, and the first two digits of the number were used to form a set of telephone numbers with a randomly generated final two digits. Beginning with the first potential control number, a trained interviewer attempted to make contact. The number was called at different times of the day (morning, afternoon, and evening) on at least three different days (one of which fell on a weekend) until one of the following endpoints was achieved: non-working number, non-residential, refusal, eligible (match), not eligible, or no answer after nine attempts. If no control was identified after the nine attempts, the interviewer proceeded to the next potential control telephone number. As with the cases, the biological mother of the control child had to be available for interview and speak English. A total of 2597 eligible controls were identified and a mother's interview was completed for 1987 subjects (76.5%). One control was excluded because his/her matched case was later found to be ineligible for the study. Reasons for non-participation of controls included: parental refusal (n = 457, 17.6%), loss to follow-up (n = 17, 0.7%), and miscellaneous reasons (n = 136, 5.2%). Matched controls could not be found for 72 (3.8%) interviewed cases. After exclusion of these non-matched cases, a total of 1842 case–control pairs (1704 sets matched 1:1, 132 sets matched 1:2, and six sets matched 1:3) remained for statistical analyses. During control selection, there were situations in which the first eligible control was not immediately available for interview, necessitating identification of the next eligible control. Some of the "first controls" were subsequently successfully interviewed, thus resulting in multiple controls per case.

Using structured questionnaires, data were collected by independent telephone interviews with mothers and, whenever available, fathers of cases and controls. The mother's questionnaire included questions relating to demographics, maternal history of disease, medication use, occupation, personal habits, household exposure prior to and during the index pregnancy and birth, reproductive and family medical history, as well as history of disease, medication use, and exposure to environmental hazards (*e.g.* pesticides and insecticides) of the index child. The father's questionnaire focused on medication use, personal habits, household exposures,

occupational history, and family medical history. The father's questionnaire was completed for 1801 of the 2081 eligible cases (86.5%) and 1813 of the 2597 eligible controls (69.8%), resulting in 1618 matched sets. The median interval between diagnosis and interview was 228 days for cases and the median interval between case interview and control interview was 292 days.

Information collected on birth-related characteristics included birth weight, gestational age, birth order, and parental age at the time of the index birth. Maternal reproductive history included birth outcomes for all pregnancies, oral contraceptive use, and other birth control methods used during the year before the index pregnancy. Information was also collected on hormone use during pregnancy and fertility issues prior to the index pregnancy, including the length of time respondents attempted to achieve a pregnancy and whether advice or treatment for infertility was sought.

Data were first analyzed by all subtypes combined, then stratified by immunophenotype and age at diagnosis (<2, 2–5, 6–10, 11–14 years). Odds ratios (ORs), as approximations of relative risk, were used to measure the association between each factor studied and risk. Conditional logistic regression was employed in the data analyses to obtain ORs and 95% confidence intervals (CIs), after adjusting for potential confounders [23]. Test of linear trend was conducted by treating a categorical variable as a continuous one in the logistic regression model.

Results

Demographic characteristics (Table 1)

Of the 1842 cases included in the analysis, early pre-B-cell leukemia (48.5%) was the most common subtype, followed by pre-B-cell (12.6%) and T-cell leukemia (9.9%). There were 231 B-cell cases (12.5%) who had insufficient information to be classified as either early pre-B or pre-B cell type. Immunophenotype was unavailable for 302 ALL cases (16.4%). Due to the heterogeneity of the last two groups, they were not included in the immunophenotypic analyses.

Table 1. Demographic characteristics of cases and controls

	Total ALL (%)		T-cell (%)		Early pre-B-cell (%)		Pre-B-cell (%)	
	Case (n = 1842)	Control (n = 1986)	Case (n = 183)	Control (n = 199)	Case (n = 893)	Control (n = 970)	Case (n = 233)	Control (n = 246)
Age at diagnosis								
<12 months	3.5	4.1	1.1	3.0	3.8	4.3	3.4	5.7
12–23 months	7.5	9.5	4.4	5.0	7.3	8.5	9.0	13.0
2–5 years	55.4	52.3	36.1	33.2	58.7	57.3	57.1	50.0
6–10 years	22.2	23.5	32.8	38.2	20.5	20.4	24.0	24.0
11+ years	11.5	10.7	25.7	20.6	9.7	9.5	6.4	7.3
Chi-square	$p = 0.07$		$p = 0.42$		$p = 0.89$		$p = 0.37$	
Gender								
Boys	55.3	52.5	75.4	67.8	52.7	52.8	51.9	50.8
Girls	44.7	45.9	24.6	32.2	47.3	47.2	48.1	49.2
	$p = 0.50$		$p = 0.10$		$p = 0.99$		$p = 0.80$	
Family income								
<$20,000	33.0	27.5	33.3	33.2	32.9	24.7	34.3	29.7
$20,000–39,000	41.6	42.5	50.8	38.2	39.8	44.2	36.5	45.1
$40,000+	25.4	30.0	15.8	28.6	27.3	31.0	29.2	25.2
Chi-square	$p < 0.01$		$p < 0.01$		$p < 0.01$		$p = 0.16$	
Mother's education								
≤High school	43.3	38.4	43.2	42.2	45.1	38.7	43.8	42.7
>High school	32.1	35.3	35.3	29.1	30.2	34.5	29.2	33.7
College+	24.6	26.3	21.3	28.6	24.6	26.8	27.0	23.6
Chi-square	$p < 0.01$		$p = 0.20$		$p < 0.05$		$p = 0.50$	
Mother's race								
White	83.8	88.9	83.6	88.4	85.1	90.0	80.3	85.0
Non-white	16.2	11.1	16.4	11.6	14.9	10.0	19.7	15.0
Chi-square	$p < 0.01$		$p = 0.17$		$p < 0.01$		$p = 0.17$	

Fifty-nine percent of patients diagnosed with T-cell ALL were between the ages of 6 and 14 years. B-cell disease was more common in younger children, with 70% of both early pre-B-cell and pre-B-cell ALL occurring among children under the age of 6. There was a slight excess of boys among both case and control groups (55.3% for cases and 52.5% for controls). However, the gender distribution among cases and controls was similar for all study participants or for immunophenotype specific subgroups.

Compared to controls, cases were more likely to have a lower family income and a lower level of maternal education, and to be non-white, with a statistically significant difference observed for early pre-B-cell and T-cell ALL (family income only) (Table 1). Mothers of pre-B-cell cases, however, had a slightly, but not significantly, higher level of education than mothers of controls. To control for the socioeconomic disparity between cases and controls we adjusted for maternal race, education, and household income throughout the following analyses.

Birth characteristics (Table 2)

Young maternal age (< 20 years old) was associated with risk of all types of ALL combined (OR = 1.4, 95% CI = 1.1–1.9), and pre-B-cell ALL (OR = 3.4, 94% CI = 1.4–8.4), while advanced maternal age (≥35) was also related to an increased risk of pre-B-cell ALL (OR = 2.6, 95% CI = 1.1–5.9). The effect of maternal age did not vary with age at diagnosis of leukemia (data not shown). There were 28 cases and five controls with Down's syndrome in this study. Further adjustment for Down's syndrome did not alter the association between maternal age and ALL risk. We did not find that gestational age is associated with the risk of ALL (data not shown).

After adjusting for maternal age, advanced paternal age was associated with an elevated risk of total ALL (OR = 1.4, 95% CI = 1.0–1.9) and of early pre-B-cell ALL (OR = 1.7, 95% CI = 1.1–2.7).

Children with birth order of fourth or higher were more prevalent among cases than among controls (OR = 1.2, 95% CI = 0.9–1.6). The elevated risk among high birth order children was more evident and reached statistical significance after adjusting for the number of live births (OR = 2.0, 95% CI = 1.3–3.0 for fourth birth compared to the first). The increased risk was mainly accounted for by the early pre-B-cell subtype, in which a dose–response relationship was observed (trend test $p = 0.01$).

Risk was significantly elevated among children weighing more that 4000 g at birth, compared to those weighing 3000 g or less (OR = 1.4, 95% CI = 1.1–1.8). The association was most pronounced, and only statistically significant, for T-cell ALL (OR = 2.4, 95% CI = 1.1–5.5); upon stratification by age at diagnosis this association remained only for children diagnosed at ages greater than 5 years. We did not find that gender modifies the birth weight effect, nor did it confer a confounding effect. In contrast, the risk of B-cell ALL was not significantly related to birth weight at any age (data not shown).

Birth control and hormone use (Table 3)

Compared to mothers of control children, mothers of cases were slightly more likely to have used birth control during the year before the index pregnancy (OR = 1.2, 95% CI = 1.0–1.3), with the elevation being significant for use of oral contraceptive (OR = 1.2) and the rhythm method (OR = 1.2). More case than control mothers reported a history of oral contraceptive use during the index pregnancy (OR = 1.5, 95% CI = 1.0–2.2); the excess was predominantly found among mothers of cases diagnosed before the age of 2 (OR = 5.1, 95% CI = 1.0–24.7). The association between oral contraceptive use during pregnancy and ALL risk was most pronounced for T-cell ALL (OR = 3.6, 95% CI = 0.9–13.7). Hormone use other than birth control pills, either in the year before or during the index pregnancy, was not associated with an elevated risk of ALL.

No significant difference was found between cases and controls in the following categories: the index pregnancy was planned, length of time spent trying to become pregnant, and whether the respondent sought medical help for conception (data not shown).

Maternal reproductive history (Table 4)

Mothers of cases of all subtypes combined, and control mothers, did not differ appreciably in the total number of live births, miscarriages, abortions, or stillbirths (data not shown). Analyses stratified by age at diagnosis, however, revealed that a maternal history of miscarriage prior to the index pregnancy was related to a significantly increased risk of ALL among very young children (≤2 years of age, OR = 1.9, 95% CI = 1.1–3.2), although the risk was not correlated to the number of miscarriages (data not shown). Immunophenotypic analyses revealed that mothers of T-cell cases were more likely to have had a history of induced abortion (OR = 2.4, 95% CI = 1.3–4.5, and OR = 2.2, 95% CI = 1.1–4.3, for ever having an abortion and abortion prior to index pregnancy, respectively) than mothers of controls.

Table 2. Odds ratios of childhood ALL associated with birth characteristics

	Total ALL			T-cell ALL			Early pre-B-cell ALL			Pre-B-cell ALL		
	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)	Cases	Controls	OR (95% CI)
Maternal age[a]												
<20	159	117	1.4 (1.1–1.9)	15	13	1.0 (0.4–2.3)	69	67	1.0 (0.6–1.4)	22	9	3.4 (1.4–8.4)
20–24	478	529	1.0 (0.8–1.1)	48	66	0.6 (0.4–1.0)	234	258	0.9 (0.7–1.2)	58	61	1.3 (0.8–2.2)
25–29	649	728	1.0 (ref.)	65	66	1.0 (ref.)	315	347	1.0 (ref.)	78	92	1.0 (ref.)
30–34	408	470	1.0 (0.9–1.2)	41	43	1.1 (0.6–2.0)	201	222	1.0 (0.8–1.3)	49	71	0.9 (0.5–1.4)
35/over	148	142	1.2 (0.9–1.6)	14	11	2.0 (0.7–5.2)	74	76	1.0 (0.7–1.2)	26	13	2.6 (1.1–5.9)
Paternal age[b]												
<25	370	347	1.2 (1.0–1.4)	32	34	1.0 (0.6–2.0)	191	169	1.3 (1.0–1.6)	47	36	1.6 (0.9–2.9)
25–29	565	603	1.0 (ref.)	60	61	1.0 (ref.)	276	296	1.0 (ref.)	70	76	1.0 (ref.)
30–34	489	541	1.1 (0.9–1.3)	48	52	1.3 (0.7–2.2)	230	251	1.2 (0.9–1.5)	61	80	0.8 (0.5–1.3)
35–39	194	233	1.0 (0.8–1.3)	23	19	2.1 (0.9–4.6)	98	125	1.0 (0.8–1.4)	19	22	0.8 (0.4–1.7)
40/over	102	84	1.4 (1.0–1.9)	6	7	1.2 (0.4–4.1)	55	37	1.7 (1.1–2.7)	17	11	1.7 (0.7–3.9)
Birth order[c]												
1st	772	865	1.0 (ref.)	70	95	1.0 (ref.)	384	422	1.0 (ref.)	92	99	1.0 (ref.)
2nd	674	688	1.3 (1.1–1.6)	60	62	1.3 (0.7–2.3)	322	328	1.3 (1.0–1.6)	100	87	1.9 (1.1–3.3)
3rd	251	298	1.5 (1.2–2.0)	37	26	1.7 (0.7–4.4)	118	153	1.5 (1.0–2.2)	24	42	1.2 (0.5–2.9)
4th/over	145	135	2.0 (1.3–3.0)	16	16	1.4 (0.4–4.9)	69	67	2.0 (1.1–3.6)	17	18	1.1 (0.3–4.0)
Trend test			$p < 0.01$			$p = 0.36$			$p = 0.01$			$p = 0.31$
Birth weight[b]												
≤3000 g	326	376	1.0 (ref.)	30	38	1.0 (ref.)	156	185	1.0 (ref.)	41	46	1.0 (ref.)
3001–3500 g	628	685	1.9 (0.9–1.3)	66	77	1.2 (0.6–2.3)	311	333	1.1 (0.8–1.4)	85	85	1.2 (0.7–2.2)
3501–4000 g	607	680	1.1 (0.9–1.4)	54	64	1.2 (0.6–2.3)	291	324	1.0 (0.8–1.4)	77	91	1.1 (0.6–2.0)
>4000 g	278	244	1.4 (1.1–1.8)	33	20	2.4 (1.1–5.5)	133	128	1.3 (0.9–1.8)	29	24	1.6 (0.8–3.4)
Trend test			$p < 0.01$			$p = 0.06$			$p = 0.16$			$p = 0.41$

[a] OR adjusted for mother's education, race, and family income.
[b] OR adjusted for maternal age, education, race, and family income.
[c] OR adjusted for maternal age, education, race, family income, and number of live births.

Table 3. Odds ratios of childhood ALL associated with maternal birth control and hormone use during 1 year before pregnancy and during pregnancy.

	Total ALL			T-cell ALL			Early pre-B-cell ALL			Pre-B-cell ALL		
	Cases	Controls	OR[a] (95% CI)	Cases	Controls	OR[a] (95% CI)	Cases	Controls	OR[a] (95% CI)	Cases	Controls	OR[a] (95% CI)
Any birth control 1 year prior to pregnancy												
No	751	835	1.0 (ref.)	67	83	1.0 (ref.)	375	421	1.0 (ref.)	99	97	1.0 (ref.)
Yes	1080	1138	1.2 (1.0–1.3)	100	99	1.4 (0.9–2.2)	535	565	1.2 (1.0–1.4)	138	151	1.1 (0.7–1.7)
Methods of birth control												
Oral contraceptive use	562	570	1.2 (1.0–1.4)	48	52	1.3 (0.7–2.4)	272	262	1.3 (1.0–1.6)	70	74	1.1 (0.7–1.8)
Jelly, cream, foam	243	260	1.1 (0.9–1.4)	20	21	1.3 (0.6–3.0)	114	130	1.0 (0.8–1.4)	32	29	1.4 (0.7–2.8)
Intrauterine device	57	58	1.1 (0.8–1.7)	6	9	0.7 (0.2–2.5)	24	29	0.9 (0.5–1.6)	6	9	0.8 (0.3–2.5)
Diaphragm, condom	477	490	1.2 (0.8–1.7)	43	38	1.2 (0.4–3.9)	246	246	1.4 (0.8–2.3)	64	62	0.7 (0.3–2.0)
Rhythm method	68	69	1.2 (1.0–1.4)	7	10	1.5 (0.8–2.7)	38	33	1.2 (1.0–1.6)	7	11	1.3 (0.8–2.2)
Other	52	59	1.1 (0.7–1.6)	4	0		29	31	1.1 (0.7–2.0)	6	11	0.7 (0.2–1.9)
Oral contraceptive use during pregnancy	71	55	1.5 (1.0–2.2)	7	4	3.6 (0.9–13.7)	30	27	1.4 (0.8–2.4)	10	8	1.3 (0.5–3.6)
Hormone use other than oral contraceptives	84	89	1.0 (0.8–1.4)	5	5	1.5 (0.4–5.9)	39	41	1.0 (0.7–1.6)	9	5	2.5 (0.8–8.4)
Hormones other than oral contraceptive use during pregnancy	40	47	0.9 (0.6–1.5)	3	2	1.8 (0.2–13.1)	20	20	1.0 (0.5–1.9)	5	3	3.2 (0.7–15.0)

[a] OR adjusted for mother's education, race, age, and family income.

Table 4. Odds ratios of childhood ALL associated with maternal reproductive history

	Total ALL			T-cell ALL			Early pre-B-cell ALL			Pre-B-cell ALL		
	Cases	Controls	OR[a] (95% CI)	Cases	Controls	OR[a] (95% CI)	Cases	Controls	OR[a] (95% CI)	Cases	Controls	OR[a] (95% CI)
Parity												
1	290	271	1.0	22	27	1.0	134	121	1.0	41	34	1.0
2	807	850	0.9 (0.8–1.1)	63	85	1.0 (0.5–2.2)	415	412	0.9 (0.7–1.2)	105	104	0.8 (0.5–1.4)
3	452	540	0.8 (0.6–1.0)	60	53	1.4 (0.7–3.1)	205	270	0.7 (0.5–0.9)	51	69	0.7 (0.4–1.2)
4	188	228	0.8 (0.6–1.0)	27	25	1.2 (0.5–2.9)	89	119	0.6 (0.4–0.9)	23	30	0.7 (0.3–1.4)
5/over	105	97	1.0 (0.7–1.4)	11	9	1.6 (0.5–5.1)	50	48	0.9 (0.5–1.4)	13	9	1.1 (0.4–3.4)
Trend test			$p = 0.24$			$p = 0.49$			$p = 0.27$			$p = 0.18$
Miscarriage prior to index pregnancy												
Never	1446	1590	1.0	141	165	1.0	706	776	1.0	181	196	1.0
Ever	396	396	1.1 (1.0–1.3)	42	34	1.8 (1.0–3.3)	187	194	1.0 (0.8–1.3)	52	50	1.2 (0.8–1.9)
1	308	306	1.1 (1.0–1.4)	33	27	1.9 (1.0–3.6)	143	145	1.1 (0.8–1.4)	42	42	1.1 (0.7–1.9)
2/over	88	90	1.1 (0.8–1.5)	9	7	1.6 (0.5–4.8)	44	49	1.0 (0.6–1.5)	10	8	1.7 (0.6–4.9)
Trend test			$p = 0.15$			$p = 0.11$			$p = 0.85$			$p = 0.34$
Induced abortion prior to index pregnancy												
Never	1536	1694	1.0	150	176	1.0	739	823	1.0	199	214	1.0
Ever	306	292	1.2 (1.0–1.4)	33	23	2.2 (1.1–4.3)	154	147	1.2 (0.9–1.5)	34	32	1.3 (0.8–2.4)
1	236	223	1.2 (1.0–1.5)	28	19	2.1 (1.0–4.3)	120	112	1.2 (0.9–1.6)	23	21	1.3 (0.7–2.6)
2/over	70	69	1.1 (0.8–1.6)	5	4	1.2 (0.3–5.2)	34	35	1.0 (0.6–1.7)	11	11	1.4 (0.5–3.7)
Trend test			$p = 0.10$			$p = 0.11$			$p = 0.40$			$p = 0.35$
Stillbirth prior to index pregnancy												
Never	1816	1959	1.0	181	197	1.0	879	960	1.0	229	241	1.0
Ever	26	27	1.0 (0.6–1.8)	2	2	0.7 (0.1–6.3)	14	10	1.8 (0.8–4.2)	4	5	0.6 (0.1–2.7)

[a] OR adjusted for maternal age, education, race, and family income.

Discussion

Although many epidemiologic studies have examined the associations between birth-related characteristics and risk of childhood ALL, the current study is one of only two that have taken into account the heterogeneity of ALL when assessing risk. In the other study, Buckley *et al.* reported that high birth weight was related to the risk of common ALL and advanced maternal age was related to the risk of T-cell ALL [1]. In the current larger and more comprehensive study we found that associations between birth characteristics and ALL risk varied with the immunophenotype. For example, advanced paternal age and high birth order were associated with the early pre-B-cell subtype, while both young and advanced maternal age at birth were related to an elevated risk of pre-B-cell ALL; high birth weight and maternal history of induced abortion (ever or prior to index pregnancy) were associated with the risk of T-cell ALL.

The bimodal association between maternal age and risk of pre-B-cell ALL risk has not been previously reported; it is reminiscent of the association between Down's syndrome and maternal age [24]. While such a conjecture would be purely speculative, it could be that children born to very young mothers and those born to older mothers are exposed to similar conditions (*e.g.* hormonal imbalances and/or inadequate nutrition) *in utero* that might account for these interesting associations. Clearly, additional epidemiologic and biologic research studies are warranted.

In 1985 Van Steensel-Moll *et al.* reported that maternal hormone use, including oral contraceptives prior to conception, and history of infertility were associated with an increased risk of childhood leukemia [3]. In contrast, we failed to find any associations with maternal history of infertility, length of time spent trying to get pregnant, or use of hormones during the year prior to the index pregnancy. We did find, however, that maternal use of oral contraceptives during the index pregnancy was associated with an elevated risk of ALL, mainly in young children. We carefully examined the data on oral contraceptive use during the index pregnancy and found that users were younger and had lower family income and lower education than non-users, although they were not differentiated by case–control status. Women who used oral contraceptives, however, did not differ from non-users in lifestyle factors, such as smoking and drinking (data not shown). We adjusted for maternal age, education, and family income in the analyses to control for the effect of socioeconomic status. Although the nature of this association is unknown, our finding appears to suggest that early *in-utero* exposure to high doses of hormone may be associated with an increased risk of ALL. *In-utero* exposure to exogenous estrogen, *e.g.* diethylstilbestrol (DES) has been found to cause cancers among both male and female offspring [25]. Oral contraceptive use during pregnancy has also been associated with an increased risk of germ-cell tumor among young adults [26, 27]. Further studies are needed to confirm this hypothesis. Alternatively, our finding may indicate that a woman's response to hormonal stimulation is related to the risk of ALL in her offspring.

Consistent with most early epidemiologic studies [1–7, 9–12], we found a positive association between high birth weight and risk of both T-cell ALL and all types of ALL combined. In contrast to studies that noted this association only among young children [5, 7, 9, 10], we found that the association did not vary with age at diagnosis except in the case of T-cell ALL, where the effect was confined to older children. A number of mechanisms have been proposed recently to explain the birth weight–ALL association. The hypothesis that an increased volume of precursor cells results from a high birth weight [2] suggests a causality, while the insulin-like growth factor-1 hypothesis suggests that high birth weight is an epiphenomenon of increased growth factor stimulation or even a consequence of ALL [28]. We propose here another hypothesis; namely, that *in-utero* exposure to high endogenous estrogen levels, one of the important predictors of birth weight [29], is involved in the etiology of childhood ALL.

Consistent with early studies [7, 8, 11], we found that maternal history of miscarriage was related to risk of all types of ALL combined among very young children (age <2 years), suggesting that common exposure(s) during pregnancy may account for both miscarriage and ALL in offspring. The association between T-cell ALL in older children and a maternal history of induced abortion has not previously been reported and needs to be confirmed in other studies.

It should be kept in mind that our study has a few limitations. First, most of the risk estimates found in this study were moderate. Given the large number of statistical analyses conducted, some of the findings might be chance findings resulting from multiple comparisons. Second, all the exposure information was self-reported and was subjective to recall biases. However, earlier studies have suggested that mothers can quite reliably recall the birth characteristics and reproductive history [30, 31]. Last, some of the observed associations, such as birth order, may reflect a potential selection bias due to the source of control subjects (random-digit dialing) and different participation rates among control and case subjects. The difference between case and control subjects in maternal education and family income may also suggest the possibility of selection

bias. The immunophenotypic specific associations found in this study, however, suggested that selection bias is probably not the sole explanation.

In summary, we found that birth characteristics and maternal reproductive factors were related to subgroups of leukemia as determined by immunophenotype. Involvement of hormonal factors in the development of childhood ALL has repeatedly been implicated, and needs to be further studied in other populations.

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Appendix: Participating principal investigators – Children's Cancer Group

Institution	Investigators	Grant no.
Group Operations Center Arcadia, California	W. Archie Bleyer, MD, Anita Khayat, PhD, Harland Sather, PhD, Mark Krailo, PhD, Jonathan Buckley, MBBS, PhD, Daniel Stram, PhD, Richard Sposto, PhD	CA 13539
University of Michigan Medical Center Ann Arbor, Michigan	Raymond Hutchinson, MD	CA 02971
University of California Medical Center San Francisco, California	Katherine Matthay, MD	CA 17829
University of Wisconsin Hospital Madison, Wisconsin	Diane Puccetti, MD	CA 05436
Children's Hospital and Medical Center Seattle, Washington	J. Russell Geyer, MD	CA 10382
Rainbow Babies and Children's Hospital Cleveland, Ohio	Susan Shurin, MD	CA 20320
Children's National Medical Center Washington, D.C.	Gregory Reaman, MD	CA 03888
Childrens Hospital Los Angeles Los Angeles, California	Paul Gaynon, MD	CA 02649
Children's Hospital of Columbus Columbus, Ohio	Frederick Ruymann, MD	CA 03750
Columbia Presbyterian College of Physicians and Surgeons New York, New York	Leonard J. Wexler, MD	CA 03526
Children's Hospital of Pittsburgh Pittsburgh, Pennsylvania	A. Kim Ritchey, MD	CA 36015
Vanderbilt University School of Medicine Nashville, Tennessee	John Lukens, MD	CA 26270
Doernbecher Memorial Hospital for Children Portland, Oregon	H. Stacy Nicholson, MD	CA 26044
University of Minnesota Health Sciences Center Minneapolis, Minnesota	Joseph P. Neglia, MD	CA 07306
Children's Hospital of Philadelphia Philadelphia, Pennsylvania	Beverly Lange, MD	CA 11796
Memorial Sloan-Kettering Cancer Center New York, New York	Peter Steinherz, MD	CA 42764
James Whitcomb Riley Hospital for Children Indianapolis, Indiana	Philip Breitfeld, MD	CA 13809
University of Utah Medical Center Salt Lake City, Utah	William Carroll, MD	CA 10198
University of British Columbia Vancouver, Canada	Christopher Fryer, MD	CA 29013
Children's Hospital Medical Center Cinninnati, Ohio	Robert Wells, MD	CA 26126
Harbor/UCLA and Miller Children's Medical Center Torrance/Long Beach, California	Jerry Finklestein, MD	CA 14560
University of California Medical Center (UCLA) Los Angeles, California	Stephen Feig, MD	CA 27678

Appendix. (Continued)

Institution	Investigators	Grant no.
University of Iowa Hospitals and Clinics Iowa City, Iowa	Raymond Tannous, MD	CA 29314
Children's Hospital of Denver Denver, Colorado	Lorrie Odom, MD	CA 28851
Mayo Clinic and Foundation Rochester, Minnesota	Gerald Gilchrist, MD	CA 28882
Izaak Walton Killam Hospital for Children Halifax, Canada	Dorothy Barnard, MD	–
University of North Carolina Chapel Hill, North Carolina	Stuart Gold, MD	–
Children's Mercy Hospital Kansas City, Missouri	Maxine Hetherington, MD	–
University of Nebraska Medical Center Omaha, Nebraska	Peter Coccia, MD	–
Wyler Children's Hospital Chicago, Illinois	James Nachman, MD	–
MD. Anderson Cancer Center Houston, Texas	Beverly Raney, MD	–
Princess Margaret Hospital Perth, Western Australia	David Baker, MD	–
New York University Medical Center New York, New York	Aaron Rausen, MD	–
Children's Hospital of Orange County Orange, California	Violet Shen, MD	–

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