Published OnlineFirst May 3, 2014; DOI: 10.1158/1055-9965.EPI-13-1330

Cancer Epidemiology, Biomarkers & Prevention

Research Article

Exposure to Infections and Risk of Leukemia in Young Children

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Abstract

Background: Epidemiologic studies indicate that infections in early childhood may protect against pediatric acute lymphoblastic leukemia (ALL).

Methods: We identified 3,402 ALL cases among children 0 to 5 years of age using the California Cancer Registry. From California birth records we randomly selected controls in a 20:1 ratio and frequency matched them to cases by birth year. We investigated markers of exposure to infections, including month of birth, timing of birth in relation to influenza and respiratory syncytial virus (RSV) seasons, and birth order based on data from California birth certificates and national infection surveillance systems.

Results: We observed an increased risk of ALL for spring and summer births, and for those first exposed to an influenza or RSV season at nine to twelve months of age compared with those exposed during the first three months of life, and this association was stronger among first born children [odds ratios (OR), 1.44 and 95% confidence intervals (CI), 1.13–1.82, for influenza exposure at nine to twelve months of age]. Decreased risk was observed with increasing birth order among non-Hispanic whites but not Hispanics (OR, 0.76 and 95% CI, 0.59–096, for fourth or higher birth order among whites).

Conclusion: Our results support the hypothesis that infections in early childhood decrease risk of ALL.

Impact: Our findings implicate early life exposure to infections as protective factors for ALL in young children. *Cancer Epidemiol Biomarkers Prev; 23(7); 1195–203. ©2014 AACR.*

Introduction

Leukemia is the most common form of childhood cancer, accounting for more than one third of all childhood cancers among those ages 0 to 14 years (1).

Pediatric leukemia arises from a diverse set of chromosomal and molecular changes. There is strong evidence that most of these are acquired, not inherited, as only a small number (about 5%) of leukemias are associated with inherited genetic syndromes (2, 3). Evidence from twin studies and studies of neonatal blood spots suggests that most initiating events occur during fetal development in utero (4–8). Infections may play a role in pediatric leukemia pathogenesis (9–13), and there are 2 main hypotheses on the nature of this etiology.

Greaves has proposed the "delayed infection" hypothesis, suggesting that delayed exposure to common childhood infections leads to an increased risk of pediatric leukemia through an abnormal immune response (14). Greaves hypothesized that lack of immune modulation in the neonatal period and in infancy may predispose the immune system to abnormal responses following subsequent "delayed" exposure to infection. Within the context of the "2 hit hypothesis," a minimum of 2 etiologic events are required for the development of acute lymphoblastic leukemia (ALL) and infection would promote the second genetic event through an aberrant or pathological immune response. A second hypothesis has been proposed by Kinlen as the "population mixing" hypothesis, which states that pediatric leukemia might arise from a rare response to common infection (15). Population mixing would result in increased risks because of contact between infected and susceptible individuals. Although Greaves' hypothesis emphasizes the timing of exposure, Kinlen's hypothesis emphasizes exposure to specific agent(s) the child has not encountered yet.

Because direct measurement of a child's actual exposure to infection is challenging in a large-scale epidemiologic setting, previous studies have used several proxies of early life exposure to infections in order to examine the link between childhood cancers and infection. Well accepted as predictors of increased early childhood exposure to infection are day care attendance, number of older siblings, and timing of birth with regard to common viral

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Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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doi: 10.1158/1055-9965.EPI-13-1330

Published OnlineFirst May 3, 2014; DOI: 10.1158/1055-9965.EPI-13-1330

infection seasons (16, 17). Here we examine the link between risk of ALL and several proxies for early life exposure to infection, including month of birth, timing of birth with regard to influenza, and respiratory syncytial virus (RSV) seasons, and birth order among California children ages 0 to 5 years.

Materials and Methods

Subjects

Using data from the California Cancer Registry, we identified all acute lymphoid leukemia (ALL) tumor cases diagnosed in California between 1988 and 2007 among children 0 to 5 years of age at diagnosis. Leukemia cases were defined as International Classification of Childhood Cancer, Third edition (ICCC-3; ref. 18) code 011 (lymphoid leukemias). Cases were part of a large case–control study of all childhood cancers ages 0 to 5 years in CA during this period, in which we successfully matched 89% of all cases to their CA birth certificate (birth years 1986–2007; ref. 19). From the same birth certificate files, we randomly selected 20 controls free of cancer by age 5 for each case, frequency matched on birth year. We cross-checked CA death records and excluded from eligible controls those who died before age 6. We also excluded improbable or likely nonviable births, defined as birth weight of <500 g or birth before 20 weeks of gestation The final ALL dataset included 3,402 ALL cases and 68,040 controls.

Because our study was based only on existing records, we did not obtain informed consent from study subjects. Our use of human subject data was approved by the UCLA Institutional Review Board and the California Health and Human Services Agency Committee for the Protection of Human Subjects.

Statistical methods

Month of birth information was collected from birth certificate data. We expect that month of birth may be associated with exposure to seasonal infections. Specifically, examples of seasonal infections and the timing of their peak include: winter months: influenza, pneumococcal disease, and rotavirus; spring: RSV and measles; summer: poliovirus and other enteroviruses; and fall: parainfluenza virus type 1 (20).

Because the timing of community infections varies from year to year, we retrieved information on influenza and RSV seasons utilizing surveillance reports from the Centers of Disease Control (CDC) and California Department of Public Health Influenza Surveillance Program (21, 22). We chose these 2 infections of interest because detailed surveillance data were available for at least part of the study period. We examined summary reports for Department of Health and Human Services Region 9 (Arizona, California, Nevada, and Hawaii) and these were available beginning with the 1997 to 1998 season (influenza) and the 1999 to 2000 season (RSV) through the 2007 to 2008 season, thus our analyses of viral seasons are restricted to these years. CDC surveillance data are based on data collection by both US World Health Organization Collaborating Laboratories and National Respiratory and Enteric Virus Surveillance System (NREVSS) laboratories. These state public health laboratories test samples and report to CDC the number of specimens tested and the number positive for each infection of interest. For each influenza and RSV season we assigned a season peak date, defined as the last day of the calendar week during which the highest percent of samples tested were positive for influenza virus or RSV isolates. Some infection seasons experienced 2 peaks of equal amplitude. In these cases, we assigned 2 peaks. We then calculated the length of time between birth and first possible exposure to an infection season, using the season peak date as the reference date for each infection season. We categorized children as having had their first possible exposure to an influenza or RSV season during the first 3 months of life, 3 to 6 months of age, 6 to 9 months of age, 9 to 12 months of age, or more than 12 months of age, as previous studies using proxies of infection exposures (such as day care attendance and level of community infections) have used similar 3-month measures (11, 23, 24).

Because detailed, week-by-week surveillance data were available for influenza, we also created a season intensity variable for each of the 11 influenza seasons from 1997 to 1998 through 2007 to 2008. We categorized each season as having low, medium, or high intensity based on the peak percentage of samples that tested positive for influenza virus isolates during the influenza season. We used cut-offs for the percentage of positive samples of <20%, 20% to 29%, and ≥30% for low-, medium-, and high-intensity seasons, respectively, and we examined whether the intensity of the influenza season modified risk for ALL among those exposed to an influenza season in the first 3 months of life. Less-detailed data are available for RSV seasons, thus we were not able to compare intensity across seasons for RSV.

Information on the mother's reproductive history is included on the birth certificate, and we used data on the number of previous live births to create a birth order variable, categorized as first, second, third, and fourth or subsequent birth.

We used unconditional logistic regression analyses to obtain odds ratios (OR) and 95% confidence intervals (CI) for risk of leukemia. We calculated measures of association for each month of birth, using the month of November as the reference value because we hypothesized that infants born in November would be most likely to be exposed to seasonal infections that peak in winter or spring months within the first few months of life. Because we do not have *a priori* evidence that any factors in our dataset are associated with timing of birth, we adjusted only for birth year in analyses related to birth month and timing of birth around infectious season peaks. For birth-order analyses, we adjusted for birth year, mother's race, and mother's age. In analyses of timing of birth in relation to infection seasons, we also stratified on mother's parity (first birth vs. second or subsequent birth) and age at

Published OnlineFirst May 3, 2014; DOI: 10.1158/1055-9965.EPI-13-1330

diagnosis (<1 year, 1 to 5 years). We also tested the interaction between timing of birth and birth order (first birth vs. second or subsequent birth) by adding a product term to the model. A previous study reported racial differences for birth order on ALL risk (25), thus we also examined birth-order associations by race/ethnicity. Because of changes in vaccination recommendations for children across the study years, we conducted a sensitivity analysis limiting to children born between 1997 and 2003 only. Finally, in additional sensitivity analyses, we excluded preterm births, defined as any birth before 37 weeks of gestation, and limited analyses to B-cell leukemia cases.

Results

ALL cases were more frequently male than their respective controls, and a higher proportion had private health insurance compared with controls. ALL cases were more frequently Hispanic (Table 1).

ALL cases were more frequently born in spring or summer months (March, June, or July) compared with November (Supplementary Table S1). Elevated but imprecise point estimates were also observed for other months. When we stratified by mother's parity, results for birth month were stronger among first born children, and we did not observe an association for ALL among second or subsequent births. Excluding cases diagnosed in infancy (less than 1 year of age) did not change our results.

When we examined the timing of births in relation to influenza and RSV seasons, we observed an increased risk of ALL among those whose first exposure to an influenza season occurred at 9 to 12 months of age compared with those exposed within the first 3 months of life (OR, 1.16 and 95% CI, 1.00–1.35; Table 2). We also observed increased point estimates for those born 3 to 6 and 6 to 9 months before an infection season, although these associations were not statistically significant. We observed a similar pattern with a stronger effect estimate among first births (OR, 1.44 and 95% CI, 1.13–1.82, for those age 9 to 12 months) and we did not observe an association among second or later births. Excluding cases diagnosed in infancy (less than 1 year of age) did not change our results (OR, 1.17 and 95% CI, 1.00–1.36, for all ALL cases exposed at 9 to 12 months). We observed very similar associations in analysis of age at first potential exposure to an RSV season (Supplementary Table S2). Children who were 9 to 12 months of age at their first exposure to an RSV season experienced increased risk of ALL (OR, 1.18 and 95% CI, 1.02–1.37) compared with those with potential exposure during the first 3 months of life, with elevated point estimates also observed for those with first exposure opportunity at 3 to 6 and 6 to 9 months. Among first births, children 9 to 12 months of age at first exposure had a 30% increase in risk (OR, 1.30 and 95% CI, 1.03–1.65) compared with those exposed at 0 to 3 months of age. We did not observe an association between ALL and age at first exposure to RSV season among children of second or higher birth order. We did not observe evidence for multiplicative interaction between timing of birth and birth order ($P = 0.12$ and 0.73 for interaction between birth order and timing of influenza and RSV seasons, respectively).

When we examined age at first exposure to influenza by season intensity, we observed that infants exposed at 6 months of age or older during a medium-intensity season had increased risk of ALL (Table 3). We also observed an elevated, though imprecise, estimate for children exposed at 9 to 12 months of age during a high-intensity season. There was a strong association between delayed exposure to influenza during medium- and high-intensity seasons among first births. Influenza season intensity did not impact ALL risk among second or higher births, and delayed age of exposure did not increase ALL risk in low-intensity influenza seasons.

Among all ALL cases combined, risk estimates decreased with increasing birth order, although confidence intervals include the null (Table 4). In non-Hispanic white children, we again observed decreased point estimates with increased birth order, with a statistically significant decrease in risk for children of fourth or higher birth order (OR, 0.76 and 95% CI, 0.59–0.96). We did not observe a birth-order association in Hispanic children.

Limiting leukemia analyses to the B-cell subtype and, in separate analyses, excluding preterm births, and limiting to birth years 1997 to 2003 did not change results for any of our analyses. We were not able to conduct analyses stratified by sex because of small numbers.

Discussion

In this large population-based study of childhood cancer in children ages 0 to 5 years in California, we investigated associations between several indirect measures of infection in early life, including month of birth, timing of birth around influenza and RSV seasons, birth order, and childhood acute lympocytic leukemia. Although we do not have data for individual level infections in our population, previous studies have demonstrated that month of birth, timing of birth around infection seasons, and birth order all increase risk of exposure to several common viral infections in childhood (16, 17). For ALL, we observed positive associations for births in the spring and summer months, births that occurred 9 to 12 months before influenza and RSV seasons, and negative associations for higher birth orders. The associations for birth month and timing of birth around infection seasons were stronger for first births.

Previous reports on the influence of season on childhood leukemia have not been consistent. Four studies have suggested seasonal variation in births for leukemia, and 3 of the 4 have suggested that the birth peak occurs in late winter or spring [February (26), March (27), and April (28)], whereas the fourth suggested 2 distinct peaks in February and August (29). The variation seen in previous studies may be because of variations between community burden of infections between countries or variation in timing of infection seasons from year to year.

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Table 1. Birth and demographic characteristics of subjects in a study of leukemia risk among California children diagnosed between 1988 and 2007

	Controls ($n = 68,040$)	ALL cases ($n = 3,402$)
	N (%)[a]	*N* (%)[a]
Sex		
Male	34,788 (51.1)	1,921 (56.5)
Female	33,252 (48.9)	1,481 (43.5)
Gestational age, wks		
≤36	6,557 (10.2)	332 (10.3)
37–42	55,191 (85.6)	2,761 (85.6)
43+	2,692 (4.2)	131 (4.1)
Missing	3,600	178
Age of mother, y		
<20	7,466 (11.0)	325 (9.6)
20–29	35,669 (52.4)	1,705 (50.1)
30–34	15,674 (23.0)	826 (24.3)
35+	9,222 (13.6)	546 (16.0)
Missing	9	0
Mother's education[b]		
≤8 years	8,166 (13.8)	410 (13.8)
Some high school (9–11 y)	10,673 (18.0)	511 (17.2)
High school diploma (12 y)	17,519 (29.6)	895 (30.2)
Some college (13–15 y)	11,616 (19.6)	553 (18.7)
College diploma or higher (16+y)	11,203 (18.9)	596 (20.1)
Missing	8,863	437
Mother's race		
White	24,695 (36.5)	1,233 (36.4)
Hispanic	30,526 (45.1)	1,680 (49.6)
Other	12,439 (18.4)	472 (13.9)
Missing	380	17
Season of birth		
Spring	16,713 (24.6)	864 (25.4)
Summer	17,500 (25.7)	924 (27.2)
Fall	17,400 (25.6)	807 (23.7)
Winter	16,427 (24.1)	807 (23.7)
Parity		
First birth	26,803 (39.4)	1,288 (37.9)
Second or third birth	32,651 (48.0)	1,669 (49.1)
Fourth or subsequent birth	8,549 (12.6)	443 (13.0)
Missing	37	2
Payment source for prenatal care[b]		
Private insurance	30,074 (50.7)	1,656 (55.6)
Other	29,238 (49.3)	1,321 (44.4)
Missing	8728	425
Age at diagnosis (cases only), y		
0		196 (5.8)
1		499 (14.7)
2		882 (25.9)
3		820 (24.1)
4		623 (18.3)
5		382 (11.2)

[a]Percentage of nonmissing.

[b]Mother's education and the payment source for prenatal care began to be collected on California birth certificates in 1989. Starting that year, 1.5% of birth certificates were missing information on maternal education, and 1.3% were missing information on payment.

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Table 2. Analysis of age at first exposure to an influenza season in a study of leukemia risk among California children diagnosed between 1997 and 2007

	All cases and controls			First births			Second or subsequent births		
	Controls (n = 31,460)	Cases (n = 1,573)	OR[a] (95% CI)	Controls (n = 12,226)	Cases (n = 585)	OR[a] (95% CI)	Controls (n = 19,222)	Cases (n = 988)	OR[a] (95% CI)
All ALL cases combined									
Age at first exposure to influenza season, mo									
0–3	9,792	455	Ref	3,814	163	Ref	5,973	292	Ref
3–6	8,018	416	1.12 (0.97–1.28)	3,151	153	1.14 (0.91–1.42)	4,864	263	1.11 (0.93–1.31)
6–9	7,543	380	1.08 (0.94–1.25)	2,896	130	1.05 (0.83–1.33)	4,645	250	1.10 (0.93–1.31)
9–12	5,444	294	1.16 (1.00–1.35)	2,087	128	1.44 (1.13–1.82)	3,355	166	1.01 (0.83–1.23)
>12	663	28	0.91 (0.62–1.34)	278	11	0.93 (0.50–1.73)	385	17	0.90 (0.55–1.49)

[a]ORs adjusted for birth year.

The association we observed between ALL and birth in the spring and summer months may be indicative of delayed exposure to seasonal infections that peak during winter months, because these infants would experience the longest timespan between birth and subsequent influenza or other infection season. Our results utilizing influenza and RSV surveillance data support this hypothesis, because we observed an increased risk estimate for those born 9 to 12 months before these infection seasons. When examining the total case population, we also observed increased point estimates for those born 3 to 6 and 6 to 9 months before an infection season, although these associations were not formally statistically significant. Associations with both virus seasons were observed among first births only, which may indicate that children with older siblings experience greater exposure to infectious agents year-round and that timing of birth in relation to infection seasons is less important for these children.

Several studies have reported reduced risk of ALL associated with higher birth order (25, 30–36), although other studies have reported either no association (26, 37–45) or a positive association (24, 46, 47). A recent pooled

Table 3. Analysis of age at first exposure to an influenza season and the intensity of that season in a study of leukemia risk among California children diagnosed between 1997 and 2007

	Low-intensity influenza season			Medium-intensity influenza season			High-intensity influenza season		
	Controls	Cases	OR (95% CI)	Controls	Cases	OR (95% CI)	Controls	Cases	OR (95% CI)
Age at first exposure to influenza season, mo									
0–3	2,923	139	Ref	3,689	164	Ref	3,180	152	Ref
3–6	2,140	109	1.07 (0.83–1.39)	3,066	150	1.10 (0.88–1.38)	2,812	157	1.17 (0.93–1.47)
6–9	1,990	99	1.05 (0.80–1.36)	2,904	158	1.22 (0.98–1.53)	2,649	123	0.97 (0.76–1.24)
9–12	2,010	101	1.06 (0.81–1.37)	1,977	117	1.33 (1.04–1.70)	837	49	1.23 (0.88–1.71)
>12	189	9	1.00 (0.50–2.00)	474	19	0.90 (0.56–1.46)	0	0	
First births									
Age at first exposure to influenza season, mo									
0–3	1,122	48	Ref	1,409	54	Ref	1,283	61	Ref
3–6	859	38	1.03 (0.67–1.60)	1,195	53	1.16 (0.79–1.70)	1,097	62	1.19 (0.83–1.71)
6–9	743	35	1.10 (0.71–1.72)	1,118	53	1.24 (0.84–1.82)	1,035	42	0.85 (0.57–1.28)
9–12	766	37	1.13 (0.73–1.75)	762	52	1.78 (1.21–2.63)	313	24	1.61 (0.99–2.63)
>12	88	2		190	9	1.24 (0.60–2.54)	0	0	
Second or subsequent births									
Age at first exposure to influenza season, mo									
0–3	1,799	91	Ref	2,280	110	Ref	1,894	91	Ref
3–6	1,280	71	1.10 (0.80–1.51)	1,871	97	1.08 (0.81–1.42)	1,713	95	1.15 (0.86–1.55)
6–9	1,247	64	1.02 (0.73–1.41)	1,786	105	1.22 (0.93–1.60)	1,612	81	1.05 (0.77–1.42)
9–12	1,243	64	1.02 (0.73–1.41)	1,215	65	1.11 (0.81–1.52)	524	25	0.99 (0.63–1.56)
>12	101	7	1.37 (0.62–3.03)	284	10	0.73 (0.38–1.41)	0	0	

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Table 4. Analysis of birth order in a study of leukemia risk among California children diagnosed between 1988 and 2007

	All cases			non-Hispanic white			Hispanic		
	Controls ($n = 68,040$)	Cases ($n = 3,402$)	OR[a] (95% CI)	Controls ($n = 24,695$)	Cases ($n = 1,233$)	OR[b] (95% CI)	Controls ($n = 30,526$)	Cases ($n = 1,680$)	OR[b] (95% CI)
Birth order									
First	26,803	1,288		10,562	534	Ref	10,904	563	Ref
Second	21,131	1,076	1.00 (0.92–1.09)	8,327	420	0.95 (0.83–1.09)	8,838	490	1.03 (0.90–1.17)
Third	11,520	593	0.95 (0.85–1.05)	3,814	195	0.94 (0.79–1.12)	5,888	326	0.99 (0.85–1.15)
≥Fourth	8,549	443	0.91 (0.81–1.03)	1,978	84	0.76 (0.59–0.96)	4,887	300	1.05 (0.89–1.24)
missing	37	2		14	0		9	1	

[a]Adjusted for birth year, maternal race, and mother's age.
[b]Adjusted for birth year and maternal age.

analysis of data from 5 US states examined associations between birth order and childhood cancers and found a decreased risk of ALL among third (OR, 0.90 and 95% CI, 0.82–0.99) and fourth or higher order (OR, 0.90 and 95% CI, 0.80–1.01) births (48). We observed a reduced risk of ALL associated with higher birth order among non-Hispanic whites but not Hispanics. This is consistent with a previous study from Northern California (25) and may indicate that birth order is a reliable predictor of infection exposure among non-Hispanic whites but not Hispanics and possibly explain differences between studies that ignore race/ethnicity when examining birth-order associations. Cultural variation may account for this difference, as Hispanic populations are more likely to have larger households that include extended family members or unrelated individuals (49, 50). Thus, even first-born children in Hispanic families may live in close contact with other nonsibling children.

Some studies that have tested the delayed infection hypothesis by examining medical or hospital records for history of infections in early life (51). However, maternal immunoglobulins, mostly IgG1, are transferred across the placenta in the third trimester of pregnancy, with maximal transport beginning at 32 weeks of gestation (52, 53). These antibodies provide passive immunity for infections to which the mother has been exposed, and their presence in the first months of life serves to protect the infant from severe disease. Nonetheless there is evidence that the neonatal system is able to mount a response to immune challenge despite passive immunity from the mother (54–56). Thus, even exposure to infections in the earliest stages of life may elicit some stimulation of the immune system and, according to Greaves' hypothesis, may contribute to a decreased risk of ALL.

We hypothesized that infants whose first exposure to influenza was during a particularly high-intensity season would experience decreased risk of ALL because a higher community burden of infection increases the likelihood of exposure. We observed that infants exposed during the second half of their first year (6 months or older) during a medium-intensity season were at increased ALL risk, particularly among first births. First born children with delayed exposure (at 9 to 12 months of age) during high-intensity seasons also experienced substantial increased risk for ALL. There is evidence from the 2009 influenza pandemic that although infants did not experience an increased burden of respiratory infections during the pandemic, parent-initiated visits for respiratory symptoms increased during that time (57). Increased parental awareness because of media reports and public health campaigns during a particularly high-intensity influenza season may result in increased precautions among parents to protect their newborn infants and thus delay their first contacts to viruses to a later time in infancy.

Breastfeeding impacts exposure to infections and immune response among infants, and it has been suggested that breastfeeding may modulate the infant's immune system thereby helping it to respond effectively to infection

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later in life (58, 59). Breast milk contains soluble and cellular compounds, including components of the maternal immune system such as leukocytes, which likely aid immune development and maturation (60). Previous studies have shown that long-term (>6 months) breastfeeding is associated with decreased risk of ALL, with a meta-analysis estimating an approximate 25% decrease in risk (OR, 0.76 and 95% CI, 0.68–0.84; ref. 58). However, a case–control study in northern California did not observe associations between breastfeeding and ALL (61). Breastfeeding rates in the United States have risen during the study period, and in a national survey, the percentage of California infants who were still breastfed at 6 months was about 40% to 49% in the year 2000 (62). We did not have information on breastfeeding among our study population and thus we were unable to examine its influence on ALL in our analyses. However, we expect that our results would be attenuated among breastfed infants and more pronounced among infants who were not breastfed.

Some of the most compelling evidence in support of an infectious ALL etiology in early childhood stems from studies of day care attendance. These studies have consistently shown a decreased risk of pediatric leukemia for regular daycare attenders, who would have a high level of exposure to infectious agents, compared with children who do not attend day care (9–12). A recent meta-analysis also found a reduced risk of ALL for day care attenders compared with nonattenders (OR, 0.76 and 95% CI, 0.67–0.87; ref. 63). We did not have information on day care attendance among our study population, although we expect that the timing of birth would have less of an effect among daycare attenders because these children are more likely to be exposed to pathogens at an early age regardless of season.

The proxies for exposure to infections in early life used in this and other studies are not actual exposures. However, high-quality influenza surveillance data were available for a subset of study years and helped us to pinpoint the specific timing of exposure opportunity to 2 common infections in early childhood and sensitivity analyses by birth order further corroborated our findings. We chose to evaluate influenza and RSV separately as the timing of their respective peak seasons is distinct. However, there is overlap in the overall duration and timing of the infection seasons and thus we cannot rule out that we are picking up the same signal in the separate analyses. In addition to having high-quality surveillance data available for these 2 infections, they represent the most common causes of respiratory illness in young children (64–68). Therefore, we believe that utilizing data on these 2 infections in particular captures important sources of immune challenge in our target population. Although we relied on several proxies for both exposure and early life immune challenge, we are confident that our approach represents one of the most comprehensive approximations to exposure opportunity and common infections in early childhood. Other approaches used to evaluate infection in early childhood include studies, which rely on maternal recall or medical records. Studies have shown that maternal recall for a child's health care utilization, vaccination status, and infections is poor (69–71). Approaches using medical records are also problematic because families may not visit a health care provider for each illness, and this may be dependent upon illness severity and other factors. Our utilization of season-specific surveillance data on 2 common sources of early childhood infection creates a unique approach to indirect exposure measurement that complements other studies using proxies for childhood infections.

We used a 3-month window to estimate the timeframe of exposure. Greaves' hypothesis is based on a lack of immune modulation in early infancy, although an optimum exposure window has not been defined. A 3-month exposure window may not represent the most biologically relevant timing for immune modulation and more work is needed to identify the biologic implications of exposure at different periods in infancy.

Our study is the largest to estimate the effect of month of birth and timing of birth around influenza and RSV seasons in childhood leukemia among young children 0 to 5 years old. Because we have data available for a wide range of years, we do not expect that our results could be influenced by chance fluctuations in monthly birth rates of a single year. In this study of a large population of childhood cancer cases, we demonstrated that timing of birth and its proximity to infection season peaks impacted risk for childhood leukemia. Although we were not able to test Kinlen's population mixing hypothesis with this study, our results support Greaves' hypothesis that delayed exposure to infections in early childhood increases risk of ALL.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: B. Ritz, M. Cockburn, J.E. Heck
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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): M. Cockburn, J.E. Heck
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Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): E.L. Marcotte, M. Cockburn
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Grant Support

This study was supported by grants from the National Institute of Environmental Health Sciences [R21ES018960 (PI: J.E. Heck), R21ES019986 (PI: B. Ritz), P30ES007048 (PI: F. Gilliland, core facilities grant supporting the working of M. Cockburn)]. E.L. Marcotte was supported by predoctoral and postdoctoral fellowships from the NIH, National Cancer Institute (T32CA09142 and T32CA099936).

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Received December 16, 2013; revised April 18, 2014; accepted April 22, 2014; published OnlineFirst May 3, 2014.

Published OnlineFirst May 3, 2014; DOI: 10.1158/1055-9965.EPI-13-1330

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Published OnlineFirst May 3, 2014; DOI: 10.1158/1055-9965.EPI-13-1330

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Cancer Epidemiol Biomarkers Prev 2014;23:1195-1203. Published OnlineFirst May 3, 2014.