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Maternal prenatal cigarette, alcohol and illicit drug use and risk of infant leukaemia: a report from the Children's Oncology Group

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Summary

Several case–control studies have evaluated associations between maternal smoking, alcohol consumption and illicit drug use during pregnancy and risk of childhood leukaemia. Few studies have specifically focused on infants (<1 year) with leukaemia, a group that is biologically and clinically distinct from older children. We present data from a Children's Oncology Group case–control study of 443 infants diagnosed with acute leukaemia [including acute lymphoblastic leukaemia (ALL) and acute myeloid leukaemia (AML)] between 1996 and 2006 and 324 population controls. Mothers were queried about their cigarette, alcohol and illicit drug use 1 year before and throughout pregnancy. Odds ratios (ORs) and 95% confidence intervals [CI] were calculated using adjusted unconditional logistic regression models. Maternal smoking (>1 cigarette/day) and illicit drug use (any amount) before and/or during pregnancy were not significantly associated with infant leukaemia. Alcohol use (>1 drink/week) during pregnancy was inversely associated with infant leukaemia overall [OR = 0.64; 95% CI 0.43, 0.94], AML [OR = 0.49; 95% CI 0.28, 0.87], and leukaemia with mixed lineage leukaemia gene rearrangements ('*MLL+*') [OR = 0.59; 95% CI 0.36, 0.97]. While our results agree with the fairly consistent evidence that maternal cigarette smoking is not associated with childhood leukaemia, the data regarding alcohol and illicit drug use are not consistent with prior reports and are difficult to interpret. It is possible that unhealthy maternal behaviours during pregnancy, some of which carry potential legal consequences, may not be adequately measured using only self-report. Future case–control studies of childhood leukaemia that pursue these exposures may benefit from incorporation of validated instruments and/or biomarkers when feasible.

Keywords

childhood cancer; infant leukaemia; maternal smoking; maternal alcohol; illicit drug use

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Introduction

With an annual incidence of about 40 cases per million children in the US, leukaemia is the second most common cancer in infants (<1 year of age) after neuroblastoma.[1] Infants with leukaemia commonly have genetic translocations involving the mixed lineage leukaemia (*MLL*) gene in their leukaemia cells. *MLL* rearrangements (*MLL*+) are found in approximately 80% of infant acute lymphoblastic leukaemias (ALLs) and 60% of infant acute myeloid leukaemias (AMLs), but in only 5% of all childhood leukaemias diagnosed after 1 year of age and 10% of adult AMLs.[2–4] *MLL* status is believed to correspond to distinct aetiologies, partly because *MLL*+ infant ALL cases typically have much poorer survival than *MLL*− cases.[5,6] Studies of identical twins[7] and stored neonatal blood spots[8,9] have indicated that *MLL* rearrangements are initiated *in utero*. Therefore, studies of infant leukaemia have focused on *in utero* exposures as potential contributing factors in leukaemogenesis.

Many previous epidemiological studies of childhood leukaemia have investigated possible connections between maternal cigarette smoking and/or maternal alcohol consumption. Most studies of maternal smoking and childhood leukaemia have found no association.[4,10] For maternal alcohol consumption, results from a 2010 meta-analysis[11] indicated that the risk of childhood AML, but not ALL, may increase with use during pregnancy. While there was heterogeneity between studies, the summary estimate for AML [odds ratio (OR) = 2.7; 95% confidence interval (CI) 1.9, 3.9] was considerably more homogenous when restricted to children aged 0–4 years (*P* heterogeneity = 0.76). The relationship between maternal illicit drug use and childhood leukaemia is less clear. A positive association between maternal marijuana use during pregnancy and childhood AML, observed in 1989,[12] was later contradicted by results from a 2006 study[13] that detected an inverse association.

Very few studies have specifically explored infant leukaemia. Shu *et al.*[14] found an inverse association for maternal smoking and a positive association for alcohol drinking, while Alexander *et al.*[15] reported null findings for both. We present data from the largest case–control study of infant leukaemia conducted to date in order to add to the limited amount of literature for these exposures.

Methods

Study population

Infants diagnosed with acute leukaemia at <1 year of age were identified at Children's Oncology Group (COG) institutions between 1 January 1996 and 13 October 2002 (phase I) and between 1 January 2003 and 31 December 2006 (phase II). Cases were eligible if they did not have Down's syndrome, if their biological mother was available for a telephone interview in English or Spanish (phase II only), and if they were diagnosed or treated at a participating COG institution in the US or Canada. Mothers of deceased cases were eligible for the study. Further aspects of subject recruitment and data collection have been described previously.[16–18]

The control recruitment strategies differed between the two phases described above. During phase I, controls were selected from the US and Canada using a standardised random digit dialling (RDD) procedure[19,20] and were frequency-matched to cases on year of birth. Phase II controls were randomly selected from 15 US state birth registries and were frequency-matched to cases on year of birth and region of residence based on the geographical and annual birth distribution of phase I cases.[17] Eligible controls did not have Down's syndrome and had a biological mother who was available for a telephone interview in English or Spanish (phase II only).

Data collection

Case and control mothers provided exposure data via structured, computer-assisted telephone interviews. Interviews were completed for 443 (64%) eligible cases (264 ALL, 172 AML, and seven with biphenotypic and acute undifferentiated leukaemia) and 324 (47%) eligible controls. Participation rates and reasons for non-participation in phases I and II have been published elsewhere.[16,17,21] Interview questions included items on demographics, reproductive history, family history of disease, and exposures during pregnancy with the index (case or control) child. For cases, pathology and cytogenetic reports from diagnosis were acquired, and *MLL* gene rearrangement status (*MLL+*, *MLL−* or indeterminate) was ascertained through central review by three independent reviewers, as previously reported.[21]

The interview queried current and past use of cigarettes, alcohol and illicit drugs such as marijuana, heroin and cocaine. Questions focused on use in the year prior to pregnancy, in early pregnancy before mothers knew they were pregnant, and from the time mothers found out they were pregnant until the index child was born. By distinguishing between the latter two time periods, we aimed to decrease under-reporting of socially undesirable behaviours, at least during early pregnancy.

Institutional review boards at the University of Minnesota and participating COG institutions approved all study procedures. The study was also approved by health departments for states providing birth certificates, as applicable. All mothers provided informed consent prior to participation.

Statistical analysis

Differences between cases and controls in potential confounders and other baseline characteristics were evaluated using Pearson's chi-squared test for categorical variables and the *t*-test for continuous variables. We compared controls with all infant leukaemias combined and with subgroups defined by leukaemia type (ALL and AML) and *MLL* status (*MLL+* and *MLL−*).

Unconditional logistic regression was used to calculate ORs and 95% CIs for the associations between maternal cigarette, alcohol and illicit drug use and development of infant leukaemia. Smokers were defined as those who smoked >1 cigarette per day, drinkers were those who consumed >1 alcoholic drink per week, and illicit drug users were those who reported any illicit drug use during the time period of interest. Dichotomous variables were created as there was no linear trend (i.e. dose response) for exposure frequency. Mothers who met the minimum criteria for smoking or drinking in at least one portion of pregnancy (i.e. before and/or after knowledge of their pregnancy) were classified as smokers or drinkers during pregnancy overall. Drug use prior to pregnancy and during pregnancy was not evaluated separately because of small cell counts. Reference groups included both never smokers/drinkers and ever smokers/drinkers not reporting use during the relevant time periods; similar results were obtained when only never smokers/drinkers were used as reference groups.

All analyses were repeated upon stratification by leukaemia type and *MLL* status. The regression models for smoking were adjusted for maternal age (continuous), education, race/ethnicity and alcohol use during pregnancy (yes or no), household income, and child's birth year (ordinal), a matching factor. For alcohol consumption, models were adjusted for maternal education and race/ethnicity and child's birth year, while for drug use, models were adjusted for maternal age and child's birth year. Child's sex, maternal smoking, maternal household use of pesticides and region of residence were also considered as potential confounders but were not included in final models because their inclusion did not change the

natural log OR estimates by >10%. All analyses were conducted using SAS software version 9.2 (SAS Institute, Inc., Cary, NC, USA).

Results

Table 1 presents descriptive characteristics for controls, all cases combined and for ALL and AML subgroups. Cases and controls were similar with respect to child's sex, household income and mother's education level. A greater percentage of cases were non-White (24% of cases vs. 16% of controls), and mothers of ALL cases were somewhat younger at the time of the child's birth compared with mothers of controls ($mean_{cases}$ = 28.7 years vs. $mean_{controls}$ = 29.8 years).

Adjusted ORs and 95% CIs for maternal prenatal cigarette, alcohol and illicit drug use are shown in Table 2. Cigarette smoking and drug use were not associated with infant leukaemia in any of the models. Alcohol use during pregnancy was inversely associated with infant leukaemia overall [OR = 0.64; 95% CI 0.43, 0.94], AML [OR = 0.49; 95% CI 0.28, 0.87] and *MLL+* leukaemia [OR = 0.59; 95% CI 0.36, 0.97]. Similar associations were observed among AML cases for alcohol use in the year prior to pregnancy [OR = 0.67; 95% CI 0.44, 1.00] and use anytime in the year prior to and/or during pregnancy [OR = 0.66; 95% CI 0.44, 0.99].

Discussion

Maternal cigarette, alcohol and illicit drug use before and during pregnancy were evaluated as potential risk factors for infant leukaemia. No statistically significant associations were observed for cigarette smoking and drug use. In contrast, alcohol use during pregnancy was inversely associated with infant leukaemia overall and specifically among AML and *MLL+* cases.

The absence of any association between maternal cigarette smoking and leukaemia mirrors most previous findings, including those in infants.[15] Only six of 25 recently reviewed[10] studies reported significant but inconsistent associations between maternal smoking and childhood leukaemia. In light of this evidence, the International Agency for Research on Cancer recently concluded that maternal cigarette smoking is not causally related to childhood leukaemia.[22]

For maternal alcohol use, a recent meta-analysis[11] of 21 case–control studies reported a positive association with childhood AML [OR = 1.56; 95% CI 1.13, 2.15] but not ALL [OR = 1.10; 95% CI 0.93, 1.29] nor 'grouped leukaemias' [OR = 1.11; 95% CI 0.88, 1.40]. The increased risk with AML was particularly strong for cases diagnosed at <5 years of age. Two studies observed inverse associations similar to ours, although children were 0–14[23] or 0–9[24] years of age instead of exclusively infants. One of these studies speculated that chance was likely to have played a role,[23] while the other suggested two distinct potential biological mechanisms.[24] First, alcohol may inhibit growth hormone/insulin-like growth factor (IGF-1), which could lead to lower birthweight and a reduced risk of childhood leukaemia. Including birthweight in our models did not change effect estimates. A second plausible mechanism involves the cancer chemopreventive activity of flavonoids (i.e. antioxidants) contained in red wine and hopped beer.[25–27] We performed a *post hoc* analysis stratified by alcohol type (data not shown). Drinking two or more servings of beer and/or red wine per week during pregnancy was inversely associated with all of the leukaemia strata, while liquor/spirits showed no associations. Thus, our overall results may lend some support to the proposed flavonoid hypothesis.

Few studies have explored maternal illicit drug use and childhood leukaemia. Maternal use of marijuana prior to or during pregnancy was positively associated with childhood AML in one study[12] and ALL in another.[28] More recently, a study designed to specifically test the hypothesis that marijuana use was associated with an increased risk of AML actually observed an inverse association.[13] While our study results did not reach statistical significance, there was a suggestion of an inverse association with any illicit drug use across most subtypes.

It is difficult to interpret our results in the context of other studies, especially in light of discrepant results. Notably, a case–control study of infant leukaemia (<18 months of age) conducted in the 1980s reported a *positive* association with maternal alcohol consumption.[14] In either study, misclassification of exposure could be an issue. Of note, misclassification of alcohol use was reported in 45% of pregnant women recalling first trimester use in their seventh month of pregnancy and at delivery.[29] This percentage could be even greater in our study population as on average the maternal interviews took place nearly 3 years after the index child's birth. We attempted to reduce misclassification by focusing on the periods prior to and after knowledge of pregnancy, although results were similar. It may be fruitful for future case–control studies like ours to consider consistency in questionnaires (ideally they would be validated questionnaires) in order to more readily compare results across studies.

There is also concern regarding recall bias, especially with regard to exposures that may be perceived as harmful. In several states, alcohol and illicit drug use are subject to mandatory reporting by health professionals during pregnancy.[30] Although our observational study was protected by a Certificate of Confidentiality from the federal government, mothers of infants with leukaemia may have been reluctant to report certain exposures for fear of repercussions. In support of this contention, one study found that mothers of sick infants might be more apt to deny alcohol and cigarette use compared with mothers of healthy children.[31] This differential misclassification could lead to ORs that are biased in unpredictable directions.[32] Because of concerns regarding reporting of these types of exposure, it may be useful to validate certain exposures in future studies, at least in a subset of cases. For example, dried blood spots, collected shortly after birth to test for metabolic and other disorders,[33] are kept in long-term storage by several health departments across the US, potentially permitting their use in aetiological research.[34] Several analytes, including cotinine in cigarette smoke[35] and cocaine,[36] have been measured in dried blood spots. Thus, with proper consideration of storage conditions, analyte half-life and stability, dried newborn blood spots could be used to provide an independent measure of certain exposures in case–control studies such as ours.[37]

Selection bias is another potential concern; however, the use of COG institutions for case ascertainment is likely to have minimised selection bias among cases as these institutions treat nearly all leukaemia patients diagnosed in the US at <5 years.38 With a response rate of 64%, however, participating cases may be fundamentally different than cases who chose not to participate. The same concern exists among controls, who had a response rate of only 47%. Previously, both the RDD and birth certificate controls from our study were compared with US National Center for Health Statistics data for all births in the year 2000.[17] Compared with the US population, control mothers were older, more often White, married, and had more years of education. Control children were more likely to be born at term and to weigh more at birth. Case and control mothers in our study were similar to each other on all measured demographic characteristics except race/ethnicity, as control mothers were more often White. This difference is of interest because, in general, White women consume alcohol more often than women of other racial/ethnic groups. In the 2009 National Survey on Drug Use and Health,[39] 60% of White women reported drinking alcohol in the past

month; only 45% of Black and Hispanic women and 40% of Asian, American Indian and Alaska Native women reported drinking. While we adjusted for race/ethnicity, residual confounding may remain.

In an *ad hoc* sensitivity analysis, we evaluated whether any differences occurred between the two study phases. Although the associations for alcohol use before pregnancy did not appear to change over time, the association between alcohol use during pregnancy and infant leukaemia was attenuated in phase II. It is unclear whether this pattern is due to an actual trend, but data from the National Survey on Drug Use and Health (formerly called the National Household Survey on Drug Abuse)[39] do not suggest any obvious trends in the prevalence of alcohol use during pregnancy over the past decade. These findings may instead be due to chance, especially given small cell counts. Nevertheless, our overall study results were driven primarily by the first phase of the study.

In conclusion, we found no evidence of an association with cigarette smoking and infant leukaemia. In contrast to some previous reports, however, we found evidence of an inverse association with maternal alcohol use during pregnancy, and no evidence of an association with illicit drug use. Because of conflicting findings across the literature and the potential for recall bias, it is important for future studies to consider consistency in questionnaires (ideally validated), as well as an independent measure of exposure, such as prediagnostic biological samples when feasible.

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Table 1

Selected characteristics of 443 infant acute leukaemia cases and 324 controls

	Controls (*n* = 324)	Combined cases[a] (*n* = 443)		ALL (*n* = 264)		AML (*n* = 172)	
	n (%)	*n* (%)	*P*[b]	*n* (%)	*P*[b]	*n* (%)	*P*[b]
Infant characteristics							
Gender							
Male	156 (48.1)	218 (49.2)	0.77	133 (50.4)	0.59	84 (48.8)	0.88
Female	168 (51.9)	225 (50.8)		131 (49.6)		88 (51.2)	
Maternal characteristics							
Age at index child's birth (years)							
Mean ± SD	29.8 ± 5.4	29.1 ± 5.8	0.07	28.7 ± 5.6	0.02	29.7 ± 5.9	0.79
Race/ethnicity							
White	273 (84.5)	334 (75.6)	0.003	199 (75.7)	0.007	130 (75.6)	0.02
Non-White	50 (15.5)	108 (24.4)		64 (24.3)		42 (24.4)	
Educational attainment							
≤High school graduate	91 (28.2)	149 (33.7)	0.12	94 (35.7)	0.12	53 (30.8)	0.31
Some post-high school	112 (34.7)	125 (28.3)		76 (28.9)		48 (27.9)	
College graduate	120 (37.1)	168 (38.0)		93 (35.4)		71 (41.3)	
Household income ($)							
≤30 000	95 (29.6)	157 (35.8)	0.16	100 (38.2)	0.09	54 (31.8)	0.43
30 000–75 000	145 (45.2)	189 (43.0)		105 (40.1)		82 (48.2)	
>75 000	81 (25.2)	93 (21.2)		57 (21.7)		34 (20.0)	

[a] Includes ALL, AML and biphenotypic or acute undifferentiated leukaemias.

[b] Comparison with controls.

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia.

Table 2

Adjusted associations between maternal preconceptual and prenatal cigarette, alcohol and illicit drug use and acute infant leukaemia

	Controls (*n* = 324)	Combined cases[a] (*n* = 443)		ALL (*n* = 264)		AML (*n* = 172)		*MLL*+ (*n* = 228)		*MLL*− (*n* = 146)	
	n	***n***	**OR [95% CI]**	***n***	**OR [95% CI]**	***n***	**OR [95% CI]**	***n***	**OR [95% CI]**	***n***	**OR [95% CI]**
Cigarette use[b]											
Any	71	87	0.89 [0.59,1.34]	58	0.97 [0.62,1.53]	28	0.83 [0.47,1.46]	49	1.00 [0.61,1.63]	27	0.84 [0.47,1.49]
Year before pregnancy	70	87	0.91 [0.60,1.37]	58	0.99 [0.63,1.56]	28	0.84 [0.48,1.49]	49	1.02 [0.63,1.66]	27	0.85 [0.48,1.52]
During pregnancy	65	74	0.80 [0.52,1.24]	50	0.87 [0.54,1.40]	23	0.74 [0.40,1.35]	39	0.83 [0.50,1.40]	26	0.89 [0.49,1.60]
Alcohol use[c]											
Any	150	168	0.78 [0.57,1.06]	106	0.86 [0.61,1.22]	60	0.66 [0.44,0.99]	86	0.74 [0.51,1.07]	56	0.82 [0.54,1.25]
Year before pregnancy	149	167	0.78 [0.57,1.06]	105	0.85 [0.60,1.20]	60	0.67 [0.44,1.00]	85	0.72 [0.50,1.06]	56	0.83 [0.54,1.26]
During pregnancy	69	63	0.64 [0.43,0.94]	43	0.75 [0.49,1.17]	19	0.49 [0.28,0.87]	32	0.59 [0.36,0.97]	20	0.65 [0.37,1.14]
Illicit drug use[d]											
Any	32	34	0.69 [0.40,1.18]	25	0.84 [0.47,1.51]	9	0.52 [0.23,1.16]	18	0.78 [0.40,1.49]	10	0.57 [0.27,1.24]

[a] Includes ALL, AML and biphenotypic or acute undifferentiated leukaemias.

[b] ORs adjusted for maternal age, education, race/ethnicity and alcohol use during pregnancy, household income and child's year of birth.

[c] ORs adjusted for maternal education and race/ethnicity and child's year of birth.

[d] ORs adjusted for maternal age and education and child's year of birth.

ALL, acute lymphoblastic leukaemia; AML, acute myeloid leukaemia; *MLL*+, mixed lineage leukaemia gene rearrangement present; *MLL*−, no mixed lineage leukaemia gene rearrangement present.