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Pre- and post-natal exposures to tobacco smoking and survival of childhood acute lymphoblastic and myeloid leukemias in California, United States

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Abstract

Background: Tobacco smoke adversely affects the prognosis of adult cancers including myeloid leukemia, but less is known in children.

Methods: We evaluated whether pre- and post-natal exposures to tobacco smoke decrease 5-year survival of 1,235 childhood acute lymphoblastic leukemia (ALL) and 188 childhood acute myeloid leukemia (AML) cases derived from a population-based case-control study in California (United States). Cases were diagnosed between 1995 and 2015 (median follow-up time of 13.2 years overall). We obtained data on tobacco smoking (before conception, during pregnancy, after birth), parental education and income, clinical features, and vital status through 2020. Cox proportional hazards regression was used to calculate hazard ratios (HR) and 95% confidence intervals (CI) for mortality associated with smoking, adjusting for sociodemographic characteristics and risk group (ALL only).

Results: About 23% of mothers and 39% of fathers reported smoking and 130 children with ALL and 52 with AML died within 5 years. For AML, increased risks of death were observed among children whose fathers smoked before conception compared to non-smoking fathers (HR=1.41; 95% CI:0.95–3.44 and 3.47; 95% CI:1.37–8.81, respectively for <20 vs. ≥20 cigarettes per day; p-trend=0.01); HR for child's passive smoking =1.74, 95% CI:0.81–3.73. Paternal preconception smoking may also reduce 5-year survival among ALL with favorable prognostic molecular subtypes (high-hyperdiploidy and absence of IKZF1 gene deletion), although the associations did not reach statistical significance (p-value for heterogeneity=0.07).

Conclusion: Paternal preconception smoking decreased 5-year survival of childhood AML.

Impact: Knowledge of exposure to tobacco smoking should be integrated in the treatment plan of childhood leukemias.

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Conflict of Interest: The authors declare no potential conflicts of interest.

Keywords

Childhood leukemia; Survival; tobacco smoking

Introduction

Leukemia is the most common childhood cancer comprised mainly of acute lymphoblastic leukemia (ALL) followed by acute myeloid leukemia (AML). Its incidence has increased in the past decades in the United States, especially in the Latinx population (1,2). Despite improvements in cancer survival, significant disparities persist by socioeconomic status (SES) and race/ethnicity (3–5). The reasons for differential clinical outcomes in childhood leukemia patients are not fully explained by disparity in care (6,7). Pre- and post-natal exposures to tobacco smoking, especially from fathers before conception and passive smoking, have been associated with increased risks of developing childhood ALL and AML (8–10) and ALL with increased number of chromosomal deletions (11,12). Yet minimal attention has been given to the possible impact of tobacco smoke on clinical outcomes following diagnosis. One study conducted among children with ALL in Spain reported that exposure to tobacco smoke—mainly maternal smoking pre- and postnatally—negatively impacted 5-year survival, relapse, and treatment-related mortality (13). Although based on small numbers of children enrolled (n=146) and reported deaths (n=8), these findings were consistent with studies in adults showing reduced survival among smokers treated for leukemia and other cancers, possibly via carcinogenic and immunologic pathways (14–25).

While the prevalence of tobacco smoking has diminished in the United States (26), tobacco use remains highly prevalent in economically deprived households and in populations of color (27–29). Notably children from these various backgrounds also experience worse event-free and overall survival following a leukemia diagnosis (3–5). We tested the hypothesis that pre- and post-natal exposures to tobacco smoke reduce ALL and AML survival in 1,449 children enrolled in a California case-control study.

Materials and Methods

Study population:

The California Childhood Leukemia Study (CCLS) is a population-based case-control study originally designed to identify environmental and genetic risk factors of childhood leukemia (1995–2015) (10); only cases were evaluated for this analysis. Childhood leukemia patients (based on the International Classification of Childhood Cancer) were rapidly identified after diagnosis at 17 hospitals and were eligible if younger than 15 years of age at diagnosis, had an English or Spanish speaking parent, lived in one of the study counties at time of diagnosis, and had no previous cancer. Among 1,709 consented cases, 1,449 were interviewed (85%). About 19% (n=50) of those without completed interviews were children who died (i.e., 26 ALL and 23 AML).

Data collection:

Interviews were conducted within 6 months of the diagnosis (on average), mainly with biological mothers, using a structured questionnaire on sociodemographic, occupational, residential, medical, and lifestyle factors. Data on child's exposure to tobacco use (defined as a minimum of 100 cigarettes/cigars/pipes in a lifetime) was collected separately from the mother and father when available; if the father was not available, the mother was interviewed regarding father's smoking. We collected information (yes/no) on paternal and maternal smoking (lifetime and before conception), maternal smoking during pregnancy and breastfeeding, and child's passive smoke exposure after birth from the mother (excluding breastfeeding) and/or anyone else (father or others) up to the time of the interview or third birthday, whichever came first. We collected start and end dates of smoking and number of cigarettes per day (cpd) for the preconception, pregnancy, and breastfeeding periods. Histologic leukemia types and white blood count (WBC) at diagnosis were abstracted from medical records and independently validated by a clinician. Determination of cytogenetic subtypes was derived from both medical records and additional testing, including fluorescence in situ hybridization (FISH) to identify leukemias with high-hyperdiploidy and the TEL-AML (ETV6-RNX1) translocation and multiplex ligation-dependent probe amplification (MLPA) to identify CDKN2A and IKZF1 deletions (10,12). To assess vital status, electronic death certificate data obtained from the California Department of Public Health Center for Health Statistics and Informatics (1995–2020) were linked to the CCLS database by child's first, middle, and last name, sex, date of birth, mother's maiden name, father's last name, and race/ethnicity, using a probabilistic linkage (Match*Pro Version 2.0.7, SEER). Ambiguous matches, usually due to misspelling of first names or surnames (n=65), were independently reviewed (by CM and LM); matches were considered definitive if consensus was achieved. Out of 1,449 participants, 191 cases were linked to death files (5 were due to external causes). This study was approved by Institutional Review Boards at the University of California, Berkeley, and the California Department of Public Health.

Statistical analysis:

The outcome evaluated was 5-year survival from all causes except external causes. Cases were considered an event if death occurred any time before end of follow-up (12/31/2020); cases were censored if alive or at date of death from external cause. The non-parametric Kaplan-Meier estimator was used to estimate the survival function, and survival curves were plotted to visualize the probability of survival comparing smoking groups. Log rank tests were performed to test the significance of differences in survival between groups. Cox proportional hazards regression was used to calculate hazard ratios (HR) and 95% confidence intervals (CI) associated with smoking, adjusting for child's sex, race/ethnicity (Latino, non-Latino white, non-Latino black, non-Latino Asians, and non-Latino others), birth year (continuous), parental highest education (dichotomized: high school or lower vs. some college or more), annual household income (6 categories), and risk group (ALL only) (categorical: "standard" defined as age >1 year and age <10 years and WBC <50,000/uL; "high" defined as age >=10 years OR age >1 year and age <10 years and WBC >=50,000/uL; and "infant" defined as age <1 year). We conducted additional analyses to assess whether other covariates acted as potential confounders including the number of persons supported by the annual household income (as a proxy for SES), year of diagnosis

(as proxy for changes in treatment protocols (30) and smoking behavior (31) over time), and hospital study site (as a proxy for treatment modalities and supportive care); none of these affected the risk estimates by more than 10%, and therefore, were not included in the final models (see Directed Acyclic Graph in Supplemental Figure 1). Stratified analyses were conducted by sex, race/ethnicity (non-Latinx White vs. Latinx), and cytogenetic characteristics (i.e., deletions in CDKN2A and IKZF1 genes, and high-hyperdiploidy; data were too sparse to analyze TEL-AML-(ETV6-RNX1) translocation separately with only 3 deaths recorded). Testing for heterogeneity between groups was conducted using likelihood ratio tests.

The study was approved by Institutional Review Boards for the California Health and Human Services and the University of California, Berkeley and San Francisco, and was conducted according to the U.S Common Rule.

Data Availability:

The epidemiologic and clinical data generated in this study are not publicly available due to terms of the informed consent signed when subjects were enrolled to the CCLS study but are available upon reasonable request from the corresponding author. The death data analyzed in this study were obtained from the California Department of Public Health (CDPH) Center for Health Statistics and Informatics (CHSI) and are not publicly available due to terms of CDPH-CHSI.

Results

Among 1,449 interviewed childhood leukemia cases (1,235 ALL, 188 AML, 26 other types), 186 children died of non-external causes within 5 years of the diagnosis (i.e., 130 ALL and 52 AML). Causes of death from death certificates were neoplasm/leukemia (n=170), infection (n=4), blood/circulatory/immune system disorders (n=4), respiratory system disorders (n=3), and others (n=5). Table 1 shows the distribution of demographic and birth characteristics by vital status. As expected, children who died were more likely to have AML or high-risk ALL, be diagnosed under one year of age, be either Latinx, non-Latinx Asian/Pacific Islanders or non-Latinx Black; and have low parental education and annual household income. Lifetime tobacco smoking was reported in 39% of fathers (65% of which were either Black, Latinx, or Asian/PI, compared to 62% among non-smokers) and 23% of mothers (46% of which were non-Latinx White); paternal smoking was more frequent in households of low education and low income compared to non-smokers; similarly maternal smoking was more frequent in low-income households (Supplemental Table 1). There was little correlation between maternal and paternal smoking but some level of correlation between pre- and post-natal maternal smoking (Supplemental Figure 2). Overall, children who died were more likely to have a history of paternal smoking, especially during preconception (29% vs. 22% in deceased vs. alive, p-value=0.06) and passive smoking after birth (24.7% vs. 17% in deceased vs. alive, p-value=0.15) (Table 2). Alive and deceased children were otherwise similar across other categories of parental smoking in univariate analyses.

Childhood AML:

Paternal preconception smoking was associated with decreased 5-year survival, especially for fathers reporting smoking more than 20 cigarettes per day (p-value for log rank test =0.067; Figure 1). Table 3 shows the HRs for 5-year survival for childhood AML with adjustment for sex and birthyear (Model A) and with additional adjustment for parental education and annual household income (Model B). In the fully adjusted Model B, the risk of dying for children with AML increased with the amount of preconception paternal smoking (HR = 1.41; 95% CI:0.95–3.44 and 3.47; 95% CI:1.37–8.81, respectively for < 20 vs. ≥20 cigarettes per day; p-trend=0.01). Overall the risk estimates were comparable with and without adjustment for SES.. Preconception paternal smoking remains an independent prognostic factor of AML after adjusting for child's passive smoking, although the magnitude of the association decreased (e.g., HR for paternal preconception smoking/20+ cigarettes per day = 2.91, 95% CI: 1.18–7.2). Further adjustment for hospital study site did not substantially modify the risk estimates (e.g., HR for paternal preconception smoking/20+ cigarettes per day = 3.60 (95% CI: 1.38–9.40). There were no notable associations between pre- and post-natal maternal smoking and AML survival.

Childhood ALL:

There were no indications of associations between ALL survival and exposure to tobacco smoke at any time pre- or postnatally in models with and without SES adjustments (Table 4). However, our data suggested differences in smoking-related risk of death by ALL molecular subgroup (favorable vs. poor prognosis; Table 5). Specifically, for paternal preconception smoking, p-values for heterogeneity in HRs were 0.07 comparing both high-hyperdiploidy status (yes/favorable vs. no/unfavorable) and IKZF1 deletion status (no/favorable vs. yes/unfavorable). When estimating the joint effect of paternal preconception smoking and these molecular types, children treated for high-hyperdiploid ALL (favorable) and exposed to paternal preconception smoking were 2.4-fold more likely to die compared to those not exposed (p-value=0.17), approaching risk levels close to ALL without high-hyperdiploid (unfavorable). A similar trend was seen for the joint effect of IKZF1 deletion negative and paternal preconception smoking, although the association did not reach statistical significance (HR=1.50, p-value=0.27). In contrast, no joint effects were seen for CDKN2A subtype and paternal preconception smoking (Table 5). Child's passive smoking did not confound associations observed for ALL subtypes. Tests for interaction with race and ethnicity reached statistical significance (p=0.03) for paternal preconception smoking and maternal smoking after birth; for Latinx children the risk was increased (HRs=1.27, 95% CI:0.70–2.31 and 1.80, 95% CI:0.86–3.74, respectively), whereas for non-Latinx White children the risk was decreased (HRs=0.22, 95% CI: 0.05–1.04 and 0.19, 95% CI:0.02–1.54, respectively) compared to those not exposed to parental smoking. In general, risk estimates associated with exposure to tobacco smoke at other times were above one for Latinx children and close to or below one for non-Latinx White children; tests for interaction, however, were not statistically significant. Results were similar for boys and girls.

Discussion

This study is the first one to report that preconception paternal smoking reduces 5-year survival of childhood AML, especially among children whose fathers were heavy smokers. Adjustment for SES and child's passive smoking had little impact on the magnitude of the association indicating that paternal preconception tobacco smoking acted independently. There was a suggestion that children treated for certain favorable molecular subtypes of ALL lost their survival advantage when fathers reported smoking before conception, although these results did not reach statistical significance and need to be replicated. Results for other windows of exposure to maternal tobacco smoking pre- and postnatally were either null or inconclusive.

Studies worldwide (8,9), including ours in California (10), have documented associations between paternal preconception smoking and increased risks of developing childhood ALL and AML. This is the first study to also report an association with reduced survival in pediatric AML, especially for heavy smokers. Our data also suggested that paternal preconception smoking reduces survival of certain ALL molecular subtypes otherwise known to have favorable prognosis, including those with high-hyperdiploidy and without IKZF1 deletion. These observations were, however, based on small numbers. The biological underpinning that may explain differences in risk by leukemia type remains unclear. The underlying mechanisms by which paternal smoking during the preconception period affect prognosis of certain childhood leukemias may include damage of paternal germ cells that could alter immune and oxidative stress pathways (32). Another potential mechanism is through paternal epigenetic programming of cardiovascular and metabolic pathways in offspring (33) that impact cancer progression, response to treatment, and treatment-related toxicity (34,35). For example, paternal preconception smoking has been associated with high body weight in offspring (36,37), suggesting that growth factors or obesity may play a mediating role.

Our data suggested that passive smoking reduced 5-year survival of childhood AML (any smokers) and ALL (Latina mothers), respectively by 1.7- to 1.8- fold, although these associations did not reach statistical significance. This is consistent with studies conducted in adults treated for acute myeloid leukemia and solid tumors showing worse clinical outcomes among smokers (14–25). Similarly, a study conducted in Spain among 146 children with ALL first reported statistically significant associations between maternal smoking during both pregnancy and after birth and poor clinical outcomes, with a 4-fold increased risk of dying, 8-fold risk of relapse, and a 14-fold increased risk of cumulative treatment-related mortality, after accounting for known prognostic factors (13). In contrast, paternal smoking was not independently associated with worse outcomes. The separate contribution of pregnancy vs. post-natal tobacco smoking could not be assessed since most mothers smoked during both periods. In our study, maternal smoking during pregnancy did not affect childhood leukemia survival. Differences in results between the study in Spain and our study in California may be due to prevalence of smoking, especially for mothers who were twice as likely to smoke in Spain compared to California (44% vs. 23%). Carcinogenic compounds found in tobacco smoke such as benzene may not only damage blood cells, but also increase genetic instability of leukemia cells and modulate immune response. Smoke

exposure has been shown to lower immunoglobulin levels and T-cell counts and delay count recovery possibly resulting in prolonged susceptibility to infection and increased risk of bleeding (14,16,21,25).

Our results should be interpreted considering limitations and strengths. Although our data on pre- and post-natal tobacco smoking are detailed and novel for the preconception period, they rely on self-report. We previously assessed the quality of recall in a subset of CCLS participants (38,39). First, we measured two biomarkers of tobacco smoking during pregnancy (i.e., 1- Cys34 protein adducts (13,39) and CpG sites in the AHRR, GFI1, and MYO1G genes (38)) in archived newborn blood samples and compared those with maternal self-reported smoking. The strong correlation between the biomarkers and self-report suggested that mother's recall was largely accurate. We also evaluated concordance between the mother's and father's reporting (among 107 leukemia cases and 108 controls) to evaluate for recall bias on father's smoking. The overall agreement for smoking (current, lifetime smoking, and three months before the mother's pregnancy) was high, with kappa statistics ranging from 0.70 to 0.76 (p-values<0.05) (40). Agreement was higher among parents of children with leukemia, those with higher education, for non-Latinx White parents, and for those with short intervals between the child's birth and diagnosis (<6 years). Since 69% of our ALL cases were diagnosed under the age of 6, mothers' recall of father's smoking should not have substantially biased our findings regarding ALL and paternal smoking. Although death at the time of interview was not an exclusion criterion, interviews were not completed for 50 children who died shortly after enrollment in the study. In our cohort, however, the 5-year survival for ALL combined was 91.8% and 69.9% for AML, which is aligned with national data for our study period (1995 to 2015) (41,42). Deceased children without interviews were similar to deceased children with interviews with respect to various birth registry data including birthweight, gestational age, and individual sociodemographic characteristics. There was a suggestion, however, that neighborhood income varied between households not interviewed and those interviewed (mean= $38,000 vs. $45,300, respectively; pooled t-test p-value=0.06), indicating the potential for selection bias among those interviewed.

Although models were adjusted for several sociodemographic characteristics known to influence both exposure to tobacco smoking and survival, there may be some residual confounding by SES. Medical insurance and access to supportive care (especially following hematopoietic stem cell transplantation and related complications such as graft-versus-host disease) may be subject to geographic and sociodemographic variations and differential adverse outcomes (43). However, our data showed that hospital study site, as a proxy for treatment modalities and supportive case, was not confounding the observed associations between tobacco smoking and survival. Also, based on a causal diagram built for our analyses, additional adjustment for medical insurance was not necessary, beyond household income, parental education, and child's race and ethnicity. Altogether, we believe that access to care should not substantially impact our results. Based on priori knowledge (44), we examined ALL molecular subtypes that are known to affect prognostic and that were available in our study (i.e., high-hyperdiploidy, CDKN2A and IKZF1 deletions). We did not have information or sufficient sample size for other prognostic subtypes such as Ph+ and Ph-like ALL, or those with TEL-AML (ETV6-RNX1) fusion gene. Also, despite a relatively

large number of childhood leukemia cases, analyses for rare subtypes (i.e., AML and ALL subgroups) and minority racial and ethnic groups were based on small numbers. Lastly, multiple comparisons may have led to false positive results.

In conclusion, our data suggest that paternal preconception smoking has a negative impact on childhood AML survival, adding to the body of evidence from previous studies mostly conducted in adults. Results for ALL subtypes need to be replicated in larger studies. Knowledge of exposure to tobacco smoke should be integrated in treatment plans to ensure that at a minimum, children undergoing cancer treatment are not exposed to the harmful effects of tobacco smoke.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations:

ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
CCLS	California Childhood Leukemia Study
CI	Confidence interval
HR	Hazards ratio
SES	Socioeconomic status
WBC	White blood count

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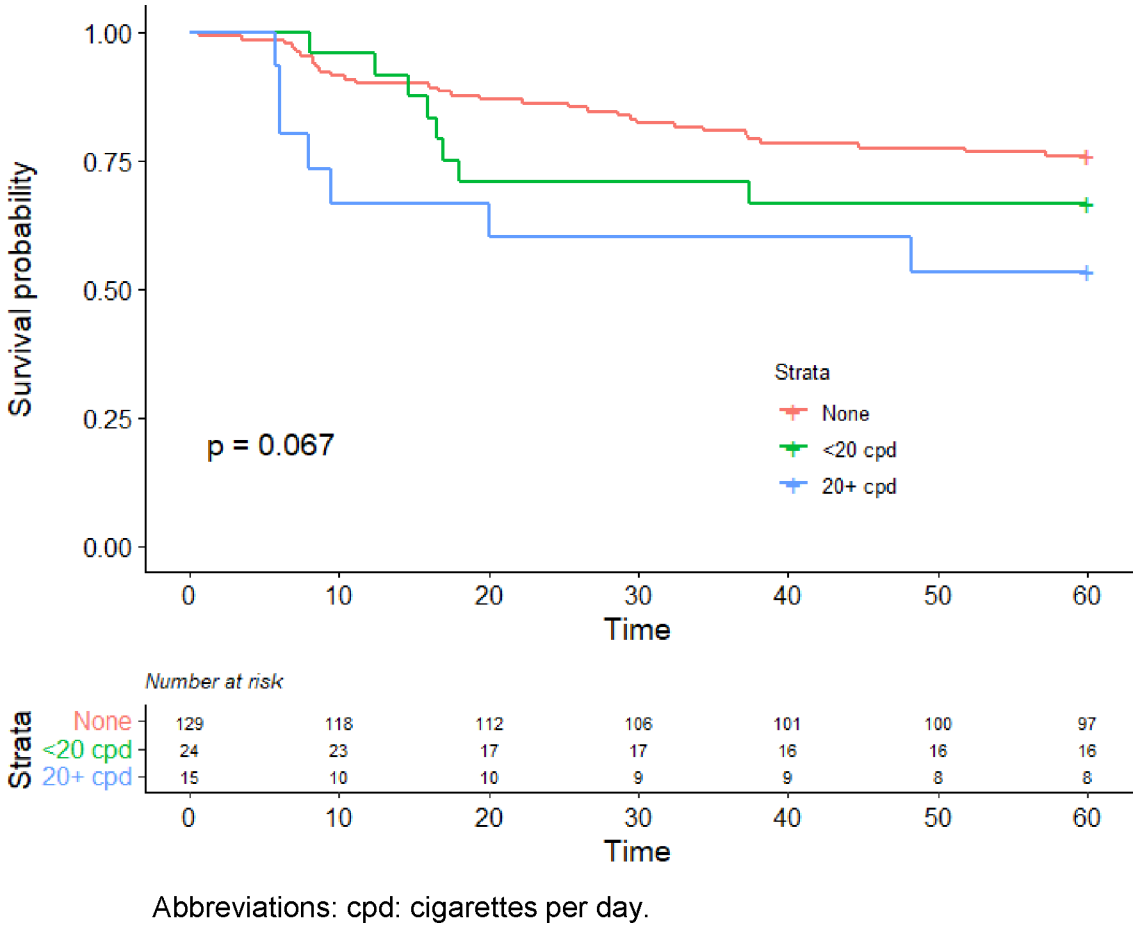

Abbreviations: cpd: cigarettes per day.

Figure 1.

Kaplan-Meier curves for level of paternal preconception smoking and childhood acute myeloid leukemia survival

Table 1.

Characteristics of children with leukemia by survival status at the end of 2020 (N=1,449).

	Alive (n=1263) n (%)	Deceased (n=186) n (%)	P-value
Leukemia type			
Acute lymphoblastic leukemia (ALL)	1105 (87.5)	130 (69.9)	<0.001
Acute myeloid leukemia (AML)	136 (10.8)	52 (28.0)	
Other types	22 (1.7)	4 (2.2)	
Sex			
Female	547 (43.3)	75 (40.3)	0.49
Male	716 (56.7)	111 (59.7)	
Race and ethnicity			
Latinx	655 (51.9)	98 (52.7)	0.04
Non-Latinx White	403 (31.9)	45 (24.2)	
Non-Latinx Asian/Pacific Islander	99 (7.8)	18 (9.7)	
Non-Latinx Black	30 (2.4)	10 (5.4)	
Other/unknown	76 (6.0)	15 (8.1)	
Birth years			
1982–1989	66 (5.2)	23 (12.4)	<0.001
1990–1999	538 (42.6)	88 (47.3)	
2000–2009	518 (41.0)	61 (32.8)	
2010–2014	141 (11.2)	14 (7.5)	
Age at diagnosis (years)			
< 1	33 (2.6)	26 (14.0)	<0.001
1 to 2	311 (24.6)	39 (21.0)	
3 to 6	550 (43.5)	46 (24.7)	
7 to 9	161 (12.7)	27 (14.5)	
10–14	208 (16.5)	48 (25.8)	
NIH group risk for ALL only			
Standard	726 (65.7)	61 (46.9)	<0.001
High	278 (25.2)	46 (35.4)	
Infant	16 (1.4)	16 (12.3)	
Unknown	85 (7.7)	7 (5.4)	
Birthweight (grams)			
<2500	66 (5.2)	12 (6.5)	0.73
2500–4000	1016 (80.4)	150 (80.6)	
4000	176 (13.9)	24 (12.9)	
Unknown	5 (0.4)	0 (0)	
Gestational age (weeks)			
<36	71 (5.6)	17 (9.1)	0.18
36–41	932 (73.8)	130 (69.9)	
41+	232 (18.4)	37 (19.9)	
Missing	28 (2.2)	2 (1.1)	

	Alive (n=1263) n (%)	Deceased (n=186) n (%)	P-value
Household annual income (USD)			
<15,000	225 (17.8)	32 (17.2)	0.09
15,000–29,999	238 (18.8)	39 (21.0)	
30,000–44,999	172 (13.6)	32 (17.2)	
45,000–59,999	165 (13.1)	31 (16.7)	
60,000–74,999	77 (6.1)	14 (7.5)	
75,000+	386 (30.6)	38 (20.4)	
Highest parental education attained			
High school or lower	479 (37.9)	76 (40.9)	0.7
Some college or more	783 (62.0)	110 (59.1)	
Missing	1 (0.1)	0 (0)	

Table 2.

Exposure to tobacco smoking by survival status at the end of 2020 (N=1,449).

Smoker type and window of exposure	Alive n (%)	Deceased n (%)	P-value
PATERNAL SMOKING			
Ever smoked (up to the time of the interview)			
No	687 (54.4)	90 (48.4)	0.10
Yes	485 (38.4)	84 (45.2)	
Unknown	91 (7.2)	12 (6.5)	
Ever smoked 3 months before conception			
No	884 (70.0)	119 (64.0)	0.06
Yes	281 (22.2)	54 (29.0)	
Unknown	98 (7.8)	13 (7.0)	
Number of cigarettes per day before conception			
Mean [SD]	2.68 [7.23]	3.51 [9.36]	0.28
Median [Min, Max]	0 [0, 80.0]	0 [0, 60.0]	
Unknown	133 (10.5)	21 (11.3)	
Smoking level before conception			
None	884 (70.0)	119 (64.0)	0.21
<20 cigarettes per day	174 (13.8)	32 (17.2)	
20 cigarettes or more per day	72 (5.7)	14 (7.5)	
Unknown	133 (10.5)	21 (11.3)	
MATERNAL SMOKING			
Ever smoked (up to the time of the interview)			
No	961 (76.1)	137 (73.7)	0.46
Yes	290 (23.0)	48 (25.8)	
Unknown	12 (1.0)	1 (0.5)	
Ever smoked 3 months before conception			
No	1107 (87.6)	165 (88.7)	0.88
Yes	144 (11.4)	20 (10.8)	
Unknown	12 (1.0)	1 (0.5)	
Number of cigarettes per day before conception			
Mean [SD]	1.10 [4.02]	0.92 [3.61]	0.53
Median [Min, Max]	0 [0, 50.0]	0 [0, 30.0]	
Unknown	15 (1.2)	1 (0.5)	
Smoking level before conception			
None	1107 (87.6)	165 (88.7)	0.77
<20 cigarettes per day	110 (8.7)	17 (9.1)	
20 cigarettes or more per day	31 (2.5)	3 (1.6)	
Unknown	15 (1.2%)	1 (0.5%)	
Ever smoked during pregnancy			
No	1161 (91.9)	169 (90.9)	0.58
Yes	90 (7.1)	16 (8.6)	

Smoker type and window of exposure	Alive n (%)	Deceased n (%)	P-value
Unknown	12 (1.0)	1 (0.5)	
Number of cigarettes per day during pregnancy			
Mean [SD]	0.45 [2.18]	0.61 [3.02]	0.48
Median [Min, Max]	0 [0, 20.0]	0 [0, 30.0]	
Unknown	15 (1.2)	1 (0.5)	
CHILD'S PASSIVE SMOKING			
Mother ever smoked during breastfeeding			
No	1168 (92.5)	169 (90.9)	0.68
Yes	39 (3.1)	4 (2.2)	
Unknown	56 (4.4)	13 (7.0)	
Number of cigarettes per day during breastfeeding			
Mean [SD]	0.19 [1.36]	0.16 [1.12]	0.79
Median [Min, Max]	0 [0, 20.0]	0 [0, 10.0]	
Unknown	58 (4.6)	13 (7.0)	
Mother ever smoked, excluding breastfeeding [1]			
No	1079 (85.4)	158 (84.9)	0.67
Yes	157 (12.4)	26 (14.0)	
Unknown	27 (2.1)	2 (1.1)	
Number of cigarettes per day, excluding breastfeeding [1]			
Mean [SD]	0.81 [3.98]	0.87 [3.95]	0.84
Median [Min, Max]	0 [0, 98.0]	0 [0, 40.0]	
Unknown	48 (3.8)	8 (4.3)	
Mother and/or anyone else ever smoked after the child's birth [1]			
No	648 (51.3)	103 (55.4)	0.15
Yes	215 (17.0)	46 (24.7)	
Unknown	400 (31.7)	37 (19.9)	

[1] Up to the child's third birthday, or time of the interview, or death, whichever occurred first.

Table 3.

Exposure to tobacco smoking and survival in children treated for acute myeloid leukemia: proportional hazards Cox models without and with adjustments for socioeconomic status (n=52 deaths out of 188 cases).

		Model A - without SES adjustment[1]		Model B - with SES adjustment[2]	
Smoker Type and Window of Exposure	**Deceased n (%)**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Paternal Smoking					
Lifetime (up to interview)					
No	24 (51.1)	Ref.		Ref.	
Yes	23 (48.9)	1.12 (0.63–2.01)	0.69	1.17 (0.65–2.11)	0.59
Preconception (y/n)					
No	31 (66.0)	Ref.		Ref.	
Yes	16 (34.0)	1.77 (0.94–3.32)	0.08	1.80 (0.95–3.44)	0.07
Preconception (cpd)					
None	31 (67.4)	Ref.		Ref.	
<20 cpd	8 (17.4)	1.59 (0.71–3.58)	0.26	1.41 (0.95–3.44)	0.42
20+ cpd	7 (15.2)	2.87 (1.21–6.80)	0.02	3.47 (1.37–8.81)	0.01
trend		0.01		0.01	
Maternal Smoking					
Lifetime (up to interview)					
No	36 (75.0)	Ref.		Ref.	
Yes	12 (25.0)	1.17 (0.59–2.34)	0.65	1.12 (0.55–2.30)	0.75
Preconception (y/n)					
No	42 (87.5)	Ref.		Ref.	
Yes	6 (12.5)	1.10 (0.46–2.63)	0.83	1.08 (0.45–2.61)	0.86
Preconception (cpd)					
None	42 (87.5)	Ref.		Ref.	
<20 cpd	5 (10.4)	1.18 (0.46–3.03)	0.73	1.17 (0.45–3.06)	0.74
20+ cpd	1 (2.1)	1.39 (0.18–10.51)	0.75	1.52 (0.18–12.69)	0.70
Pregnancy					
No	42 (87.5)	Ref.		Ref.	
Yes	6 (12.5)	1.50 (0.63–3.60)	0.36	1.47 (0.61–3.56)	0.39
Child's Passive Smoking					
Mother - during breastfeeding					
No	45 (97.8)	Ref.		Ref.	
Yes	1 (2.2)	0.56 (0.08–4.19)	0.57	0.53 (0.07–4.01)	0.54
Mother - excluding breastfeeding[3]					
No	40 (83.3)	Ref.		Ref.	
Yes	8 (16.7)	1.31 (0.59–2.89)	0.51	1.33 (0.58–3.06)	0.51
Mother and/or anyone else[3]					
No	21 (61.8)	Ref.		Ref.	
Yes	13 (38.2)	1.68 (0.81–3.47)	0.16	1.74 (0.81–3.73)	0.15

Abbreviations: cpd: cigarettes per day; HR: hazards ratio; CI: confidence interval; ref: reference; SES: socioeconomic status.

[1] Adjusted for sex, birthyear, race/ethnicity

[2] Adjusted for sex, birthyear, race/ethnicity, highest parental education attained (binary), and income (6 categories).

[3] Up to the child's third birthday, or time of the interview, or death, whichever occurred first.

Table 4.

Exposure to tobacco smoking and survival in children treated for acute lymphoblastic leukemia: proportional hazards Cox models without and with adjustments for socioeconomic status (n=130 deaths out of 1235 cases).

		Model A - without SES adjustment[1]		Model B - with SES adjustment[2]	
Smoker Type and Window of Exposure	**Deceased n(%)**	**HR (95% CI)**	**p-value**	**HR (95% CI)**	**p-value**
Paternal Smoking					
Lifetime (up to interview)					
No	50 (52.1)	Ref.		Ref.	
Yes	46 (47.9)	1.09 (0.72–1.65)	0.67	1.02 (0.67–1.55)	0.93
Preconception (y/n)					
No	68 (70.8)	Ref.		Ref.	
Yes	28 (29.2)	1.04 (0.66–1.64)	0.86	0.93 (0.59–1.48)	0.77
Preconception (cpd)					
None	68 (74.7)	Ref.		Ref.	
<20 cpd	19 (20.9)	1.05 (0.62–1.77)	0.87	0.97 (0.56–1.66)	0.90
20+ cpd	4 (4.4)	0.69 (0.25–1.92)	0.47	0.58 (0.20–1.63)	0.30
p-trend		0.76		0.53	
Maternal Smoking					
Lifetime (up to interview)					
No	74 (71.8)	Ref.		Ref.	
Yes	29 (28.2)	1.26 (0.80–1.97)	0.32	1.18 (0.75–1.85)	0.48
Preconception (y/n)					
No	90 (87.4)	Ref.		Ref.	
Yes	13 (12.6)	1.07 (0.59–1.94)	0.83	0.90 (0.48–1.67)	0.73
Preconception (cpd)					
None	90 (87.4)	Ref.		Ref.	
<20 cpd	12 (11.7)	1.19 (0.63–2.22)	0.59	1.02 (0.53–1.95)	0.95
20+ cpd	1 (1.0)	0.53 (0.07–3.81)	0.52	0.40 (0.05–2.93)	0.37
Pregnancy					
No	94 (91.3)	Ref.		Ref.	
Yes	9 (8.7)	1.19 (0.58–2.43)	0.64	1.03 (0.50–2.15)	0.93
Child's Passive Smoking					
Mother - during breastfeeding					
No	92 (97.9)	Ref.		Ref.	
Yes	2 (2.1)	0.82 (0.20–3.36)	0.78	0.74 (0.18–3.06)	0.68
Mother - excluding breastfeeding[3]					
No	88 (86.3)	Ref.		Ref.	
Yes	14 (13.7)	1.04 (0.59–1.86)	0.89	0.89 (0.49–1.62)	0.70
Mother and/or anyone else[3]					
No	62 (72.1)	Ref.		Ref.	
Yes	24 (27.9)	1.08 (0.66–1.76)	0.77	0.92 (0.56–1.53)	0.76

Abbreviations: cpd: cigarettes per day; HR: hazards ratio; CI: confidence interval; ref: reference; SES: socioeconomic status.

[1] Adjusted for sex, birthyear, race/ethnicity, and NCI risk group status.

[2] Adjusted for sex, birthyear, race/ethnicity, NCI risk group status, highest parental education attained (binary), and income (6 categories).

[3] Up to the child's third birthday, or time of the interview, or death, whichever occurred first.

Table 5.

Joint effects of paternal preconception smoking and molecular type of childhood acute lymphoblastic leukemia (favorable vs. poor prognosis) on survival: proportional hazards Cox models.

Molecular Type/Paternal Preconception Smoking Status	Alive N (%)	Deceased N (%)	HR (95% CI)[1]	p-value	p-value hetero-geneity
High- hyperdiploidy/Smoke					
Yes (favorable)/No	223 (26.8)	5 (50.0)	Ref.		
Yes (favorable)/Yes	58 (7.0)	5 (50.0)	2.44 (0.69–8.63)	0.17	p=0.07[2]
No (poor)/No	402 (48.2)	51 (64.6)	4.06 (1.60–10.33)	<0.01	
No (poor)/Yes	150 (18.0)	18 (22.8)	2.82 (1.02–7.79)	0.05	
IKZF1 deletion/Smoke					
No (favorable)/No	333 (65.9)	23 (47.9)	Ref.		
No (favorable)/Yes	103 (20.4)	14 (29.2)	1.50 (0.73–3.08)	0.27	p=0.07[3]
Yes (poor)/No	45 (8.9)	10 (20.8)	2.67 (1.20–5.92)	0.02	
Yes (poor)/Yes	24 (4.8)	1 (2.1)	0.53 (0.07–4.04)	0.54	
CDKN2A deletion/Smoke					
No (favorable)/No	279 (55.2)	20 (40.0)	Ref.		
No (favorable)/Yes	90 (17.8)	9 (18.0)	0.99 (0.43–2.30)	0.99	p=0.95[4]
Yes (poor)/No	99 (19.6)	14 (28.0)	1.58 (0.77–3.26)	0.21	
Yes (poor)/Yes	37 (7.3)	7 (14.0)	1.63 (0.65–4.08)	0.30	

Abbreviations: HR: hazards ratio; CI: confidence interval; ref: reference.

[1]Adjusted for sex, birthyear, NCI risk group status, highest parental education attained (binary), and income (6 categories).

[2]Test for heterogeneity comparing the effect of smoking between childhood ALL with and without high-hyperdiploidy.

[3]Test for heterogeneity comparing the effect of smoking between childhood ALL with and without IKZF1 deletion.

[4]Test for heterogeneity comparing the effect of smoking between childhood ALL with and without CDKN2A deletion.