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Maternal use of illicit drugs, tobacco or alcohol and the risk of childhood cancer before 6 years of age

Nathalie Auger[a,b,c,*], Catherine Goudie[d], Nancy Low[e], Jessica Healy-Profitós[a,b], Ernest Lo[b,c], Thuy Mai Luu[f]

[a] University of Montreal Hospital Research Centre, School of Public Health, Montreal, Quebec, Canada
[b] Institut national de santé publique du Québec, Montreal, Quebec, Canada
[c] Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Quebec, Canada
[d] Department of Pediatrics, Division of Hematology-Oncology, McGill University Health Centre, Montreal, Quebec, Canada
[e] Department of Psychiatry, McGill University, Montreal, Quebec, Canada
[f] Department of Pediatrics, Sainte Justine Hospital Research Centre, University of Montreal, Montreal, Quebec, Canada

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ABSTRACT

Background: Previous studies provide conflicting evidence of a link between maternal substance use and risk of childhood cancer.
Methods: We analyzed a cohort of 785,438 newborns in Quebec (2006–2016). We identified infants whose mothers had problematic illicit drug, tobacco, or alcohol use before or during pregnancy. The primary outcomes were childhood hematopoietic cancer or solid tumors within 0–5 years of age. Using Cox proportional hazards models, we computed hazard ratios (HR) and 95% confidence intervals (CI) for the association between maternal substance use and childhood cancer, adjusted for potential confounders.
Results: A total of 925 cases of cancer occurred during 3.5 million person-years of follow-up. Children exposed to any maternal substance use had marginally elevated cancer incidence rates compared with unexposed children (29.4 vs. 26.1 per 100,000 person-years). Maternal illicit drug use was associated with the risk of acute lymphoblastic leukemia (HR 1.63, 95% CI 0.79–3.36) and fibrosarcoma (HR 2.11, 95% CI 0.86–5.16). Maternal tobacco use was associated with acute myeloid leukemia (HR 2.01, 95% CI 0.72–5.60) and fibrosarcoma (HR 2.13, 95% CI 1.05–4.32), but a weak association with neuroblastoma (HR 1.21, 95% CI 0.61–2.40) and renal tumors (HR 1.14, 95% CI 0.42–3.13) also appeared to be present.
Conclusions: We found a potential association between maternal substance use and certain types of early childhood cancer. Although effects were modest, maternal substance use may contribute to some types of childhood cancer, especially leukemia and fibrosarcoma.

1. Introduction

Substance use among pregnant women is widespread, but the health implications for children are poorly understood. Around 10% of women report drinking or smoking during pregnancy, and 1–2% report using illicit drugs (Ordean et al., 2017; Public Health Agency of Canada, 2009). Maternal substance use has the potential to influence the risk of childhood cancer. Pediatric cancer is one of the largest contributors to early childhood mortality, and the incidence appears to be increasing over time (Health Canada, 2017). Few risk factors have been clearly identified (Health Canada, 2017) apart from ionizing radiation, chemotherapy agents, and constitutional genetic alterations, which together contribute to only a small proportion of cancers (Bunin, 2004; Health Canada, 2017; Stiller, 2004). The opioid epidemic and a continuing move towards marijuana legalization in North America have renewed concerns about the short- and long-term effects of maternal substance use on infants (Huang et al., 2015; Ordean et al., 2017), including the potential to increase childhood cancer rates.

The period of greatest risk for childhood cancer is the first few years of life, with children under age 5 diagnosed at twice the rate of those aged 5–15 years (Health Canada, 2017). The proclivity to appear so early in life suggests that many childhood cancers may relate to in utero or even periconceptional exposures (Bunin, 2004; Stiller, 2004). In utero exposure to substance use is linked with a number of adverse short- and long-term outcomes in children (Ordean et al., 2017), yet the rarity of childhood cancer makes it difficult to draw conclusive links

* Corresponding author at: Institut national de santé publique du Québec, 190 Cremazie Blvd E., Montreal, Quebec, H2P 1E2, Canada.
E-mail address: nathalie.auger@inspq.qc.ca (N. Auger).

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with maternal substance use (Karalexi et al., 2017; Mucci et al., 2004; Trivers et al., 2006).

Existing studies on the association of maternal substance use with different childhood cancers are conflicting (Bluhm et al., 2006; Brooks et al., 2004; Grufferman et al., 1993; Karalexi et al., 2017; Mucci et al., 2004; Müller-Schulte et al., 2018; Slater et al., 2011; Tettamanti et al., 2016; Trivers et al., 2006). While most studies find a relationship between illicit drugs, tobacco, or alcohol and neuroblastoma (Bluhm et al., 2006; Buck et al., 2001; Chu et al., 2016; Müller-Schulte et al., 2018; Schwartzbaum, 1992; Yang et al., 2000), studies of childhood leukemia are more heterogeneous (Infante-Rivard et al., 2002; Karalexi et al., 2017; Latino-Martel et al., 2010; MacArthur et al., 2008; Milne et al., 2013; Mucci et al., 2004; Shu et al., 1996). A Swedish study found that smoking in pregnancy increased the risk of acute myeloid but not lymphoblastic leukemia (Mucci et al., 2004), whereas a Canadian study found an increased risk of both cancers (MacArthur et al., 2008). We therefore investigated the association between maternal substance use and risk of childhood cancer within 0–5 years of age in a large cohort of newborns. We defined substance use as use of illicit drugs, tobacco, and alcohol but not prescription or over-the-counter medications.

2. Materials and methods

2.1. Study design and population

We performed an observational cohort study using data from the Maintenance and Use of Data for the Study of Hospital Clientele registry, which contains all children born in Quebec, Canada, from 2006 to 2016 (N = 785,438). We followed the children from birth until age 5 years, death, or March 31, 2017, whichever came first. The database is an administrative registry that has discharge abstracts for all hospitalizations in the province, including 99% of deliveries. Discharge abstracts for newborns are linked with the mother's delivery abstract and contain both the mother and infant's encrypted medical insurance numbers (Ministry of Health and Social Services, 2017). We used medical insurance numbers, which are permanently assigned by the provincial government and do not change over time, to track the infants for future hospitalizations. Children who died at birth, had an invalid health insurance number, or were linked to mothers with an invalid health insurance number were not included, as they could not be followed over time and lacked full information on maternal exposures.

We collected information on maternal exposures from the obstetric discharge abstract. The abstracts contain information related to maternal exposures during antenatal follow-up as well as during delivery (Collège des médecins du Québec, 2005). Moreover, we collected information on maternal exposures before pregnancy from discharge abstracts of previous hospitalizations. We identified all previous hospitalizations dating back to 1989, the earliest year in which data became available.

2.2. Substance use

We identified women who had problematic use of illicit drugs, alcohol, or tobacco during previous hospitalizations or during pregnancy using the 9th and 10th revisions of the International Classification of Diseases (Table S1). During antenatal visits, women were asked about any substance use in pregnancy, whether mild or problematic. Before pregnancy, however, we could only capture problematic substance use that led to hospitalization. Most cases of mild substance use do not require hospitalization. In this study, we could not fully identify women with mild or undocumented substance use.

We analyzed substance use as a binary exposure (yes, no) as well as by type of exposure (illicit drugs, tobacco use without illicit drugs, no problematic substance use). Previous literature indicates tobacco is more strongly related to cancers such as hepatoblastoma (Spector and Birch, 2012). Due to the rarity of the outcome, we were unable to examine associations for specific illicit drugs or analyze alcohol as a separate category.

2.3. Childhood cancer

We followed children from birth to identify future hospitalizations for any type of cancer before their sixth birthday, as a large proportion of cancers manifest within 0–5 years. Early onset cancers are more likely to be attributable to prenatal exposures than later cancers. The main outcome measure was the occurrence of any cancer expressed as a binary variable (yes, no). We further divided cancers into two major types (hematopoietic vs. solid tumors) and several narrower subtypes (acute lymphoblastic leukemia, acute myeloid leukemia, other leukemias; lymphoma, central nervous system tumors, retinoblastoma, soft tissue sarcoma, neuroblastoma; other solid tumors of the renal, hepatic, bone, germ cell, skin and respiratory systems). Soft tissue sarcomas included rhabdomyosarcoma, fibrosarcoma, and other specified soft tissue sarcomas. We defined the outcomes using topography and morphology codes in the International Classification of Diseases for Oncology-3, classified following a modified version of the World Health Organization's 3rd edition of the International Classification of Childhood Cancer (Steliarova-Foucher et al., 2005). Most children with cancer are hospitalized in Quebec.

2.4. Covariates

We obtained maternal and infant birth characteristics from the delivery abstract and considered several covariates that could confound the association between substance use and early childhood cancer. We included infant sex (male, female) (Kaatsch, 2010), maternal age (< 25, 25–34, ≥ 35 years), parity (0, 1, ≥ 2), preexisting/gestational diabetes (Contreras et al., 2016; Johnson et al., 2009; Stiller, 2004), and socioeconomic status (most disadvantaged quintile, not disadvantaged, unknown) (Bunin, 2004). Socioeconomic status was based on a composite score of mean income, education, and employment rate for neighborhoods in the Canada Census (Auger et al., 2015). We did not adjust for birth weight or congenital anomalies detected at birth or during later hospitalizations (Table S1), as these factors likely lie on the pathway between maternal substance use and childhood cancer (Fisher et al., 2012; VanderWeele et al., 2012).

2.5. Data analysis

We calculated the incidence of early childhood cancer per 100,000 person-years. We used Cox models to calculate unadjusted and adjusted hazard ratios comparing children exposed to maternal substance use with children who were unexposed. Models were adjusted for infant sex, maternal pre-existing or gestational diabetes, maternal age at delivery, parity, and socioeconomic status. We used the number of days since birth as the timescale and verified the assumption of proportional hazards using Schoenfeld residuals and time interaction terms. We analyzed the first hospitalization for cancer, censoring children who did not develop the outcome by the end of the study period and specifying deaths as a competing risk using the Fine and Gray method (So et al., 2014). We accounted for clustering of outcomes in siblings using robust sandwich estimators (Zou, 2004).

In a secondary analysis, we assessed if associations varied with the timing of substance use, distinguishing women whose substance use was present during pregnancy versus those whose substance use was documented only during pre-pregnancy hospitalizations. We did so because a proportion of women with problematic substance use may cease using substances before conception. However, we could only perform this analysis for illicit drugs due to small cell counts. In a sensitivity analysis, we examined the impact of excluding infants born after March 31, 2012 who did not have a full 5 years of follow-up.

We used two-sided hypothesis tests and 95% confidence intervals

Table 1
Incidence of childhood cancer according to maternal and newborn characteristics.

		Any cancer		Hematopoietic cancer		Solid tumors	
	No. children	No. cancer	Incidence per 100,000 person-years (95% confidence interval)	No. cancer	Incidence per 100,000 person-years (95% confidence interval)	No. cancer	Incidence per 100,000 person-years (95% confidence interval)
Maternal substance use							
Any	59,698	77	29.4 (25.1-34.4)	29	11.1 (8.6-14.3)	48	18.3 (15.0-22.4)
Illicit drugs	18,601	24	27.6 (20.8-36.6)	10	11.5 (7.4-17.8)	14	16.1 (11.1-23.3)
Tobacco	40,361	52	30.3 (25.0-36.6)	19	11.1 (8.1-15.2)	33	19.2 (15.1-24.5)
No	725,740	848	26.1 (24.9-27.4)	289	8.9 (8.2-9.6)	564	17.4 (16.4-18.4)
Maternal age							
< 25	125,282	153	26.8 (24.0-30.0)	48	8.4 (6.9-10.3)	106	18.6 (16.2-21.2)
25-34	525,246	618	26.2 (24.8-27.7)	222	9.4 (8.6-10.3)	399	16.9 (15.8-18.1)
≥35	134,910	154	26.4 (23.6-29.5)	48	8.2 (6.7-10.1)	107	18.3 (16.0-21.0)
Maternal diabetes[a]							
Yes	61,218	83	32.3 (27.8-37.6)	31	12.1 (9.4-15.5)	53	20.6 (17.1-25.0)
No	724,220	842	25.9 (24.7-27.1)	287	8.8 (8.1-9.6)	559	17.2 (16.2-18.2)
Parity							
0	384,047	471	27.4 (25.7-29.2)	162	9.4 (8.4-10.5)	311	18.1 (16.7-19.6)
1	275,097	316	25.7 (23.8-27.8)	115	9.4 (8.2-10.6)	204	16.6 (15.1-18.3)
≥2	126,294	138	24.6 (21.8-27.7)	41	7.3 (5.9-9.1)	97	17.3 (15.0-19.9)
Infant sex							
Male	402,747	478	26.5 (24.9-28.3)	167	9.3 (8.3-10.3)	312	17.3 (16.0-18.7)
Female	382,691	447	26.1 (24.5-27.9)	151	8.8 (7.9-9.9)	300	17.5 (16.2-19.0)
Birth weight							
≥4000g	76,554	109	31.3 (27.4-35.8)	25	7.2 (5.4-9.5)	84	24.1 (20.7-28.1)
2500-3999g	671,853	765	25.5 (24.2-26.8)	279	9.3 (8.6-10.1)	491	16.4 (15.4-17.4)
< 2500g	37,030	51	31.4 (25.9-38.2)	14	8.6 (6.0-12.5)	37	22.8 (18.2-28.6)
Congenital anomaly							
Chromosomal	1,222	23	446.4 (334.4-596.0)	16	310.5 (219.6-439.1)	7	135.9 (80.5-229.4)
Structural	103,271	346	76.0 (70.5-81.9)	59	13.0 (10.8-15.5)	290	63.7 (58.7-69.1)
No	680,945	556	18.2 (17.2-19.3)	243	8.0 (7.3-8.7)	315	10.3 (9.5-11.2)
Socioeconomic status							
High	139,327	153	24.4 (21.8-27.3)	38	6.1 (4.8-7.6)	116	18.5 (16.3-21.0)
Mid-High	155,137	189	27.1 (24.5-30.0)	72	10.3 (8.8-12.2)	120	17.2 (15.2-19.5)
Middle	153,457	179	26.0 (23.5-28.9)	66	9.6 (8.1-11.4)	114	16.6 (14.6-18.9)
Mid-low	152,462	187	27.4 (24.8-30.3)	69	10.1 (8.6-12.0)	118	17.3 (15.2-19.7)
Low	154,866	186	26.9 (24.3-29.8)	64	9.3 (7.8-11.0)	122	17.7 (15.6-20.0)
Total	785,438	925	26.3 (25.2-27.6)	318	9.1 (8.4-9.8)	612	17.4 (16.5-18.4)

[a] Preexisting or gestational diabetes.

(CI) to assess statistical significance. We analyzed the data in SAS version 9.4 (SAS Institute Inc., Cary, NC). Due to the anonymized nature of the data, the institutional review board of the University of Montreal Hospital Centre waived the need for ethics review.

3. Results

There were 3,511,487 person-years of follow-up in the study and 925 incident cases of cancer (26.3 per 100,000 person-years). This number included 318 hematopoietic cancers (9.1 per 100,000 person-years) and 612 solid tumors (17.4 per 100,000 person-years) (Table 1). Cancer incidence tended to be greater for children exposed to maternal substance use, including illicit drugs and tobacco, but differences were small.

The adjusted hazard ratio for childhood cancer overall was minimally elevated for any maternal substance use (Table 2). Substance use was associated with 1.09 times the risk of any cancer (95% CI 0.86–1.38). Maternal substance use appeared to be more strongly associated with hematopoietic cancer than solid tumors. Illicit drug use was associated with 1.23 times the risk of hematopoietic cancer (95% CI 0.65–2.34), and tobacco use was associated with 1.17 times the risk (95% CI 0.74–1.86). Children exposed to maternal tobacco use had 1.09 times the risk of solid tumors (95% CI 0.76–1.56).

Maternal substance use appeared to be most associated with acute lymphoblastic leukemia, soft tissue sarcomas, and neuroblastoma (Table 3). Associations differed somewhat for illicit drug versus tobacco use. Illicit drug use was associated with 1.63 times the risk of acute lymphoblastic leukemia (95% CI 0.79–3.36) and 2.11 times the risk of fibrosarcoma (95% CI 0.86–5.16). In contrast, maternal tobacco use was not associated with acute lymphoblastic leukemia but was associated with 2.01 times the risk of acute myeloid leukemia (95% CI 0.72–5.60) and 1.52 times the risk of other leukemias (95% CI 0.70–3.31). Similar to illicit drugs, tobacco use was associated with 2.13 times the risk of fibrosarcoma (95% CI 1.05–4.32). Maternal tobacco use was also associated with an increased risk of neuroblastoma and renal tumors.

When we accounted for the possibility of changes in the hazard over time, both maternal illicit drug and tobacco use appeared to be associated with a greater risk of acute lymphoblastic leukemia with age, supporting a stronger link with this cancer after infancy (Fig. 1). Both maternal illicit drug and tobacco use were associated with over 2 times the risk of acute lymphoblastic leukemia at 5 years of age. Maternal tobacco use appeared to be associated with a greater risk of fibrosarcoma over time, whereas illicit drug use was more strongly associated with fibrosarcoma earlier in life. There was no evidence of a change in the hazard over time for other specific cancers.

When we assessed the timing of substance use (Table 4), illicit drug use before pregnancy was associated with 1.87 times the risk of acute lymphoblastic leukemia (95% CI 0.76–4.60) and 3.13 times the risk of fibrosarcoma (95% CI 1.15–8.48). Illicit drug use during pregnancy tended to be associated with neuroblastoma (HR 1.23, 95% CI 0.30–5.00). In sensitivity analyses, restricting the analysis to children with a full 5 years of follow-up also tended to strengthen the associations somewhat.

Table 2
Association between maternal substance use and childhood cancer.

	Unadjusted hazard ratio (95% confidence interval)			Adjusted hazard ratio (95% confidence interval)[a]		
	Any cancer	Hematopoietic cancer	Solid tumors	Any cancer	Hematopoietic cancer	Solid tumors
Any maternal substance use						
Yes	1.10 (0.87-1.38)	1.18 (0.81-1.72)	1.04 (0.78-1.40)	1.09 (0.86-1.38)	1.20 (0.81-1.74)	1.04 (0.77-1.40)
No	Reference	Reference	Reference	Reference	Reference	Reference
Type of substance use						
Illicit drugs	1.03 (0.69-1.54)	1.23 (0.65-2.30)	0.92 (0.54-1.55)	1.04 (0.69-1.56)	1.23 (0.65-2.34)	0.92 (0.54-1.57)
Tobacco	1.13 (0.85-1.50)	1.18 (0.74-1.87)	1.09 (0.77-1.56)	1.12 (0.85-1.49)	1.17 (0.74-1.86)	1.09 (0.76-1.56)
No	Reference	Reference	Reference	Reference	Reference	Reference

[a] Adjusted for infant sex, maternal preexisting or gestational diabetes, maternal age at delivery, parity, and socioeconomic status. Sample sizes are provided in Table S2.

Table 3
Association between maternal substance use and child cancer subtypes.

	Hazard ratio (95% confidence interval)[a]		
	Illicit drugs	Tobacco	No use
Any cancer	1.04 (0.69-1.56)	1.12 (0.85-1.49)	Reference
Hematopoietic cancer	1.23 (0.65-2.34)	1.17 (0.74-1.86)	Reference
Acute lymphoblastic leukemia	1.63 (0.79-3.36)	1.02 (0.54-1.93)	Reference
Acute myeloid leukemia	–	2.01 (0.72-5.60)	Reference
Other leukemias	0.86 (0.21-3.50)	1.52 (0.70-3.31)	Reference
Lymphoma	–	0.48 (0.07-3.43)	Reference
Solid tumors[b]	0.92 (0.54-1.57)	1.09 (0.76-1.56)	Reference
Central nervous system	0.48 (0.12-1.96)	0.73 (0.32-1.66)	Reference
Retinoblastoma	0.66 (0.09-4.81)	0.62 (0.15-2.56)	Reference
Soft tissue sarcomas	1.86 (0.82-4.19)	1.46 (0.73-2.93)	Reference
Rhabdomyosarcoma	2.55 (0.35-18.76)	–	Reference
Fibrosarcoma	2.11 (0.86-5.16)	2.13 (1.05-4.32)	Reference
Other sarcomas[c]	–	0.76 (0.10-5.68)	Reference
Neuroblastoma	0.86 (0.27-2.71)	1.21 (0.61-2.40)	Reference
Renal	0.53 (0.07-3.93)	1.14 (0.42-3.13)	Reference
Germ	–	1.30 (0.31-5.45)	Reference

[a] Adjusted for infant sex, maternal preexisting or gestational diabetes, maternal age at delivery, parity, and socioeconomic status. Sample sizes are provided in Table S3.

[b] Hepatic, bone, skin, and respiratory tumors were rare and could not be shown separately.

[c] Glomangiosarcoma; pigmented dermatofibrosarcoma protuberans; myxomatous, lipomatous, myomatous, and synovial-like neoplasms; osteochondroma; mesenchymal chondrosarcoma.

4. Discussion

In this population-based cohort study of 785,438 children with over 3.5 million years of follow-up, we found some association between maternal substance use and risk of certain childhood cancers. While associations were imprecise due to small case numbers, our data nonetheless point to elevated risks of hematopoietic cancer, neuroblastoma, and fibrosarcoma for children exposed to maternal illicit drug and tobacco use. The association with fibrosarcoma is particularly novel, as little is known about risk factors for this type of cancer (Loeb et al., 2008). Children exposed to tobacco also had an elevated risk of renal tumors.

Our results generally align with cohort studies that prospectively collected information on maternal substance use. We found an increased risk of acute myeloid leukemia in tobacco-exposed children, an association also found in a Swedish study of 1.4 million children (Mucci et al., 2004). The study moreover found a lower risk of acute lymphoblastic leukemia similar to our nearly null association. Two separate studies using the same population of Swedish children found that maternal tobacco use was associated with an increased risk of brain tumors (Brooks et al., 2004; Tettamanti et al., 2016). In our data, illicit drugs and tobacco were not associated with central nervous system tumors; however, our sample size was smaller. Nonetheless, our results resemble findings of recent systematic reviews and meta-analyses. The relationship we found between prenatal tobacco exposure and neuroblastoma is similar to a meta-analysis of 7 case-control studies (Chu et al., 2016). Another meta-analysis reported a very similar risk of neuroblastoma following tobacco exposure, but in contrast we found a weaker association with illicit drugs (Müller-Schulte et al., 2018).

Our results align with some but not all case-control studies where recall and selection bias may have been a concern. In a case-control study of 517 cases and 610 controls, marijuana use was not associated with acute myeloid leukemia (Trivers et al., 2006), a finding that resembles ours. However, the authors concluded in sensitivity analyses that recall bias had the potential to explain the low odds ratios. Studies of neuroblastoma generally yield findings that differ from ours. Marijuana use in the first trimester has been associated with neuroblastoma (Bluhm et al., 2006), but we found much weaker associations with illicit drugs. Studies of maternal substance use and soft tissue sarcomas are rarer. In a Spanish report of 4 children with congenital fibrosarcoma, all cases were exposed to parental tobacco use (Ortega-Garcia et al., 2012). Similarly, tobacco and illicit drugs were associated with nearly twice the risk of fibrosarcoma in our study.

Understanding the impact of maternal substance use on childhood cancer can be challenging. In observational studies, underreporting of substance use frequently cannot be circumvented. Misclassification of exposed children as unexposed may attenuate the difference between groups and minimize the ability to detect an association. For this reason, statistically nonsignificant results should not necessarily be interpreted as null associations (Alderson, 2004). Our results were not statistically significant, but the elevated risks may nonetheless be clinically meaningful and reflect conservative estimates of the association between maternal substance use and child cancer.

Moreover, an association between maternal substance use and specific cancers is biologically plausible. Alcohol, tobacco, and several illicit drugs have known teratogenic potential, raising the possibility that prenatal exposure to these substances may also induce genetic damage that potentiates the later development of cancer (Karalexi et al., 2017; Mucci et al., 2004; Müller-Schulte et al., 2018). Unlike congenital anomalies, however, it is less clear if there is a critical window of exposure during pregnancy that is more likely to increase cancer risk (Müller-Schulte et al., 2018). Studies evaluating the effect of maternal substance use during specific trimesters on the risk of cancer are rare. A study of maternal marijuana use found that the risk of neuroblastoma was greater among children exposed in the first trimester and that risks were elevated but nonsignificant in the second and third trimesters (Bluhm et al., 2006). Cancer risk may also depend on factors such as parental gene polymorphisms and gene-environment interactions. A study of 491 children with acute lymphoblastic leukemia found that maternal genetic polymorphisms could increase the burden of prenatal alcohol exposure in women who consumed alcohol

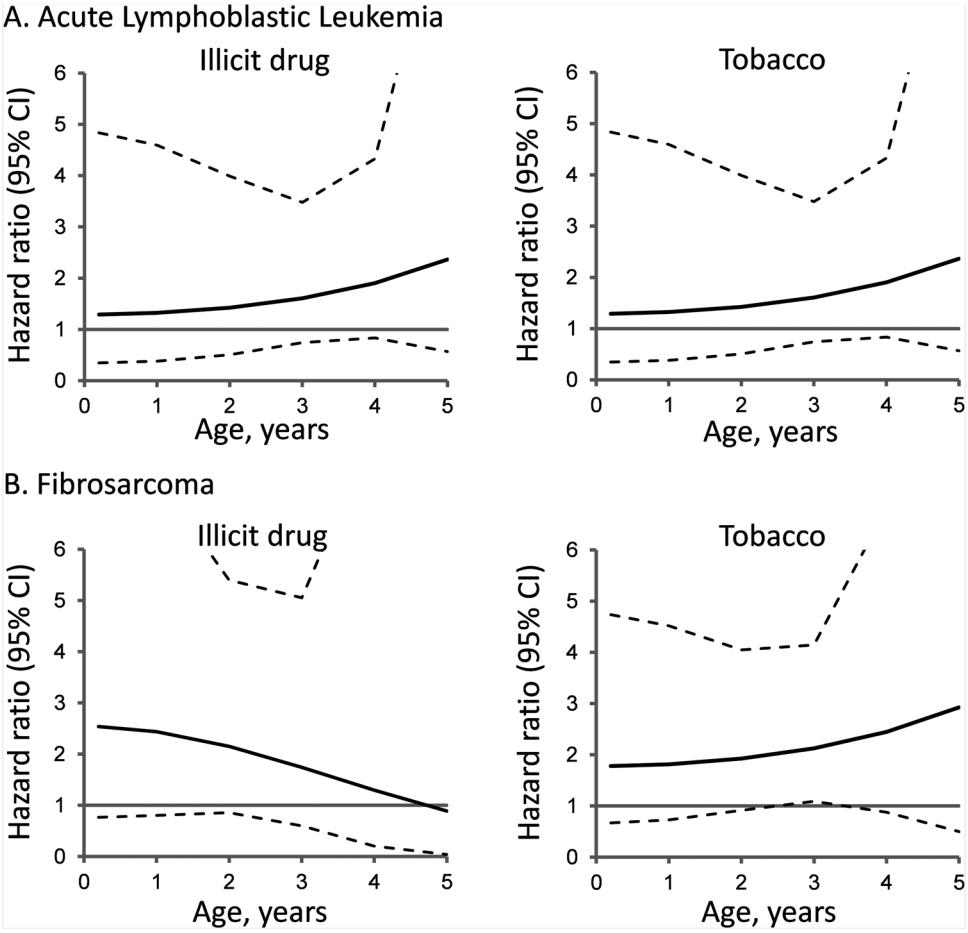

Fig. 1. Association of maternal substance use with acute lymphoblastic leukemia and fibrosarcoma by age of child at diagnosis.
Panels show the change in hazard ratios (solid lines) over time, with upper and lower confidence intervals (dashed lines). Hazard ratios are adjusted for infant sex, maternal preexisting or gestational diabetes, maternal age at delivery, parity, and socioeconomic status.

Table 4
Association between maternal illicit drug use and child cancer subtypes, according to timing of maternal substance use.

	Hazard ratio (95% confidence interval)[a]	
	Illicit drugs before pregnancy only	Illicit drugs during pregnancy[b]
Any cancer	1.13 (0.66-1.92)	0.93 (0.50-1.73)
Hematopoietic cancer	1.37 (0.61-3.11)	1.07 (0.40-2.86)
Acute lymphoblastic leukemia	1.87 (0.76-4.60)	1.34 (0.42-4.21)
Acute myeloid leukemia	–	–
Other leukemias	0.83 (0.11-6.11)	0.89 (0.13-6.18)
Lymphoma	–	–
Solid tumors[c]		
Central nervous system	0.45 (0.06-3.26)	0.52 (0.07-3.70)
Retinoblastoma	–	1.39 (0.19-10.16)
Soft tissue sarcomas	2.85 (1.17-6.93)	0.67 (0.10-4.72)
Rhabdomyosarcoma	4.54 (0.62-33.16)	–
Fibrosarcoma	3.13 (1.15-8.48)	0.90 (0.13-6.34)
Other specific sarcomas[d]	–	–
Neuroblastoma	0.53 (0.07-3.83)	1.23 (0.30-5.00)
Renal	1.01 (0.14-7.48)	–
Germ	–	–

[a] Hazard ratios are relative to no substance use, adjusted for infant sex, maternal preexisting or gestational diabetes, maternal age at delivery, parity, and socioeconomic status. Sample sizes are provided in Table S4.

[b] With or without prior illicit drug use.

[c] Hepatic, bone, skin, and respiratory tumors were rare and could not be shown separately.

[d] Glomangiosarcoma; pigmented dermatofibrosarcoma protuberans; myxomatous, lipomatous, myomatous, and synovial-like neoplasms; osteochondroma; mesenchymal chondrosarcoma.

during pregnancy and breastfeeding (Infante-Rivard et al., 2002).

Several associations strengthened in analyses restricted to illicit drug use during pre-pregnancy hospitalizations. Some women in our cohort had illicit drug use documented five years or more before pregnancy, raising the possibility that chronic substance use was not reported during pregnancy or that past drug use was a risk factor even if women stopped using substances before pregnancy. Substance use has been shown to cause long-term epigenetic changes that are passed on to future offspring, some of which could increase cancer risk (Nielsen et al., 2012; Yiu and Li, 2015). It is also possible that women with illicit drug use have chronic health disorders that contribute to the increased cancer risk in offspring. Stigma around admitting illicit drug use during pregnancy may, however, be prominent and explain the weaker associations compared with pre-pregnancy use of drugs.

This study had several important limitations. We could not fully identify women with mild substance use, making it difficult to compare our results with studies that had different exposure definitions. We could not assess exposure to illicit drugs or alcohol during breastfeeding due to lack of data on this covariate. Similarly, we did not know the proportion of women who successfully stopped using illicit drugs, tobacco, or alcohol, although most Canadian women report quitting smoking and drinking during pregnancy (Public Health Agency of Canada, 2009). We did not have information on paternal substance use or environmental smoke exposure after the child's birth. We also did not have data on prescription medications. We had limited knowledge of polysubstance use and no information on dose and frequency. We could not analyze alcohol separately due to limited sample size and could not determine if in utero exposure occurred during only part of pregnancy or continuously throughout. We could not track patients that moved out of Quebec or were hospitalized in another province. We also could not account for competing risks such as miscarriage,

terminations, and stillbirth. We controlled for potential confounders, but residual bias may remain, as we did not have data on ethnicity and prenatal care. Use of ICD codes may have resulted in misclassification of exposures or outcomes. The data reflect a multiethnic Canadian province with universal publicly funded health care, but we do not know if similar associations would be found in areas with different characteristics.

In this cohort study of nearly 800,000 children, we found some evidence of an association between maternal substance use and the risk of cancer in offspring. Risks were elevated for illicit drugs and tobacco, particularly for certain hematopoietic cancers and soft tissue sarcomas. Due to probable underreporting of substance use, the results reflect a conservative estimate of the association with childhood cancer. Our results suggest maternal substance use may play a role in the development of childhood cancer, although the extent is unclear. Women should abstain from any substance use during pregnancy to minimize any potential risk.

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Contributors

NA, NL, JHP, and TML conceived and designed the study, and JHP performed the statistical analysis with input from NA. EL provided statistical expertise. CG helped interpret the results. JHP and NA drafted the manuscript, and CG, NL, EL, and TML revised it for critical intellectual content. All authors contributed to and approved the final version submitted.

Conflict of interest

No conflict declared.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drugalcdep.2019.03.008.

References

Alderson, P., 2004. Absence of evidence is not evidence of absence. BMJ 328, 476–477.
Auger, N., Fraser, W., Healy-Profitós, J., Arbour, L., 2015. Association between preeclampsia and congenital heart defects. JAMA 314, 1588–1598.
Bluhm, E.C., Daniels, J., Pollock, B.H., Olshan, A.F., 2006. Maternal use of recreational drugs and neuroblastoma in offspring: a report from the Children's Oncology Group (United States). Cancer Causes Control 17, 663–669.
Brooks, D.R., Mucci, L.A., Hatch, E.E., Cnattingius, S., 2004. Maternal smoking during pregnancy and risk of brain tumors in the offspring. A prospective study of 1.4 million Swedish births. Cancer Causes Control 15, 997–1005.
Buck, G.M., Michalek, A.M., Chen, C.J., Nasca, P.C., Baptiste, M.S., 2001. Perinatal factors and risk of neuroblastoma. Paediatr. Perinat. Epidemiol. 15, 47–53.
Bunin, G.R., 2004. Nongenetic causes of childhood cancers: evidence from international variation, time trends, and risk factor studies. Toxicol. Appl. Pharmacol. 199, 91–103.
Chu, P., Wang, H., Han, S., Jin, Y., Lu, J., Han, W., Shi, J., Guo, Y., Ni, X., 2016. Maternal smoking during pregnancy and risk of childhood neuroblastoma: systematic review and meta-analysis. J. Cancer Res. Ther. 12, 999–1005.
Collège des Médecins du Québec, 2005. La tenue des dossiers par le médecin en centre hospitalier de soins généraux et spécialisés. Collège des Médecins du Québec, Montreal.
Contreras, Z.A., Ritz, B., Virk, J., Cockburn, M., Heck, J.E., 2016. Maternal pre-pregnancy and gestational diabetes, obesity, gestational weight gain, and risk of cancer in young children: a population-based study in California. Cancer Causes Control 27, 1273–1285.
Fisher, P.G., Reynolds, P., Von Behren, J., Carmichael, S.L., Rasmussen, S.A., Shaw, G.M., 2012. Cancer in children with nonchromosomal birth defects. J. Pediatr. 160, 978–983.
Grufferman, S., Schwartz, A.G., Ruymann, F.B., Maurer, H.M., 1993. Parents' use of cocaine and marijuana and increased risk of rhabdomyosarcoma in their children. Cancer Causes Control 4, 217–224.
Health Canada, 2017. Cancer in Young People in Canada: A Report from the Enhanced Childhood Cancer Surveillance System. Health Canada, Ottawa.
Huang, Y.-H.J., Zhang, Z.-F., Tashkin, D.P., Feng, B., Straif, K., Hashibe, M., 2015. An epidemiologic review of marijuana and cancer: an update. Cancer Epidemiol. Biomarkers Prev. 24, 15–31.
Infante-Rivard, C., Krajinovic, M., Labuda, D., Sinnett, D., 2002. Childhood acute lymphoblastic leukemia associated with parental alcohol consumption and polymorphisms of carcinogen-metabolizing genes. Epidemiology 13, 5.
Johnson, K.J., Carozza, S.E., Chow, E.J., Fox, E.E., Horel, S., McLaughlin, C.C., Mueller, B.A., Puumala, S.E., Reynolds, P., Von Behren, J., Spector, L.G., 2009. Parental age and risk of childhood cancer: a pooled analysis. Epidemiology 20, 475–483.
Kaatsch, P., 2010. Epidemiology of childhood cancer. Cancer Treat. Rev. 36, 277–285.
Karalexi, M.A., Dessypris, N., Thomopoulos, T.P., Ntouvelis, E., Kantzanou, M., Diamantaras, A.-A., Moschovi, M., Baka, M., Hatzipantelis, E., Kourti, M., Polychronopoulou, S., Stiakaki, E., Mora, A.-M., Wunsch-Filho, V., Infante-Rivard, C., Loutradis, D., Petridou, E.T., 2017. Parental alcohol consumption and risk of leukemia in the offspring: a systematic review and meta-analysis. Eur. J. Cancer Prev. 26, 433.
Latino-Martel, P., Chan, D.S., Druesne-Pecollo, N., Barrandon, E., Hercberg, S., Norat, T., 2010. Maternal alcohol consumption during pregnancy and risk of childhood leukemia: systematic review and meta-analysis. Cancer Epidemiol. Biomarkers Prev. 19, 1238–1260.
Loeb, D.M., Thornton, K., Shokek, O., 2008. Pediatric soft tissue sarcomas. Surg. Clin. North Am. 88, 615–627.
MacArthur, A.C., McBride, M.L., Spinelli, J.J., Tamaro, S., Gallagher, R.P., Theriault, G., 2008. Risk of childhood leukemia associated with parental smoking and alcohol consumption prior to conception and during pregnancy: the cross-Canada childhood leukemia study. Cancer Causes Control 19, 283–295.
Milne, E., Greenop, K.R., Scott, R.J., de Klerk, N.H., Bower, C., Ashton, L.J., Heath, J.A., Armstrong, B.K., 2013. Parental alcohol consumption and risk of childhood acute lymphoblastic leukemia and brain tumors. Cancer Causes Control 24, 391–402.
Ministry of Health and Social Services, 2017. Med-Echo System Normative Framework–Maintenance and Use of Data for the Study of Hospital Clientele. Government of Quebec, Quebec.
Mucci, L.A., Granath, F., Cnattingius, S., 2004. Maternal smoking and childhood leukemia and lymphoma risk among 1,440,542 Swedish children. Cancer Epidemiol. Biomarkers Prev. 13, 1528–1533.
Müller-Schulte, E., Kurlemann, G., Harder, A., 2018. Tobacco, alcohol and illicit drugs during pregnancy and risk of neuroblastoma: systematic review. Arch. Dis. Child. Fetal Neonatal Ed. 103, F467–F473.
Nielsen, D.A., Utrankar, A., Reyes, J.A., Simons, D.D., Kosten, T.R., 2012. Epigenetics of drug abuse: predisposition or response. Pharmacogenomics 13, 1149–1160.
Ordean, A., Wong, S., Graves, L., 2017. No. 349– substance use in pregnancy. J. Obstet. Gynaecol. Can. 39, 922–937.
Ortega-Garcia, J.A., Soldin, O.P., López-Hernández, F.A., Trasande, L., Ferrís-Tortajada, J., 2012. Congenital fibrosarcoma and history of prenatal exposure to petroleum derivatives. Pediatrics 130, e1019–e1025.
Public Health Agency of Canada, 2009. What Mothers Say: The Canadian Maternity Experiences Survey. Public Health Agency of Canada, Ottawa.
Schwartzbaum, J.A., 1992. Influence of the mother's prenatal drug consumption on risk of neuroblastoma in the child. Am. J. Epidemiol. 135, 1358–1367.
Shu, X.O., Ross, J.A., Pendergrass, T.W., Reaman, G.H., Lampkin, B., Robison, L.L., 1996. Parental alcohol consumption, cigarette smoking, and risk of infant leukemia: a Childrens Cancer Group study. J. Natl. Cancer Inst. 88, 24–31.
Slater, M.E., Linabery, A.M., Blair, C.K., Spector, L.G., Heerema, N.A., Robison, L.L., Ross, J.A., 2011. Maternal prenatal cigarette, alcohol and illicit drug use and risk of infant leukaemia: a report from the Children's Oncology Group. Paediatr. Perinat. Epidemiol. 25, 559–565.
So, Y., Lin, G., Johnston, G., 2014. Using the PHREG Procedure to Analyze Competing-Risks Data. SAS Institute Inc., Cary, NC.
Spector, L.G., Birch, J., 2012. The epidemiology of hepatoblastoma. Pediatr. Blood Cancer. 59, 776–779.
Steliarova-Foucher, E., Stiller, C., Lacour, B., Kaatsch, P., 2005. International classification of childhood cancer, third edition. Cancer 103, 1457–1467.
Stiller, C.A., 2004. Epidemiology and genetics of childhood cancer. Oncogene 23, 6429–6444.
Tettamanti, G., Ljung, R., Mathiesen, T., Schwartzbaum, J., Feychting, M., 2016. Maternal smoking during pregnancy and the risk of childhood brain tumors: results from a Swedish cohort study. Cancer Epidemiol. 40, 67–72.
Trivers, K.F., Mertens, A.C., Ross, J.A., Steinbuch, M., Olshan, A.F., Robison, L.L., 2006. Parental marijuana use and risk of childhood acute myeloid leukaemia: a report from the Children's Cancer Group (United States and Canada). Paediatr. Perinat. Epidemiol. 20, 110–118.
VanderWeele, T.J., Mumford, S.L., Schisterman, E.F., 2012. Conditioning on intermediates in perinatal epidemiology. Epidemiology 23, 1–9.
Yang, Q., Olshan, A.F., Bondy, M.L., Shah, N.R., Pollock, B.H., Seeger, R.C., Look, A.T., Cohn, S.L., 2000. Parental smoking and alcohol consumption and risk of neuroblastoma. Cancer Epidemiol. Biomarkers Prev. 9, 967–972.
Yiu, T.T., Li, W., 2015. Pediatric cancer epigenome and the influence of folate. Epigenomics 7, 961–973.
Zou, G., 2004. A modified Poisson regression approach to prospective studies with binary data. Am. J. Epidemiol. 159, 702–706.