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Research Article

Tobacco Smoke Exposure and the Risk of Childhood Acute Lymphoblastic and Myeloid Leukemias by Cytogenetic Subtype

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Abstract

Background: Tobacco smoke contains carcinogens known to damage somatic and germ cells. We investigated the effect of tobacco smoke on the risk of childhood acute lymphoblastic leukemia (ALL) and myeloid leukemia (AML), especially subtypes of prenatal origin such as ALL with translocation t(12;21) or high-hyperdiploidy (51–67 chromosomes).

Methods: We collected information on exposures to tobacco smoking before conception, during pregnancy, and after birth in 767 ALL cases, 135 AML cases, and 1,139 controls (1996–2008). Among cases, chromosome translocations, deletions, or aneuploidy were identified by conventional karyotype and fluorescence *in situ* hybridization.

Results: Multivariable regression analyses for ALL and AML overall showed no definite evidence of associations with self-reported (yes/no) parental prenatal active smoking and child's passive smoking. However, children with history of paternal prenatal smoking combined with postnatal passive smoking had a 1.5-fold increased risk of ALL [95% confidence interval (CI), 1.01–2.23], compared to those without smoking history (ORs for pre- or postnatal smoking only were close to one). This joint effect was seen for B-cell precursor ALL with t(12;21) (OR = 2.08; 95% CI, 1.04–4.16), but not high hyperdiploid B-cell ALL. Similarly, child's passive smoking was associated with an elevated risk of AML with chromosome structural changes (OR = 2.76; 95% CI, 1.01–7.58), but not aneuploidy.

Conclusions: Our data suggest that exposure to tobacco smoking was associated with increased risks of childhood ALL and AML; and risks varied by timing of exposure (before and/or after birth) and cytogenetic subtype, based on imprecise estimates.

Impact: Parents should limit exposures to tobacco smoke before and after the child's birth. *Cancer Epidemiol Biomarkers Prev; 22(9); 1600–11. ©2013 AACR.*

Introduction

The predominant phenotype of childhood acute lymphoblastic leukemia (ALL) is B-cell precursor ALL. It occurs primarily in young children 2 to 5 years of age, whereas the incidence of the less common T-cell phenotype increases with age (1). B-cell precursor ALL tends to have numerical and structural chromosomal abnormalities such as high hyperdiploidy (defined by the presence of 51–67 chromosomes, referred to as 51+) and translocation t(12;21)/*ETV6-RUNX1* (also referred to as the *TEL-AML1* gene fusion, a molecular cytogenetic abnormality not detectable in conventional cytogenetics), which represent the most common cytogenetic subtypes of B-cell precursor ALL (2). Acute myeloid leukemia (AML) is rare in children, and occurs uniformly across all ages. Childhood AML is often characterized by recurrent chromosomal abnormalities such as *MLL* fusions located at chromosome 11q23, t(8;21), t(15;17), and inv(16) (2).

Genetic mutations leading to leukemic clones take place either during fetal development [e.g., (t12;21)/*ETV6-RUNX1*], after birth [e.g., t(1;19)/*E2A-PBX1*], or possibly during both periods [e.g., *MLL* fusion (3)]. Although molecular markers are used for diagnostic and prognostic

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purposes, little is known about the underlying mechanisms leading to childhood ALL and AML with specific chromosome abnormalities. The distinctive natural history of ALL and AML subtypes may provide clues in identifying periods of susceptibility to certain leukemogenic agents.

Mainstream tobacco smoke (exhaled by the smoker) and sidestream smoke (emitted from a burning tobacco product) contain a mixture of human carcinogens, such as benzene, formaldehyde, 1,3 butadiene, polycyclic aromatic hydrocarbons, and polonium (4, 5). Benzene is known to damage cells of myeloid lineage and pluripotent hematopoietic stem cells (6–8), thus potentially playing a role in the development of both childhood AML and ALL. Understanding the effect of tobacco smoke on the risk of childhood leukemia is complex because exposure to tobacco-specific chemicals may affect either somatic or germ cells during critical periods of a child's development (preconception, pregnancy, after birth). Although epidemiologic studies conducted worldwide have generally reported no association between maternal smoking during pregnancy and the risk of ALL and AML in the offspring (9), evidence is accumulating in favor of an association between paternal active tobacco smoking before conception and childhood ALL, suggesting a role of germline mutations in disease development (10, 11). Data on the relation of tobacco smoking to the risk of specific immunophenotypes (11–13) or cytogenetic subtypes (11, 14) of childhood leukemia, however, are sparse.

This analysis is an expansion of a previous report (15) to assess whether various phenotypic and molecular subtypes of childhood leukemia have distinct associations with child's and parents' exposure to passive (involuntary) and active (voluntary) smoking.

Materials and Methods

Study population

The Northern California Childhood Leukemia Study (NCCLS) is a case–control study conducted in 17 counties in Northern California in phase I (1995–1999) and an additional 18 counties in Central California (35 counties total) in phase II (2000–2008). Cases were identified within 72 hours after diagnosis at 7 (phase I) or 9 (phase II) hospitals, and were eligible for participation if they were younger than 15 years of age at diagnosis, had an English or Spanish speaking parent or guardian, lived in one of the 35 counties that comprised the population base at the time of diagnosis, and had never been previously diagnosed with cancer. Comparison of case ascertainment in the 35-county study area to the California Cancer Registry (1997–2003) showed that the NCCLS ascertained 96% of children diagnosed with leukemia in the phase I participating hospitals and 93% in the phase II hospitals. When considering both participating and nonparticipating hospitals within the 35 study counties, 76% of all diagnosed cases were ascertained in the NCCLS. Eighty-six percent of cases determined to be eligible consented to participate.

Eligibility criteria for controls were similar as those for cases. Controls were randomly selected using birth certificates obtained through the California Office of Vital Records, and 1 or 2 controls were matched to each case on child's date of birth, sex, Hispanic ethnicity (defined as either one or both parents being Hispanic, as indicated on the birth certificate record), and maternal race (as indicated on the birth certificate record). Out of all potential controls searched, 12% could not be located, 20% refused to participate, and 68% were successfully contacted and considered eligible. Among those contacted and eligible, 86% agreed to participate. The overall control participation rate was estimated to be 59%, where the numerator was defined as the number of confirmed eligible controls (68% of controls contacted) and those presumed to be eligible controls (68% of controls not located or refusals), and the denominator was defined as all potential controls searched (16). We determined that participating controls were representative of the source population with respect to reproductive and demographic characteristics (17). 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 participating hospitals. Written informed consent was obtained from the parents of all participating subjects.

Data collection

Interviews. During phase I, a self-administered questionnaire was used to collect tobacco smoking histories, followed by a home-based, in-person interview administered by trained personnel to obtain additional information. During phase II, all information was collected through home-based, in-person interviews. Information on tobacco was collected separately for each parent: paternal smoking was obtained from the mother in phase I, and from the father (69%), or mother when the father was not available (31%) in phase II. Calendar aids were provided to enhance recall of time-specific exposures. The median time between date of enrollment and interview was 4 months for cases and 14 months for controls. For mothers and fathers, we collected information on active smoking during lifetime (defined as smoking at least 100 cigarettes, pipes, or cigars), 3 months before conception, and pregnancy, as well as passive smoking at home or in the workplace before or during pregnancy. For children, passive smoking at home was determined by the presence of a person (i.e., mother, father, or other person) who smoked at least once a week or more for at least 3 months from birth to the diagnosis/reference date or third birthday, whatever occurred first. In phase II, similar information on passive smoking in cars and public places was collected for the child and parents (before or during the mother's pregnancy). The number of cigarettes, pipes, and cigars smoked was collected for paternal smoking 3 months before the pregnancy, as well as maternal smoking before, during, and after the pregnancy.

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Medical record abstraction. Clinical and laboratory data relevant to immunophenotypic and cytogenetic classification were abstracted from case children's medical records, and reviewed for accuracy by a consulting clinical oncologist (J. Schiffman). Immunophenotype was determined for ALL cases (754 B-cell ALL and 77 T-cell ALL) according to the WHO classification using flow cytometry profiles provided in the pathology report. Cytogenetic classification was determined in pretreated bone marrow specimens at the time of diagnosis using karyotypes ascertained from conventional G-banding and occasional FISH.

Additional FISH analyses. Childhood ALL cases were selected for FISH screening at the University of California, Berkeley laboratory (L. Zhang, M.T. Smith) if the medical records showed a normal cytogenetic report at diagnosis, failed to provide any data, or had no observed high hyperdiploidy (51+) and/or a common translocation. Of the leukemia cases that met these criteria, only those with available pretreatment bone marrow aspirate smears had FISH analysis. Specifically, FISH assays were designed to detect both t(12;21)/*ETV6-RUNX1* and high hyperdiploidy simultaneously among B-lineage ALL cases (>1 year of age), using probes for chromosome 12p13, chromosome 21q22, and the centromere of chromosome X (Vysis). Additional probes for chromosomes 6, 10, and 18 were applied to cases ambiguous for hyperdiploidy.

Cytogenetic classification. Diagnostic karyotype for each patient was classified according to clonal genetic aberrations using the International System for Human Cytogenetic Nomenclature 1995 criteria (18). Details on classification of cytogenetic abnormalities by FISH have been described previously (19). Cases having chromosome gains or structural abnormalities required 2 or more metaphases for designation of clonality, whereas loss of chromosomes necessitated a minimum of 3 metaphases. Patients having translocations, inversions, deletions, or insertions involving the 11q23/*MLL* chromosome region were classified as having 11q23/*MLL* rearrangements. Patients with diploid karyotypes required a minimum of 20 banded metaphases. Classification of ploidy level was made according to the simplest clone. Conventional cytogenetics was used to assign ploidy status, unless the patient had available FISH data and a normal karyotype (or no available sample), whereby FISH was used to assign ploidy. Among the ALL cases with adequate karyotypes, G-banding assigned ploidy to 48.2% of cases and FISH (done by either a collaborating hospital or University of California, Berkeley, CA) assigned ploidy for the remaining 51.8% of cases. Classifications were conducted by 2 individuals (M.C. Aldrich, K. Bartley); ambiguous cases (~9%) were separately reviewed by an independent reviewer (X. Ma) and inconsistencies were resolved after discussion.

Karyotpe and FISH data were available for 777 ALL and 138 AML. The remaining 62 ALL cases and 6 AML cases had inadequate information or samples and were excluded from analyses stratified by cytogenetic subtype. Table 1 lists the frequency distribution of common cytogenetic types for B-cell precursor ALL and AML reported in the NCCLS from 1995 to 2008.

Statistical analysis

Because the information on paternal preconception smoking was collected 12 months after the study began, this analysis includes children enrolled in 1996 and after: 767 ALL cases (689 B-cell ALL and 70 T-cell ALL), 135 AML cases, and 1,139 healthy controls (of these, 975 controls were matched to ALL cases and 164 controls matched to AML cases). Analyses were conducted for ALL and AML, and by immunophenotype (for ALL) and cytogenetic subtype. ORs and approximate 95% confidence intervals (CI) were calculated from unconditional logistic regression models adjusted for child's age at diagnosis, sex, Hispanic ethnicity, maternal race (i.e., Black, White, and other), and household income. Parental education, parental age at child's birth, child's birth weight, home use of paints and solvents, and paternal exposures to organic solvents at work were not included in the final models because they did not change the OR between tobacco exposure and childhood leukemia.

Parental active smoking was highly correlated before and during pregnancy (66% of mothers and 97% for fathers smoked both before and during pregnancy). Therefore, we present ORs for maternal and paternal smoking during the prenatal period as a whole. For leukemia subtypes with 5 or more observations per cell, we assessed the joint effect of exposure to tobacco during the prenatal and postnatal periods, using likelihood ratio tests. To assess homogeneity between leukemia subtypes, we computed χ^2 tests based on the Woolf's method (P-value > 0.05 indicates homogeneity). Numbers of cigarettes smoked per day were modeled as counts, and there was no evidence of a departure from linearity.

Results

Case and control participants were similar with respect to matching characteristics, but differed by household income and maternal education, both of which were higher among controls (Table 2). Household income and parental education was slightly correlated with maternal active smoking (r: 0.01–0.15) or passive smoking (r: 0.08–0.16) and moderately correlated with paternal active smoking (r: 0.11–0.21) and passive smoking (r: 0.15–0.25).

The case–control distribution of tobacco smoke exposures and the corresponding ORs and 95% CIs are presented for ALL overall and immunophenotypes (Tables 3 and 4), cytogenetic subtypes of B-cell precursor ALL (Table 5), and AML overall and cytogenetic subtypes (Table 6). In multivariable models for ALL (Table 3), most ORs for exposure to tobacco smoking at various times were equal or close to 1, with possibly the exception of nonstatistically significant increased risks of T-cell precursor ALL with prenatal maternal smoking (OR = 1.69;

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Table 1. Common cytogenetic subtypes of B-cell precursor ALL and AML: the NCCLS, 1995–2008

B-cell precursor ALL ($n = 701$[a])		AML ($n = 138$[b])	
	N (%)[c]		*N* (%)[c]
No apparent abnormality	73 (10.4)	No apparent abnormality	25 (18.1)
Total structural changes	397 (56.6)	Total structural changes	103 (74.6)
Translocation t(12;21)	143 (20.4)	Translocation t(8;21)	21 (15.2)
Translocations other than t(12;21)	87 (12.4)	Translocation t(15;17)	14 (10.1)
t(1;19)	23 (3.3)	Inversion inv(16)	7 (5.1)
t(9;22)	8 (1.1)		
11q23/*MLL* rearrangement	22 (3.1)	11q23/*MLL* rearrangement	17 (12.3)
Any deletion	75 (10.7)	Any deletion	21 (15.2)
del(12p)	36 (5.1)	del(9q)	5 (3.6)
del(6q)	17 (2.4)		
del(9p)	17 (2.4)		
Total numerical changes	413 (58.9)	Total numerical changes	55 (39.9)
Trisomy 8	52 (7.4)	Trisomy 8	18 (13.0)
Monosomy 7	18 (2.6)		
Ploidy level			
High hyperdiploidy (51–67 chr.)	237 (33.8)		
Low hyperdiploidy (47–50 chr.)	112 (16.0)	Low hyperdiploidy (47–50 chr.)	31 (22.5)
Hypodiploidy (45 chr.)	28 (4.0)	Hypodiploidy (45 chr.)	9 (6.5)
Pseudodiploid	183 (26.1)	Pseudodiploid	71 (51.4)

Abbreviation: chr., chromosome.

[a]Includes 145 cases in phase I (1995–1999) and 556 cases in phase II (2000–2008).

[b]Includes 39 cases in phase I (1995–1999) and 99 cases in phase II (2000–2008).

[c]Leukemia case may have more than one chromosome abnormality.

95% CI, 0.64–4.46), and B-cell precursor ALL with passive smoking at home (OR = 1.30; 95% CI, 0.90–1.88). The model assessing a possible joint effect of paternal prenatal smoking and child's postnatal passive smoking showed that exposure during both periods, compared to none, was associated with an increased risk of ALL overall and B-cell precursor ALL (OR = 1.50; 95% CI, 1.01–2.23 and OR = 1.60; 95% CI, 1.07–2.04, respectively); however, no increased risks were observed with exposure *solely* to prenatal paternal smoking or child's passive smoking (*P*-values for interaction$\leq$0.05; Table 3). No joint effect of prenatal maternal smoking and child's passive smoking was reported for childhood ALL. The ORs for every increase in 5 cigarettes smoked per day was 1.06 (95% CI, 0.98–1.14) for preconception paternal smoking.

Among nonsmoking parents, nonstatistically significant increased risks of childhood ALL (OR = 1.50; 95% CI, 0.84–2.69) and B-cell precursor ALL (OR = 1.66; 95% CI, 0.92–3.00) were observed when fathers were exposed to tobacco smoke in cars during the preconception period (Table 4); mothers' exposure to passive smoking in cars was rare. Children exposed to tobacco smoke in cars but not at home also experienced a 1.5-fold nonstatistically significant increased risk of B-cell precursor ALL (95% CI, 0.71–3.54; 11 cases and 16 controls). There were no associations between childhood ALL and a father's or mother's passive smoking at home, work, or in public areas.

Exposure to tobacco smoke before and after birth was not associated with an elevated risk of childhood B-ALL with high hyperdiploidy, in contrast to other cytogenetic subtypes (Table 5). Paternal prenatal smoking *combined* with child's passive smoking was associated with an increased risk of childhood B-cell precursor with t(12;21) (OR = 2.08; 95% CI, 1.04–4.16), but not for B-cell precursor ALL with high hyperdiploidy (OR = 1.01; 95% CI, 0.54–1.87; *P*-value for homogeneity = 0.04; Table 5). Maternal prenatal smoking was associated with no or reduced risks of all B-cell ALL cytogenetic subtypes; specifically, we observed a deficit of B-cell ALL with chromosome translocations other than t(12:21) (OR = 0.24; 95% CI, 0.06–0.89).

Nonstatistically significant increased risks of childhood AML were observed with prenatal maternal and paternal active smoking, and child's passive smoking at home (Table 6). The latter association was of a larger magnitude for AML with recurrent chromosome aberrations known to confer a favorable prognosis (OR = 2.76; 95% CI, 1.01–7.58; 15 exposed cases). No associations were found between tobacco smoke and AML with aneuploidy. Finally, childhood leukemias (ALL or AML) with *MLL* fusion ($n = 34$) were not associated with any exposure to tobacco smoke (data not shown).

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Table 2. Sociodemographic characteristics of children with leukemia and controls recruited in the NCCLS, 1996–2008

	Acute lymphoblastic leukemia		Acute myeloid leukemia	
	Cases *N*[a] (%)	Controls *N*[a] (%)	Cases *N*[b] (%)	Controls *N*[b] (%)
	767	975	135	164
Child's sex				
Male	431 (56)	560 (57)	72 (53)	89 (54)
Female	336 (44)	415 (43)	63 (47)	75 (46)
Child's age at diagnosis (years)				
0–1	83 (11)	105 (11)	38 (30)	51 (31)
>1–2	436 (57)	561 (58)	28 (19)	32 (20)
>2–5	110 (14)	144 (15)	17 (13)	22 (13)
>5–14	138 (18)	165 (17)	52 (38)	59 (36)
Mean	5.5 (SD 3.5)	5.4 (SD 3.4)	6.6 (SD 4.9)	6.3 (SD 4.8)
Child's race/ethnicity				
Hispanic	362 (47)	416 (43)	61 (45)	69 (42)
Non-Hispanic White	267 (35)	391 (40)	50 (37)	64 (39)
Non-Hispanic others	138 (18)	168 (17)	24 (18)	31 (19)
Household annual income (USD)				
<15,000	119 (16)	96 (10)	28 (21)	13 (8)
15,000–29,999	136 (18)	123 (13)	24 (18)	25 (15)
30,000–44,999	120 (16)	120 (12)	20 (15)	17 (10)
45,000–59,999	110 (14)	136 (14)	14 (10)	26 (16)
60,000–74,999	56 (7)	108 (11)	12 (9)	14 (9)
≥75,000	226 (29)	392 (40)	37 (27)	69 (42)
Mother's age at birth (years)				
Mean	28.3 (SD 6.2)	29.2 (SD 6.1)	27.8 (SD 6.6)	29.7 (SD 5.9)
Mother's education				
No schooling or elementary school	91 (12)	75 (8)	13 (10)	16 (10)
High school or similar	248 (32)	269 (28)	48 (36)	44 (27)
College or similar	215 (28)	302 (31)	33 (24)	43 (26)
Bachelor's degree or higher	213 (28)	328 (34)	41 (30)	61 (37)
Unknown	0	1 (0)	0	0
Father's age at birth (years)				
Mean	31 (SD 7.0)	31.7 (SD 7.2)	30.7 (SD 7.3)	32.0 (SD 6.4)
Father's education			0	
No schooling or elementary school	93 (12)	102 (10)	15 (11)	17 (10)
High school or similar	269 (35)	295 (30)	56 (41)	52 (32)
College or similar	152 (20)	247 (25)	19 (14)	38 (23)
Bachelor's degree or higher	230 (30)	302 (31)	42 (31)	54 (33)
Unknown	23 (3)	29 (3)	3 (2)	3 (2)

Abbreviation: USD, United States dollars.

[a]Includes 113 cases/146 controls in phase I (1996–1999; 1995 excluded from the analyses) and 654 cases/829 controls in phase II (2000–2008).

[b]Includes 32 cases/37 controls in phase I (1996–1999; 1995 excluded from the analyses) and 103 cases/127 controls in phase II (2000–2008).

Discussion

Subtypes of childhood ALL exhibit specific molecular characteristics known to be important in risk stratification and treatment specification at diagnosis. These molecular characteristics may have distinctive mechanistic origins and could be useful stratification criteria for epidemiologic analysis as well. Indeed, hyperdiploidy results from a presumed "chaotic" mitosis, which contrasts sharply with the mechanism of translocations, which involve double-stranded DNA breaks and DNA repair (3). We previously reported an association between home use of paints and the risk of B-cell precursor ALL, with marked

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Table 3. Risk of childhood ALL associated with parents' and child's exposure to tobacco smoking, by immunophenotype: the NCCLS, 1996–2008

		Overall		B-cell precursor ALL		T-cell ALL	
	Controls	Cases		Cases		Cases	
Exposure to tobacco smoking	***N* = 975**	***N* = 767**	**OR[a] (95% CI)**	***N* = 689**	**OR[a] (95% CI)**	***N* = 70**	**OR[a] (95% CI)**
Multivariable model							
Maternal prenatal smoking[b]							
No	856	661	1.00 (—)	594	1.00 (—)	59	1.00 (—)
Yes	118	106	0.83 (0.56–1.24)	95	0.78 (0.52–1.19)	11	1.69 (0.64–4.46)
Paternal prenatal smoking[b]							
No	703	498	1.00 (—)	445	1.00 (—)	47	1.00 (—)
Yes	222	218	1.17 (0.91–1.50)	199	1.19 (0.92–1.54)	18	1.12 (0.58–2.19)
Child's passive smoking at home[c]							
No	798	599	1.00 (—)	536	1.00 (—)	55	1.00 (—)
Yes	163	161	1.20 (0.84–1.72)	148	1.30 (0.90–1.88)	13	0.61 (0.23–1.58)
Joint effect of maternal prenatal smoking and child's passive smoking[d]							
No exposure during both periods	777	588	1.00 (—)	527	1.00 (—)		
Maternal prenatal smoking only	21	11	0.60 (0.27–1.35)	9	0.59 (0.22–1.28)		
Child's passive smoking only	67	67	1.11 (0.75–1.65)	63	1.14 (0.80–1.79)		
Exposure during both periods	96	94	1.04 (0.74–1.47)	85	1.05 (0.74–1.51)		
		P-value for interaction	0.35		0.31		
Joint effect of paternal prenatal smoking and child's passive smoking[d]							
No exposure during both periods	670	498	1.00 (—)	444	1.00 (—)		
Paternal prenatal smoking only	127	98	0.91 (0.68–1.22)	90	0.94 (0.69–1.27)		
Child's passive smoking only	74	46	0.80 (0.51–1.09)	44	0.90 (0.57–1.41)		
Exposure during both periods	88	115	1.50 (1.01–2.23)	104	1.60 (1.07–2.38)		
		P-value for interaction	0.02		0.05		

NOTE. Shaded areas when insufficient data (≤5 observations per cell).

Abbreviations: CI, confidence interval.

[a]OR adjusted for child's age at diagnosis/reference date, sex, and Hispanic status, maternal race, and household annual income.

[b]Three months before conception and/or during pregnancy.

[c]Any smokers including mother, father, and others.

[d]Model with maternal smoking is adjusted for paternal prenatal smoking; model with paternal smoking is adjusted for maternal prenatal smoking.

differences in risk between (t12;21)/*ETV6-RUNX1* and hyperdiploid subtypes (20). Similarly, the observed association between home use of petroleum solvents and childhood AML was limited to those with chromosomal structural changes (20).

Time- and subtype-specific analyses in our study suggested that the risk of childhood ALL was associated with a history of paternal prenatal active smoking *combined* with child's postnatal exposure to passive smoking at home, and that the magnitude of association was the strongest for B-cell precursor ALL harboring t(12;21). No association was found with high-hyperdiploid ALL, and associations seen with other cytogenetic subtypes did not reach statistical significance. Most individual studies and meta-analyses have reported no association between maternal smoking during pregnancy and childhood ALL (9, 21), and small to moderate positive associations between preconception paternal smoking and childhood ALL (10, 11). However, evaluations of the risk by main immunophenotype or cytogenetic subtype remain sparse. In a French study, elevated risks following paternal smoking from 1 year before conception to the time of the interview, were reported for both B-cell precursor ALL ($n = 545$), and T-cell ALL [$n = 67$ (13)]. An Australian study reported an increased risk of ALL overall with paternal smoking during the conception year, and no difference in risk by immunophenotype [$n = 294$ pre-B-cell ALL; number of T-cell ALL not provided (11)]. The lack of association we observed between preconception paternal smoking and childhood T-cell ALL ($n = 69$) is in contrast with these earlier observations. Other childhood leukemia studies have investigated *in utero* exposures specific to infant leukemia with *MLL* rearrangements, showing associations with maternal consumption of food that contains topoisomerase II inhibitors during pregnancy (22, 23) and transplacental chemical exposures (24), but not maternal smoking (14). We also reported no associations with any sources of tobacco smoking and childhood

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Table 4. Risk of childhood ALL overall and B-cell precursor ALL associated with father's passive smoking 3 months before conception among nonsmoking parents: the NCCLS, 2000–2008 (phase II)

		Overall		B-cell precursor ALL	
	Controls	Cases		Cases	
Sources of passive smoking	*N* = 392	*N* = 300	OR[a] (95% CI)	*N* = 268	OR[a] (95% CI)
Home					
No	379	293	1.00 (—)	261	1.00 (—)
Yes	10	7	0.82 (0.30–2.22)	7	0.92 (0.34–2.54)
Work place(s)					
No	312	232	1.00 (—)	209	1.00 (—)
Yes	68	59	1.08 (0.73–1.62)	52	1.05 (0.69–1.59)
Car(s)					
No	359	265	1.00 (—)	235	1.00 (—)
Yes	23	30	1.50 (0.84–2.69)	29	1.66 (0.92–3.00)
Public area(s)					
No	301	224	1.00 (—)	200	1.00 (—)
Yes	87	71	1.04 (0.72–1.51)	63	1.04 (0.71–1.53)

Abbreviation: CI, confidence interval.

[a]OR adjusted for child's age at diagnosis/reference date, sex, and Hispanic status, maternal race, and household annual income.

leukemia with *MLL* rearrangement. To our knowledge, only the study by Milne and colleagues (11) has examined the risk of childhood ALL by cytogenetic type in older children. Although limited by small sample sizes, the authors reported no apparent differences in risks associated with paternal smoking for ALL with high hyperdiploidy ($n = 82$) and those with t(12;21) [$n = 60$ (11)].

Results published on a limited subset of children with AML enrolled in the NCCLS ($n = 46$) showed a 3-fold increased risk following preconception paternal active smoking, based on unstable risk estimates (15). This updated analysis reports a nonstatistically significant increased risk of AML with paternal prenatal active smoking, as well as child's passive smoking at home (Table 6). With the exception of one study (25), all studies have reported no association between paternal smoking and childhood AML (26). The main limitation of studies of childhood AML is the lack of statistical power due to the rarity of the disease, further complicated by its molecular heterogeneity. Although our observation of differential AML risks by cytogenetic profile is based on imprecise estimates, several case-only studies of tobacco smoking and the risk of adult AML have also reported a higher risk for AML with any chromosome abnormalities (27), complex karyotype (28, 29), or specific aberrations such as t(8;21) (27, 30), -7/del(7q) (28–30), +8 (27, 29), t(8:21), t(15;17), or inv(16) (28) (not all associations reached statistical significance).

It is well established that tobacco-related contaminants can damage DNA in human somatic cells, and there is growing evidence that tobacco affects germ cells not only in animals, but in humans (31). Biologic studies (3, 32) investigating the origin of leukemic clones in children have also detected molecular lesions in the neonatal blood spots, supporting the hypothesis that an "initiating genetic hit" occurs before birth. Common prenatal lesions include (t12;21)/*ETV6-RUNX1* and hyperdiploidy in childhood ALL and t(8;21)/*AML1-ETO* in childhood AML, whereas t(1;19)/*E2A-PBX1*, the second most frequent translocation in childhood ALL, seems to occur after birth. The translocation t(12;21)/*ETV6-RUNX1* is present in about 20% of children with B-cell precursor ALL, yet on a population level is much more prevalent at birth (33), suggesting that a "second genetic hit" after birth is likely to be necessary to cause leukemia. This data are consistent with our earlier observation (15) showing that the combination of paternal preconception smoking and child's passive smoking distinctly increased the risk of childhood ALL with t(12;21), supporting the two-step model for childhood leukemia. In this instance, the first genetic hit would occur before conception via genotoxic effects of tobacco smoke on germ cells (the sperm), and the second hit would occur after the child's birth via carcinogenic effects on somatic cells through passive smoking. Because fathers in our study usually smoke before and during pregnancy, we cannot rule out that exposure to tobacco smoke via the mother's passive smoking may also affect the fetus (although this alternative explanation is weakened by the fact that mother's active smoking does not seem to be associated with an increased risk of childhood ALL). Also, information on the total number of cigarettes smoked per day after the child's birth was not available, limiting our ability to assess differences with respect to prenatal and/or postnatal exposure to tobacco smoke. We observed a decreased risk of B-cell precursor ALL harboring translocations other than (t12;21) following maternal prenatal smoking, however findings for rare cytogenetic subtypes should be interpreted with caution due to small numbers.

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Table 5. Risk of childhood B-cell precursor ALL associated with exposure to tobacco smoking, by cytogenetic subtype: the NCCLS, 1996–2008

		High hyperdiploidy		t(12;21)		Other translocation(s)		Any chromosome deletion		No apparent cytogenetic anomalies	
	Controls	Cases		Cases		Cases		Cases		Cases	
Exposure to tobacco smoking	$N = 975$	$N = 222$	OR[a] (95% CI)	$N = 130$	OR[a] (95% CI)	$N = 82$	OR[a] (95% CI)	$N = 70$	OR[a] (95% CI)	$N = 68$	OR[a] (95% CI)
Multivariable model											
Maternal prenatal smoking[b]											
No	856	197	1.00 (—)	107	1.00 (—)	79	1.00 (—)	59	1.00 (—)	58	1.00 (—)
Yes	118	25	0.83 (0.44–1.58)	23	1.00 (0.48–20.6)	3	0.24 (0.06–0.89)	11	0.76 (0.30–1.95)	10	0.79 (0.81–2.67)
Paternal prenatal smoking[b]											
No	703	155	1.00 (—)	81	1.00 (—)	58	1.00 (—)	42	1.00 (—)	39	1.00 (—)
Yes	222	51	0.95 (0.64–1.41)	40	1.21 (0.75–1.96)	22	1.20 (0.68–2.12)	24	1.38 (0.76–2.56)	24	1.47 (0.31–2.03)
Child's passive smoking at home[c]											
No	798	185	1.00 (—)	94	1.00 (—)	71	1.00 (—)	53	1.00 (—)	52	1.00 (—)
Yes	163	36	0.98 (0.56–1.71)	34	1.5 (0.79–3.00)	10	0.93 (0.40–2.15)	17	1.30 (0.57–2.95)	16	1.20 (0.56–2.95)
Joint effect of paternal prenatal smoking and child's passive smoking[d]											
No exposure during both periods	670	157	1.00 (—)	82	1.00 (—)						
Paternal prenatal smoking only	127	26	0.74 (0.47–1.19)	12	0.69 (0.36–1.32)						
Child's passive smoking only	74	12	0.67 (0.33–1.35)	8	0.85 (0.35–2.03)						
Exposure during both periods	88	24	1.01 (0.54–1.87)	26	2.08 (1.04–4.16)						
		P-value for interaction	0.17		0.01						

NOTE. Shaded areas when insufficient data (≤5 observations per cell).

Abbreviation: CI, confidence interval.

[a]OR adjusted for child's age at diagnosis/reference date, sex, and Hispanic status, maternal race, and household annual income.

[b]Three months before conception and/or during pregnancy.

[c]Any smokers including mother, father, and others.

[d]Model with maternal smoking is adjusted for paternal prenatal smoking; model with paternal smoking is adjusted for maternal prenatal smoking.

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Table 6. Risk of childhood AML associated with exposure to tobacco smoking, by cytogenetic subtype: the NCCLS, 1996–2008

		Overall		Abnormal chromosome numbers		Recurrent structural chromosome changes[a]		No apparent cytogenetic anomalies	
	Controls	Cases		Cases		Cases		Cases	
Exposure to tobacco smoking	*N* = 164	*N* = 135	OR[b] (95% CI)	*N* = 52	OR[b] (95% CI)	*N* = 39	OR[b] (95% CI)	*N* = 24	OR[b] (95% CI)
Multivariable model									
Maternal prenatal smoking[c]									
No	146	114	1.00 (—)	47	1.00 (—)	35	1.00 (—)	19	1.00 (—)
Yes	22	30	1.46 (0.77–2.74)	4	0.78 (0.16–3.87)	4	0.45 (0.10–2.02)	5	0.83 (0.17–3.91)
Paternal prenatal smoking[c]									
No	112	77	1.00 (—)	33	1.00 (—)	27	1.00 (—)	11	1.00 (—)
Yes	50	51	1.36 (0.82–2.24)	13	1.28 (0.54–3.01)	9	0.87 (0.33–2.34)	11	2.52 (0.83–7.66)
Child's passive smoking at home[d]									
No	134	100	1.00 (—)	43	1.00 (—)	26	1.00 (—)	14	1.00 (—)
Yes	32	41	1.41 (0.80–2.49)	8	0.70 (0.21–2.35)	13	2.76 (1.01–7.58)	10	1.32 (0.31–5.58)
Joint effect of paternal prenatal smoking and child's passive smoking[e]									
No exposure during both periods	111	78	1.00 (—)						
Paternal prenatal smoking only	20	16	1.14 (0.55–2.39)						
Child's passive smoking only	12	16	1.57 (0.65–3.79)						
Exposure during both periods	19	22	1.60 (0.63–4.05)						
	P-value for interaction		0.86						

NOTE. Shaded areas when insufficient data (≤5 observations per cell).

Abbreviation: CI, confidence interval.

[a]Includes any translocation involving chromosome 21, t(15;17), t(8;16), and inv(16).

[b]OR adjusted for child's age at diagnosis/reference date, sex, and Hispanic status, maternal race, and household annual income.

[c]Three months before conception and/or during pregnancy.

[d]Any smokers including mother, father, and others.

[e]Model is adjusted for maternal prenatal smoking.

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Although epidemiologic data may corroborate current knowledge about the natural history of specific leukemia subtypes, the mechanisms through which chemicals in tobacco smoke cause selected chromosomal break points remain unclear. Subtype-specific associations may result from other means than breaking chromosomes such as protein modification, signal transduction changes, or cell toxicity in which specific subtypes display more sensitivity.

Children may be exposed to second-hand smoke in the presence of a smoker at home, as well as to residues deposited on surfaces [referred to as third-hand smoking (34)]. In our study, about 6% of children were also exposed to smoke while inside a car, and those uniquely exposed to passive smoking in cars (not at home) were at higher risk of B-cell precursor ALL than children exposed at home. Similarly, nonsmoking fathers exposed to tobacco smoke in cars (but not at home, workplace, and public areas) were at increased risk of having children with B-cell precursor ALL. Possible mechanisms to explain this observation include germ cell damage during the preconception period as described earlier, and/or child's exposure to third-hand smoke via particle tracked into the child's environment. Sidestream and mainstream smoke contain similar mixtures of chemicals, but their concentrations vary depending on the smoke emission rates (35). Measurement studies of fine particulate matter and other markers of tobacco exposure have documented that smoking in a confined space like cars results in exposure to very high levels of tobacco-related chemicals (36, 37).

Our results should be interpreted in the context of the limitations and strength of the study. The NCCLS is the largest epidemiologic study to examine the association between exposure to tobacco smoke and the risk of leukemia harboring common chromosomal abnormalities. We recognize that replication of our observations in other large studies, individual, or pooled such as in the Childhood Leukemia International Consortium (CLIC), are needed to provide more precise estimates. Differential recall of tobacco smoking history between case and control families is a valid concern in case–control studies. Although tobacco smoking is a multiple organ site carcinogen, its association with hematologic malignancies is probably not well known to the general public. Also, the fact that we observed both positive and negative findings by leukemia subtype may be an indication that differential recall bias has limited influence on the results. Information on paternal tobacco smoking was collected through the mother or father depending on the phase of the study and availability of the father (see Materials and Methods section). A subset of parents of 107 cases and 108 controls from the NCCLS was recruited to assess the agreement between the mother's and father's self-reported information on father's smoking. Using κ statistics, the overall agreement for father's current smoking, father's lifetime smoking, and father's smoking during the 3 months prior to mother's pregnancy was substantial based on the scale proposed by Landis and Koch (38), with $\kappa = 0.76$ (95% CI, 0.60–0.91); 0.73 (95% CI, 0.63–0.83); and 0.70 (95% CI, 0.56–0.84), respectively. Agreement was higher among parents of cases, with higher education, and non-Hispanic Whites, as well as when the interval between the child's birth and diagnosis for cases (or reference date for controls) was less than 6 years. As the peak incidence of ALL is observed in children 2 to 5 years old, our findings about ALL should not have been substantially affected by who completed the interview (i.e., mother vs. father). Also we found no apparent difference in risks between Hispanics and non-Hispanic children.

In this analysis, controls have significantly higher household income and maternal education levels than cases, which may reflect a true observation or alternatively result from selection bias. Also, history of paternal and maternal smoking was associated with markers of socioeconomic status. In particular, the combination of prenatal paternal smoking and passive smoking was more frequent in households with low income and father's education, whereas smoking only during one period (before or after the child's birth) was more common in households with higher income and father's education. However, this observation was true for both cases and controls, and may not have substantially biased the results. All models were adjusted for household income, and additional adjustment for other socioeconomic markers such as parental education and age at child's birth did not influence the risk estimates.

The strengths of our study include the ultra-rapid ascertainment of children diagnosed with incident leukemia, the high participation rate (95%) of cases in the participating hospitals, the centralized review of medical abstracts by a pediatric oncologist to confirm the histology, immunophenotype, and karyotype of all leukemias, and additional FISH analyses conducted at a central laboratory to complete cytogenetic characterization on over 90% of leukemia cases, using pretreatment bone marrow and blood specimens. We collected detailed information on tobacco smoking history, including data on parent's passive smoking in various locations.

Our data suggest that combined exposures to tobacco smoking before the child's birth—including during the preconception period—and after birth are involved in the etiology of childhood ALL, consistent with the two-step model for leukemogenesis. The associations with tobacco smoking varied by cytogenetic subtype of B-cell ALL and possibly AML, although based on imprecise estimates.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

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References

1. Ries LAG, SEER Program (National Cancer Institute, United States). Cancer incidence and survival among children and adolescents: United States SEER program 1975–1995. Vol. vi. Bethesda, MD: National Cancer Institute SEER Program; 1999. p. 182.
2. Pui C-H. Childhood leukemias. Vol. xii. Cambridge, UK: Cambridge University Press; 1999. p. 567.
3. Greaves MF, Wiemels J. Origins of chromosome translocations in childhood leukaemia. Nat Rev Cancer 2003;3:639–49.
4. Cogliano VJ, Baan R, Straif K, Grosse Y, Lauby-Secretan B, El Ghissassi F, et al. Preventable exposures associated with human cancers. J Natl Cancer Inst 2011;103:1827–39.
5. Zaga V, Lygidakis C, Chaouachi K, Gattavecchia E. Polonium and lung cancer. J Oncol 2011;2011:860103.
6. International Agency for Research on Cancer. Overall evaluation of carcinogenicity: an updating of IARC monographs, vol. 1 to 42. Lyon, France: IARC; 1987. p. 440.
7. Goldstein BD. Benzene as a cause of lymphoproliferative disorders. Chem Biol Interact 2010;184:147–50.
8. Smith MT. Advances in understanding benzene health effects and susceptibility. Annu Rev Public Health 2010;31:133–48.
9. Klimentopoulou A, Antonopoulos CN, Papadopoulou C, Kanavidis P, Tourvas AD, Polychronopoulou S, et al. Maternal smoking during pregnancy and risk for childhood leukemia: a nationwide case-control study in Greece and meta-analysis. Pediatr Blood Cancer 2012;58:344–51.
10. Liu R, Zhang L, McHale CM, Hammond SK. Paternal smoking and risk of childhood acute lymphoblastic leukemia: systematic review and meta-analysis. J Oncol 2011;2011:854584.
11. Milne E, Greenop KR, Scott RJ, Bailey HD, Attia J, Dalla-Pozza L, et al. Parental prenatal smoking and risk of childhood acute lymphoblastic leukemia. Am J Epidemiol 2012;175:43–53.
12. Brondum J, Shu XO, Steinbuch M, Severson RK, Potter JD, Robison LL. Parental cigarette smoking and the risk of acute leukemia in children. Cancer 1999;85:1380–8.
13. Rudant J, Clavel J, Infante-Rivard C. Selection bias in case-control studies on household exposure to pesticides and childhood acute leukemia. J Expo Sci Environ Epidemiol 2010;20:299–309.
14. Slater ME, Linabery AM, Blair CK, Spector LG, Heerema NA, Robison LL, et al. Maternal prenatal cigarette, alcohol and illicit drug use and risk of infant leukaemia: a report from the Children's Oncology Group. Paediatr Perinat Epidemiol 2011;25:559–65.
15. Chang JS, Selvin S, Metayer C, Crouse V, Golembesky A, Buffler PA. Parental smoking and the risk of childhood leukemia. Am J Epidemiol 2006;163:1091–100.
16. Bartley K, Metayer C, Selvin S, Ducore J, Buffler P. Diagnostic X-rays and risk of childhood leukaemia. Int J Epidemiol 2010;39:1628–37.
17. Ma X, Buffler PA, Layefsky M, Does MB, Reynolds P. Control selection strategies in case-control studies of childhood diseases. Am J Epidemiol 2004;159:915–21.
18. Mitelman F, editor. An International System for Human Cytogenetic Nomenclature. Basel, Switzerland: S. Karger; 1995:1–114;49.
19. Aldrich MC, Zhang L, Wiemels JL, Ma X, Loh ML, Metayer C, et al. Cytogenetics of Hispanic and White children with acute lymphoblastic leukemia in California. Cancer Epidemiol Biomarkers Prev 2006;15:578–81.
20. Scelo G, Metayer C, Zhang L, Wiemels JL, Aldrich MC, Selvin S, et al. Household exposure to paint and petroleum solvents, chromosomal translocations, and the risk of childhood leukemia. Environ Health Perspect 2009;117:133–9.
21. Bonaventure A, Goujon-Bellec S, Rudant J, Orsi L, Leverger G, Baruchel A, et al. Maternal smoking during pregnancy, genetic polymorphisms of metabolic enzymes, and childhood acute leukemia: the ESCALE study (SFCE). Cancer Causes Control 2012;23:329–45.
22. Ross JA. Dietary flavonoids and the MLL gene: a pathway to infant leukemia? Proc Natl Acad Sci U S A 2000;97:4411–3.
23. Spector LG, Xie Y, Robison LL, Heerema NA, Hilden JM, Lange B, et al. Maternal diet and infant leukemia: the DNA topoisomerase II inhibitor hypothesis: a report from the children's oncology group. Cancer Epidemiol Biomarkers Prev 2005;14:651–5.
24. Alexander FE, Patheal SL, Biondi A, Brandalise S, Cabrera ME, Chan LC, et al. Transplacental chemical exposure and risk of infant leukemia with MLL gene fusion. Cancer Res 2001;61:2542–6.
25. Sorahan T, Prior P, Lancashire RJ, Faux SP, Hulten MA, Peck IM, et al. Childhood cancer and parental use of tobacco: deaths from 1971 to 1976. Br J Cancer 1997;76:1525–31.
26. Chang JS. Parental smoking and childhood leukemia. Methods Mol Biol 2009;472:103–37.
27. Crane MM, Strom SS, Halabi S, Berman EL, Fueger JJ, Spitz MR, et al. Correlation between selected environmental exposures and karyotype in acute myelocytic leukemia. Cancer Epidemiol Biomarkers Prev 1996;5:639–44.
28. Bjork J, Albin M, Mauritzson N, Stromberg U, Johansson B, Hagmar L. Smoking and acute myeloid leukemia: associations with morphology and karyotypic patterns and evaluation of dose-response relations. Leuk Res 2001;25:865–72.
29. Bjork J, Johansson B, Broberg K, Albin M. Smoking as a risk factor for myelodysplastic syndromes and acute myeloid leukemia and its relation to cytogenetic findings: a case-control study. Leuk Res 2009;33:788–91.
30. Lebailly P, Willett EV, Moorman AV, Roman E, Cartwright R, Morgan GJ, et al. Genetic polymorphisms in microsomal epoxide hydrolase and susceptibility to adult acute myeloid leukaemia with defined cytogenetic abnormalities. Br J Haematol 2002;116:587–94.

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31. DeMarini DM. Genotoxicity of tobacco smoke and tobacco smoke condensate: a review. Mutat Res 2004;567:447–74.
32. Wiemels JL, Leonard BC, Wang Y, Segal MR, Hunger SP, Smith MT, et al. Site-specific translocation and evidence of postnatal origin of the t(1;19) E2A-PBX1 fusion in childhood acute lymphoblastic leukemia. Proc Natl Acad Sci U S A 2002;99:15101–6.
33. Mori H, Colman SM, Xiao Z, Ford AM, Healy LE, Donaldson C, et al. Chromosome translocations and covert leukemic clones are generated during normal fetal development. Proc Natl Acad Sci U S A 2002;99:8242–7.
34. Matt GE, Quintana PJ, Destaillats H, Gundel LA, Sleiman M, Singer BC, et al. Thirdhand tobacco smoke: emerging evidence and arguments for a multidisciplinary research agenda. Environ Health Perspect 2011; 119:1218–26.
35. Pieraccini G, Furlanetto S, Orlandini S, Bartolucci G, Giannini I, Pinzauti S, et al. Identification and determination of mainstream and sidestream smoke components in different brands and types of cigarettes by means of solid-phase microextraction-gas chromatography-mass spectrometry. J Chromatogr A 2008;1180:138–50.
36. Muller D, Klingelhofer D, Uibel S, Groneberg DA. Car indoor air pollution—analysis of potential sources. J Occup Med Toxicol. 2011; 6:33.
37. Semple S, Apsley A, Galea KS, Maccalman L, Friel B, Snelgrove V. Secondhand smoke in cars: assessing children's potential exposure during typical journey conditions. Tob Control 2012 Jan 6. [Epub ahead of print]
38. Landis JR, Koch GG. The measurement of observer agreement for categorical data. Biometrics 1977;33:159–74.

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