Varying Impact of Gestational Diabetes Mellitus on Incidence of Childhood Cancers: An Age-Stratified Retrospective Cohort Study

Sophie Marcoux,[1,2] Gabriel Côté-Corriveau,[1] Jessica Healy-Profitós,[2,3] and Nathalie Auger[2–5]

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OBJECTIVE

We studied the association between gestational diabetes mellitus and early versus late childhood cancer.

RESEARCH DESIGN AND METHODS

We conducted a retrospective cohort study of 1 million children born between 2006 and 2019 in Quebec, Canada. We identified children who were exposed to gestational diabetes mellitus in utero and followed them from birth up to 14 years of age to identify new-onset cancers. We estimated hazard ratios (HRs) for the association between gestational diabetes mellitus and childhood cancer using Cox proportional regression models with adjustment for covariates through inverse propensity score weights.

RESULTS

A total of 83,626 children (8.2%) were exposed to gestational diabetes mellitus, and 1,702 developed cancer during 7.6 million person-years of follow-up. Children exposed to gestational diabetes mellitus had a higher risk of any cancer (HR 1.19, 95% CI 1.01–1.40), with signals present for blood cancer (HR 1.27, 95% CI 0.92–1.76) and solid tumors (HR 1.14, 95% CI 0.94–1.40). The association between gestational diabetes mellitus and cancer was strongest early in life and decreased with age. Gestational diabetes mellitus was associated with 1.47 times the risk of any cancer (95% CI 1.21–1.79), 1.44 times the risk of solid cancer (95% CI 1.12–1.87), and 1.61 times the risk of blood cancer (95% CI 1.09–2.36) in children age <2 years. Gestational diabetes mellitus was not significantly associated with blood or solid cancers after 2 years of age, and all associations disappeared after 6 years.

CONCLUSIONS

Hyperglycemia may be carcinogenic in utero and may be a novel risk factor for early childhood cancer.

Cancer is a leading cause of morbidity and mortality in childhood, but the association with gestational diabetes mellitus is poorly understood (1). Most childhood cancers are unexplained, as only 5–10% are caused by inherited syndromes (2).

[1]Faculty of Medicine, University of Montreal, Montreal, Quebec, Canada
[2]University of Montreal Hospital Research Centre, Montreal, Quebec, Canada
[3]Institut national de santé publique du Québec, Montreal, Quebec, Canada
[4]Department of Social and Preventive Medicine, University of Montreal, Montreal, Quebec, Canada
[5]Department of Epidemiology, Biostatistics, and Occupational Health, McGill University, Montreal, Quebec, Canada

Corresponding author: Nathalie Auger, nathalie.auger@inspq.qc.ca

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The possibility that pregnancy hyperglycemia is related to unexplained cancers has been understudied (3). Exposure to hyperglycemia is common in utero, as up to 17% of pregnancies are affected by gestational diabetes mellitus (4). Hyperglycemia is known for its carcinogenic properties outside of pregnancy (5). Elevated blood glucose levels in adults increase the production of reactive oxygen species and the risk of DNA damage (6). Adults with type 1 and 2 diabetes have an increased risk of several types of cancer (7,8). However, the possibility that gestational diabetes mellitus is a risk factor for childhood cancer has received limited attention.

Previous studies have not shown a consistent association between maternal diabetes and childhood cancer (3,9–12). In a recent literature review, investigators found that children of mothers with diabetes had an overall increased risk of cancer, but most studies did not distinguish between gestational diabetes mellitus and preexisting diabetes (3). Studies with a focus on gestational diabetes mellitus have yielded mixed findings suggesting either positive or neutral associations with childhood cancer (9–12). These analyses either did not stratify child cancers by age of onset or were not large enough to investigate specific cancers. In the only meta-analysis on this topic, investigators reported that gestational diabetes mellitus was associated with a nonsignificant risk of child cancer, but cancers at older ages were included, which may have masked associations (3). As exposure to hyperglycemia from gestational diabetes mellitus stops upon delivery (4), elevated glucose levels may promote the development of cancers that appear early in life rather than later in childhood. Our objective was to determine the association between gestational diabetes mellitus and the risk of childhood cancer with stratification by age.

RESEARCH DESIGN AND METHODS

Study Design and Population

We performed a retrospective cohort study of 1,030,537 children born in hospitals between 1 April 2006 and 31 March 2019 in Quebec, Canada. We followed the children from birth up to 14 years of age using data from the Maintenance and Use of Data for the Study of Hospital Clientele medico-administrative database (13). The cohort includes nearly all children born in Quebec, as the province provides universal health care coverage and >98% of births occur in hospital. Maternal and infant birth discharge abstracts are linked, with provision of all diagnoses and procedures during prenatal follow-up and delivery (14). In addition, information on all hospitalizations for childhood cancer is available in the data.

We included children born at 28 weeks or more of gestation, the gestational age by which most women have undergone gestational diabetes mellitus screening (4). We excluded children without maternal data. Follow-up began at birth and ended at the first hospitalization for cancer, death from other causes, or the study end on 31 March 2020.

Gestational Diabetes Mellitus

The main exposure measure was gestational diabetes mellitus, defined as glucose intolerance with onset during pregnancy (4). We identified children whose mothers had gestational diabetes mellitus based on diagnostic codes in ICD-10. The reference group included children whose mothers did not have any type of diabetes. We placed children whose mothers had type 1 or 2 diabetes in a separate category.

Current guidelines in Canada recommend one- or two-step approaches for gestational diabetes mellitus screening between 24 and 28 weeks of gestation. In the one-step approach, fasting glucose levels are measured just before a 75-g glucose challenge, followed by glucose measurements 1 h and 2 h later. Gestational diabetes mellitus is diagnosed if blood glucose levels are ≥5.3 mmol/L (95 mg/dL) for fasting, ≥10.6 mmol/L (≥191 mg/dL) 1 h postchallenge, or ≥9.0 mmol/L (≥162 mg/dL) 2 h postchallenge. In the two-step approach, women are screened with use of a 50-g glucose challenge and diagnosed with gestational diabetes mellitus if glucose levels are ≥11.0 mmol/L (≥198 mg/dL) 1 h postchallenge. Women with glucose levels between 7.8 and 11.0 mmol/L (140–198 mg/dL) undergo the 75-g glucose challenge (4). These guidelines have been in place since 2013. Prior to 2013, guidelines recommended only two-step screening and two abnormal blood glucose values for diagnosis of gestational diabetes mellitus (15).

Childhood Cancer

The main outcome was hospitalization for cancer before 14 years. We classified cancers using codes for neoplasm histology (morphology) and origin (topography) in the World Health Organization's 3rd Edition of the International Classification of Childhood Cancers (16). We categorized cancers into two main subgroups: blood cancer or solid tumors. We also included categories for the most common types of cancer in children under 14 years: leukemia (acute lymphoblastic, acute myeloid, other), lymphoma, central nervous system tumors, sarcoma, retinoblastoma, neuroblastoma and renal and hepatic tumors. The data captured almost all childhood cancers, as hospital services are required for diagnosis, treatment, and management in Quebec.

Covariates

We adjusted for several covariates that could confound the association between gestational diabetes mellitus and childhood cancer, including maternal age (<25, 25–34, ≥35 years), parity (0, 1, ≥2), birth weight (<2,500, 2,500–3,999, ≥4,000 g), cesarean section (yes, no), congenital or chromosomal anomalies (yes, no), maternal comorbidity (yes, no), maternal history of cancer (yes, no), socioeconomic disadvantage (yes, no, unknown), place of residence (rural, urban, unknown), prenatal exposure to air pollution (particulate matter$_{2.5}$ <0.14, 0.14–0.22, >0.23 μg/m^3, unknown), and birth year (2). We defined maternal comorbidity as preeclampsia, preexisting hypertension, obesity, or dyslipidemia using ICD-10 codes (17). Socioeconomic disadvantage was defined as the most materially disadvantaged fifth of the population based on an index of neighborhood income, education, and employment (17). We adjusted for birth year as a continuous variable using quadratic splines (18).

Data Analysis

We calculated the incidence of childhood cancer per 100,000 person-years. We estimated hazard ratios (HRs) and 95% CIs for the association between gestational diabetes mellitus and childhood cancer using Cox proportional hazards regression. We defined the timescale as

the number of days between birth and the date of hospitalization for cancer, death from other causes, or study end. We censored children without events at the end of the study and treated death as a competing risk. We verified the proportionality of hazards using log (−log survival) plots and used quadratic time interaction terms to assess changes in HRs over time. We adjusted for maternal age, parity, birth weight, cesarean section, congenital or chromosomal anomaly, maternal comorbidity, maternal history of cancer, socioeconomic disadvantage, place of residence, pollution, and birth year using stabilized inverse propensity weights derived from a logistic regression model (19). We ensured that weights were balanced and used robust sandwich estimators to account for the possibility of hospital-based clustering in preferred screening or diagnostic protocols between institutions (15).

In sensitivity analysis, we excluded children with congenital and chromosomal anomalies, as these conditions are common risk factors for childhood cancer (2). In addition, we stratified the analysis before and after 2013 to determine whether changes in diabetes screening and diagnosis criteria affected the associations. We performed analyses with SAS, version 9.4 (SAS Institute, Cary, NC), and determined statistical significance through two-tailed tests with 95% CIs. We received an ethics waiver from the institutional review board of the University of Montreal Hospital Centre due to use of anonymized data.

RESULTS

The cohort comprised 1,030,537 children with 7,657,495 person-years of follow-up, including 83,626 children (8.2%) exposed to gestational diabetes mellitus, 7,272 exposed to type 1 or 2 diabetes (0.71%), and 1,702 with cancer (0.17%) (Table 1). Cancer incidence was higher in children exposed to gestational diabetes mellitus (26.5 per 100,000 person-years) or preexisting diabetes (25.3 per 100,000 person-years) than in children not exposed to any diabetes (21.9 per 100,000 person-years). Cancer incidence rates were also higher in infants with low or high birth weight, congenital or chromosomal anomalies, cesarean section, and maternal comorbidity or history of cancer. Cancer rates did not vary with maternal age, parity, socioeconomic disadvantage, or other characteristics. After application of stabilized inverse propensity score weights, there was no imbalance in the distribution of covariates between exposed and unexposed children (Supplementary Table 1).

Children exposed to gestational diabetes mellitus had a higher incidence of cancer overall, including blood cancer, solid tumors, and most specific types of cancer (Table 2). Exceptions were rates of lymphoma, central nervous system tumors, retinoblastoma, and hepatic tumors, which were either lower or no different between exposed and unexposed children.

In adjusted regression models, gestational diabetes mellitus was associated with a higher risk of any cancer (HR 1.19, 95% CI 1.01–1.40) (Table 3). A signal was present with both blood cancer (HR 1.27, 95% CI 0.92–1.76) and solid tumors (HR 1.14, 95% CI 0.94–1.40). Gestational diabetes mellitus was most strongly associated with other leukemias (HR 1.90, 95% CI 1.13–3.20). A trend was also present for acute lymphoblastic leukemia and renal tumors.

The strength of the association between gestational diabetes mellitus and childhood cancer decreased over time (Supplementary Fig. 1). Gestational diabetes mellitus was most strongly associated with blood cancer and solid tumors diagnosed before 6 years of age.

When we stratified the analysis by age-group, associations between gestational diabetes mellitus and child cancer were more marked early in life (Table 4). Compared with those not exposed to any diabetes, children exposed to gestational diabetes mellitus had 1.47 times the risk of any cancer (95% CI 1.21–1.79), 1.61 times the risk of blood cancer (95% CI 1.09–2.36), and 1.44 times the risk of solid cancer (95% CI 1.12–1.87) before 2 years of age. Gestational diabetes mellitus was most strongly associated with, among other cancers, other leukemia (HR 2.46, 95% CI 1.37–4.40) and sarcoma (HR 1.58, 95% CI 0.90–2.78) before age 2 years. Associations with gestational diabetes mellitus disappeared in older age-groups for most types of cancer, although some HRs remained elevated. Gestational diabetes mellitus trended toward an association with renal tumors between 2 and 5 years (HR 2.17, 95% CI 0.95–4.97). Preexisting diabetes was associated with an elevated but nonsignificant risk of cancer before 2 years (HR 1.34, 95% CI 0.61–1.93).

In sensitivity analyses where we excluded children with chromosomal and congenital anomalies, associations with gestational diabetes mellitus were attenuated for several cancers but persisted for any cancer (HR 1.34, 95% CI 1.06–1.70) and other leukemia before age 2 years (HR 2.24, 95% CI 1.14–4.41) (Supplementary Table 2). The association with any cancer before age 2 years was stronger prior to 2013 (HR 1.79, 95% 1.32–2.43) than after (HR 1.08, 95% 0.72–1.63) (Supplementary Table 3). Associations with blood cancer and solid tumors followed the same pattern.

CONCLUSIONS

In this cohort of 1,030,537 children followed from birth until 14 years of age, exposure to maternal hyperglycemia due to gestational diabetes mellitus in the second and third trimesters of pregnancy was associated with an increased risk of early childhood cancer. Gestational diabetes mellitus was associated with blood cancer and solid tumors before 2 years of age. Gestational diabetes mellitus was more strongly associated with other leukemias and sarcomas in children age <2 years and renal tumors in children age <6 years. In contrast, gestational diabetes mellitus was not strongly associated with cancers that developed later in childhood. The findings provide evidence that gestational diabetes mellitus may be a risk factor for early childhood cancer and that the risk is concentrated for cancers that develop before 2–6 years of age.

Results of studies have shown an inconsistent relationship between gestational diabetes mellitus and childhood cancer (9–12,20,21). Two recent case-control studies with large numbers of children in Finland and the U.S. had results similar to ours, with data suggesting that gestational diabetes mellitus confers a somewhat increased risk of childhood cancer (9,10). However, a number of other studies were underpowered by a small number of cancer cases in the group exposed to gestational diabetes mellitus (11,12,21). Lack of age stratification is an important gap in all these studies, as associations with cancers that develop early in childhood

Table 1—Cancer incidence rate according to patient characteristics

	No. of children	No. with cancer	Person-years	Cancer rate per 100,000 person-years (95% CI)
Maternal diabetes				
Gestational diabetes mellitus	83,626	142	535,893	26.5 (22.4–31.2)
Type 1 and 2 diabetes	7,272	13	51,462	25.3 (14.7–43.5)
No	939,639	1,547	7,070,140	21.9 (20.8–23.0)
Maternal age, years				
<25	158,236	270	1,236,734	21.8 (19.4–24.6)
25–34	685,409	1,136	5,127,308	22.2 (20.9–23.5)
≥35	186,892	296	1,293,453	22.9 (20.4–25.6)
Parity				
0	503,145	841	3,753,454	22.4 (20.9–24.0)
1	359,335	581	2,678,231	21.7 (20.0–23.5)
≥2	168,057	280	1,225,811	22.8 (20.3–25.7)
Birth weight, g				
<2,500	50,850	107	359,927	29.7 (24.6–35.9)
2,500–3,999	883,248	1,393	6,549,604	21.3 (20.2–22.4)
≥4,000	96,439	202	747,964	27.0 (23.5–31.0)
Cesarean section				
Yes	247,843	461	1,802,139	25.6 (23.3–28.0)
No	782,694	1,241	5,855,357	21.2 (20.0–22.4)
Congenital or chromosomal anomaly				
Yes	58,384	154	424,982	36.2 (30.9–42.4)
No	972,153	1,548	7,232,513	21.4 (20.4–22.5)
Maternal comorbidity*				
Yes	87,059	144	563,162	25.6 (21.7–30.1)
No	943,478	1,558	7,094,334	22.0 (20.9–23.1)
Maternal history of cancer				
Yes	4,355	11	30,405	36.2 (20.0–65.3)
No	1,026,182	1,691	7,627,091	22.2 (21.1–23.3)
Socioeconomic disadvantage				
Yes	206,418	345	1,517,744	23.0 (20.7–25.5)
No	782,801	1,300	5,868,438	22.3 (21.1–23.5)
Place of residence				
Urban	824,922	1,351	6,132,368	22.0 (20.9–23.2)
Rural	188,226	331	1,413,691	23.4 (21.0–26.1)
Air pollution†				
Low	348,980	561	2,627,727	21.3 (19.7–23.2)
Middle	304,270	522	2,308,388	22.6 (20.8–24.6)
High	355,681	601	2,641,664	22.8 (21.0–24.6)
Total	1,030,537	1,702	7,657,495	22.2 (21.2–23.3)

*Preeclampsia, preexisting hypertension, obesity, dyslipidemia. †Particulate matter$_{2.5}$ (low <0.14, middle 0.14–0.22, high ≥0.23 μg/m^3).

may be obscured when age-groups are combined. Only one study included investigation of rates in different age-groups, with findings that gestational diabetes mellitus was more strongly associated with cancer before 6 years (21). Associations were attenuated when follow-up was extended to 20 years of age.

The mechanisms underlying the association between gestational diabetes mellitus and risk of child cancer remain uncertain, but exposure to maternal hyperglycemia and hyperinsulinemia may play a role. Hyperglycemia is associated with production of reactive oxygen species, which may increase the risk of DNA damage (6). Maternal hyperglycemia impacts fetal growth and metabolism through activation of insulin receptors and overproduction of IGF-I (9,10). High birth weight is associated with several types of childhood cancer, suggesting that increased insulin receptor signaling may be important for a range of cancers (22). Insulin can contribute to carcinogenesis by activating insulin receptors and IGF-I receptors that are overexpressed on malignant cells (3,23). Cancer-promoting effects of hyperglycemia may act on precancerous cells already present in utero, increasing the risk of cancers early in life. However, the effect may fade after birth when gestational exposure ends, which would explain the gradual decrease in cancer risk over time. The importance of a hyperglycemic intrauterine environment is further supported by studies suggesting that only maternal diabetes, and not paternal diabetes, is associated with an increased risk of child cancer (12,24).

In addition to hyperglycemia and hyperinsulinemia, other factors may be

Table 2—Incidence of cancer for children with and without exposure to gestational diabetes mellitus

	Gestational diabetes mellitus		No maternal diabetes	
	No. of children with cancer	Incidence per 100,000 person-years (95% CI)	No. of children with cancer	Incidence per 100,000 person-years (95% CI)
Any cancer*	142	26.5 (22.5–31.2)	1,547	21.9 (20.8–23.0)
Blood cancer	52	9.7 (7.4–12.7)	544	7.7 (7.1–8.4)
Leukemia, any	47	8.8 (6.6–11.7)	461	6.5 (5.9–7.1)
Acute lymphoblastic leukemia	29	5.4 (3.8–7.8)	345	4.9 (4.4–5.4)
Acute myeloid leukemia	7	1.3 (0.6–2.7)	69	1.0 (0.8–1.2)
Other or unspecified leukemia	18	3.4 (2.1–5.3)	108	1.5 (1.3–1.8)
Lymphoma	6	1.1 (0.5–2.5)	90	1.3 (1.0–1.6)
Solid cancer†	91	17.0 (13.8–20.8)	1,011	14.3 (13.4–15.2)
Neuroblastoma	20	3.7 (2.4–5.8)	188	2.7 (2.3–3.1)
Sarcoma	23	4.3 (2.8–6.5)	240	3.4 (3.0–3.8)
Central nervous system	25	4.7 (3.1–6.9)	335	4.7 (4.2–5.3)
Renal	12	2.2 (1.3–3.9)	100	1.4 (1.2–1.7)
Retinoblastoma	5	0.9 (0.4–2.2)	70	1.0 (0.8–1.2)
Hepatic	<5	0.2 (0.0–1.3)	19	0.3 (0.2–0.4)

*Cancers are not mutually exclusive, as some children had more than two tumors. †Additionally includes rare bone, germ, skin, and respiratory tumors.

involved in promoting childhood cancer. In our data, gestational diabetes mellitus was most strongly associated with leukemias before 2 years of age. Prior studies have found that gestational diabetes mellitus is associated with the risk of acute lymphoblastic leukemia (9,10,21,24), suggesting that hematopoietic tumors may be more responsive to gestational diabetes mellitus. Hematopoietic cells may be particularly sensitive to increased levels of IGF-1, as this growth factor is important for the production and regulation of blood cells (10). Higher IGF-1 levels are also associated with greater birth weight, a risk factor for leukemia (9,10,21,22,24). Gestational diabetes mellitus may also modulate CD26/DPP4, a regulator of hematopoiesis (25) found in lower levels in newborns of women with gestational diabetes mellitus (26). However, these pathways remain to be validated, as we primarily found associations with other leukemias—in contrast to existing literature that has focused on acute lymphoblastic leukemia (9,10,21,24).

Table 3—Association between gestational diabetes mellitus and childhood cancer

	HR (95% CI)	
	Unadjusted	Adjusted*
Any cancer	1.15 (0.97–1.37)	1.19 (1.01–1.40)
Blood cancer	1.22 (0.92–1.62)	1.27 (0.92–1.76)
Leukemia, any	1.29 (0.96–1.74)	1.38 (1.04–1.84)
Acute lymphoblastic leukemia	1.09 (0.74–1.59)	1.24 (0.88–1.74)
Acute myeloid leukemia	1.27 (0.58–2.76)	1.06 (0.45–2.50)
Other or unspecified leukemia	2.03 (1.23–3.34)	1.90 (1.13–3.20)
Lymphoma	0.90 (0.39–2.05)	0.95 (0.39–2.30)
Solid cancer	1.20 (0.90–1.39)	1.14 (0.94–1.40)
Neuroblastoma	1.25 (0.79–1.98)	1.16 (0.69–1.97)
Sarcoma	1.20 (0.78–1.84)	1.12 (0.69–1.82)
Central nervous system	0.97 (0.65–1.46)	0.96 (0.60–1.54)
Renal	1.48 (0.81–2.69)	1.31 (0.67–2.57)
Retinoblastoma	0.82 (0.33–2.04)	1.07 (0.48–2.41)
Hepatic	0.61 (0.08–4.57)	1.82 (0.35–9.41)

*HR for gestational diabetes mellitus vs. no diabetes, with adjustment for maternal age, parity, birth weight, cesarean section, congenital or chromosomal anomaly, maternal comorbidity, maternal history of cancer, socioeconomic disadvantage, place of residence, pollution, and birth year.

In our study, children exposed to gestational diabetes mellitus were at risk for solid tumors before age 2 years and possibly renal cancer between 2 and 5 years of age. It has been reported from prior studies that gestational diabetes mellitus is associated with increased risk of renal tumors in children (9,10). While fetal growth pathways are thought to connect gestational diabetes mellitus and childhood renal cancer (9,10,22), organ-specific sensitivity to epigenetic changes induced by hyperglycemia is another potential route. Kidney development

Table 4—Association between gestational diabetes mellitus and childhood cancer with stratification by age

	Age <2 years (*n* = 665 children with cancer)	Age 2–5 years (*n* = 702 children with cancer)	Age ≥6 years (*n* = 322 children with cancer)
Any cancer	1.47 (1.21–1.79)	1.02 (0.77–1.36)	0.97 (0.63–1.48)
Blood cancer	1.61 (1.09–2.36)	1.12 (0.74–1.70)	1.22 (0.55–2.70)
Leukemia, any	1.74 (1.13–2.67)	1.12 (0.73–1.72)	1.72 (0.73–4.04)
Acute lymphoblastic leukemia	1.09 (0.41–2.92)	1.12 (0.69–1.82)	1.86 (0.73–4.74)
Acute myeloid leukemia	1.48 (0.51–4.25)	0.67 (0.09–5.12)	0.87 (0.17–4.33)
Other or unspecified leukemia	2.46 (1.37–4.40)	1.45 (0.56–3.74)	1.03 (0.20–5.19)
Lymphoma	0.84 (0.11–6.30)	0.88 (0.28–2.76)	1.07 (0.24–4.87)
Solid cancer	1.44 (1.12–1.87)	0.95 (0.60–1.51)	0.82 (0.44–1.51)
Neuroblastoma	1.31 (0.73–2.34)	0.99 (0.32–3.05)	—
Sarcoma	1.58 (0.90–2.78)	0.77 (0.37–1.62)	1.14 (0.33–3.96)
Central nervous system	1.11 (0.52–2.38)	0.54 (0.26–1.09)	1.31 (0.67–2.54)
Renal	0.98 (0.31–3.10)	2.17 (0.95–4.97)	—
Retinoblastoma	1.05 (0.43–2.59)	1.22 (0.16–9.33)	—
Hepatic	2.65 (0.60–11.72)	—	—

Data are HRs (95% CI) for gestational diabetes mellitus vs. no diabetes, with adjustment for maternal age, parity, birth weight, cesarean section, congenital or chromosomal anomaly, maternal comorbidity, maternal history of cancer, socioeconomic disadvantage, place of residence, pollution, and birth year. Dashes indicate that there were no cancer events in the exposed category.

occurs throughout gestation up to 36 weeks of pregnancy, with most nephrons forming rapidly between 18 and 32 weeks (27). This developmental window overlaps with the gestational age at which the hyperglycemia of gestational diabetes mellitus becomes apparent (4,28). Wilms tumor, the most common renal tumor in childhood, is believed to follow a two-hit model with the first hit occurring during embryonic development (29). Maternal hyperglycemia may act as the second hit that occurs later during fetal kidney development, resulting in renal tumors that present early in childhood (27).

There are methodological challenges that make it challenging to measure the true effect of gestational diabetes mellitus on childhood cancer. Women with gestational diabetes mellitus frequently have more intensive prenatal follow-up than women without diabetes (28). Efforts to screen and manage gestational diabetes mellitus may interfere in the natural course of carcinogenesis. Women can be treated initially with physical activity and dietary control of blood glucose levels (28). If hyperglycemia persists, women may be prescribed pharmacological drugs such as insulin, metformin, and glyburide (28,30). While insulin does not cross the placenta, metformin and glyburide do (30). In adults, the evidence is mixed on whether antidiabetes drugs affect cancer risk (31). One study found that use of insulin and metformin in pregnant women with diabetes lowered the risk of childhood cancer compared with no diabetes medication, particularly for women with gestational diabetes mellitus (9). As 8–20% of women require insulin treatment (32), our findings may be conservative estimates of the association between gestational diabetes mellitus and child cancer.

A related issue is that women with poorly controlled diabetes may be induced early or receive cesarean sections to prevent pregnancy complications, lowering the length of time a fetus is exposed to hyperglycemia. Preterm birth due to early induction shortens the duration of exposure to maternal hyperglycemia, reducing the ability to measure the true effect on childhood cancer. In a French study, investigators found that women with insulin-treated gestational diabetes mellitus had higher cesarean section rates than woman with diet-controlled gestational diabetes mellitus (33). Women who are treated with insulin may have more difficulty maintaining normal blood glucose levels, greater fetal growth, and more macrosomia requiring cesarean section (33). Others have proposed that cesarean section limits mucosal colonization of newborns and leads to dysbiosis and immune dysfunction (34). As the immune system is involved in cancer development, it is possible that cesarean section mediates part of the association between gestational diabetes mellitus and childhood cancer by altering mucosal colonization. However, even with adjustment for cesarean section, we found an association with cancer, which suggests that much of the effect of gestational diabetes mellitus occurs outside of this pathway.

This study was free of selection bias, as we included nearly all children born in Quebec. We had ample follow-up time and >1,700 children with cancer. However, we were limited by lack of information on the treatment and control of hyperglycemia. We do not know the extent to which blood glucose levels may be more important for the development of cancer than a diagnosis of gestational diabetes mellitus. The weaker associations after 2013 when Diabetes Canada lowered the threshold to diagnose gestational diabetes mellitus suggest that more severe hyperglycemia may confer increased risk. As with any registry-based study, there may be misclassification of undiagnosed gestational diabetes mellitus, and type 2 diabetes may be incorrectly diagnosed as gestational diabetes mellitus (10). Undiagnosed cases would attenuate the difference between groups, whereas misdiagnosis of type 2 diabetes may result in some overestimation of associations. The infrequency of some childhood cancers limited our ability to measure the association between gestational diabetes mellitus and tumor subtypes with small case counts.

We did not have complete information on confounders such as maternal weight gain and occupation and cannot rule out residual confounding. Prior research suggests that the association between maternal diabetes and childhood cancer is independent of maternal weight (10), although gestational weight gain could contribute. When we calculated E-values to assess the impact of residual confounding (35), we found that an unmeasured confounder would have to be associated with 2.9 times the risk of gestational diabetes mellitus and leukemia to

explain away the association between gestational diabetes mellitus and leukemia. As no suspected risk factor has such strong associations, residual confounding is likely minimal.

This study suggests that in utero exposure to gestational diabetes mellitus in pregnancy may be associated with a greater risk of early childhood cancer. In our cohort, gestational diabetes mellitus was primarily associated with risk of blood and solid cancers before 2 years of age. Gestational diabetes mellitus may be a novel risk factor for early childhood cancer. More data are needed to determine whether child cancer rates may be lowered through improved control of maternal glycemic levels.

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