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Authors

Morimoto, Libby M
Kwan, Marilyn L
Deosaransingh, Kamala
et al.

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Original Contribution

History of Early Childhood Infections and Acute Lymphoblastic Leukemia Risk Among Children in a US Integrated Health-Care System

Libby M. Morimoto*, Marilyn L. Kwan, Kamala Deosaransingh, Julie R. Munneke, Alice Y. Kang, Charles Quesenberry, Jr., Scott Kogan, Adam J. de Smith, Catherine Metayer, and Joseph L. Wiemels

* Correspondence to Dr. Libby M. Morimoto, School of Public Health, University of California, Berkeley, 1995 University Avenue, Suite 460, Berkeley, CA 94704 (e-mail: libbym@berkeley.edu).

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Surrogate measures of infectious exposures have been consistently associated with lower childhood acute lymphoblastic leukemia (ALL) risk. However, recent reports have suggested that physician-diagnosed early-life infections increase ALL risk, thereby raising the possibility that stronger responses to infections might promote risk. We examined whether medically diagnosed infections were related to childhood ALL risk in an integrated health-care system in the United States. Cases of ALL ($n = 435$) diagnosed between 1994–2014 among children aged 0–14 years, along with matched controls ($n = 2{,}170$), were identified at Kaiser Permanente Northern California. Conditional logistic regression was used to estimate risk of ALL associated with history of infections during first year of life and across the lifetime (up to diagnosis). History of infection during first year of life was not associated with ALL risk (odds ratio (OR) = 0.85, 95% confidence interval (CI): 0.60, 1.21). However, infections with at least 1 medication prescribed (i.e., more "severe" infections) were inversely associated with risk (OR = 0.42, 95% CI: 0.20, 0.88). Similar associations were observed when the exposure window was expanded to include medication-prescribed infections throughout the subjects' lifetime (OR = 0.52, 95% CI: 0.32, 0.85).

childhood ALL; childhood leukemia; early-life infections; medical record

Abbreviations: ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; CI, confidence interval; KPNC, Kaiser Permanente Northern California; OR, odds ratio; VDW, Virtual Data Warehouse.

A rich and consistent literature has shown that patterns of infection influence childhood acute lymphoblastic leukemia (ALL) risk. Greaves proposed a "delayed infection" hypothesis that leukemia follows a 2-hit model, in which the first hit occurs in utero, producing a preleukemic clone, and a second hit occurs postnatally (1, 2). Exposure to infectious agents might influence the occurrence of that second hit during early childhood. It is surmised that early exposure to a variety of infections "educates" and modulates the immune system, thereby lessening any leukemogenic-stimulating, aberrantly strong reactions to infections or other environmental factors that might lead to damaging mutations. This idea is strongly supported by several studies of reduced risk of ALL and exposure to childhood contacts, and other surrogate measures of early immune stimulation such as daycare attendance (3–5), larger family size/higher birth order (6, 7), and vaccinations (8, 9). Studies of population mixing within new towns provide evidence that specific infections might influence risk (10); however, no specific postnatal infection has yet been identified that precipitates ALL.

While surrogate measures of postnatal infectious exposures have consistently been associated with ALL risk, the lack of a specific infection or leukemic agent has made it difficult to directly measure the association of exposure to infectious agents and subsequent responses. Most studies have used history of infections as a measure of exposure, with generally mixed results (3, 11). However, in an examination of the United Kingdom Childhood Cancer Study (UKCCS), the number of physician-diagnosed infections during the first year of life was higher among case children (odds ratio (OR) = 1.4, 95% confidence interval (CI): 1.1, 1.9; $P < 0.05$) relative to controls (12); a subsequent UKCCS

analysis found that this increased risk was specific to developing ALL after 2 years of age (13). Similar results were observed in a population-based analysis of national health records in Taiwan. When compared with controls, Taiwanese children who developed leukemia were more likely to have had infections diagnosed by a physician in their first year of life (OR = 3.18, 95% CI: 2.17, 4.66) and in any period before diagnosis (censored 1 year prior to diagnosis, OR = 3.90, 95% CI: 2.61, 5.81) with a dose-response relationship (14). These results from unbiased population clinical records are provocative and raise the question of whether physician-diagnosed infections early in life are not a measure of exposure to infectious agents, but rather, a reflection of a stronger immune response to common pathogens due to differences in innate immunity at birth. This hypothesis is suggested by differences in serum immune factors in neonatal samples (15–17).

Infection history ascertained from medical record abstraction and administrative databases can be superior to self-report because it is less susceptible to recall bias. Therefore, in the present analysis, we asked whether medically diagnosed infections were related to ALL risk in an integrated and multiethnic health-care system in the United States. Infection history from medical records of childhood ALL cases (and matched nonleukemia controls) from Kaiser Permanente Northern California (KPNC) were examined in relation to ALL status and compared with results for acute myeloid leukemia (AML), which is not known to have an infection-related etiology.

METHODS

Study population

Childhood leukemia cases and matched controls were selected from the KPNC member population. KPNC is one of the largest integrated health-care systems in the United States, with 4.3 million members covering the greater San Francisco–Oakland Bay Area and Sacramento Area and including over 6,000 physicians, 21 hospitals, and 233 outpatient clinics covering a 14-county region in Northern California. The KPNC Cancer Registry, which reports to the Bay Area and State of California's Surveillance, Epidemiology, and End Results Program Cancer Registries, has information on tumor characteristics such as American Joint Committee on Cancer stage, morphology, and grade (18). Data are collected, coded, and then added to the KPNC Cancer Registry approximately 4–6 months after diagnosis. Details on invasive and in-situ cancers diagnosed in the KPNC population are available from 1947 through the present. Eligible cases were those diagnosed with childhood leukemia at ages 0–14 years from 1994–2014 (beginning the year that tumor, node, and metastasis staging defined by American Joint Committee on Cancer criteria were required to be collected in National Cancer Institute's Surveillance, Epidemiology, and End Results Program registries, as well as KPNC Cancer Registries) (19). They were identified from the KPNC Cancer Registry using *International Classification of Diseases for Oncology, 3rd Edition*, morphology codes (9811, 9812, 9814, 9813, 9815, 9816, 9817, 9818). Cases were excluded if the child had Down syndrome ($n = 35$), had a prior history of cancer ($n = 4$), or was not continuously enrolled in the KPNC health plan for at least 1 year after birth ($n = 10$). Five control subjects for each case were randomly sampled with replacement from the membership data set, individually matched by age at diagnosis (within 365 days), calendar year of cancer diagnosis, sex, race, Hispanic ethnicity, and age at KPNC enrollment, using the incidence-density sampling technique to obtain a set of controls representative of the underlying pool of eligible cohort members (20). Web Figure 1 (available at https://academic.oup.com/aje) describes the relationships between ALL, infections, and potential confounders/mediators. All subjects had to have at least 1 year of continuous KPNC enrollment to be included in the study. The final matched cohort had 579 cases and 2,891 controls. After excluding 2 cases (for previous use of anticancer medications) and their matched controls, the final analytical cohort consisted of 575 cases and 2,870 controls. This study was approved by the KPNC and University of California, Berkeley, institutional review boards.

Data collection

Data on infection history and associated medications dispensed were obtained from the KPNC Virtual Data Warehouse (VDW). The VDW is a data source for research maintained by the KPNC Division of Research and other health-care systems (21). It consists of content areas and data elements from KPNC electronic databases that have been harmonized to facilitate research use. The VDW data warehouse includes files on membership enrollment, utilization of health services and pharmacy, verifiable in situ and invasive cancer data, laboratory results, vital signs, mortality information, census, member demographics, and provider information.

Diagnoses for common infections for each subject were obtained from the VDW diagnosis file using *International Classification of Diseases, Ninth Revision* (ICD-9), diagnosis codes. The following 18 infection categories were identified and included: intestinal infectious diseases, other bacterial diseases, septicemia, bacterial infections, meningitis, viral diseases, other diseases due to viruses, fungal infections, other infectious and parasitic diseases, conjunctivitis, otitis media, hearing loss, acute respiratory infections, pneumonia and influenza, unspecified bronchitis, infections of skin and subcutaneous tissue, other inflammatory conditions of skin and subcutaneous tissue, and perinatal infections. Categories composed of allergies and asthma were excluded. Web Table 1 shows the groupings of specific ICD-9 diagnosis codes per category. Diagnoses resulting from all types of patient encounters (inpatient, outpatient, telephone encounters, and other visit types) were included. Medications commonly used to treat the infections described above were obtained for each subject from the VDW pharmacy file; these included systemic antibiotics, topical/external antibiotics, nonsteroidal antiiflammatory drugs, steroidal respiratory drugs, and nonsteroidal respiratory drugs. Finally, study covariates including age at cancer diagnosis or reference date, date of birth, sex, and race/ethnicity were obtained from the VDW demographic file.

Table 1. Characteristics of Leukemia Cases and Controls, Kaiser Permanente Northern California, 1994–2014

Characteristic	Total ($n = 3,445$)		Cases ($n = 575$)		Controls ($n = 2,870$)	
	No.	%	No.	%	No.	%
Age at diagnosis, years						
<1	132	3.83	22	3.83	110	3.83
1–3	1,146	33.27	191	33.22	955	33.28
4–6	867	25.17	145	25.22	722	25.16
7–9	516	14.98	86	14.96	430	14.98
10–12	510	14.80	85	14.78	425	14.81
13–14	274	7.95	46	8.00	228	7.94
Race						
Asian/Pacific Islander	545	15.82	91	15.83	454	15.82
Black	300	8.71	50	8.70	250	8.71
Multiracial	14	0.41	3	0.52	11	0.38
Native American/Alaska Native	293	8.51	49	8.52	244	8.50
White	2,293	66.56	382	66.43	1911	66.59
Hispanic						
Yes	1,052	30.54	176	30.61	876	30.52
No	2,393	69.46	399	69.39	1994	69.48
Diagnosis year						
1994–1997	678	19.68	113	19.65	565	19.69
1998–2001	612	17.76	102	17.74	510	17.77
2002–2005	648	18.81	108	18.78	540	18.82
2006–2009	752	21.83	126	21.91	626	21.81
2010–2014	755	21.92	126	21.91	629	21.92
Sex						
Male	1859	53.96	310	53.91	1,549	53.97
Female	1,586	46.04	265	46.09	1,321	46.03
Leukemia subtype						
Acute lymphoblastic leukemia	2,605	75.62	435	75.65	2,170	75.61
Acute myeloid leukemia	401	11.64	67	11.65	334	11.64
Other/not otherwise specified	439	12.74	73	12.70	366	12.75

Statistical analysis

Odds ratios and 95% confidence intervals were estimated using conditional logistic regression. History of infection (excluding asthma and allergies) was assessed in relation to leukemia risk, parameterized as any infection (yes/no) and number of infections diagnosed. Number of medications dispensed (including all drug classes described above but excluding formulations specific for asthma and allergies) was also evaluated in relation to risk, independent of infection status. Individual infections or medications prescribed on the same date were considered independent and counted separately in analyses. Because the premise behind this investigation was that children with an "uneducated" immune system might have a more severe response to infectious exposures as well as an increased risk of ALL, we created a classification system for infection severity based upon whether medications were prescribed. By linking the KPNC pharmacy and infection diagnosis data, we inferred infection severity based upon whether medications were dispensed on the same day and up to 2 days following infection diagnosis date. Infections "requiring" 0 medications were classified as "mild" and infections requiring at least 1 medication were classified as "medication-prescribed." For severity analyses, multiple medications and multiple infections dispensed/diagnosed on the same day were collapsed into a single medication/diagnosis instance, because it was not possible, without chart review, to determine which medications were prescribed for which infection, and counting them separately might result in double (or more) counting.

We evaluated infections occurring 1) in the first year of life, and 2) during the child's lifetime. For all analyses, infections diagnosed within 6 months of leukemia diagnosis date/reference date were excluded because they might represent prodromes of the leukemia. Infections diagnosed only during a telephone visit (as opposed to an in-person encounter in the clinic, emergency room, or hospital admission) were excluded. We also conducted analyses stratified by child's Hispanic ethnicity status, limited to cases diagnosed between ages 2 and 5 years ("common" ALL). In an attempt to isolate infections most likely to be of bacterial origin, we conducted analyses limited to medication use defined as systemic antibiotics only.

RESULTS

In our cohort of 575 leukemia cases and 2,870 matched controls, there were 435 ALL cases and 2,170 matched controls, 67 AML cases and 334 matched controls, and 74 leukemia cases with unknown subtype and 366 matched controls. Years of diagnosis ranged from 1994 to 2014. There were 33,831 unique infection diagnoses and 17,992 unique prescriptions dispensed. Because of matching, cases and controls were similar with respect to age, race, ethnicity, calendar year of diagnosis, age at enrollment, and sex. A total of 34% of the cases and controls were non-White (16% Asian/Pacific Islander, 9% Black, 8.5% Native American/Alaskan); 31% were Hispanic (Table 1).

Neither a history of any infection during the first year of life (OR = 0.85, 95% CI: 0.60, 1.21) nor increasing numbers of infections diagnosed during the first year of life (5 or more vs. none OR = 0.72, 95% CI: 0.46, 1.12) were significantly associated with risk of ALL overall (Table 2), although there was a suggestion of an inverse association with increasing numbers of infections (P value for trend = 0.10). When infections were classified by "severity," this inverse association appeared to be stronger for infections requiring medication, with 3 or more severe infections associated with a 58% decrease in ALL risk (OR = 0.42, 95% CI: 0.20, 0.88). Again, the P value for trend fell short of statistical significance, possibly due to the small number of infections within each cell. When the exposure window was expanded to include infections occurring throughout the subjects' lifetime (up to diagnosis/reference date minus 6 months), the observed association remained (for 3 or more medication-prescribed infections vs. none, OR = 0.52, 95% CI: 0.32, 0.85) and the P value for trend was significant ($P < 0.003$) (Table 3). For these "lifetime" analyses, sensitivity analyses were conducted, excluding children with discontinuous enrollment (i.e., who were not continuously enrolled in KPNC from birth to diagnosis). Because results were similar to analyses including all subjects, but with wider confidence intervals, only results with all subjects are presented. Independent of infections, neither numbers of medications dispensed during the first year of life (OR = 0.79, 95% CI: 0.44, 1.40) nor through the subjects' lifetime (OR = 0.72, 95% CI: 0.50, 1.03) were associated with ALL risk.

Similar to ALL, any infections, increasing number of infections, and increasing number of medications prescribed during the first year of life and in the subjects' lifetime were not statistically significantly related to AML risk (Tables 2 and 3). There was a suggestion of a U-shaped relationship between medication-prescribed infections and AML, with both 1 medication-prescribed infection (OR = 4.51, 95% CI: 0.95, 21.44) and 3 or more medication-prescribed infections (OR = 4.62, 95% CI: 0.71, 30.18) associated with a greater than 4-fold increased risk of AML, and 2 medication-prescribed infections associated with a 1.4-fold increased risk (OR = 1.37, 95% CI: 0.11, 16.66), during the first year of life. Similar trends were observed when infections over the subjects' lifetime were evaluated. However, given the extremely small numbers of AML cases and matched controls in each exposure stratum, all point estimates were imprecise, with wide confidence intervals.

In stratified analyses, there was no evidence that the relationships between infections, medications, and ALL risk were modified by Hispanic ethnicity for exposures occurring in the first year or during their lifetime (Web Tables 2 and 3). Similarly, no significant associations were observed when analyses were limited to cases diagnosed between ages 2 and 5 years ("common" ALL) (Web Table 4). When medications were limited to only systemic antibiotics during first year of life (Web Table 5), results were similar to the main associations (e.g., suggestion of inverse association with increasing numbers of infections, particularly those requiring medications) but attenuated.

DISCUSSION

In this ethnically diverse cohort from an integrated healthcare system, increasing number of infections, especially infections requiring medication, was inversely associated with risk of childhood ALL. This relationship was observed for both infections occurring during the first year of life and those occurring through the child's lifetime (up to 6 months prior to diagnosis). Conversely, the increasing number of medication-prescribed infections was associated with increased risk of AML, although results were imprecise due to small sample sizes.

Several assessments of infections ascertained from medical record abstraction or administrative databases and risk of ALL have been conducted, with studies in the United Kingdom (12) and Taiwan (14) reporting positive associations with increasing numbers of early-life infections, studies in Denmark, Scotland, New Zealand, and France reporting inverse associations (22–25), and studies in the United Kingdom and Denmark reporting no association (26, 27). While the present study does little to clarify the direction of this association, it does underscore the significant heterogeneity across studies that makes comparisons between them problematic. In our present analysis, we attempted to distinguish weak from strong responses to infections to help assess infections that might be healthy modulators of immune development (weak) from those that can be damaging by causing extensive inflammation, reactive metabolites, and cytokine-induced cell growth (strong). Therefore, we hypothesized that we would find evidence of differential associations by severity. Instead, our data provide

Table 2. History of Childhood Infections, Associated Prescriptions (All Medications) During the First Year of Life, and Risk of Childhood Leukemia, Kaiser Permanente Northern California, 1994–2014

Infection and Medication History	Acute Lymphoblastic Leukemia							Acute Myeloid Leukemia						
	Cases ($n = 435$)		Controls ($n = 2,170$)[a]		OR[b]	95% CI	*P* Value	Cases ($n = 67$)		Controls ($n = 334$)[a]		OR[b]	95% CI	*P* Value
	No.	%	No.	%				No.	%	No.	%			
Any infection diagnosed[c]														
No	281	64.6	1,370	63.1	1.00	Referent		46	68.7	238	71.3	1.00	Referent	
Yes	154	35.4	800	36.9	0.85	0.60, 1.21	0.36	21	31.3	96	28.7	1.37	0.53, 3.51	0.52
No. of infections diagnosed[c]														
0	281	64.6	1,370	63.1	1.00	Referent		46	68.7	238	71.3	1.00	Referent	
1	35	8.0	156	7.2	0.99	0.62, 1.58	0.97	5	7.5	32	9.6	0.94	0.27, 3.27	0.93
2–4	67	15.4	335	15.4	0.87	0.58, 1.30	0.49	12	17.9	37	11.1	1.94	0.69, 5.46	0.21
≥5	52	12.0	309	14.2	0.72	0.46, 1.12	0.14	4	6.0	27	8.1	0.87	0.21, 3.68	0.85
P for trend						0.10							0.73	
No. of medications prescribed for infections														
0	318	73.1	1,576	72.6	1.00	Referent		50	74.6	266	79.6	1.00	Referent	
1–2	64	14.7	308	14.2	1.00	0.69, 1.46	0.98	10	14.9	39	11.7	1.79	0.65, 4.89	0.26
3–5	35	8.0	176	8.1	0.95	0.60, 1.52	0.84	5	7.5	19	5.7	1.92	0.53, 6.93	0.32
≥6	18	4.1	110	5.1	0.79	0.44, 1.40	0.42	2	3.0	10	3.0	1.43	0.25, 8.13	0.68
P for trend						0.17							0.42	
Frequency of mild infections (no medications prescribed)														
0[d]	281	64.6	1,370	63.1	1.00	Referent		46	68.7	238	71.3	1.00	Referent	
1	54	12.4	242	11.2	0.99	0.65, 1.51	0.96	8	11.9	41	12.3	1.24	0.40, 3.82	0.71
2	30	6.9	183	8.4	0.70	0.42, 1.16	0.17	4	6.0	19	5.7	1.28	0.31, 5.34	0.73
≥3	53	12.2	284	13.1	0.84	0.54, 1.29	0.42	5	7.5	26	7.8	1.10	0.29, 4.16	0.88
P for trend						0.43							0.68	
Frequency of medication-prescribed infections (≥1 medications prescribed)														
0[d]	281	64.6	1,370	63.1	1.00	Referent		46	68.7	238	71.3	1.00	Referent	
1	43	9.9	214	9.9	0.86	0.52, 1.42	0.56	8	11.9	20	6.0	3.50	0.88, 13.88	0.07
2	27	6.2	103	4.7	1.13	0.62, 2.04	0.69	1	1.5	10	3.0	0.99	0.09, 10.56	0.99
≥3	20	4.6	170	7.8	0.46	0.24, 0.87	0.02	5	7.5	16	4.8	3.40	0.63, 18.21	0.15
P for trend						0.06							0.26	

Table continues

Table 2. Continued

Infection and Medication History	Acute Lymphoblastic Leukemia							Acute Myeloid Leukemia						
	Cases ($n = 435$)		Controls ($n = 2,170$)[a]		OR[b]	95% CI	*P* Value	Cases ($n = 67$)		Controls ($n = 334$)[a]		OR[b]	95% CI	*P* Value
	No.	%	No.	%				No.	%	No.	%			
Frequency of mild infections, adjusted for medication-prescribed infections														
0[d]	281	64.6	1,370	63.1	1.00	Referent		46	68.7	238	71.3	1.00	Referent	
1	54	12.4	242	11.2	1.04	0.68, 1.59	0.86	8	11.9	41	12.3	1.15	0.36, 3.64	0.81
2	30	6.9	183	8.4	0.75	0.45, 1.25	0.27	4	6.0	19	5.7	1.22	0.29, 5.14	0.79
3	53	12.2	284	13.1	0.93	0.59, 1.47	0.75	5	7.5	26	7.8	0.94	0.22, 3.96	0.93
P for trend						0.76							0.34	
Frequency of medication-prescribed infections, adjusted for mild infections														
0[d]	281	64.6	1,370	63.1	1.00	Referent		46	68.7	238	71.3	1.00	Referent	
1	43	9.9	214	9.9	0.82	0.47, 1.41	0.47	8	11.9	20	6.0	4.51	0.95, 21.44	0.06
2	27	6.2	103	4.7	1.05	0.54, 2.04	0.88	1	1.5	10	3.0	1.37	0.11, 16.66	0.80
3	20	4.6	170	7.8	0.42	0.20, 0.88	0.02	5	7.5	16	4.8	4.62	0.71, 30.18	0.11
P for trend						0.08							0.15	

Abbreviations: CI, confidence interval; OR, odds ratio

[a] Controls matched 5:1 to case on sex, race, Hispanic ethnicity, age at KPNC enrollment, calendar year of leukemia diagnosis.

[b] From conditional logistic regression.

[c] From *International Classification of Diseases, Ninth Revision,* diagnosis codes.

[d] Reference group = no infections; does not add to 100% because not all infection and medication groupings shown.

Table 3. History of Childhood Infections, Associated Prescriptions (All Medications) During Lifetime, and Risk of Childhood Leukemia, Kaiser Permanente Northern California, 1994–2014

Infection and Medication History	Acute Lymphoblastic Leukemia							Acute Myeloid Leukemia						
	Cases ($n = 435$)		Controls ($n = 2,170$)[a]		OR[b]	95% CI	*P* Value	Cases ($n = 67$)		Controls ($n = 334$)[a]		OR[b]	95% CI	*P* Value
	No.	%	No.	%				No.	%	No.	%			
Any infection diagnosed[c]														
No	136	31.3	648	29.9	1.00	Referent		22	32.8	134	40.1	1.00	Referent	
Yes	299	68.7	1,522	70.1	0.88	0.64, 1.22	0.44	45	67.2	200	59.9	1.94	0.84, 4.5	0.12
No. of infections diagnosed[c]														
0	136	31.3	648	29.9	1.00	Referent		22	32.8	134	40.1	1.00	Referent	
1	40	9.2	203	9.4	0.90	0.59, 1.38	0.64	11	16.4	32	9.6	2.71	1.02, 7.23	0.05
2–4	83	19.1	417	19.2	0.89	0.61, 1.29	0.54	12	17.9	65	19.5	1.47	0.54, 3.96	0.45
≥5	176	40.5	902	41.6	0.86	0.59, 1.24	0.41	22	32.8	103	30.8	1.74	0.64, 4.75	0.28
P for trend						0.14							0.72	
No. of medications prescribed for infections														
0	176	40.5	836	38.5	1.00	Referent		29	43.3	165	49.4	1.00	Referent	
1–2	77	17.7	389	17.9	0.89	0.63, 1.24	0.48	13	19.4	56	16.8	1.57	0.66, 3.69	0.31
3–5	76	17.5	326	15.0	1.01	0.70, 1.44	0.97	5	7.5	37	11.1	1.03	0.32, 3.36	0.96
≥6	106	24.4	620	28.6	0.72	0.50, 1.03	0.07	20	29.9	76	22.8	2.11	0.81, 5.45	0.13
P for trend						0.03							0.57	
Frequency of mild infections (no medications prescribed)														
0[d]	136	31.3	648	29.9	1.00	Referent		22	32.8	134	40.1	1.00	Referent	
1	65	14.9	342	15.8	0.84	0.57, 1.23	0.37	15	22.4	42	12.6	3.12	1.24, 7.85	0.02
2	53	12.2	215	9.9	1.09	0.71, 1.67	0.68	8	11.9	39	11.7	1.70	0.57, 5.06	0.34
≥3	162	37.2	843	38.8	0.83	0.57, 1.21	0.32	19	28.4	103	30.8	1.38	0.52, 3.65	0.52
P for trend						0.93							0.42	
Frequency of medication-prescribed infections (≥1 medications prescribed)														
0[d]	136	31.3	648	29.9	1.00	Referent		22	32.8	134	40.1	1.00	Referent	
1	59	13.6	309	14.2	0.76	0.49, 1.18	0.23	11	16.4	41	12.3	2.60	0.74, 9.14	0.14
2	58	13.3	198	9.1	1.19	0.74, 1.91	0.48	4	6.0	24	7.2	1.80	0.37, 8.68	0.47
≥3	103	23.7	640	29.5	0.59	0.37, 0.93	0.02	17	25.4	71	21.3	2.81	0.72, 10.96	0.14
P for trend						0.01							0.39	

Table continues

Table 3. Continued

Infection and Medication History	Acute Lymphoblastic Leukemia							Acute Myeloid Leukemia						
	Cases ($n = 435$)		Controls ($n = 2,170$)[a]		OR[b]	95% CI	*P* Value	Cases ($n = 67$)		Controls ($n = 334$)[a]		OR[b]	95% CI	*P* Value
	No.	%	No.	%				No.	%	No.	%			
Frequency of mild infections, adjusted for medication-prescribed infections														
0[d]	136	31.3	648	29.9	1.00	Referent		22	32.8	134	40.1	1.00	Referent	
1	65	14.9	342	15.8	0.88	0.60, 1.30	0.52	15	22.4	42	12.6	3.03	1.2, 7.65	0.02
2	53	12.2	215	9.9	1.16	0.76, 1.78	0.49	8	11.9	39	11.7	1.60	0.53, 4.82	0.40
≥3	162	37.2	843	38.8	0.97	0.66, 1.45	0.90	19	28.4	103	30.8	1.18	0.42, 3.31	0.75
P for trend						0.12							0.13	
Frequency of medication-prescribed infections, adjusted for mild infections														
0[d]	136	31.3	648	29.9	1.00	Referent		22	32.8	134	40.1	1.00	Referent	
1	59	13.6	309	14.2	0.73	0.47, 1.14	0.17	11	16.4	41	12.3	2.87	0.81, 10.21	0.10
2	58	13.3	198	9.1	1.13	0.70, 1.82	0.63	4	6.0	24	7.2	2.02	0.41, 9.83	0.39
≥3	103	23.7	640	29.5	0.52	0.32, 0.85	0.01	17	25.4	71	21.3	3.48	0.85, 14.27	0.08
P for trend						0.003							0.10	

Abbreviations: CI, confidence interval; OR, odds ratio

[a] Controls matched 5:1 to case on sex, race, Hispanic ethnicity, age at KPNC enrollment, calendar year of leukemia diagnosis.

[b] From conditional logistic regression.

[c] From *International Classification of Diseases, Ninth Revision,* diagnosis codes.

[d] Reference group = no infections; does not add to 100% because not all infection and medication groupings shown.

moderate support for infections in general modulating risk downwards, with no effect modulation by severity. These observations support the original Greaves' hypothesis.

Differences in health-care utilization practices in different countries could explain some of the heterogeneity across studies. Whether and when an individual seeks medical attention for illness might vary by national, cultural, and economic health-care utilization practices. Parents might be more likely to take their child to the doctor in countries with public or universal health care than those without (28). Among the studies using medical record or administrative databases to ascertain or confirm infection history, only the present study was conducted in a country without some form of public health care. While KPNC is an integrated health-care delivery system, in which all primary to tertiary clinical care is provided to subscribers, the consumer frequently assumes a copayment at the point of service (which varies by insurance plan). Even within a single health-care system, predictors of utilization are complex and can include patient and system-level factors such as distance from medical facility, available transportation, education, health literacy, and acculturation—factors that we could not account for in this analysis. Finally, the lack of a consistent association among studies might indicate that history of infection is not a valid indicator of exposure to infectious agents and/or an individuals' response to immune system stimulation in some study settings.

Our population for this study was not large but did indicate a different relationship of infection to leukemia risk for AML versus ALL. Medication-prescribed infections were nonsignificantly related to AML incidence, with consistently high risk ratios for infections occurring during the first year and lifetime. AML is not a disease thought to have risk reduction from exposure to infectious stimuli; in fact, the only study showing a relationship with infections indicates strong (OR of approximately 6) risk from physician-diagnosed infection (14). Our results here are consistent with infection-related damage, like damage from chemical exposures, inducing risk to AML.

Strengths of this study include the case-control design, with subjects selected from a well-defined cohort; the integrated health-care delivery system with clinical and administrative information from the electronic medical record mapped to a common format for accurate and efficient data extraction; and the large and ethnically diverse population comprising approximately 23% of the Northern California population (29). Some limitations should also be considered. Similar to other studies using medical record abstraction or administrative databases, little data were available on other childhood leukemia risk factors, and confounding might have affected risk estimates. Specifically, geocoded income as a measure of socioeconomic status, both a risk factor for childhood leukemia and associated with health-care utilization patterns, was missing for a large proportion of the population; therefore, matching or adjusting for this variable was not possible. However, among those with geocoded income groups, case and control distributions were similar. If there are any impacts on risk estimates, our inability to assess unmeasured confounders should likely bias our reported results toward the null.

As discussed above, our findings are concordant with significant prior data indicating that infants' daycare attendance, larger family size/higher birth order, and vaccinations (all of which elicit immune responses) are associated with decreased risk of ALL. In light of the large proportion of childhood leukemia that is ALL, our findings should reassure families that early infections leading to a physician visit do not place children at increased risk of leukemia. In addition, given that studies to date have not elucidated the mechanisms through which exposure to infections or response to infections influence childhood leukemia risk, further investigations in this area should include ancillary and contributory information to help clarify responder status of the child in addition to the infections themselves. Examination of additional variables of interest might permit the identification of characteristics of infectious agents and of hosts that alone or in combination are indicative of protection or susceptibility. Such additional information might include immune profiles of mothers and their children, detection of subclinical congenital infections (e.g., cytomegalovirus), assessment of microbiomes of mothers and infants, and identification of prenatally acquired preleukemic genetic lesions. Ultimately, it is hoped that these studies will lead to interventions that reverse the incidence trends of ALL, which have increased in the past 50 years (30, 31).

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Author affiliations: Division of Epidemiology and Biostatistics, School of Public Health, University of California, Berkeley, Berkeley, California (Libby M. Morimoto, Alice Y. Kang, Catherine Metayer); Division of Research, Kaiser Permanente Northern California, Oakland, California (Marilyn L. Kwan, Kamala Deosaransingh, Julie R. Munneke, Charles Quesenberry Jr.); Department of Laboratory Medicine, University of California San Francisco, San Francisco, California (Scott Kogan); Helen Diller Family Comprehensive Cancer Center, University of California San Francisco, San Francisco, California (Scott Kogan); and Center for Genetic Epidemiology, Department of Preventive Medicine, University of Southern California, Los Angeles, California (Adam J. de Smith, Joseph L. Wiemels).

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