Title

Cesarean Section and Risk of Childhood Acute Lymphoblastic Leukemia in a Population-Based, Record-Linkage Study in California

Journal

American Journal of Epidemiology, 185(2)

ISSN

0002-9262

Authors

Wang, Rong
Wiemels, Joseph L
Metayer, Catherine
et al.

Publication Date

2017-01-15

DOI

10.1093/aje/kww153

Peer reviewed

American Journal of Epidemiology

Vol. 185, No. 2
DOI: 10.1093/aje/kww153
Advance Access publication:
December 16, 2016

Original Contribution

Cesarean Section and Risk of Childhood Acute Lymphoblastic Leukemia in a Population-Based, Record-Linkage Study in California

Rong Wang, Joseph L. Wiemels, Catherine Metayer, Libby Morimoto, Stephen S. Francis, Nina Kadan-Lottick, Andrew T. DeWan, Yawei Zhang, and Xiaomei Ma*

* Correspondence to Dr. Xiaomei Ma, Yale School of Public Health, P.O. Box 208034, 60 College Street, New Haven, CT 06520-8034, United States (e-mail: xiaomei.ma@yale.edu).

Initially submitted March 18, 2016; accepted for publication July 11, 2016.

The relationship of mode of delivery to risk of childhood acute lymphoblastic leukemia (ALL) is uncertain. After linking birth records and cancer registry data from California, we conducted a population-based case-control study to investigate the role of delivery by cesarean section (C-section) in the etiology of childhood ALL. This study included 5,081 cases and 18,927 matched controls born in 1978–2009; more detailed data were available on type of C-section (i.e., elective vs. emergency) for a subset of 1,552 cases and 5,688 controls. No association was observed between C-section overall and childhood ALL risk (<15 years of age), but elective C-section was associated with a significantly elevated risk of ALL (odds ratio (OR) = 1.17, 95% confidence interval (CI): 1.01, 1.36). At the peak ages of ALL incidence (2–4 years), C-section was associated with an 11% higher risk of ALL (OR = 1.11, 95% CI: 1.01, 1.22) compared with vaginal delivery, and the magnitude of the association was larger for elective C-section (OR = 1.38, 95% CI: 1.11, 1.70). Emergency C-section was not associated with childhood ALL. Because of design features minimizing nonparticipation and inaccurate recall, this record linkage–based study is less prone to bias. Our results suggest that delivery by elective C-section was associated with a higher risk of childhood ALL, especially at the peak ages of incidence. It is important to evaluate possible mechanisms, because this potential risk factor is modifiable.

acute lymphoblastic leukemia; case-control studies; cesarean section; child; leukemia; microbiome

Abbreviations: ALL, acute lymphoblastic leukemia; C-section, cesarean section; CCR, California Cancer Registry; CI, confidence interval; OR, odds ratio.

In the United States, acute lymphoblastic leukemia (ALL) accounts for one-fourth of all cancers diagnosed in children <15 years of age (1), with a sharp incidence peak at ages 2–4 years across all racial/ethnic groups (2). A similar incidence peak has been observed in other industrialized nations but not in developing countries (3), which has engendered the "delayed infection" hypothesis proposed by Greaves et al. (4). The essence of the Greaves hypothesis is that improper developmental modulation of the immune system due to early-life immunological isolation results in aberrantly strong reactions to infections later in childhood and an increased risk of childhood ALL (4). Moreover, immune function may play an important role in the etiology of childhood ALL (5, 6).

The early onset of childhood ALL has motivated studies on the possible etiological role of prenatal and perinatal factors. Here, we focus on the mode of delivery, for multiple reasons. First, compared with vaginal delivery, cesarean section (C-section) drastically modifies an infant's first bacterial community by preventing normal exposure to the vaginal microbiome (7), alters levels of stress hormone at birth (8–11), may influence epigenetic regulation of gene expression (12–14), and finally may be a marker for conditions that predispose the mother to birthing difficulties ranging from infections to morphological abnormalities (15). Previous studies have found associations between C-section and an increased risk of several immune system–related diseases, including asthma (16–18), allergies (19),

and type 1 diabetes mellitus (20). Second, the rate of delivery by C-section has increased dramatically in the United States over the last 4 decades, from 5.8% in 1970 (21) to 32.9% in 2009 (22), and the incidence rate of childhood ALL has also increased continuously (2). Third, the relationship of C-section to the risk of childhood ALL has not been evaluated in many studies, and most of those studies did not find an association (23–30). In a recent Greek investigation, Thomopoulos et al. (30) observed an elevated risk of early-onset childhood ALL among children delivered by C-section, especially prelabor (i.e., elective) C-section. This observation was replicated in a pooled analysis from the Childhood Leukemia International Consortium, which included the Greek study and 3 other case-control studies (31), but because of the potential for bias in these studies, the uncertainty about categorization of elective and emergency C-section, and concern about the focus on the age group of 0–3 years (in which biologically distinct subtypes of ALL are found) (32), the finding is far from conclusive.

The distinction of elective versus emergency C-section can be important, because these events represent different exposure scenarios. A newborn delivered by elective C-section usually does not experience rupture of the amniotic membrane until surgery, significantly limiting microbial colonization from the birth canal (7), whereas a large proportion of emergency C-sections are performed after the onset of physical labor and the rupture of membranes, thus exposing the fetus to the mother's vaginal flora. Additionally, a newborn delivered by elective C-section will not experience the physical trauma of labor, which is known to trigger a stress response (33). Furthermore, emergency C-section may be a surrogate measure of birth complications or fetal distress.

Inspired by these observations and potential biological mechanisms, we hypothesized that C-section, especially elective C-section, would be associated with an increased risk of childhood ALL. We tested this hypothesis in a population-based, statewide case-control study from California, with a particular focus on childhood ALL that occurred at the ages of peak incidence (ages 2–4 years).

METHODS

Study population

We developed the California Childhood Cancer Record Linkage Project by linking statewide birth records maintained by the vital statistics division of the California Department of Public Health (for the years 1978–2009) to statewide cancer diagnosis data from the California Cancer Registry (CCR) for the years 1988–2011. Included in this analysis were children born in California and diagnosed with their first, primary ALL before the age of 15 years, as reported to the CCR. For each case of leukemia, up to 4 control subjects were randomly selected from the statewide birth records and matched to the case participant on year and month of birth, sex, and race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic, Asian/Pacific Islander, or other). None of the controls had been diagnosed with any childhood cancer according to data from the CCR. The study protocol was approved by the institutional review boards at the California Health and Human Services Agency; the University of California, Berkeley; the University of California, San Francisco; and Yale University.

From a total of 5,439 identified cases, we excluded cases using the following criteria: 1) length of gestation outside the range of 22–44 weeks ($n = 309$) (34); 2) unknown values for mode of delivery ($n = 5$), birth weight ($n = 1$), birth order ($n = 4$), or mother's country of birth ($n = 3$); 3) presence of Down syndrome, an established, strong risk factor for childhood ALL (35) ($n = 29$); or 4) mother's residence was outside of California at the time of delivery (out of concern that these children would not have been reported to the CCR had they developed childhood ALL) ($n = 7$). The final sample included 5,081 cases. The same exclusion criteria were applied to a total of 20,352 matched control subjects selected for the 5,081 cases, and 18,927 controls remained in the final sample. In the final study population, each case had at least 1 matched control, and approximately 75% of cases had 4 matched controls.

Variables of interest

Information on mode of delivery was obtained from birth records. Data on C-section versus vaginal delivery were available for all birth years (1978–2009).

Data-collection forms used by the California Department of Public Health changed over time, and additional details of delivery data that allowed us to categorize C-sections as elective versus emergency were available only for birth years 1978–1988 and 2005–2009 (Appendix Table 1). During 1978–1981, a variable in birth records called "C-section" categorized C-sections as emergency ("primary, emergency" or "repeat, emergency"), elective ("primary, elective" or "repeat, elective"), or unknown. During 1982–1988, the word "nonelective" was used instead of "emergency", and we defined nonelective ("nonelective primary" or "nonelective repeat") C-sections as emergency C-sections. In 2005–2009, a variable called "method of delivery" provided information on whether a trial of labor was attempted. For this period, we defined C-sections with a trial of labor attempted as emergency C-sections and C-sections without a trial of labor attempted as elective C-sections.

Because we did not have detailed information on the type of C-section for all birth years, we evaluated the validity of an approximate approach that was used in the pooled analysis by the Childhood Leukemia International Consortium (31) to categorize elective versus emergency C-section based on maternal history of C-section and the number of offspring in the index delivery. This approach categorized a C-section as elective if the mother had a history of C-section in the past or if the index child was part of a multiple birth (e.g., twins or triplets); otherwise it would be considered emergent. We then compared the 2 sets of definitions for the birth years of 1978–1988, for which there was a clear indication of elective versus emergency C-section in the birth records (the gold standard). Among the 1,148 C-sections that occurred during 1978–1988, the

type of C-section was misclassified for 340 (29.6%) when we used the approximate approach. Additionally, among 434 C-sections that were deemed elective based on the gold standard, fewer than half (n = 202, 46.5%) were correctly classified as elective C-sections by the approximate approach. An additional evaluation using data for birth years 2005–2009 also suggested poor validity of the approximate approach, which prompted us not to use it in this analysis.

To account for potential confounding by other birth characteristics, we also abstracted data on birth weight, length of gestation, singleton versus multiple birth, birth order, maternal age at the time of delivery, maternal country of birth, and maternal education.

Statistical analysis

Pearson's χ^2 test was used to compare demographic and socioeconomic characteristics between cases and controls. Odds ratios and 95% confidence intervals were obtained from conditional logistic regression models, which accounted for the matched design. Separate analyses were conducted for ALL diagnosed at the ages <15 years, 0–1 year, 2–4 years, and 5–14 years, motivated by recognized differences in ALL subtype and pathophysiology by age at diagnosis (36, 37). Potential confounders considered in the models included birth weight (<2,500, 2,500–2,999, 3,000–3,499, 3,500–3,999, or ≥4,000 g), length of gestation (22–36, 37–41, or 42–44 weeks), birth order (first, second, or third or higher), maternal country of birth (United States or a foreign country), maternal age at the time of delivery (<20, 20–24, 25–29, 30–34, or ≥35 years), and maternal education (up to 8th grade, 9th–12th grade, at least some college, or unknown).

Because maternal education was missing for over 23% of the subjects, we conducted multiple imputation for the missing values. First, we used a correlation coefficient of 0.4 as the threshold to identify variables that were correlated with maternal education, and those included race/ethnicity, maternal age at the time of delivery, and mother's country of birth. Subsequently, we used Proc MI with the monotone discriminant method in SAS, version 9.4 (SAS Institute, Inc., Cary, North Carolina), to create 10 complete data sets, analyzed the 10 data sets with Proc Phreg, and finally used Proc MIANALYZE to combine results from the 10 analyses. No other variables had missing data.

We initially adjusted for all covariates simultaneously in the models and then conducted sensitivity analyses by using the SAS stepwise function to retain only covariates that were statistically significant. Because the estimated odds ratios for mode of delivery, the primary exposure of interest, from the 2 sets of analyses were essentially the same, we decided to present only the results from the models that included all covariates. As a sensitivity analysis, we also compared the results derived from models with maternal education in its original format with the results from models with maternal education in its imputed format. The 2 sets of results were extremely similar, and we chose to present the results using imputed maternal education. Furthermore, regression analysis using locally weighted scatterplot smoothing was applied to show the prevalence ratio for elective C-section in cases versus controls for the different ages at ALL diagnosis. SAS was used for all analyses. All tests were 2-sided, and $P < 0.05$ indicated statistical significance.

RESULTS

The 5,081 cases and 18,927 controls were comparable in terms of sex, race/ethnicity, and year of birth—characteristics on which they were matched (Table 1). Compared with controls, cases had higher birth weight. Mothers of case patients were more likely to have been born outside the United States, to have been older at the time of delivery, and to have had less education. No significant differences were observed with regard to length of gestation, plurality of birth (singleton vs. multiple), birth order, or percentage of individuals living in poverty at the zip code level. In terms of mode of delivery, a slightly higher percentage of children with ALL (24.6% of cases vs. 23.6% of controls) had been delivered by C-section.

For the 1,552 cases and 5,688 controls with detailed information on type of C-section, a slightly higher percentage of children with ALL (14.2% of cases vs. 12.9% in controls) had been delivered by elective C-section. However, the difference did not reach statistical significance (Table 1). There was a considerable change over time in the proportion of newborns delivered by C-section. In our study population, the proportion of deliveries by C-section among all births increased from 17% (16.9% in cases vs. 17.1% in controls) in 1978–1982 to more than 30% (34.7% in cases vs. 30.6% in controls) in 2005–2009. Among those delivered by C-section, the proportion delivered by elective C-section increased among both cases (from 22.9% to 90.4%) and controls (from 40.7% to 88.5%) over the two 5-year periods. As shown in Figure 1, the prevalence ratio for elective C-section in cases versus controls had a peaking pattern similar to that of ALL incidence in California.

Of the 5,081 cases, 592 (11.7%), 2,296 (45.2%), and 2,193 (43.2%) were diagnosed at the ages of 0–1 year, 2–4 years, and 5–14 years, respectively (Table 2). No association was observed between delivery by C-section and the risk of overall childhood ALL (<15 years of age; odds ratio (OR) = 1.03, 95% confidence interval (CI): 0.96–1.10). In analyses stratified by the age at diagnosis, delivery by C-section was associated with an increased risk of ALL in the age group 2–4 years (OR = 1.11, 95% CI: 1.01, 1.22) but not in the 2 other age groups (0–1 year or 5–14 years; Table 2).

Among the subset of 1,552 cases and 5,688 controls who had more detailed data on the type of C-section (i.e., elective vs. emergency), C-section was associated with an increased risk of ALL diagnosis in the age group 2–4 years (OR = 1.20, 95% CI: 1.01, 1.44). Compared with vaginal delivery, the odds ratios for elective and emergency C-section were 1.17 (95% CI: 1.01, 1.36) and 1.01 (95% CI: 0.85, 1.19), respectively, for overall childhood ALL (<15 years of age). No significant association was observed between either type of C-section and the risk

Table 1. Characteristics of Children With Childhood Acute Lymphoblastic Leukemia and Control Participants, California, 1978–2009

Characteristic	ALL Group (n = 5,081)		Control Group (n = 18,927)		*P* Value
	No. of Participants	%	No. of Participants	%	
Sex					0.98
Female	2,220	43.7	8,273	43.7	
Male	2,861	56.3	10,654	56.3	
Race/ethnicity					0.98
Non-Hispanic white	1,734	34.1	6,473	34.2	
Non-Hispanic black	184	3.6	659	3.5	
Hispanic	2,627	51.7	9,784	51.7	
Asian/Pacific Islander	484	9.5	1,828	9.7	
Other	52	1.0	183	1.0	
Year of birth					0.72
1978–1989	1,404	27.6	5,125	27.1	
1990–1999	2,386	47.0	8,980	47.4	
2000–2009	1,291	25.4	4,822	25.5	
Birth weight, g					<0.01
<2,500	249	4.9	1,133	6.0	
2,500–2,999	1,904	37.5	7,063	37.3	
3,000–3,499	695	13.7	2,820	14.9	
3,500–3,999	1,574	30.9	5,733	30.3	
≥4,000	659	13.0	2,178	11.5	
Length of gestation, weeks					0.19
22–36	574	11.3	2,094	11.1	
37–41	4,070	80.1	15,343	81.1	
42–44	437	8.6	1,490	7.9	
Birth plurality					0.60
Singleton	4,958	97.6	18,444	97.4	
Multiple birth	123	2.4	483	2.6	
Birth order					
First	2,046	40.3	7,532	39.8	0.75
Second	1,586	31.2	5,901	31.2	
Third or higher	1,449	28.5	5,494	29.0	
Mother's country of birth					<0.01
United States	2,981	58.7	10,586	55.9	
Foreign country	2,100	41.3	8,341	44.1	
Age of mother at delivery, years					<0.01
<20	495	9.7	2,011	10.6	
20–24	1,147	22.6	4,769	25.2	
25–29	1,483	29.2	5,362	28.3	
30–34	1,211	23.8	4,258	22.5	
≥35	745	14.7	2,527	13.4	
Mother's education					
Up to 8th grade	466	9.2	2,122	11.2	0.34
9th–12th grade	1,846	36.3	6,871	36.3	
At least some college	1,569	30.9	5,552	29.3	
Unknown	1,200	23.6	4,382	23.2	

Table continues

Table 1. Continued

Characteristic	ALL Group (n = 5,081)		Control Group (n = 18,927)		P Value
	No. of Participants	%	No. of Participants	%	
Mode of delivery					
Vaginal	3,833	75.4	14,462	76.4	0.15
Cesarean section	1,248	24.6	4,465	23.6	
Mode of delivery[a]					
Vaginal	1,161	74.8	4,342	76.3	0.51
Emergency cesarean section	169	10.9	607	10.7	
Elective cesarean section	221	14.2	733	12.9	

Abbreviation: ALL, acute lymphoblastic leukemia.
[a] Reported for a subset of 1,552 cases and 5,688 controls for whom detailed delivery information was available.

of ALL in age groups 0–1 year or 5–14 years. However, among children aged 2–4 years, the peak ages of ALL incidence, delivery by elective C-section was associated with an increased risk (OR = 1.38, 95% CI: 1.11, 1.70) compared with vaginal delivery, whereas emergency C-section showed no association (OR = 0.98, 95% CI: 0.74, 1.29) (Table 3). We also conducted separate analyses for birth years 1978–1988 and 2005–2009. For children delivered by elective C-section and aged 2–4 years at diagnosis, an increased risk was observed among those born in 1978–1988 (OR = 1.71, 95% CI: 1.24, 2.37). For children born in 2005–2009, we observed an odds ratio of 1.18 (95% CI: 0.90, 1.56) (detailed results not shown).

DISCUSSION

In this large, population-based case-control study, we found that delivery by C-section, especially elective C-section, was associated with an increased risk of childhood ALL being diagnosed at ages 2–4 years, the peak ages of ALL incidence in the United States.

We did not observe an association between C-section overall and risk of childhood ALL across the entire age range <15 years, which is consistent with the results from several existing studies (23–30). Similarly, in a Greek study, Thomopoulos et al. (30) reported no association between C-section and overall childhood ALL but observed a nearly 60% elevated risk of early-onset ALL (defined as ALL diagnosed at ≤3 years of age). A previous study in California

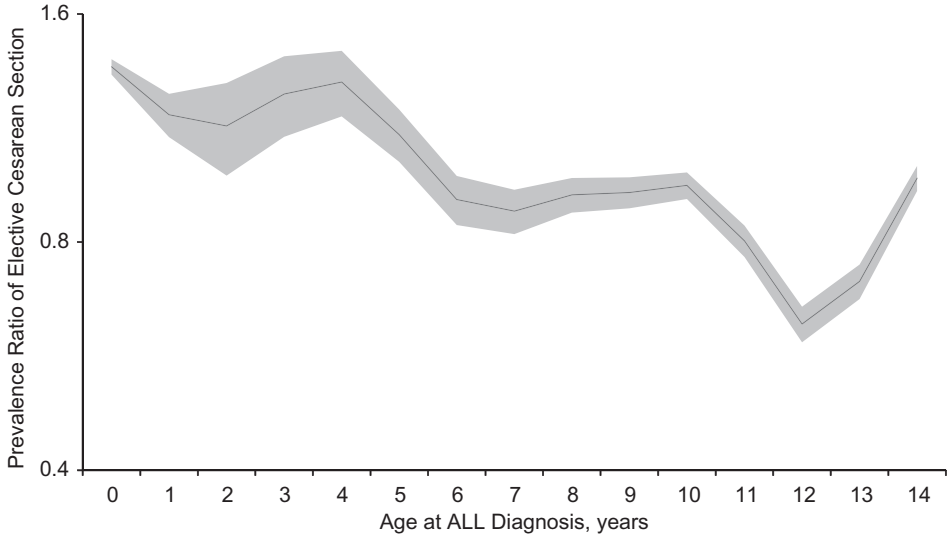

Figure 1. Prevalence ratios for elective cesarean section by age at diagnosis of acute lymphoblastic leukemia (ALL) in a subset of 1,552 cases and 5,688 controls, California, 1978–2009. The relationship between the prevalence ratio and age at ALL diagnosis was smoothed by means of locally weighted scatterplot smoothing. The thickness of the shaded area is proportional to the age-specific incidence of ALL in California.

Table 2. Odds Ratios for the Risk of Childhood Acute Lymphoblastic Leukemia According to Mode of Delivery and Age at Diagnosis, California, 1978–2009

Age at Diagnosis and Mode of Delivery	ALL Group (n = 5,081)		Control Group (n = 18,927)		Unadjusted		Adjusted[a]	
	No. of Participants	%	No. of Participants	%	OR	95% CI	OR	95% CI
0–14								
Vaginal	3,833	75.4	14,462	76.4	1.00	Referent	1.00	Referent
Cesarean section	1,248	24.6	4,465	23.6	1.06	0.98, 1.14	1.03	0.96, 1.10
0–1								
Vaginal	433	73.1	1,610	72.7	1.00	Referent	1.00	Referent
Cesarean section	159	26.9	606	27.3	0.97	0.79, 1.19	0.94	0.78, 1.14
2–4								
Vaginal	1,678	73.1	6,490	75.5	1.00	Referent	1.00	Referent
Cesarean section	618	26.9	2,104	24.5	1.14	1.02, 1.26	1.11	1.01, 1.22
5–14								
Vaginal	1,722	78.5	6,362	78.4	1.00	Referent	1.00	Referent
Cesarean section	471	21.5	1,755	21.6	1.00	0.89, 1.12	0.97	0.87, 1.07

Abbreviations: ALL, acute lymphoblastic leukemia; CI, confidence interval; OR, odds ratio.

[a] Adjusted for birth weight (<2,500, 2,500–2,999, 3,000–3,499, 3,500–3,999, or ≥4,000 g), length of gestation (22–36, 37–41, or 42–44 weeks), birth order (first, second, or third or higher), mother's country of birth (United States or a foreign country), maternal age at the time of delivery (<20, 20–24, 25–29, 30–34, or ≥35 years), and maternal education (up to 8th grade, 9th–12th grade, or at least some college).

with hospital-based case ascertainment found an increased risk (OR = 1.44, 95% CI: 1.0, 2.06) of common ALL (CD10+ and CD19+) among children delivered by C-section (24).

Thomopoulos et al. and, in a Swedish study, Naumburg et al. (28) evaluated the potential role of elective versus emergency C-section in the etiology of childhood ALL. Thomopoulos et al. found a positive association between "prelabor" (i.e., elective) C-section, but not "during labor" (i.e., emergency) C-section, and early-onset ALL (30). Naumburg et al. did not observe any association between either elective or emergency C-section and the risk of childhood lymphatic leukemia (age range: 0–16 years) (28). Compared with the Swedish study, in which only approximately 10% of participants were delivered by C-section, both the Greek study and our study involved higher C-section rates and included many more participants. In addition, Naumburg et al. did not conduct analyses stratified by age at diagnosis (28). In the pooled analysis from the Childhood Leukemia International Consortium, which included the Greek study, Marcotte et al. (31) also reported a significantly increased risk of ALL in children delivered by prelabor C-section (OR = 1.23, 95% CI: 1.04, 1.47). An advantage of the studies included in this pooled analysis was the availability of data on indications for the C-sections, which our study did not have. This difference may help explain the poor validity for the classification of elective versus emergency C-section when we attempted to use the approximate approach that had been used in the pooled analysis. In the subset population with detailed information on type of C-section, we observed an increased risk of overall childhood ALL among children delivered by elective C-section; this increase was driven mainly by the age group of 2–4 years, among whom common ALL (CD10+ and CD19+) is the primary subtype (32).

The distinction of elective versus emergency C-section may be crucial. A newborn delivered by elective C-section neither acquires microbial colonization from the birth canal nor experiences stress from labor, while a newborn delivered by emergency C-section is likely to be exposed to the mother's microbial flora and be subjected to stress from labor. During vaginal delivery and emergency C-section with ruptured amniotic membranes, a newborn will have direct contact with maternal vaginal flora. Mode of delivery is a major determinant of the initial microbiota composition of newborns. In 2 different studies, within the first 24 hours after delivery, vaginally delivered newborns harbored bacterial communities resembling those of the maternal vagina, whereas newborns delivered by C-section acquired skin microbiota—which might resemble those of the delivery environment (7, 34). The composition of infants' gut microflora during the first 6 months of life differs considerably by the mode of delivery (38), and even at 7 years of age, clostridia were higher in vaginally delivered children than in children delivered by C-section (39). Although these studies did not distinguish between elective and emergency C-section, it is reasonable to expect that the difference between vaginal delivery and elective C-section would be more profound than that between vaginal delivery and emergency C-section, in terms of the role in an infant's first bacterial community and possibly moderation of the immune system. In addition, contraction of the uterus and fetal hypoxia during labor trigger a stress response in both the mother and the fetus, resulting in markedly increased levels of cortisol and catecholamine in

Table 3. Odds Ratios for the Risk of Childhood Acute Lymphoblastic Leukemia According to Specific Type of Cesarean Section in a Subset of Children With Detailed Delivery Information, California, 1978–1988 and 2005–2009

Age at Diagnosis and Mode of Delivery	ALL Subgroup (n = 1,552)		Control Subgroup (n = 5,688)		Unadjusted		Adjusted[a]	
	No. of Participants	%	No. of Participants	%	OR	95% CI	OR	95% CI
0–14								
Vaginal	1,161	74.8	4,342	76.3	1.00	Referent	1.00	Referent
C-section[b]	391	25.2	1,346	23.7	1.11	0.98, 1.27	1.09	0.97, 1.23
Emergency C-section	169	10.9	607	10.7	1.04	0.86, 1.25	1.01	0.85, 1.19
Elective C-section	221	14.2	733	12.9	1.18	1.00, 1.40	1.17	1.01, 1.36
0–1								
Vaginal	115	67.3	452	71.0	1.00	Referent	1.00	Referent
C-section	56	32.7	185	29.0	1.19	0.83, 1.71	1.21	0.88, 1.67
Emergency C-section	14	8.2	45	7.1	1.19	0.62, 2.26	1.24	0.69, 2.25
Elective C-section	42	24.6	140	22.0	1.19	0.80, 1.79	1.20	0.84, 1.71
2–4								
Vaginal	426	70.0	1,666	73.4	1.00	Referent	1.00	Referent
C-section[b]	183	30.0	603	26.6	1.21	0.99, 1.47	1.20	1.01, 1.44
Emergency C-section	62	10.2	238	10.5	0.99	0.73, 1.35	0.98	0.74, 1.29
Elective C-section	121	19.9	363	16.0	1.37	1.08, 1.73	1.38	1.11, 1.70
5–14								
Vaginal	620	80.3	2,224	79.9	1.00	Referent	1.00	Referent
C-section[b]	152	19.7	558	20.1	1.00	0.82, 1.23	0.97	0.81, 1.16
Emergency C-section	93	12.0	324	11.6	1.04	0.81, 1.34	0.99	0.79, 1.24
Elective C-section	58	7.5	230	8.3	0.94	0.69, 1.28	0.94	0.72, 1.22

Abbreviations: ALL, acute lymphoblastic leukemia; C-section, cesarean section; CI, confidence interval; OR, odds ratio.

[a] Adjusted for birth weight (<2,500, 2,500–2,999, 3,000–3,499, 3,500–3,999, or ≥4,000 g), length of gestation (22–36, 37–41, or 42–44 weeks), birth order (first, second, or third or higher), mother's country of birth (United States or a foreign country), maternal age at the time of delivery (<20, 20–24, 25–29, 30–34, or ≥35 years), and maternal education (up to 8th grade, 9th–12th grade, or at least some college).

[b] Due to a small number of C-sections with unknown type, the numbers of elective and emergency C-sections did not always add up to the total number of C-sections.

newborns (33). Multiple studies have found lower levels of cortisol and catecholamine in neonates delivered by C-section than in neonates who underwent vaginal delivery (8–11). Cortisol may eliminate preleukemic clones arising in utero (40). Moreover, differences in levels of stress hormones at birth may alter immune responses and affect the immune system later in life (15), and there is evidence of altered methylation patterns after C-section in genes important to immune regulation (12–14). From the perspective of stress hormones, elective C-section is more different from vaginal delivery than is emergency C-section. Given the possible biological pathways, it is critical to consider elective and emergency C-section as distinct exposures.

Strengths of the current study include a large sample size, a population-based design, no refusal to participate, reliance on data from preexisting birth records, and the ability to adjust for multiple covariates. Because our study was based on record linkage, we were able to obtain nonidentifying data without active consent. As a result, this study was less prone to selection bias (due to nonparticipation of subjects) or information bias (due to general difficulty in recall or differential reporting related to case-vs.-control status).

Despite the strengths of this study, the record-linkage design also led to several inherent limitations. First, we were restricted to the use of existing data without confirmation, although we did exclude subjects whose length of gestation was outside a plausible range, and a previous study found a near perfect agreement on mode of delivery when comparing birth records with medical records (41). Within our study population, we observed a change in the percentage of newborns delivered by C-section over time, which mirrors the trend reported by the California Department of Public Health (42). Second, data on elective versus emergency C-section were available only for a subset of 1,552 cases and 5,688 controls, although our sample was still larger than any of the other individual studies evaluating the role of C-section in the etiology of

childhood ALL (23–30). Third, it is possible that some of the controls could have moved out of California and developed childhood ALL elsewhere, or they could have developed childhood ALL within California but not have been captured by the CCR. However, childhood ALL (<15 years of age) is a rare disease, with an annual incidence of approximately 35 per million (2); fewer than 10 cases would have been expected to develop among the 18,927 controls if they had been observed from birth to before age 15 years. In addition, there is no reason to suspect that the possibility of misclassifying actual cases as controls would be different based on a child's mode of delivery, and nondifferential misclassification would have biased the risk estimates towards the null. Last, we were limited to data available in existing records, and therefore we could not adjust for additional potential confounders such as breastfeeding, which has been linked to a lower risk of childhood ALL (43), or indications for C-section.

In summary, in this large, population-based case-control study, which had a low susceptibility to bias, delivery by elective C-section was associated with an increased risk of childhood ALL, especially at the peak ages of ALL incidence (ages 2–4 years). It is important to conduct additional studies to further evaluate this association and to identify potential underlying mechanisms, because such analyses may point toward a preventable aspect in the etiology of childhood ALL. Until more is known, it is probably prudent to perform C-sections only when they are medically justifiable, especially when considering the multiple other types of disease to which they have been linked (16–20).

ACKNOWLEDGMENTS

Author affiliations: Department of Chronic Disease Epidemiology, Yale School of Public Health, New Haven, Connecticut (Rong Wang, Andrew T. DeWan, Xiaomei Ma); Department of Epidemiology and Biostatistics, School of Medicine, University of California, San Francisco, San Francisco, California (Joseph L. Wiemels, Stephen S. Francis); Division of Epidemiology, School of Public Health, University of California, Berkeley, Berkeley, California (Catherine Metayer, Libby Morimoto); Yale Cancer Center, Yale School of Medicine, Yale University, New Haven, Connecticut (Nina Kadan-Lottick, Yawei Zhang, Xiaomei Ma); Section of Pediatric Hematology/Oncology, Yale School of Medicine, Yale University, New Haven, Connecticut (Nina Kadan-Lottick); and Department of Environmental Health Sciences, Yale School of Public Health, New Haven, Connecticut (Yawei Zhang).

This work was supported by research grants from the National Institutes of Health (grants R01 CA155461, R01 CA175737, T32 CA151022, and P01 ES018172) and the Environmental Protection Agency (grant RD83451101). The collection of cancer incidence data used in this study was supported by the California Department of Public Health as part of the statewide cancer reporting program mandated by California Health and Safety Code Section 103885; the National Cancer Institute's Surveillance, Epidemiology, and End Results Program under contract HHSN261201000140C awarded to the Cancer Prevention Institute of California, contract HHSN261201000035C awarded to the University of Southern California, and contract HHSN261201000034C awarded to the Public Health Institute; and the Centers for Disease Control and Prevention's National Program of Cancer Registries, under agreement U58DP003862-01 awarded to the California Department of Public Health.

The ideas and opinions expressed herein are those of the author(s), and no endorsement by the California Department of Public Health, the National Cancer Institute, or the Centers for Disease Control and Prevention or their contractors and subcontractors is intended or should be inferred.

Conflict of interest: none declared.

REFERENCES

1. Howlader N, Noone AM, Krapcho M, et al., eds. *SEER Cancer Statistics Review 1975–2010*. Bethesda, MD: National Cancer Institute; 2013.
2. Ward E, DeSantis C, Robbins A, et al. Childhood and adolescent cancer statistics, 2014. *CA Cancer J Clin*. 2014; 64(2):83–103.
3. Stiller CA, Parkin DM. Geographic and ethnic variations in the incidence of childhood cancer. *Br Med Bull*. 1996;52(4): 682–703.
4. Greaves MF, Alexander FE. An infectious etiology for common acute lymphoblastic leukemia in childhood? *Leukemia*. 1993;7(3):349–360.
5. O'Connor SM, Boneva RS. Infectious etiologies of childhood leukemia: plausibility and challenges to proof. *Environ Health Perspect*. 2007;115(1):146–150.
6. Greaves M. Infection, immune responses and the aetiology of childhood leukaemia. *Nat Rev Cancer*. 2006;6(3):193–203.
7. Dominguez-Bello MG, Costello EK, Contreras M, et al. Delivery mode shapes the acquisition and structure of the initial microbiota across multiple body habitats in newborns. *Proc Natl Acad Sci USA*. 2010;107(26):11971–11975.
8. Vogl SE, Worda C, Egarter C, et al. Mode of delivery is associated with maternal and fetal endocrine stress response. *BJOG*. 2006;113(4):441–445.
9. Mears K, McAuliffe F, Grimes H, et al. Fetal cortisol in relation to labour, intrapartum events and mode of delivery. *J Obstet Gynaecol*. 2004;24(2):129–132.
10. Zanardo V, Solda G, Trevisanuto D. Elective cesarean section and fetal immune-endocrine response. *Int J Gynaecol Obstet*. 2006;95(1):52–53.
11. Bird JA, Spencer JA, Mould T, et al. Endocrine and metabolic adaptation following caesarean section or vaginal delivery. *Arch Dis Child Fetal Neonatal Ed*. 1996;74(2):F132–F134.
12. Almgren M, Schlinzig T, Gomez-Cabrero D, et al. Cesarean delivery and hematopoietic stem cell epigenetics in the newborn infant: implications for future health? *Am J Obstet Gynecol*. 2014;211(5):502.e1–502.e8.
13. Schlinzig T, Johansson S, Gunnar A, et al. Epigenetic modulation at birth—altered DNA-methylation in white blood cells after Caesarean section. *Acta Paediatr*. 2009; 98(7):1096–1099.

14. Franz MB, Poterauer M, Elhenicky M, et al. Global and single gene DNA methylation in umbilical cord blood cells after elective caesarean: a pilot study. *Eur J Obstet Gynecol Reprod Biol*. 2014;179:121–124.
15. Cho CE, Norman M. Cesarean section and development of the immune system in the offspring. *Am J Obstet Gynecol*. 2013;208(4):249–254.
16. Thavagnanam S, Fleming J, Bromley A, et al. A meta-analysis of the association between Caesarean section and childhood asthma. *Clin Exp Allergy*. 2008;38(4):629–633.
17. Metsälä J, Kilkkinen A, Kaila M, et al. Perinatal factors and the risk of asthma in childhood—a population-based register study in Finland. *Am J Epidemiol*. 2008;168(2):170–178.
18. Kolokotroni O, Middleton N, Gavatha M, et al. Asthma and atopy in children born by caesarean section: effect modification by family history of allergies—a population based cross-sectional study. *BMC Pediatr*. 2012;12(2):179.
19. Bager P, Wohlfahrt J, Westergaard T. Caesarean delivery and risk of atopy and allergic disease: meta-analyses. *Clin Exp Allergy*. 2008;38(4):634–642.
20. Cardwell CR, Stene LC, Joner G, et al. Caesarean section is associated with an increased risk of childhood-onset type 1 diabetes mellitus: a meta-analysis of observational studies. *Diabetologia*. 2008;51(5):726–735.
21. Placek PJ, Taffel SM. Trends in cesarean section rates for the United States, 1970–78. *Public Health Rep*. 1980;95(6):540–548.
22. Martin JA, Hamilton BE, Ventura SJ, et al. Births: final data for 2009. *Natl Vital Stat Rep*. 2011;60(1):1–70.
23. Ajrouche R, Rudant J, Orsi L, et al. Childhood acute lymphoblastic leukaemia and indicators of early immune stimulation: the Estelle study (SFCE). *Br J Cancer*. 2015;112(6):1017–1026.
24. Francis SS, Selvin S, Metayer C, et al. Mode of delivery and risk of childhood leukemia. *Cancer Epidemiol Biomarkers Prev*. 2014;23(5):876–881.
25. Johnson KJ, Soler JT, Puumala SE, et al. Parental and infant characteristics and childhood leukemia in Minnesota. *BMC Pediatr*. 2008;8:7.
26. Kaye SA, Robison LL, Smithson WA, et al. Maternal reproductive history and birth characteristics in childhood acute lymphoblastic leukemia. *Cancer*. 1991;68(6):1351–1355.
27. McKinney PA, Juszczak E, Findlay E, et al. Pre- and perinatal risk factors for childhood leukaemia and other malignancies: a Scottish case control study. *Br J Cancer*. 1999;80(11):1844–1851.
28. Naumburg E, Bellocco R, Cnattingius S, et al. Supplementary oxygen and risk of childhood lymphatic leukaemia. *Acta Paediatr*. 2002;91(12):1328–1333.
29. Reynolds P, Von Behren J, Elkin EP. Birth characteristics and leukemia in young children. *Am J Epidemiol*. 2002;155(7):603–613.
30. Thomopoulos TP, Skalkidou A, Dessypris N, et al. Prelabor cesarean delivery and early-onset acute childhood leukemia risk. *Eur J Cancer Prev*. 2016;25(2):155–161.
31. Marcotte EL, Thomopoulos TP, Infante-Rivard C, et al. Caesarean delivery and risk of childhood leukaemia: a pooled analysis from the Childhood Leukemia International Consortium (CLIC). *Lancet Haematol*. 2016;3(4):e176–e185.
32. Wiemels J, Ma X. Stressful exit from the womb and risk of childhood leukaemia. *Lancet Haematol*. 2016;3(4):e155–e156.
33. Hyde MJ, Mostyn A, Modi N, et al. The health implications of birth by Caesarean section. *Biol Rev Camb Philos Soc*. 2012;87(1):229–243.
34. Shin H, Pei Z, Martinez KA 2nd, et al. The first microbial environment of infants born by C-section: the operating room microbes. *Microbiome*. 2015;3:59.
35. Cnattingius S, Zack MM, Ekbom A, et al. Prenatal and neonatal risk factors for childhood lymphatic leukemia. *J Natl Cancer Inst*. 1995;87(12):908–914.
36. Forestier E, Schmiegelow K; Nordic Society of Paediatric Haematology and Oncology NOPHO. The incidence peaks of the childhood acute leukemias reflect specific cytogenetic aberrations. *J Pediatr Hematol Oncol*. 2006;28(8):486–495.
37. Chiaretti S, Vitale A, Cazzaniga G, et al. Clinico-biological features of 5202 patients with acute lymphoblastic leukemia enrolled in the Italian AIEOP and GIMEMA protocols and stratified in age cohorts. *Haematologica*. 2013;98(11):1702–1710.
38. Gronlund MM, Lehtonen OP, Eerola E, et al. Fecal microflora in healthy infants born by different methods of delivery: permanent changes in intestinal flora after cesarean delivery. *J Pediatr Gastroenterol Nutr*. 1999;28(1):19–25.
39. Salminen S, Gibson GR, McCartney AL, et al. Influence of mode of delivery on gut microbiota composition in seven year old children. *Gut*. 2004;53(9):1388–1389.
40. Schmiegelow K, Vestergaard T, Nielsen SM, et al. Etiology of common childhood acute lymphoblastic leukemia: the adrenal hypothesis. *Leukemia*. 2008;22(12):2137–2141.
41. DiGiuseppe DL, Aron DC, Ranbom L, et al. Reliability of birth certificate data: a multi-hospital comparison to medical records information. *Matern Child Health J*. 2002;6(3):169–179.
42. Boumediene B, Chow J, Frideman M, et al. *Trends in Maternal Morbidity in California 1999–2005*. Sacramento, CA: California Department of Public Health, Center for Family Health, Maternal, Child, and Adolescent Health Branch; 2011. https://www.cdph.ca.gov/programs/mcah/Documents/MO-CAPAMR-TrendsinMaternalMorbidityinCalifornia-1999-2005-TechnicalReport.pdf. Accessed May 1, 2016.
43. Amitay EL, Keinan-Boker L. Breastfeeding and childhood leukemia incidence: a meta-analysis and systematic review. *JAMA Pediatr*. 2015;169(6):e151025.

(Appendix follows)

Appendix Table 1. Designation as Emergency or Elective for the Variables for Cesarean Section Used in California Birth Records, 1978–2009

Date Range	Variable Name	Type of Cesarean Section		
		Emergency	Elective	Unknown
1978–1981	Cesarean	Primary, emergency	Elective primary	Unknown
		Repeat, emergency	Elective repeat	
1982–1988	Cesarean	Nonelective primary	Elective primary	Yes, unspecified
		Nonelective repeat	Elective repeat	Unknown or unreported
2005–2009	Method of delivery	Cesarean—primary, with trial of labor attempted Cesarean—primary, vacuum, with trial of labor attempted Cesarean—repeat, with trial of labor attempted Cesarean—repeat, vacuum, with trial of labor attempted	Cesarean—primary Cesarean—primary, vacuum Cesarean—repeat Cesarean—repeat, vacuum	