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Original Contribution

Parental Smoking and the Risk of Childhood Leukemia

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Cigarette smoke has been linked to adult myeloid leukemia; however, the association between parental smoking and childhood leukemia remains unclear. Parental smoking and the risk of childhood leukemia were examined in the Northern California Childhood Leukemia Study, a case-control study, between 1995 and 2002. The present analysis included 327 acute childhood leukemia cases (281 acute lymphoblastic leukemia (ALL) and 46 acute myeloid leukemia (AML)) and 416 controls matched on age, sex, maternal race, and Hispanic ethnicity. Maternal smoking was not associated with an increased risk of either ALL or AML. Paternal preconception smoking was significantly associated with an increased risk of AML (odds ratio = 3.84, 95% confidence interval: 1.04, 14.17); an increased risk for ALL was suggestive for paternal preconception smoking (odds ratio = 1.32, 95% confidence interval: 0.86, 2.04). Greater risks of ALL were observed compared with the risk associated with paternal preconception smoking alone, when paternal preconception smoking was combined with maternal postnatal smoking ($p_{interaction} = 0.004$) or postnatal passive smoking exposure ($p_{interaction} = 0.004$). These results strongly suggest that exposure to paternal preconception smoking alone or in combination with postnatal passive smoking may be important in the risk of childhood leukemia.

case-control studies; child; leukemia; smoking

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

Tobacco smoke contains more than 60 known human or animal carcinogens (1) and is known to increase the risk of various adult cancers including myeloid leukemia (2). The role of parental smoking in childhood cancer is less certain, although the association may be biologically plausible. Newborns of smoking mothers have increased frequencies of chromosomal abnormalities (3, 4). Smoking is also associated with oxidative damage and aneuploidy of sperm (5, 6).

Epidemiologic studies to date have found inconsistent results regarding the association between parental smoking and childhood leukemia. A case-control study from China in which none of the mothers smoked showed that the risk of childhood acute leukemia increased if the father smoked for 5 or more pack-years before conception (7). A large case-control study from the United Kingdom based on 1,630 leukemia cases and 6,987 controls reported a nonsignificant increasing trend for risk of childhood leukemia associated with paternal preconception smoking and a significant decreasing trend for maternal smoking during pregnancy (8). In contrast, a large case-control study from the United States based on approximately 2,500 leukemia cases and 2,500 controls did not find evidence of an association between paternal or maternal smoking before or during pregnancy and childhood leukemia (9). Recently, a population-based cohort study of 1,440,542 Swedish children indicated that

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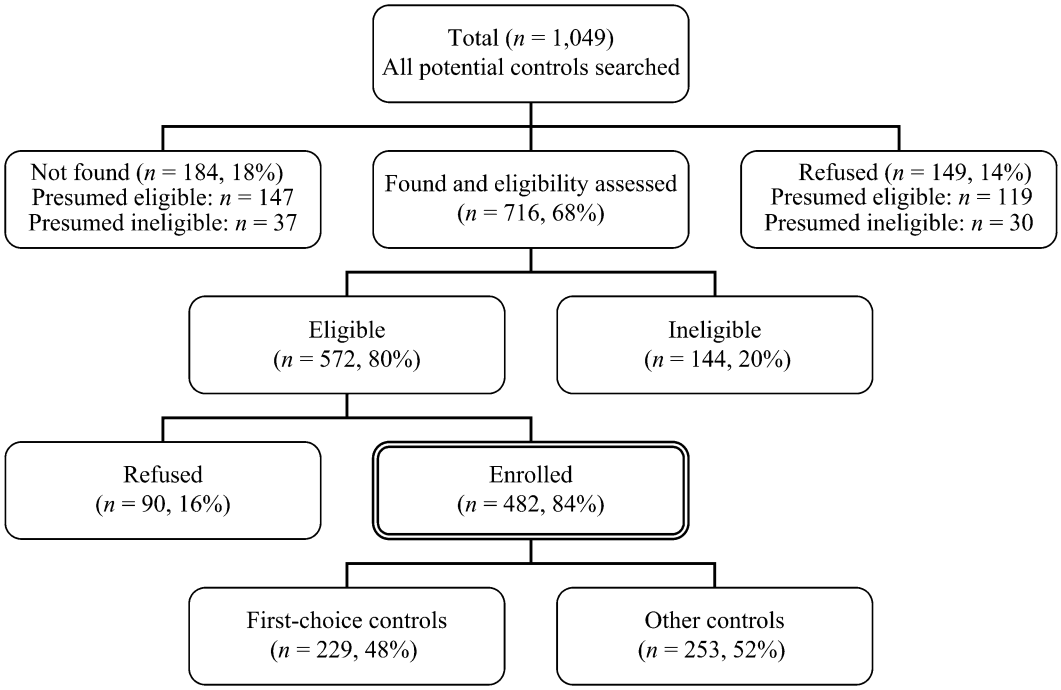

FIGURE 1. Selection of controls for the Northern California Childhood Leukemia Study in the period of August 19, 1995, to November 30, 2002. "Presumed eligible" and "presumed ineligible" determined by assuming the same percentage of eligible as that in potential controls who were located and whose eligibilities were assessed.

maternal smoking between the eighth and 12th week of gestation was associated with a significantly lower risk for acute lymphoblastic leukemia (ALL) and a higher risk for acute myeloid leukemia (AML) (10).

Only two studies to date have examined the joint influence between paternal and maternal smoking on the risk of childhood leukemia (9, 11), and only one emphasized the sequence of exposure (11). In the current analysis, we examined the association between paternal and maternal smoking and the risk of ALL and AML. Particular emphasis is placed on the timing of exposure (before conception, during pregnancy, and after birth). In addition, the current analysis focused on the joint influence between paternal smoking exposure before conception and the child's in utero or postnatal smoking exposure.

MATERIALS AND METHODS

Study population

The Northern California Childhood Leukemia Study is an ongoing case-control study. Phase I of the study (1995–1999) included 17 counties in the San Francisco Bay Area, and phase II of the study (1999–2002) included 18 additional counties in the California Central Valley. The study population of the Northern California Childhood Leukemia Study is racially and ethnically diverse, and 40 percent of the study participants are Hispanic. Case subjects were originally ascertained usually within 72 hours of diagnosis from seven hospitals (phase I) and later expanded to include nine hospitals (phase II) in the study area. For each case, one or two control subjects were randomly selected from birth certificates through the California Office of Vital Records, matched on age, sex, Hispanic ethnicity, and maternal race. There were four eligibility criteria for cases and controls: 1) being a resident of the study area; 2) being less than 15 years of age at the time of case diagnosis (referent date for controls); 3) having at least one English- or Spanish-speaking parent or guardian; and 4) having no previous diagnosis of cancer. Eighty-six percent of the eligible cases consented to participate in the study. For every control subject search, a set of four birth certificates meeting the matching criteria was randomly generated. One of the four birth certificates was randomly chosen as a potential control to be recruited. If the recruitment with the first-choice control was not successful, another birth certificate from those remaining was randomly selected. Additional sets of four birth certificates were requested if recruitment was not successful with the first set of birth certificates. Figure 1 presents a detailed flow chart of the search process and the results for selection of controls. Of the 572 eligible controls contacted, 482 (84 percent) enrolled in the study. The overall participation for the controls was 58 percent (the number of the enrolled controls divided by the total number of control subjects excluding the known and presumed ineligibles). A recent publication from the Northern California Childhood Leukemia Study indicated that no evidence exists that the participating controls were different from the sampled population

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in terms of parental age, parental education, and mother's reproductive history (12).

The study was approved by the University of California Committee 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 all the participating hospitals. Written, informed consent was obtained from the parents of all participating subjects.

Data collection and management

Paternal smoking exposure information was collected from biologic mothers through self-administered questionnaires in phase I and through in-person interviews with biologic mothers in phase II. For fathers who ever smoked (defined as ever smoked 100 cigarettes before the case child's diagnosis of leukemia), additional smoking exposure information (yes/no, number of cigarettes smoked per day) was obtained for the preconception period (3 months prior to the mother's pregnancy). Maternal smoking exposure information was collected using the same method through in-person interviews with biologic mothers for both phases of the study. For mothers who ever smoked, additional smoking exposure information was obtained for the preconception period, during pregnancy, while breastfeeding, and during the postnatal period (between the child's birth and the child's third birthday or the date on which the case child was diagnosed with leukemia, whichever came first). In addition, biologic mothers were asked about the presence (yes/no) of other smokers (anyone else besides the mother, including the father) in the household during the postnatal period. Data on parental job title, maternal dietary intake 1 year before pregnancy, maternal alcohol consumption during pregnancy, and maternal medication/recreational drug use during pregnancy were also collected.

The analysis consists of the two largest racial/ethnic groups (Hispanic and non-Hispanic White) from the Northern California Childhood Leukemia Study. Two chronic myeloid leukemia cases were excluded. Subjects diagnosed at less than 2 months of age (two ALL cases and two AML cases) were excluded from the analyses involving postnatal exposure, since it is uncertain whether the postnatal exposure, if any, occurred during this short period before diagnosis. Those with missing smoking data were excluded from the analysis (16/647 or 2.5 percent for fathers and 1/745 or 0.1 percent for mothers). The collection of paternal smoking exposure data did not commence until 12 months after the study began; thus, the number of subjects available is smaller than that for maternal smoking analyses. The final sample included 327 case-control sets (238 pairs and 89 triplets) for maternal smoking and 267 case-control sets (184 pairs and 83 triplets) for paternal smoking. Of the 327 cases of leukemia, 281 were ALL and 46 were AML.

Statistical analysis

Data on ALL and AML were analyzed separately, as these subtypes are clinically and epidemiologically distinct (13). Conditional logistic regression models were used to estimate the odds ratios measuring the risk of childhood leukemia associated with parental smoking during the preconception, pregnancy, and postnatal period while adjusting for the influence of household income. Likelihood ratio tests were used to compare specific models to assess the role of different combinations of analytical variables. Because adjustment for parental age and education had minimal impact on the results, only household income was included in the final model. In our study population, mothers who smoked were more likely to use recreational drugs, to consume alcohol during pregnancy, and to have a lower folate intake. Fathers who smoked were more likely to work in construction and dusty occupations and to have less occupational exposure to electromagnetic fields. None of these variables changed the results significantly, and thus they were not retained in the final statistical models.

Most analyses focus only on ALL cases because of the small numbers of AML cases. Three periods of maternal smoking were included in the same additive conditional logistic model to examine the contribution of time period-specific exposure. Maternal smoking in the postnatal period was examined by breastfeeding status to differentiate exposure through inhalation and through breast milk. The joint influence of paternal and maternal smoking on the risk of ALL was assessed on the multiplicative scale with an odds ratio (OR) for interaction $= OR_{AB}/(OR_A \times OR_B)$ using conditional logistic regression. A significant upward departure from one for the odds ratio for interaction indicates that the joint effect of paternal and maternal smoking is greater than their individual effects.

RESULTS

Cases and controls were comparable for all the demographic characteristics evaluated except for annual household income ($p < 0.05$) (table 1).

Among the 224 mothers who ever smoked, 82 (36.6 percent) did not smoke during the three exposure periods (3 months before conception, during pregnancy, and during the postnatal period as defined previously); 84 (37.5 percent) smoked throughout all three periods; 24 (10.7 percent) smoked before and after pregnancy but not during pregnancy; 22 (9.8 percent) smoked only after pregnancy; and the remaining 12 (5.4 percent) smoked in a combination of various time periods. Information on paternal smoking during pregnancy and during the postnatal period was not collected; however, information on smoking by other household members (including the father) besides the mother was available. Among the children of 255 fathers who ever smoked (three had missing information on smoking by other household members), 86 (33.7 percent) were not exposed to either paternal preconception smoking or smoking by other household members during the postnatal period; 98 (38.4 percent) were exposed only to paternal preconception smoking; two (0.8 percent) were exposed only to smoking by other household members during the postnatal period; and 69 (27 percent) had exposures to both. These results indicate that parental smoking patterns vary sufficiently to warrant examining the association between parental smoking and the risk of childhood leukemia by specific time periods.

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TABLE 1. Characteristics of cases and controls by leukemia type, the Northern California Childhood Leukemia Study, Berkeley, California, 1995–2002

	Acute lymphoblastic leukemia					Acute myeloid leukemia				
	Cases		Controls		*p* value*	Cases		Controls		*p* value*
	No.	%	No.	%		No.	%	No.	%	
Age (years)†										
<2	29	10	38	10		11	24	12	23	
2–5.9	161	57	213	59		9	20	11	21	
6–9.9	53	19	64	18		13	28	16	31	
10–15	38	14	49	13		13	28	13	25	
Mean (SE‡)	5.4 (0.2)		5.4 (0.2)			6.8 (0.7)		6.7 (0.6)		
Sex†										
Male	141	50	181	50		26	56	29	56	
Female	140	50	183	50		20	44	23	44	
Race/ethnicity†										
Non-Hispanic White	148	53	192	53		27	59	30	58	
Hispanic	133	47	172	47		19	41	22	42	
Household income ($)										
<15,000	41	15	36	10	0.001	11	24	5	10	0.17
15,000–29,999	57	20	54	15		6	13	7	13	
30,000–44,999	47	17	43	12		8	17	9	17	
45,000–59,999	49	17	58	16		3	7	12	23	
60,000–74,999	27	10	46	13		7	15	6	12	
≥75,000	60	21	127	35		11	24	13	25	
Maternal education										
High school or less	127	45	137	38	0.15	21	46	21	40	0.48
Some college	87	31	128	35		10	22	17	33	
College or postgraduate	67	24	99	27		15	32	14	27	
Paternal education										
High school or less	114	52	130	44	0.25	20	54	20	48	0.45
Some college	49	22	79	27		4	11	9	21	
College or postgraduate	58	26	84	29		13	35	13	31	
Maternal age (years) at birth										
<20	31	11	27	7	0.24	3	7	5	10	0.42
20–24.9	66	23	77	21		12	26	7	13	
25–29.9	67	24	108	30		16	35	18	35	
30–34.9	86	31	104	29		10	22	11	21	
≥35	31	11	48	13		5	11	11	21	
Mean (SE)	27.9 (0.4)		28.6 (0.3)		0.12	27.8 (0.9)		29.1 (0.9)		0.33
Paternal age (years) at birth										
<20	13	6	14	5	0.80	2	5	1	2	0.46
20–24.9	42	19	46	15		4	11	7	16	
25–29.9	53	23	71	23		13	35	9	21	
30–34.9	66	29	94	31		10	27	12	27	
≥35	53	23	78	26		8	22	15	34	
Mean (SE)	30.3 (0.5)		31.0 (0.4)		0.29	31.0 (1.1)		31.8 (1.0)		0.61

* *p* values derived from chi-squared tests for categorical variables and *t* tests for continuous variables.
† Matching variables.
‡ SE, standard error.

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TABLE 2. Paternal smoking and the risk of childhood leukemia by histologic type, the Northern California Childhood Leukemia Study, Berkeley, California, 1995–2002

Paternal smoking	Acute lymphoblastic leukemia				Acute myeloid leukemia			
	Cases (no.)	Controls (no.)	Odds ratio*	95% confidence interval	Cases (no.)	Controls (no.)	Odds ratio	95% confidence interval
Ever/never								
No	124	187	Referent		18	30	Referent	
Yes	104	119	1.25	0.85, 1.82	21	14	2.64	0.98, 7.12
Preconception								
No	153	234	Referent		23	36	Referent	
Yes	74	70	1.32	0.86, 2.04	16	8	3.84	1.04, 14.17
CPD†			1.03	1.00, 1.06			1.05	0.98, 1.13

* The odds ratios were derived from conditional logistic regression models, adjusting for household income.
† CPD, number of cigarettes smoked per day.

Since Hispanics and non-Hispanic Whites had similar risks associated with paternal and maternal smoking, the two ethnic groups were combined (test for heterogeneity for ALL: $p = 0.39$ for paternal smoking and 0.27 for maternal smoking). Excluding children with Down's syndrome (12 and six case-control sets for ALL and AML, respectively) did not change the results of this analysis.

Paternal preconception smoking was significantly associated with an increased risk of AML (OR = 3.84, 95 percent confidence interval (CI): 1.04, 14.17), although this risk was based on only 16 exposed cases and eight exposed controls (table 2). The assessment using the number of cigarettes smoked per day also showed an increasing trend (OR associated with a one-cigarette/day increment = 1.05, 95 percent CI: 0.98, 1.13; OR associated with a 10-cigarette/day increment = 1.65, 95 percent CI: 0.83, 3.28). Further analysis with AML using the lifetime nonsmoker group as the referent (18 cases/30 controls) indicated that the AML cases of fathers who smoked but who did not smoke during the 3-month preconception period (five cases/six controls) had an odds ratio = 1.56 (95 percent CI: 0.39, 6.16), while the cases of fathers who smoked during the 3-month preconception period (16 cases/eight controls) had an odds ratio = 4.05 (95 percent CI: 1.07, 15.27).

A positive association between paternal preconception smoking and ALL was suggestive but not statistically significant by use of a binary smoking exposure variable (OR = 1.32, 95 percent CI: 0.86, 2.04). However, a more powerful analysis using the number of cigarettes smoked per day provided stronger evidence of an association (OR associated with a one-cigarette/day increment = 1.03, 95 percent CI: 1.00, 1.06; OR associated with a 10-cigarette/day increment = 1.34, 95 percent CI: 1.02, 1.74). Further analysis with ALL using the lifetime nonsmoker group as the referent (124 cases/187 controls) showed that the cases of fathers who smoked but who did not smoke during the 3-month preconception period (29 cases/48 controls) had an odds ratio = 1.10 (95 percent CI: 0.63, 1.91), while the cases of fathers who smoked during the 3-month preconception period (74 cases/70 controls) had an odds ratio = 1.35 (95 percent CI: 0.86, 2.10).

Maternal smoking was not associated with an increased risk of childhood leukemia with respect to smoking before the child's diagnosis and the three windows of exposure (before conception, during pregnancy, and postnatal) (table 3). The multivariable model including all three time periods for maternal smoking showed that no specific time window was significantly associated with an increased risk or decreased risk for ALL (data not shown). No significant association was found between maternal smoking during breastfeeding and ALL, although the total number of mothers who smoked while breastfeeding was small (table 4). Finally, the effect of paternal preconception smoking was examined together with each of the three windows of exposures for maternal smoking. Paternal preconception smoking, combined with maternal postnatal smoking, was associated with a greater risk of ALL than was paternal preconception smoking alone (table 5). The $OR_{expected} = 0.72 \times 0.88 = 0.63$ when there is no evidence of a joint influence between paternal preconception smoking and maternal postnatal smoking. The $OR_{observed} = 3.94$, which was significantly different from the expected odds ratio ($OR_{interaction} = OR_{observed}/OR_{expected} = 3.94/0.63 = 6.25$; $p_{interaction} = 0.004$, adjusted for household income and maternal smoking before conception and during pregnancy), suggesting strong evidence for a joint influence between paternal preconception smoking and maternal postnatal smoking. To reduce the misclassification of a child's postnatal exposure to passive smoking, we combined maternal postnatal smoking and the child's postnatal exposure to other smokers in the household to form a summary postnatal passive smoking variable. The joint influence of paternal preconception smoking and the child's postnatal passive smoking was also significant ($OR_{observed} = 1.67$, $OR_{expected} = 0.41 \times 0.84 = 0.34$, $OR_{interaction} = OR_{observed}/OR_{expected} = 1.67/0.34 = 4.91$; $p_{interaction} = 0.004$, adjusted for household income and maternal smoking before conception and during pregnancy).

DISCUSSION

Our results showed that maternal smoking alone was not associated with an increased risk in either ALL or AML.

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TABLE 3. Maternal smoking and the risk of childhood leukemia by histologic type, the Northern California Childhood Leukemia Study, Berkeley, California, 1995–2002

Maternal smoking	Acute lymphoblastic leukemia				Acute myeloid leukemia			
	Cases (no.)	Controls (no.)	Odds ratio*	95% confidence interval	Cases (no.)	Controls (no.)	Odds ratio	95% confidence interval
Ever/never								
No	189	259	Referent		33	38	Referent	
Yes	92	105	1.12	0.79, 1.59	13	14	1.00	0.41, 2.44
Preconception								
No	235	304	Referent		40	45	Referent	
Yes	46	60	0.88	0.57, 1.36	6	7	0.79	0.21, 2.95
CPD†			1.02	0.98, 1.06			1.02	0.93, 1.12
Pregnancy								
No	245	320	Referent		41	45	Referent	
Yes	36	44	0.93	0.58, 1.51	5	7	0.60	0.15, 2.44
CPD			1.01	0.95, 1.07			1.01	0.92, 1.11
Postnatal‡								
No	227	302	Referent		35	41	Referent	
Yes	52	60	0.99	0.64, 1.52	9	9	0.94	0.32, 2.81
CPD			1.02	0.98, 1.06			1.05	0.94, 1.17

* The odds ratios were derived from conditional logistic regression models, adjusting for household income.
† CPD, number of cigarettes smoked per day.
‡ Two cases and two matched controls from the acute lymphoblastic leukemia group and two cases and two matched controls from the acute myeloid leukemia group under the age of 2 months were excluded from the analysis.

Paternal preconception smoking was associated with a significantly increased risk of AML and a nonsignificantly increased risk of ALL. Paternal preconception smoking, combined with maternal postnatal smoking or postnatal passive smoking in general, was associated with a significantly increased risk of ALL.

TABLE 4. Relation of maternal smoking while breastfeeding to acute lymphoblastic leukemia, the Northern California Childhood Leukemia Study, Berkeley, California, 1995–2002*

Smoking characteristic in the postnatal period	Cases (no.)	Controls (no.)	Odds ratio†	95% confidence interval
No smoking postnatally	225	299	Referent	
Smoked postnatally, excluding breastfeeding period	35	46	0.88	0.53, 1.45
Smoked postnatally, including breastfeeding period	16	14	1.26	0.59, 2.67
CPD‡ while breastfeeding			1.04	0.95, 1.14
Pack-months§			1.16	0.92, 1.45

* Two cases and two matched controls under the age of 2 months were excluded.
† The odds ratios were derived from conditional logistic regression models, adjusting for household income.
‡ CPD, number of cigarettes smoked per day.
§ One pack-month = one pack (20 cigarettes) per day for 1 month.

Of the seven studies of paternal smoking and AML, two studies also found a positive association (7, 14), while five others did not (9, 15–18). Seven studies found a positive association with paternal smoking and ALL (7, 11, 14–16, 19, 20), while four others did not (8, 9, 18, 21). It is recognized that childhood ALL and AML are two distinct diseases with different histologic presentations, age distributions, and prognoses (13). Studies of adult leukemia have also reported that smoking is associated with myeloid leukemia, while its relation with lymphocytic leukemia is still unclear (2). Tobacco smoke contains a high level of benzene (1). A smoker is exposed, on average, to 2 mg of benzene per day, of which 90 percent (1.8 mg) is from mainstream smoke, whereas a nonsmoker is exposed, on average, to only 0.2 mg of benzene per day from sources including outdoor air, indoor air, driving a car, and passive smoke (22). Benzene is a well-established chemical leukemogen, specifically for myeloid leukemia (23). Workers exposed to benzene were found to have increased levels of cytogenetic abnormalities associated with AML (24, 25) even at a low level of benzene exposure (<3.25 mg/m^3 (1 ppm)) (26), and myeloid progenitor cells are more sensitive than mature white blood cells to the toxicity of benzene (27).

Fraga et al. (5) reported that the level of 8-hydroxy-2′-deoxyguanosine, a product of oxidative DNA damage, was 50 percent higher in the sperm of smokers compared with that of nonsmokers. Shi et al. (6) reported that, compared with nonsmoking men, light- and heavy-smoking men were more likely to produce abnormal sperm with disomy of

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TABLE 5. Relation of paternal preconception smoking and maternal postnatal smoking or postnatal passive smoking to acute lymphoblastic leukemia, the Northern California Childhood Leukemia Study, Berkeley, California, 1995–2002*

Smoking exposure			Cases (no.)	Controls (no.)	Odds ratio†	95% confidence interval
Paternal preconception	Maternal postnatal	Postnatal passive‡				
Analysis 1: paternal preconception and maternal postnatal smoking						
No	No		144	205	Referent	
No	Yes		8	27	0.72	0.22, 2.38
Yes	No		36	47	0.88	0.51, 1.52
Yes	Yes		37	23	3.94	1.25, 12.37
Analysis 2: paternal preconception and postnatal passive smoking						
No		No	141	197	Referent	
No		Yes	11	34	0.41	0.17, 0.97
Yes		No	24	36	0.84	0.47, 1.52
Yes		Yes	48	34	1.67	0.79, 3.50

* Two cases and two controls under the age of 2 months were excluded.

† All odds ratios were adjusted for household income and maternal smoking during preconception and pregnancy by conditional logistic models.

‡ Postnatal passive smoking is either maternal postnatal smoking or other smokers in the household during the postnatal period or both.

chromosome 13. Zenzes et al. (28) investigated the transmission of benzo[*a*]pyrene diol epoxide-DNA adducts in early human preimplantation embryos and found evidence for preferential gametic transmission through smoking fathers. These data are consistent with a possible mechanism linking paternal preconception smoking to an increased risk of childhood leukemia.

Maternal smoking was not found to increase the risk of childhood ALL or AML, which is consistent with the results reported by the majority of studies of childhood leukemia (14, 29), both studies of ALL (9, 15, 20, 21, 30) and studies of AML (9, 15, 17). A few studies reported a positive association for childhood ALL (11, 31) and AML (10, 32). Others reported that maternal smoking is inversely associated with the development of ALL (10) or all childhood leukemia (8, 19, 33, 34). Of possible relevance, maternal smoking during pregnancy is strongly associated with an increased risk of spontaneous abortion (35). In addition, our study and previous studies (36, 37) have indicated an association between the history of previous fetal loss and childhood leukemia. If the same fetal abnormality induced by smoking, which increases the risk of spontaneous abortion, also predisposes the child to develop childhood leukemia, then the cases ascertained in the final study population may not represent all the subjects who could have developed leukemia. This potential selection bias could weaken a true positive association or, in the more extreme case, give rise to an inverse association between maternal smoking during pregnancy and childhood leukemia, as was observed with ALL in the Swedish cohort study (10).

In our study, the median number of cigarettes smoked per day for mothers who smoked during pregnancy was six, while the median number of cigarettes smoked for fathers before conception was 10. The lower number of cigarettes smoked per day by mothers may partially explain the lack of association between maternal smoking during pregnancy and the risk of childhood leukemia in our study.

The association between maternal smoking and childhood leukemia could also be influenced by the child's genetic makeup. To date, only two published studies have examined the influence of genetic polymorphisms on the relation between maternal smoking and childhood leukemia (21, 38). The need for a large number of leukemia cases to detect gene-environment interaction may be a limitation to the information currently available. For example, assuming risk of 1/2,000 for a child to develop leukemia (39), a maternal smoking prevalence of 15 percent, variant allele frequency ranging from 0.2 to 0.5, a dominant mode of inheritance, marginal relative risk of 1.5 for smoking, marginal relative risk of 1.0 for the gene variant, alpha = 0.05, and power = 0.80, a sample size of approximately 1,500 would be required to detect an odds ratio for interaction of 2.0 (40). This sample size may be achieved through collaboration between study groups, especially for the rarer types of childhood leukemia such as AML; however, careful planning must be undertaken to pool such data. Important issues such as population stratification must also be considered, as pooled subjects may come from different geographic locations, and an additional adjustment for race by genetic methods may be needed (41).

The current analysis suggests that most of the paternal preconception effect on the risk of ALL results from the combined paternal preconception smoking and postnatal passive smoking exposure (table 5). This two-step effect is consistent with the development of childhood leukemia as hypothesized by Greaves (42); that is, the development of childhood leukemia may require two events, an initiating event occurring before birth and a promoting event occurring

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after birth. If the occurrence of childhood leukemia requires at least two events, which can be viewed as two complement component causes, then the strength of one component cause will depend on the prevalence of its causal complement (43). This causal model may partly explain the inconsistent results with parental smoking across studies, as different study populations may have different exposure profiles.

Children with Down's syndrome are known to carry a higher risk of childhood leukemia (44). The major chromosomal abnormality among children with Down's syndrome is trisomy of chromosome 21, which is a chromosome frequently involved in ALL (t(12;21)) and AML (t(8;21)) that is not associated with Down's syndrome. Children with Down's syndrome are often considered to have experienced the first event in utero that leads to childhood leukemia (44). A recent study showed that Down's syndrome children exposed to passive smoke postnatally had a significantly increased risk of leukemia (OR = 2.42, 95 percent CI: 1.03, 5.69) (45). Similarly, our data indicate that passive smoking after birth could serve as a promoting event for the development of childhood leukemia. One study reported that children exposed to an average of 10.5 cigarettes per day by mothers and 6.5 cigarettes per day by regular visitors had higher levels of serum cotinine, 4-aminobiphenyl-hemoglobin adduct, and polycyclic aromatic hydrocarbon-albumin adducts (46).

There are several limitations to this study. First, the controls in our study have a higher household income compared with the cases, which is in contrast to some of the previous studies that reported lower socioeconomic status among controls (47, 48), thereby raising the possibility of participation bias in that controls of higher socioeconomic status are more likely to participate; however, our analyses indicated that participating controls in the Northern California Childhood Leukemia Study are not significantly different from the ideal controls for both paternal and maternal education, two indicators of socioeconomic status, suggesting that bias resulting from participation bias may be minimal in our study (12). In addition, results on the association between socioeconomic status and childhood leukemia are inconsistent in previous studies that used different surrogates for socioeconomic status measured at different levels (individuals vs. groups) and different study designs (48). Second, differential reporting between case mothers and control mothers is a possibility. Since both overreporting and underreporting by the case mothers are likely, the direction of bias cannot be determined. Third, mothers' reporting of paternal smoking may not be an ideal assessment of smoking exposure; however, two previous studies reported high agreement between self and partner in the reporting of paternal smoking (kappa coefficient = 0.84–0.90) (49, 50). Fourth, paternal information was collected from biologic mothers by use of different methods (self-administered questionnaire in phase I and face-to-face interview in phase II); however, the prevalence of paternal preconception smoking among controls was comparable (22.1 percent for phase I and 23.5 percent for phase II). The 1994 National Household Survey on Drug Abuse showed that there was no significant difference in the prevalence of smoking between data collected from the self-administered questionnaire and data obtained by face-to-face interviews among the nonadolescent population (18 years or older) (51). Finally, information regarding paternal alcohol consumption, folate intake, and recreational use of drugs was not collected, and thus their potential confounding effects could not be ruled out.

There are several strengths to the study. The cases appear to be representative of the source population from which they arose, that is, the pediatric population of the 35-county study area. A previous comparison of cases ascertained by the study with cases identified by the population-based California Cancer Registry indicated that 88 percent of the childhood leukemia cases listed in the cancer registry were included in this study. In addition, the selection of controls in the Northern California Childhood Leukemia Study is population based, utilizing birth certificates matched to the cases residing in the 35 counties at the time of diagnosis, and appears to provide a representative sample of the control population from the study area (12).

In conclusion, results from the current analysis suggest that the timing and the sequence of exposure to paternal and maternal smoking are likely important in the development of childhood leukemia. Currently, the public is generally more aware of the detrimental effect of maternal smoking during pregnancy on the health of the fetus. The knowledge of a potentially harmful effect of paternal smoking exposure may provide men with a stronger incentive to quit smoking. Public health measures targeting smoking fathers could achieve additional improvements in the health of children, including improvements for diseases such as asthma, respiratory tract infection, and otitis media that are more prevalent among children (52).

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