American Journal of Epidemiology

Vol. 165, No. 1
DOI: 10.1093/aje/kwj336
Advance Access publication October 11, 2006

Original Contribution

Maternal Illness and Drug/Medication Use during the Period Surrounding Pregnancy and Risk of Childhood Leukemia among Offspring

Marilyn L. Kwan[1,2], Catherine Metayer[2], Vonda Crouse[3], and Patricia A. Buffler[2]

[1] Division of Research, Kaiser Permanente, Oakland, CA.
[2] Division of Epidemiology and Biostatistics, School of Public Health, University of California, Berkeley, CA.
[3] Department of Pediatric Hematology/Oncology, Children's Hospital Central California, Madera, CA.

Received for publication October 31, 2005; accepted for publication May 8, 2006.

Maternal illness and drug/medication use (prescription, over-the-counter, and illicit) during pregnancy might be related to childhood leukemia risk. These issues were evaluated using data (1995–2002) from the Northern California Childhood Leukemia Study. The authors selected 365 children under age 15 years who had been diagnosed with incident leukemia and birth certificate controls who were matched to them on age, sex, Hispanic ethnicity, and maternal race. Data on maternal illnesses and drug use from before pregnancy through breastfeeding were obtained by interview with the biologic mother and were analyzed by conditional logistic regression. Maternal history of influenza/pneumonia was associated with a statistically significant increased risk of acute lymphoblastic leukemia (ALL) in the offspring (odds ratio (OR) = 1.89, 95% confidence interval (CI): 1.24, 2.89), although the risk was nonsignificant for common ALL (OR = 1.41, 95% CI: 0.75, 2.63). A similar pattern of increased risk was found for history of sexually transmitted disease. Use of iron supplements was indicative of decreased ALL risk (OR = 0.67, 95% CI: 0.47, 0.94). Observing an increased risk of leukemia in children of mothers reporting a history of influenza/pneumonia and sexually transmitted disease around the time of pregnancy suggests that maternal infection might contribute to the etiology of leukemia. Furthermore, maternal iron supplement use may be protective against childhood leukemia.

drugs, non-prescription; influenza, human; leukemia, lymphocytic, acute, L1; pharmaceutical preparations; pregnancy; prenatal exposure delayed effects; sexually transmitted diseases; street drugs

Abbreviations: ALL, acute lymphoblastic leukemia; cALL, common acute lymphoblastic leukemia; CI, confidence interval; LSD, lysergic acid diethylamide; NCCLS, Northern California Childhood Leukemia Study; OR, odds ratio.

Childhood leukemia is the primary cause of cancer for children under the age of 15 years (1). It is a heterogeneous disease; 78 percent of case children are diagnosed with acute lymphoblastic leukemia (ALL), which has a peak incidence at ages 2–5 years, and over 15 percent of case children are diagnosed with acute myeloid leukemia (1). Evidence now indicates that ALL, especially common ALL (cALL), which represents B-lineage ALL diagnosed at ages 2–5 years and expressing CD10 surface antigen (2, 3), might be initiated prenatally by characteristic genetic rearrangements (4–7). These genetic changes might arise from illness of the mother during pregnancy. Maternal history of influenza/pneumonia before and during pregnancy may be associated with an increased risk of childhood leukemia in the offspring (8–10), although three studies found no association or a decreased risk (11–13). Urinary tract infections appear to be not associated with childhood leukemia risk (12–14).

Other prepregnancy and pregnancy events, such as maternal drug use (prescription, over-the-counter, and illicit), have been linked to adverse outcomes such as birth defects, low

Correspondence to Dr. Marilyn Kwan, Division of Research, Kaiser Permanente, 2000 Broadway, First Floor, Oakland, CA 94612 (e-mail: marilyn.l.kwan@kp.org).

birth weight, and physical and developmental delays (15–17) and might contribute to leukemogenesis as well (18). Investigators have previously assessed the roles of recreational drugs, antibiotics, and iron supplements before and during pregnancy. In three studies, use of recreational drugs by the mother was indicative of an increased risk of childhood leukemia in the offspring (18–20), but in one study, the finding was not statistically significant (18). Among eight studies on maternal antibiotic use (9, 10, 12, 18–22), only one found a significant association with elevated risk of childhood leukemia in progeny (21). For maternal use of iron supplements, several investigators reported a reduction in risk of childhood leukemia, yet none of the findings were statistically significant (10, 20, 23).

We conducted a comprehensive analysis of 365 cases and 460 matched controls within the Northern California Childhood Leukemia Study (NCCLS) to replicate and further elucidate these potential maternal associations in a large case-control study of childhood leukemia. We expanded on previous studies by assessing a more diverse list of maternal illnesses, by analyzing maternal illness and drug use during breastfeeding as well as before pregnancy and during pregnancy, and by further categorizing ALL into cALL, an important distinction to make in order to fully examine the suggested infectious etiology of childhood leukemia (3). Since maternal illness and drug use are related exposures that represent both the health status and the lifestyle of the mother, we report the two sets of results concurrently.

MATERIALS AND METHODS

Study population

The NCCLS is an ongoing, population-based case-control study that began in 1995. This analysis consisted of data from two phases: phase 1 (August 19, 1995–November 30, 1999), covering 17 counties in northern California, and phase 2 (December 1, 1999–November 30, 2002), covering an additional 18 counties in central California. Incident cases of childhood leukemia were identified on the basis of *International Classification of Diseases for Oncology* criteria (24) using rapid case ascertainment procedures in seven (phase 1) to nine (phase 2) pediatric hospitals in the northern and central California study region. Comparison with the statewide California Cancer Registry for 2000 showed that 95 percent and 76 percent of eligible cases among residents in the five-county San Francisco-Oakland Metropolitan Statistical Area and in the other 30 counties of the study area, respectively, were identified by the NCCLS protocol. Case children were eligible if they were under 15 years of age, had no previous cancer, and lived within the study region and if their parents spoke either English or Spanish. The study was approved by the University of California Office for the Protection of Human Subjects, the California Health and Human Services Agency Committee for the Protection of Human Subjects, and the institutional review boards of the collaborating hospitals. Written informed consent was obtained from the parents of all participating subjects.

Control subjects who resided within the study area were randomly selected from birth certificates supplied by the California Department of Health Services and were individually matched to cases on date of birth, sex, Hispanic ethnicity (the child was classified as Hispanic if either parent was Hispanic), maternal race, and maternal county of residence at birth (phase 1 only). Matching on maternal county of residence at birth was not pursued in phase 2 because of concerns regarding overmatching on potential environmental exposures related to leukemia risk. Initially in phase 1, one birth certificate control and one friend control were selected. Because of evidence of selection bias, use of the friend control group was discontinued (25). A second birth certificate control was then added in phase 2 to increase statistical power. Therefore, the data available included 282 1:1 matched case-control sets and 100 1:2 matched case-control sets, for which interviews were completed by December 1, 2002. For cases not born in California (7 percent), controls were selected from the case county of residence at diagnosis. Inclusion of case children born out of state was demonstrated to not modify study results in earlier analyses (26, 27).

The overall case participation rate was 86 percent, while the overall control participation rate (defined as the number of eligible participating controls divided by the total number of eligible controls) was 85 percent (482/570). Including all potential controls (eligible, not located, and refused; $n = 840$ ($570 + 149 + 121$)) by assuming that the same percentage of controls would be eligible as the percentage of controls whose eligibility was confirmed yielded a response rate of 57 percent (482/840) (see figure 1 for details). Reasons for nonresponse of the eligible and presumed-eligible controls included refusal (25 percent) and nonlocatability (18 percent). Further description of NCCLS control recruitment is provided in a previous publication (25).

Data collection and management

Information on maternal illness and drug/medication use (prescription, over-the-counter, and illicit) 3 months before pregnancy, during all trimesters of pregnancy, and while breastfeeding was collected by in-home interview with the biologic mother of the index child. For seven illnesses (influenza/pneumonia, urinary tract infection, spotting/cramping/bleeding, nausea/vomiting, swelling, anemia, and sexually transmitted diseases (data collected only in phase 1)), respondents were asked, ''In the 3 months before your pregnancy with [*child*], during your pregnancy (or while breastfeeding), did you have any of the following health problems or conditions?'' For six classes of prescription, over-the-counter, or illicit drugs (birth control pills, nausea medication, iron supplements (excluding prenatal vitamins), antibiotics, herbal medication or natural remedies, and recreational drugs), respondents were asked, ''We are interested in drugs taken 3 months before pregnancy or during pregnancy (or while breastfeeding), including those prescribed by a doctor, over-the-counter drugs, and drugs you may have obtained from a friend. Did you take [*drug*]?'' If the respondent reported ever having a sexually transmitted disease or taking any drug, she was asked to provide the type of disease or the name of the drug, respectively. Data on frequency of illness

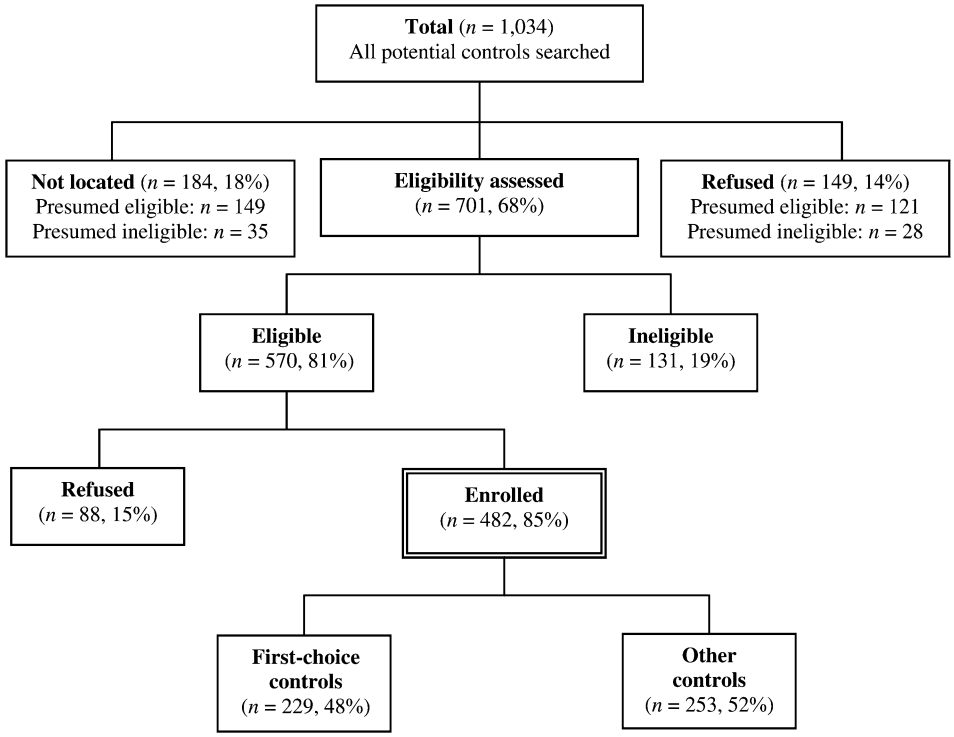

FIGURE 1. Control selection strategy for an analysis of the associations of maternal illness and drug/medication use with childhood leukemia, Northern California Childhood Leukemia Study, Berkeley, California, 1995–2002. For calculation of the proportions of controls "Presumed eligible" and "presumed ineligible," it was assumed that the percentages eligible and ineligible would be the same as those for potential controls whose eligibility was assessed (81% and 19%, respectively).

(but not of drug use) were also collected, but numbers were insufficient for analysis.

The trimester periods were collapsed into a general pregnancy period because of a small sample size. Since mothers may potentially misclassify their pregnancy status by up to 2 weeks on the basis of the female menstrual cycle (28), we combined the period of 3 months before pregnancy with the period of pregnancy to minimize misclassification of exposure. For the purposes of this analysis, the term "overall period" refers to the period of 3 months before pregnancy through the end of breastfeeding, and "peripregnancy" refers to the period of 3 months before pregnancy through the end of pregnancy. The final data set for analysis consisted of 365 cases and 460 controls for childhood leukemia, 311 cases and 398 controls for ALL, and 145 cases and 191 controls for cALL. We evaluated the cALL subgroup separately to specifically address the infectious hypothesis in the development of childhood leukemia.

Statistical analysis

Baseline characteristics of cases and controls were compared using the Pearson chi-square test. Associations between maternal illnesses and drug use, along with socioeconomic characteristics of participants (household income and maternal education), were evaluated with Pearson correlation coefficients and frequency tables, respectively, to characterize the data set prior to regression modeling. To assess the associations between maternal history of illnesses and drug use and risk of childhood leukemia, we constructed conditional logistic regression models. Separate models of childhood leukemia, ALL, and cALL (maternal illness analysis only) were created for each of the exposure periods of interest (peripregnancy and breastfeeding) and for the overall time period. Odds ratios were considered statistically significant if the 95 percent confidence interval excluded 1.00 and the p value was 0.05 or less. Confounding was examined by using chi-square tests to compare the likelihood ratio statistics of the models with and without inclusion of a priori confounding factors (annual household income, maternal education, maternal age at the birth of the child, and maternal smoking). An additive conditional logistic model was assumed adjusting for household income, maternal education, and maternal age at the birth of the child (29). The categories of confounders included in the model are displayed in table 1.

RESULTS

The study sample was 36 percent Hispanic, 50 percent non-Hispanic White, 4 percent non-Hispanic Black, and 10 percent other race/ethnicity. The childhood leukemia cases

TABLE 1. Selected characteristics of children with leukemia and matched controls, Northern California Childhood Leukemia Study, Berkeley, California, 1995–2002

	Childhood leukemia					Acute lymphoblastic leukemia				
	Cases		Controls		*p* value*	Cases		Controls		*p* value*
	No.	%	No.	%		No.	%	No.	%	
Child's age (years)†										
<1	19	5	21	5		13	4	15	4	
1–<2	36	10	47	10		26	8	34	8	
2–5	189	52	246	53		179	58	234	59	
6–10	79	22	95	21		65	21	78	20	
11–14	42	11	51	11		28	9	37	9	
Mean (SD‡)	5.4 (3.6)		5.4 (3.6)			5.2 (3.4)		5.2 (3.4)		
Child's sex†										
Male	168	46	216	47		164	53	206	52	
Female	197	54	244	53		147	47	192	48	
Child's race/ethnicity†										
Hispanic	130	36	171	37		113	36	149	37	
Non-Hispanic White	188	51	231	50		161	52	203	51	
Non-Hispanic Black	13	4	16	4		9	3	11	3	
Other	34	9	42	9		28	9	35	9	
Breastfeeding (months)					0.43					0.48
None	38	12	43	10		33	12	36	10	
<6	174	53	216	51		148	53	188	51	
>6	113	35	167	39		99	35	146	39	
Mean (years) (SD)	6.7 (7.9)		7.4 (8.1)			6.9 (8.0)		7.3 (7.7)		
Maternal age (years) at child's birth					0.15					0.16
<25	123	34	124	27		106	34	109	27	
25–29	90	25	135	29		74	24	117	29	
30–34	104	28	131	29		91	29	113	28	
≥35	48	13	70	15		40	13	59	15	
Mean (SD)	28.1 (6.1)		28.9 (6.0)			28.0 (6.0)		28.8 (5.9)		
Maternal education					0.04					0.08
High school or less	159	44	161	35		134	43	139	35	
Some post-high-school education	100	27	153	33		89	29	135	34	
College graduate	106	29	146	32		88	28	124	31	
Maternal smoking					0.36					0.51
Never	256	70	336	73		218	70	288	72	
Ever	109	30	124	27		93	30	110	28	
Annual household income (dollars)					<0.001					0.002
<15,000	55	15	42	9		42	13	36	9	
15,000–29,999	69	19	68	15		62	20	59	15	
30,000–44,999	61	17	55	12		49	16	46	11	
45,000–59,999	57	15	73	16		55	18	62	16	
60,000–74,999	39	11	63	14		31	10	51	13	
≥75,000	84	23	159	34		72	23	144	36	
Total	365§		460§			311§		398§		

* Pearson χ^2 test; two-sided.

† For phase 1 (August 19, 1995–November 30, 1999), cases and controls were matched 1:1 on date of birth, sex, Hispanic ethnicity, maternal race, and maternal county of residence at birth. For phase 2 (December 1, 1999–November 30, 2002), cases and controls were matched 1:1 and 1:2 on date of birth, sex, Hispanic ethnicity, and maternal race. Age is age at diagnosis for cases and age at the corresponding date for controls.

‡ SD, standard deviation.

§ A total of 270 1:1 case-control pairs and 95 1:2 case-control triplets of childhood leukemia and 224 pairs and 87 triplets of the acute lymphoblastic leukemia subtype.

TABLE 2. Associations between history of maternal illness and risk of leukemia among offspring, Northern California Childhood Leukemia Study, Berkeley, California, 1995–2002

Maternal illness (ever vs. never)	Childhood leukemia				Acute lymphoblastic leukemia				Common acute lymphoblastic leukemia			
	No. of exposed cases	No. of exposed controls	OR*,†	95% CI*	No. of exposed cases	No. of exposed controls	OR†	95% CI	No. of exposed cases	No. of exposed controls	OR†	95% CI
Influenza/pneumonia												
Overall‡	82	69	1.74	1.18, 2.57	73	58	1.89	1.24, 2.89	33	36	1.41	0.75, 2.63
Peripregnancy‡	71	53	1.77	1.17, 2.68	64	44	2.02	1.28, 3.18	30	28	1.36	0.70, 2.65
Urinary tract infection												
Overall	46	65	0.78	0.51, 1.21	39	57	0.81	0.51, 1.29	21	27	0.95	0.48, 1.89
Peripregnancy	36	53	0.68	0.42, 1.09	31	47	0.70	0.42, 1.17	17	23	0.78	0.36, 1.68
Spotting/cramping/bleeding												
Overall	92	101	1.16	0.81, 1.64	83	88	1.25	0.86, 1.81	40	39	1.24	0.70, 2.23
Peripregnancy	88	92	1.16	0.81, 1.65	79	82	1.20	0.82, 1.75	38	34	1.22	0.66, 2.24
Nausea/vomiting												
Overall	113	140	0.95	0.68, 1.32	96	124	0.90	0.63, 1.28	36	54	0.81	0.44, 1.49
Peripregnancy	107	131	0.94	0.67, 1.32	92	116	0.91	0.63, 1.31	36	49	0.90	0.48, 1.68
Swelling												
Overall	40	59	0.82	0.52, 1.30	33	51	0.77	0.46, 1.29	15	22	1.01	0.45, 2.28
Peripregnancy	38	56	0.81	0.51, 1.30	32	49	0.77	0.46, 1.30	14	22	0.91	0.40, 2.08
Anemia												
Overall	88	115	0.88	0.62, 1.25	74	100	0.86	0.59, 1.26	35	47	0.92	0.50, 1.69
Peripregnancy	81	103	0.90	0.63, 1.29	69	92	0.87	0.59, 1.29	33	44	1.03	0.55, 1.91
Sexually transmitted diseases§												
Overall	16	3	6.33	1.65, 24.27	13	3	4.85	1.24, 18.96	9	2	7.04	0.87, 56.98
Peripregnancy	13	2	7.59	1.58, 36.56	12	2	6.65	1.37, 32.38	8	1	13.58	0.93, 198.71

* OR, odds ratio; CI, confidence interval.

† Derived from conditional logistic regression adjusting for household income, maternal education, and maternal age at the birth of the child as presented in table 1.

‡ Overall: 3 months before pregnancy, during pregnancy, and while breastfeeding; peripregnancy: 3 months before pregnancy and during pregnancy.

§ Includes chlamydia, genital herpes, and human papillomavirus. Data were collected only in phase 1.

and their matched controls were similar with respect to birth weight, breastfeeding, and maternal smoking (table 1). Compared with controls, more leukemia cases came from families with lower annual household income ($p < 0.001$) and were born to younger mothers ($p = 0.15$) with fewer years of education ($p = 0.04$). When the ALL cases were compared with their matched controls, the distributions of these characteristics were similar (table 1).

Antibiotic use was correlated with influenza/pneumonia ($r = 0.14$; $p < 0.001$), urinary tract infection ($r = 0.45$; $p < 0.001$), spotting/cramping/bleeding ($r = 0.12$; $p < 0.001$), nausea/vomiting ($r = 0.14$; $p < 0.001$), and sexually transmitted disease ($r = 0.16$; $p < 0.002$). Anemia and nausea/vomiting were correlated with use of iron supplements ($r = 0.55$; $p < 0.001$) and nausea medication ($r = 0.29$; $p < 0.001$), respectively. Birth control pills (25 percent), iron supplements (27 percent), antibiotics (35 percent), herbal medications or natural remedies (29 percent), and recreational drugs (26 percent) were more commonly used by women with higher family incomes (≥$75,000/year) than by women with lower incomes. Birth control pills (41 percent), nausea medication (45 percent), iron supplements (41 percent), and recreational drugs (38 percent) were more often used by women with lower education (high school or less) than by women with higher education.

The associations between maternal history of illnesses and risk of childhood leukemia, ALL, and cALL are shown in table 2. During the overall period, maternal influenza/pneumonia was associated with a significantly increased risk of both childhood leukemia (odds ratio (OR) = 1.74, 95 percent confidence interval (CI): 1.18, 2.57) and ALL (OR = 1.89, 95 percent CI: 1.24, 2.89). After the results were stratified by antibiotic use, the effect was still elevated and did not vary by ever/never use of antibiotics (p for interaction = 0.95). Maternal history of sexually transmitted diseases such as chlamydia, genital herpes, and human papillomavirus was also associated with significantly increased risks of childhood leukemia (OR = 6.33, 95 percent

TABLE 3. Associations between history of maternal drug use and risk of leukemia among offspring, Northern California Childhood Leukemia Study, Berkeley, California, 1995–2002

Maternal drug/ medication use (ever vs. never)	Childhood leukemia				Acute lymphoblastic leukemia			
	No. of exposed cases	No. of exposed controls	OR*,†	95% CI*	No. of exposed cases	No. of exposed controls	OR†	95% CI
Birth control pills								
Overall‡	66	82	0.96	0.66, 1.42	58	71	0.98	0.65, 1.47
Peripregnancy‡	59	77	0.95	0.64, 1.43	55	67	1.01	0.66, 1.54
Nausea medication								
Overall	23	24	1.12	0.58, 2.14	20	18	1.38	0.68, 2.79
Peripregnancy	20	24	1.01	0.51, 2.02	18	18	1.33	0.64, 2.76
Iron supplements								
Overall	99	152	0.70	0.51, 0.97	83	133	0.67	0.47, 0.94
Peripregnancy	69	102	0.76	0.52, 1.11	57	88	0.72	0.47, 1.09
Antibiotics								
Overall	100	125	1.12	0.79, 1.59	87	105	1.28	0.88, 1.86
Peripregnancy	57	71	1.00	0.66, 1.52	48	65	0.96	0.62, 1.50
Herbal medication								
Overall	32	54	0.76	0.47, 1.23	25	46	0.72	0.42, 1.25
Peripregnancy	20	25	1.01	0.53, 1.94	13	22	0.73	0.34, 1.56
Recreational drugs§								
Overall	49	39	1.50	0.94, 2.38	44	31	1.74	1.04, 2.92
Peripregnancy	30	35	1.12	0.65, 1.92	28	27	1.42	0.78, 2.59

* OR, odds ratio; CI, confidence interval.

† Derived from conditional logistic regression adjusting for household income, maternal education, and maternal age at the birth of the child as presented in table 1.

‡ Overall: 3 months before pregnancy, during pregnancy, and while breastfeeding; peripregnancy: 3 months before pregnancy and during pregnancy.

§ Includes marijuana, cocaine, heroin, methamphetamine/amphetamine (“speed”/“crank”), 3,4-methylenedioxymethamphetamine (“ecstasy”), and lysergic acid diethylamide (LSD).

CI: 1.65, 24.27) and ALL (OR = 4.85, 95 percent CI: 1.24, 18.96), although these odds ratios were based on only 16 and 13 exposed cases, respectively, and three and two exposed controls. The positive association between maternal influenza/pneumonia and sexually transmitted disease and risk of childhood leukemia persisted when we examined only cALL cases and controls, yet with the smaller numbers of cases and controls, the odds ratios were no longer significant. The other illnesses examined were not related to risk of leukemia during childhood. Restricting the exposure period to peripregnancy revealed similar associations as those observed in the overall period. After limiting the analysis to the breastfeeding period, the odds ratios for maternal influenza/pneumonia and sexually transmitted disease were elevated yet nonsignificant (not shown).

The associations between maternal drug use and risk of childhood leukemia and ALL are presented in table 3. During the overall period, taking iron supplements was significantly associated with decreased risks of childhood leukemia (OR = 0.70, 95 percent CI: 0.51, 0.97) and ALL (OR = 0.67, 95 percent CI: 0.47, 0.94). A significantly elevated risk was observed only for ALL with use of recreational drugs during the overall period (OR = 1.74, 95 percent CI: 1.04, 2.92). Adjustment for maternal smoking did not appreciably alter the effect estimates (not shown). Mothers reported using such illegal substances as marijuana (79 percent), methamphetamine/amphetamine (“speed”/“crank”; 9 percent), cocaine (4 percent), lysergic acid diethylamide (LSD; 3 percent), 3,4-methylenedioxymethamphetamine (“ecstasy”; 3 percent), and heroin (2 percent). None of the other drugs queried about were associated with risk of childhood leukemia during this overall time period. Examination of maternal use of iron supplements and recreational drugs during peripregnancy reflected similar trends, but the odds ratios were not significant. The associations observed for use of iron supplements and recreational drugs during the breastfeeding period were of the same magnitude as those of the overall and peripregnancy periods but were not significantly associated with childhood leukemia or ALL risk (not shown).

DISCUSSION

In this study, we examined the associations between maternal illness and drug use and risk of childhood leukemia in

offspring. Maternal history of influenza/pneumonia during the overall period of 3 months before pregnancy through the end of breastfeeding, as well as only the peripregnancy period of 3 months before pregnancy through the end of pregnancy, was associated with increased risks of childhood leukemia, ALL, and cALL in the offspring, but the latter risk was not significant. Maternal history of sexually transmitted disease was also associated with elevated risks of childhood leukemia, ALL, and cALL, although the limited number of exposed cases and controls produced wide confidence intervals and the effect estimate for cALL was not significant. Maternal use of iron supplements during the overall period was significantly associated with a reduced risk of childhood leukemia in progeny, while maternal use of recreational drugs during the overall period was associated with an increased risk of childhood ALL.

The possible association between maternal influenza and risk of childhood leukemia in offspring was first suggested two decades ago in an ecologic analysis (30). Using population-based data to classify influenza epidemics and construct influenza cohorts for 1,317 leukemic children, the authors identified excess leukemia cases diagnosed at ages 0–4 years in the influenza cohort when the first trimester coincided with an influenza epidemic. A relative risk of 3.4 was reported for the exposed cohort in the first trimester as compared with the nonexposed cohort.

Six case-control studies based on medical records (8–10, 12, 13) or personal interviews (11) have examined the effect of maternal influenza or pneumonia before or during pregnancy on childhood leukemia or cancer risk. Investigators from three studies reported associations between respiratory tract (10) or viral (9) infections and increased risk of childhood leukemia and between acute respiratory infections and increased risk of childhood cancer (8). In contrast, other investigators reported negative results for influenza (11, 12) and influenza-like symptoms of pneumonia, gastroenteritis, sinusitis, and rhinitis (13).

A group of Nordic investigators has directly examined the association between maternal viral infections and risk of childhood leukemia in offspring (31, 32). In a case-control study of 342 ALL cases and 61 other leukemia cases and 1,216 matched controls, Lehtinen et al. (31) analyzed serum samples collected during the first trimester of pregnancy for antibodies to herpesviruses. The presence of maternal Epstein-Barr virus immunoglobulin M was significantly associated with an increased risk of ALL in offspring, while cytomegalovirus immunoglobulin M was associated with a borderline-significant increased risk of ALL. No association was found for maternal herpesvirus 6 immunoglobulin M. Using the same archive of first-trimester sera, Lehtinen et al. (32) reported that *Mycoplasma pneumoniae* immunoglobulin M was marginally significantly associated with an increased risk of childhood leukemia in progeny, while no association was noted for *Chlamydia trachomatis*. In another case-control study, Dockerty et al. (11) reported no association between the presence of maternal cold sores/oral herpes immediately prior to or during pregnancy and the risk of childhood leukemia. To our knowledge, no previous studies have examined the relation between maternal human papillomavirus and risk of childhood leukemia.

Maternal infections during pregnancy could initiate an in utero infection that might increase cALL risk by occurring during a specific stage of B-cell development or a period of immunologic competency of the fetus (3). Influenza or pneumonia and specific sexually transmitted diseases such as human papillomavirus and herpes can be transmitted across the placenta and thus might play an etiologic role in this infectious model (33, 34). Furthermore, human papillomavirus has been shown to be a primary cause of cervical cancer through viral interference with essential regulatory mechanisms of cellular growth, DNA repair, and immunologic function (35). In our study, we observed an increased risk of cALL in offspring of mothers who reported a history of influenza/pneumonia or sexually transmitted disease. The results were not statistically significant compared with those for childhood leukemia and ALL, but the lack of statistical significance might have been due to limited numbers for the cALL analysis. It is also possible that the proposed infectious etiology of childhood leukemia might not be specific for cALL. Timing or other factors that affect the second leukemogenetic event may play a stronger role.

Maternal use of iron supplements overall was significantly associated with decreased risks of both childhood leukemia and ALL in the NCCLS population. Three previous studies found a reduced yet nonsignificant risk of ALL with maternal use of iron supplements during pregnancy (10, 20, 23), while three other studies suggested an increased risk with ALL (22), no association with leukemic Down syndrome (36), and no association with acute nonlymphoblastic leukemia (19). In a previous analysis of NCCLS phase 1 data on maternal diet in the year before pregnancy, use of iron supplements was not associated with ALL risk (26). Those authors noted that the prepregnancy results on vitamin supplements might not be valid for pregnancy, since supplementation does increase during pregnancy (26). Mothers who take iron supplements while pregnant may decrease the risk of leukemia in their children, since this mineral is necessary to prevent anemia, which was observed in a medical record study to be associated with a significant increase in risk of childhood leukemia (9). In our analysis, anemia was not associated with childhood leukemia risk; this may have been due to self-report inaccuracies, since anemia usually requires a medical diagnosis. Furthermore, maternal self-reports of anemia were found to have low validity in a medical record validation study of infant leukemia (37). While there is currently no direct biologic evidence that iron supplements decrease childhood leukemia risk, our results suggest that iron intake might be essential in establishing a healthy in utero environment for the developing fetus.

Our results were consistent with those of previous studies observing an association between maternal use of recreational drugs during pregnancy and increased risk of childhood leukemia (19, 20). Marijuana was the most prevalent illicit drug used by mothers in these studies, as well as in our study (79 percent). In animal experiments, marijuana smoke has been shown to be a mutagenic and fetotoxic substance (38). In a study of umbilical cord blood lymphocytes, five newborns of marijuana smokers had a significantly higher frequency of mutant lymphocytes than did five newborns of nonsmokers (39). This observation suggests that smoking

marijuana during pregnancy can cause in utero DNA damage, leading to elevated risk of childhood cancers such as leukemia.

As in all case-control designs, recall bias cannot be ruled out, especially considering the sensitive nature of the data collected (i.e., sexually transmitted disease status and recreational drug use while pregnant). Since an underlying social stigma might be attached to these exposures, reporting could have been distorted among both cases and controls, although it is unknown whether recall would be differential. A study assessing sources of self-report bias using recreational drug-use data observed that social desirability concerns were primarily associated with underreporting of drug use, while memory difficulties were mainly related to overreporting of drug use (40). Another limitation is that information on maternal illness was collected by self-report via in-person interviews rather than from medical records. A paper on maternal reporting of pregnancy-related events found lower validity and reliability for pregnancy complications, but reassuringly, little evidence of differential misclassification was noted (37). Lastly, frequency of drug use during each time period was not obtained in our study, precluding a dose-response assessment.

Our analyses presented several strengths. First, compared with previous studies which examined influenza/pneumonia (11–13), our exposure category was more homogeneous, consisting of persons who reported having influenza, pneumonia, or any related symptoms. In addition, we assessed a more diverse list of illnesses, within which we conducted a subgroup analysis of cALL cases and controls. Second, this study evaluated maternal illness and drug use during breastfeeding as well as prior to and during pregnancy. Analysis of this overall window of exposure is more comprehensive, especially considering that mothers can potentially transfer viral agents and excrete drugs to their infants via breast milk (41, 42). Finally, the NCCLS is distinguished by the use of population-based birth certificate controls that have been shown to be representative of our source population (25).

In conclusion, we observed that any maternally reported episode of influenza/pneumonia or sexually transmitted disease in the overall period of 3 months before pregnancy through the end of breastfeeding was associated with significantly increased risks of childhood leukemia and ALL in progeny. Additionally, maternal use of iron supplements in the overall period of 3 months before pregnancy through breastfeeding was associated with significantly decreased risks of childhood leukemia and ALL in offspring, while use of recreational drugs was associated with a significantly elevated risk of ALL only. In the future, we plan to assess genetic susceptibility genes of drug metabolism and infection (cytochrome P450, glutathione *S*-transferases, and chemokines) to further and more directly examine these potential maternal associations with risk of childhood leukemia.

ACKNOWLEDGMENTS

This study was supported by research grants PS42 ES04705 and R01 ES09137 from the National Institute of Environmental Health Sciences (Research Triangle Park, North Carolina) and by grant 019165 from Children with Leukaemia (London, United Kingdom).

The authors thank the following persons for their assistance with patient recruitment: Dr. Jim Feusner at Children's Hospital Oakland; Dr. Gary Dahl at Packard Children's Hospital; Drs. Katherine Matthay and Mignon Loh at the University of California, San Francisco; Dr. Kenneth Leung at Kaiser San Francisco Hospital; Dr. Stacy Month at Kaiser Oakland Hospital; Drs. Carolyn Russo and Alan Wong at Kaiser Santa Clara Hospital; Dr. Jonathan Ducore at the University of California, Davis, Medical Center; and Dr. Vincent Kiley at Kaiser Sacramento Hospital. The authors also thank the study staff for their hard work and dedication, Monique Does for supervising the fieldwork and interviews, and Dr. Anand Chokkalingam for providing helpful comments and suggestions on the manuscript.

Conflict of interest: none declared.

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