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Future risk of cancer in women who have children with birth defects

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ABSTRACT

Purpose: We studied whether having an infant with birth defects was associated with the risk of maternal cancer.
Methods: We carried out a longitudinal cohort study of 1,214,506 women who delivered infants between 1989 and 2016 in Quebec, Canada. We identified women whose infants had birth defects and followed the mothers over time to identify cancers up to 28 years after delivery. We used Cox regression to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between birth defects and maternal cancer, adjusted for maternal characteristics.
Results: A total of 36,050 women developed cancer during 19,251,851 person-years of follow-up. Relative to no birth defects, women whose infants had defects did not have an elevated risk of cancer overall (HR 1.03, 95% CI 0.99–1.06). However, associations were present with placental cancer (HR 2.23, 95% CI 1.04–4.77) and lymphoid leukemia (HR 1.61, 95% CI 1.03–2.51). Among specific birth defects, women whose infants had heart (HR 1.12, 95% CI 1.03–1.21) or sensory (HR 1.16, 95% CI 1.04–1.30) defects had a higher risk of cancer.
Conclusions: We found inconsistent evidence of a clinically meaningful association between having an infant with birth defects and the risk of early maternal cancer.
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Introduction

Cancer is the leading cause of death in women between 40 and 80 years of age [1]; but prevention remains a challenge. Many cancer risk factors appear when women are of reproductive age, with recent data suggesting that pregnancy outcomes such as preterm birth and macrosomia are associated with future cancer [2, 3]. However, risks associated with other reproductive outcomes receive limited attention. The lack of evidence is particularly prominent for birth defects. Birth defects occur in about 4% of newborns [4] and may involve genetic pathways that are similar to those in cancer. Some studies suggest that infants with congenital anomalies are at risk of cancer because of a genetic predisposition [5, 6]. Moreover, birth defects and cancer have common behavioral determinants such as smoking, alcohol, and suboptimal diet [4, 7]. The special care required for infants with birth defects may also impact maternal health and well-being [8, 9].

Whether having an infant with birth defects is linked with the risk of maternal cancer is poorly understood. A recent study of 455,250 women found that having an infant with a major congenital anomaly was associated with a higher risk of maternal death from cancer, compared with no anomaly [10]. However, the study could not assess cancer incidence. Another analysis of 795,607 women found no association overall, but women whose infants had heart or central nervous system defects had higher risks of respiratory and digestive cancers [11]. Many of the associations with specific birth defects disappeared when the study sample was increased to include a broader range of women [11]. A number of

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other studies provide inconsistent evidence of a link between specific birth defects and different maternal cancers [12–15]. To clarify this relationship, we assessed whether having an infant with a birth defect was associated with the future risk of maternal cancer in a cohort of 1.2 million parous women.

Material and methods

Data

We used a retrospective cohort design to analyze women who delivered infants in hospitals of Quebec, Canada, between 1989 and 2016. We extracted data on all pregnant women and used encrypted health insurance numbers to follow up the women over time for future cancer hospitalizations. Follow-up extended up to 28 years after delivery and stopped when the woman was hospitalized for cancer, died, or the study ended on March 31, 2017. Data on the women were drawn from discharge abstracts in the Maintenance and Use of Data for the Study of Hospital Clientele registry [16]. For each hospitalization, we had information on up to 40 diagnostic and 35 procedural codes, three cancer topography and morphology codes, and death during hospitalization. In Quebec, around 99% of women deliver in hospital.

Women without health insurance numbers were not included because they could not be followed up over time. We further excluded 12,321 women who themselves had congenital anomalies and 773 women who had cancer before cohort entry. We also excluded 1663 women who only had stillbirths, as data on birth defects in stillborn infants were not available.

Birth defects

To identify congenital anomalies, we used diagnostic codes of the International Classification of Diseases (9th and 10th revisions), and procedure codes of the Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures and the Canadian Classification of Health Interventions included on the discharge summaries of newborns (Table S1). Birth defects were categorized by leading sites, including the central nervous system, heart, genitourinary, musculoskeletal, chromosomal, and other remaining anomalies (orofacial cleft, respiratory, digestive, sensory, and abdominal wall defect). Abdominal wall defects included gastroschisis, omphalocele, and diaphragmatic hernia.

We captured all women whose infants had anomalies detected during pregnancy or at birth but could not identify defects that were diagnosed during childhood. Women were considered exposed if at least one infant had a birth defect. The comparison group included women whose infants had no birth defects in any pregnancy. In the analyses of various types of defects, women who had multiple infants with defects, or whose infant had multiple defects (chromosomal or other), were included in each exposure category in the analyses of various types of defects.

Maternal cancer

The outcome was cancer that required in-hospital treatment during future admissions. Validation studies with cancer registration data have shown that 92% of incident cancers are present in Quebec hospitalization data [17]. The exception is melanoma, which may be treated in ambulatory settings and is therefore underrepresented in the data [17]. We identified women with cancer using morphology and topography codes in the first, second, and third revisions of the International Classification of Diseases for Oncology (Table S2). We did not analyze nonmelanoma skin cancer.

We analyzed cancer by site, including breast, lung, colorectum, head and neck, thyroid, upper gastrointestinal tract, cervix, uterus, placenta, ovary, other reproductive, bladder, kidney and ureter, hepatobiliary, pancreas, melanoma, eye, brain and central nervous system, heart and thorax, bone, connective and soft tissue, hemolymphopoietic, and other or ill-defined cancers [18, 19]. We further divided hemolymphopoietic cancers as leukemia (lymphoid leukemia, myeloid leukemia, other), multiple myeloma, lymphoma (Hodgkin's, non-Hodgkin's), and other hemopoietic cancers. We analyzed the first hospitalization for incident cancer and included women with different cancers in each outcome category.

Covariates

We accounted for maternal age at first delivery (<20, 20–24, 25–29, 30–34, 35–39, ≥40 years), total parity (1, 2, ≥3 deliveries), multiple birth (yes, no), comorbidity, including obesity, diabetes, tobacco, alcohol, or substance use (yes, no; Table S1), neighborhood material deprivation (yes, no, unknown), and period at first delivery (1989–1998, 1999–2007, 2008–2016). We used total parity as a measure of baseline health, as higher parity is associated with better health in women [7]. Material deprivation was defined as residence in the most deprived quintile of the population based on a composite score of census data on mean neighborhood income, employment rate, and proportion with no high school diploma [20].

Data analysis

We calculated the incidence of cancer per 1000 person-years and the cumulative incidence after 28 years accounting for death as a competing event [21]. We estimated hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between infant birth defects and maternal risk of cancer using Cox proportional hazards regression models adjusted for maternal age at first delivery, total parity, multiple birth, comorbidity, material deprivation, and period at first delivery. We verified the proportional hazards assumption using log (−log survival) plots. We used the Fine and Gray method to account for death as a competing event [22] and defined the time scale as the number of days since the first delivery. Women were censored if they were not diagnosed with cancer before the end of the study.

We considered the possibility that women with more than one pregnancy had more than one opportunity to have infants with birth defects. We therefore performed secondary analyses in which we considered the number of infants with birth defects as the exposure in regression models.

In sensitivity analyses, we restricted the data to women with a minimum follow-up of 5 years, and stratified the analysis by maternal age at first pregnancy (<35, ≥35 years). We performed subset analyses for specific anomalies that were too rare to consider in the main analysis, including orofacial clefts, respiratory, digestive, sensory, abdominal wall, and multiple defects. We also examined finer categories of cancer, including colon, rectosigmoid junction, rectum, anus, salivary gland, larynx, and lip, tongue, and mouth cancer. We used SAS, version 9.4 (SAS Institute Inc., Cary, NC), to perform the analyses. Hospital data were deidentified. We obtained an ethics waiver from the Institutional Review Board of the University of Montreal Hospital Center.

Results

In this study of 1,214,506 women comprising 19,251,851 person-years of follow-up, 117,508 had infants with birth defects and 36,050 developed cancer (Table 1). A total of 2,148,358 infants was

Table 1
Cancer incidence according to characteristics of women

Characteristic	No. of women with cancer	Total no. of women	Person-years	Cancer incidence per 1000 person-years (95% confidence interval)
Women who had infants with a birth defect				
Yes*	3282	117,508	1,885,386	1.74 (1.68–1.80)
No	32,768	1,096,998	17,366,465	1.89 (1.87–1.91)
Maternal age at first delivery, y				
<20	810	67,554	1,128,221	0.72 (0.67–0.77)
20–24	4640	261,526	4,313,861	1.08 (1.05–1.11)
25–29	12,536	449,360	7,265,831	1.73 (1.70–1.76)
30–34	11,649	306,820	4,723,640	2.47 (2.42–2.51)
35–39	5269	109,251	1,564,075	3.37 (3.28–3.46)
≥40	1146	19,995	256,223	4.47 (4.22–4.74)
Total parity				
1	18,172	530,584	7,892,039	2.30 (2.27–2.34)
2	13,605	495,446	7,976,406	1.71 (1.68–1.73)
≥3	4273	188,476	3,383,406	1.26 (1.23–1.30)
Multiple birth				
Yes	789	28,821	447,162	1.76 (1.65–1.89)
No	35,261	1,185,685	18,804,689	1.88 (1.86–1.89)
Comorbidity†				
Yes	3038	66,230	1,038,909	2.92 (2.82–3.03)
No	33,012	1,148,276	18,212,942	1.81 (1.79–1.83)
Material deprivation				
Yes	5948	229,256	3,516,877	1.69 (1.65–1.73)
No	25,701	889,248	13,698,430	1.88 (1.85–1.90)
Period at first delivery				
1989–1998	28,310	563,899	13,271,134	2.13 (2.11–2.16)
1999–2007	6044	327,567	4,356,996	1.39 (1.35–1.42)
2008–2016	1696	323,040	1,623,721	1.04 (1.00–1.10)
Total	36,050	1,214,506	19,251,851	1.87 (1.85–1.89)

* Represents a total of 2,148,358 infants, for a prevalence of birth defects in infants of 57.5 per 1000.
† Obesity, diabetes, tobacco, alcohol, or substance use.

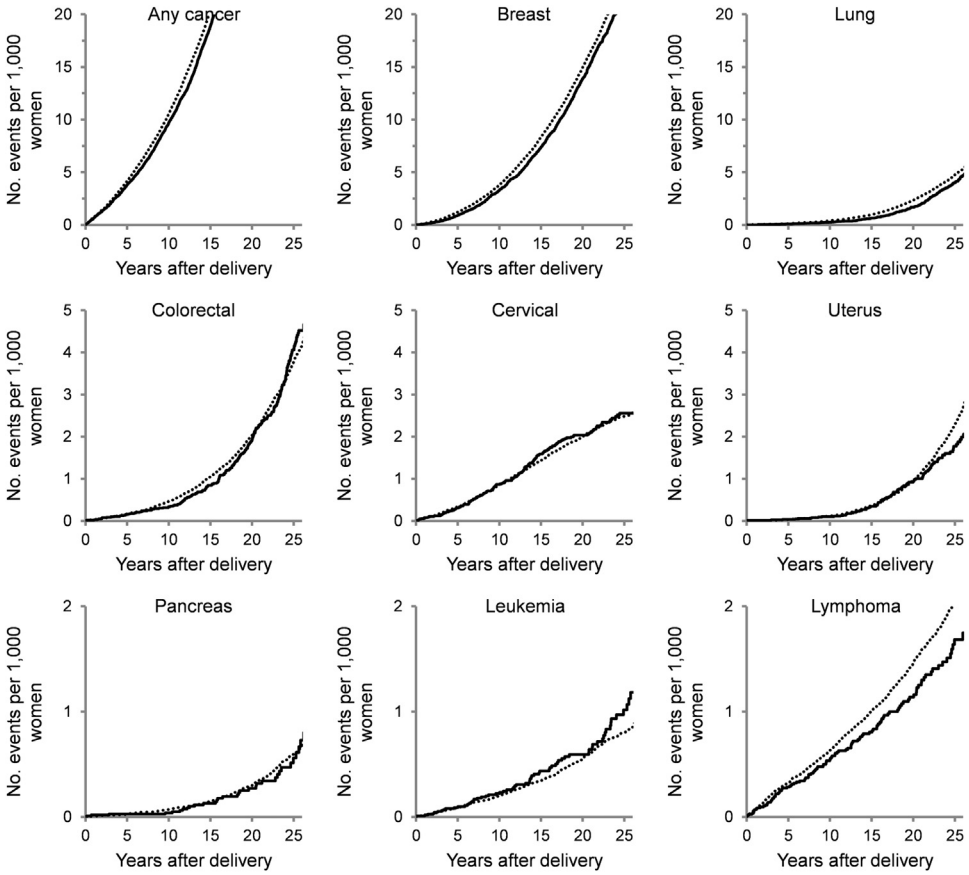

Fig. 1. Cumulative incidence of cancer in women according to presence of birth defects in infants. Figure 1 shows the cumulative incidence of cancer for women whose infants had birth defects (black line) and women whose infants had no birth defects (dotted line) according to the number of years after delivery. Top row shows the cumulative incidence for any, breast, and lung cancer; middle row for colorectal, cervical, and uterus cancer; bottom row for pancreas cancer, leukemia, and lymphoma.

born, of whom 5.7% had congenital anomalies. The average length of follow-up was 14.4 years for incident cancers. Cancer incidence was slightly lower for women whose infants had birth defects (1.74 per 1000 person-years) than for women whose infants had no defects (1.89 per 1000 person-years).

Women whose infants had birth defects had a similar cumulative incidence of cancer compared with no defects (Fig. 1). After 15 years, the cumulative incidence of any cancer was 18.9 (95% CI 18.0–19.8) for women whose infants had birth defects and 20.4 (95% CI 20.1–20.7) for women whose infants had no birth defect. The cumulative incidence associated with birth defects was higher only for leukemia. There was no apparent difference in the cumulative incidence curves for other types of cancer, except for uterine cancer and lymphoma which appeared to be less frequent in women whose infants had birth defects.

Having an infant with birth defects was not associated with the risk of cancer in adjusted models (Table 2). Women whose infants had birth defects had 1.03 times the risk of any cancer compared with no birth defects (95% CI 0.99–1.06). There was no association for the majority of cancers, although having an infant with birth defects was associated with the risk of lymphoid leukemia (HR 1.61; 95% CI 1.03–2.51) and placental cancer (HR 2.23; 95% CI 1.04–4.77).

No single birth defect was consistently associated with the risk of maternal cancer (Table 3). Central nervous system, genitourinary, musculoskeletal, chromosomal, and other anomalies were not associated with the risk of maternal cancer. However, women whose infants had heart defects had 1.12 times the risk of any cancer (95% CI 1.03–1.21), 1.37 times the risk of cervical cancer (95% CI 1.00–1.89), and 1.72 times the risk of leukemia (95% CI 1.02–2.89) compared with no birth defect.

We found no evidence that women who had more than one infant with birth defects had a higher risk of cancer (Table 4). Among women with two or more pregnancies, having two or more infants with birth defects was not associated with the risk of cancer. Similarly, having one infant with birth defects had no impact. Compared with two or more pregnancies, women with only one pregnancy had a higher risk of most cancers regardless of birth defects. Although the risk of lymphoid leukemia in women with only one pregnancy was somewhat stronger for birth defects (HR 2.51; 95% CI 1.30–4.86), a similar trend was present in women with two or more pregnancies.

In sensitivity analyses, restricting the data to women with a minimum follow-up of 5 years had no impact on results, nor did stratifying by maternal age at first pregnancy. Having an infant with orofacial cleft, respiratory, digestive, abdominal wall, or multiple defects was not clearly associated with the overall risk of maternal cancer (Table S3). However, women whose infants had sensory defects had 1.16 times the risk of any cancer (95% CI 1.04–1.30), 1.53 times the risk of cervical cancer (95% CI 1.01–2.31), and 4.89 times the risk of placental cancer (95% CI 1.20–19.91). Analysis of finer cancer categories did not yield substantially meaningful results.

Discussion

In this cohort of more than 1.2 million parous women, having an infant with birth defects was not associated with the overall risk of maternal cancer. Birth defects appeared to be associated with the future risk of leukemia and placental cancer, but there was no

Table 2
Association of infant birth defects with future risk of maternal cancer

Cancer site	Total no. of women	No. of women whose infants have birth defects	Hazard ratio (95% confidence interval)	
			Unadjusted	Adjusted*
Breast	14,955	1328	0.92 (0.87–0.97)	1.01 (0.96–1.07)
Lung	2738	210	0.81 (0.70–0.93)	1.00 (0.87–1.16)
Colorectal	2307	220	1.01 (0.88–1.16)	1.14 (0.99–1.32)
Head and neck	643	58	0.95 (0.72–1.24)	1.02 (0.78–1.34)
Thyroid	4676	469	1.04 (0.94–1.14)	1.00 (0.91–1.10)
Upper gastrointestinal tract	373	31	0.86 (0.60–1.24)	0.96 (0.66–1.39)
Cervical	1880	188	1.02 (0.88–1.19)	1.09 (0.93–1.27)
Uterus	1280	96	0.79 (0.65–0.98)	0.95 (0.77–1.17)
Placenta	44	9	2.35 (1.13–4.88)	2.23 (1.04–4.77)
Ovarian	1179	112	0.99 (0.81–1.20)	1.15 (0.94–1.40)
Other reproductive	299	28	1.00 (0.67–1.47)	1.04 (0.70–1.54)
Bladder	293	21	0.73 (0.47–1.14)	0.86 (0.55–1.35)
Kidney and ureter	769	65	0.89 (0.69–1.14)	0.93 (0.72–1.20)
Hepatobiliary	233	23	1.06 (0.69–1.63)	1.15 (0.74–1.79)
Pancreas	358	33	0.98 (0.68–1.40)	1.09 (0.77–1.56)
Melanoma	1377	140	1.06 (0.89–1.26)	1.10 (0.92–1.31)
Eye, brain, and central nervous system	810	70	0.88 (0.69–1.13)	0.93 (0.72–1.19)
Heart and thorax	49	5	1.05 (0.42–2.65)	1.20 (0.47–3.05)
Bone	171	12	0.71 (0.40–1.28)	0.77 (0.43–1.39)
Connective and soft tissue	300	25	0.85 (0.56–1.28)	0.89 (0.59–1.35)
Hemolymphopoietic	2480	219	0.91 (0.79–1.05)	0.97 (0.84–1.12)
Leukemia	575	67	1.24 (0.96–1.60)	1.32 (1.02–1.71)
Lymphoid leukemia	174	24	1.52 (0.99–2.34)	1.61 (1.03–2.51)
Myeloid leukemia	388	42	1.13 (0.82–1.56)	1.22 (0.88–1.69)
Other leukemia	61	5	0.83 (0.33–2.08)	0.83 (0.34–2.02)
Multiple myeloma	178	9	0.51 (0.26–1.00)	0.54 (0.28–1.05)
Lymphoma	1461	116	0.81 (0.67–0.97)	0.85 (0.70–1.03)
Hodgkin's	521	42	0.81 (0.59–1.10)	0.81 (0.59–1.11)
Non-Hodgkin's	970	76	0.80 (0.63–1.01)	0.87 (0.69–1.11)
Other hemopoietic	379	33	0.91 (0.64–1.30)	1.00 (0.69–1.43)
Other or ill-defined	892	328	0.94 (0.75–1.18)	1.09 (0.86–1.37)
Any cancer	36,050	3511	0.94 (0.91–0.98)	1.03 (0.99–1.06)

* Adjusted for maternal age at first delivery, total parity, multiple birth, comorbidity, material deprivation, and period at first delivery.

Table 3
Type of birth defect and future risk of maternal cancer

Cancer site	Hazard ratio (95% confidence interval)*					
	Central nervous system defect (n = 4368)	Heart defect (n = 19,231)	Genitourinary defect (n = 22,257)	Musculoskeletal defect (n = 55,047)	Chromosomal anomaly (n = 4000)	Other anomaly (n = 18,436)
Breast	0.93 (0.69–1.25)	1.11 (0.98–1.26)	0.99 (0.86–1.14)	0.99 (0.91–1.07)	1.03 (0.80–1.34)	1.01 (0.88–1.17)
Lung	0.98 (0.49–1.96)	0.85 (0.59–1.21)	0.95 (0.65–1.37)	1.01 (0.83–1.22)	0.83 (0.41–1.65)	1.33 (0.98–1.79)
Colorectal	0.42 (0.14–1.30)	1.15 (0.83–1.59)	1.19 (0.85–1.67)	1.07 (0.88–1.30)	1.04 (0.54–2.00)	1.44 (1.06–1.95)
Head and neck	1.95 (0.73–5.25)	0.75 (0.36–1.58)	1.15 (0.62–2.15)	1.02 (0.70–1.48)	0.43 (0.06–3.05)	1.76 (1.06–2.94)
Thyroid	0.94 (0.57–1.54)	1.06 (0.85–1.31)	0.95 (0.76–1.19)	1.04 (0.91–1.18)	0.67 (0.38–1.19)	1.07 (0.85–1.34)
Upper gastrointestinal tract	1.68 (0.42–6.78)	1.49 (0.73–3.03)	1.57 (0.78–3.17)	0.68 (0.37–1.25)	0.71 (0.10–5.03)	0.21 (0.03–1.46)
Cervical	1.13 (0.54–2.37)	1.37 (1.00–1.89)	1.13 (0.80–1.60)	1.02 (0.82–1.27)	0.82 (0.34–1.98)	1.15 (0.80–1.64)
Uterus	1.79 (0.85–3.77)	1.46 (0.98–2.17)	0.76 (0.42–1.38)	0.85 (0.63–1.15)	0.66 (0.21–2.05)	0.97 (0.58–1.61)
Placenta	—	1.43 (0.19–10.88)	2.61 (0.61–11.28)	1.56 (0.48–5.13)	—	3.14 (0.75–13.24)
Ovarian	1.40 (0.58–3.38)	1.11 (0.70–1.78)	1.14 (0.71–1.85)	1.10 (0.84–1.44)	1.25 (0.52–3.02)	1.62 (1.08–2.43)
Other reproductive	0.95 (0.13–6.80)	0.85 (0.32–2.29)	0.72 (0.23–2.24)	1.05 (0.61–1.82)	0.79 (0.11–5.67)	1.46 (0.65–3.27)
Bladder	1.08 (0.15–7.74)	1.24 (0.50–3.04)	0.85 (0.27–2.63)	0.96 (0.54–1.72)	—	0.54 (0.14–2.18)
Kidney and ureter	1.12 (0.36–3.49)	1.17 (0.69–1.98)	0.74 (0.37–1.49)	0.93 (0.65–1.32)	0.67 (0.17–2.69)	1.14 (0.64–2.03)
Hepatobiliary	1.16 (0.16–8.19)	2.51 (1.26–4.99)	0.67 (0.17–2.67)	0.41 (0.15–1.09)	3.24 (1.04–10.11)	1.62 (0.66–3.98)
Pancreas	—	1.14 (0.51–2.58)	1.32 (0.59–2.96)	0.96 (0.56–1.63)	—	1.09 (0.45–2.64)
Melanoma	1.38 (0.62–3.07)	0.98 (0.63–1.52)	1.26 (0.85–1.85)	1.09 (0.86–1.39)	1.08 (0.45–2.59)	1.12 (0.73–1.72)
Eye, brain, and central nervous system	1.83 (0.76–4.43)	1.11 (0.66–1.89)	0.57 (0.27–1.20)	0.82 (0.58–1.18)	1.43 (0.53–3.85)	1.49 (0.92–2.41)
Heart and thorax	6.69 (0.88–51.05)	—	—	1.91 (0.68–5.33)	—	1.60 (0.21–11.96)
Bone	1.84 (0.25–13.25)	0.81 (0.20–3.27)	0.81 (0.20–3.28)	1.03 (0.50–2.10)	—	0.43 (0.06–3.02)
Connective and soft tissue	3.86 (1.43–10.43)	0.86 (0.32–2.31)	0.64 (0.21–2.01)	1.02 (0.59–1.74)	—	0.47 (0.12–1.90)
Hemolymphopoietic	0.95 (0.47–1.90)	0.94 (0.68–1.31)	1.06 (0.77–1.46)	0.91 (0.74–1.11)	0.79 (0.38–1.66)	0.99 (0.70–1.39)
Leukemia	1.53 (0.49–4.75)	1.72 (1.02–2.89)	1.33 (0.73–2.42)	1.12 (0.76–1.64)	0.49 (0.07–3.45)	1.29 (0.69–2.41)
Lymphoid leukemia	3.16 (0.79–12.64)	2.25 (0.97–5.22)	1.22 (0.39–3.84)	1.07 (0.52–2.20)	—	1.70 (0.62–4.64)
Myeloid leukemia	0.79 (0.11–5.68)	1.56 (0.80–3.03)	1.43 (0.71–2.88)	1.18 (0.75–1.86)	0.74 (0.11–5.27)	0.96 (0.40–2.33)
Other leukemia	—	1.93 (0.46–8.14)	—	0.35 (0.05–2.44)	—	2.21 (0.55–8.87)
Multiple myeloma	3.06 (0.75–12.51)	0.34 (0.05–2.38)	0.81 (0.20–3.28)	0.37 (0.12–1.16)	—	0.80 (0.20–3.20)
Lymphoma	0.20 (0.03–1.44)	0.80 (0.50–1.27)	0.94 (0.61–1.45)	0.91 (0.71–1.18)	0.99 (0.41–2.38)	0.63 (0.36–1.09)
Hodgkin's	—	0.81 (0.39–1.72)	0.99 (0.51–1.91)	0.87 (0.57–1.34)	0.59 (0.08–4.21)	0.75 (0.34–1.68)
Non-Hodgkin's	0.32 (0.05–2.26)	0.83 (0.47–1.47)	0.88 (0.49–1.55)	0.91 (0.66–1.25)	1.16 (0.43–3.11)	0.61 (0.30–1.23)
Other hemopoietic	2.25 (0.72–7.08)	0.51 (0.16–1.61)	0.96 (0.40–2.32)	0.73 (0.41–1.30)	0.70 (0.10–5.04)	2.16 (1.18–3.96)
Other or ill-defined	1.07 (0.34–3.33)	1.11 (0.65–1.89)	0.71 (0.35–1.42)	1.14 (0.84–1.56)	0.61 (0.15–2.43)	1.32 (0.79–2.21)
Any cancer	1.04 (0.87–1.25)	1.12 (1.03–1.21)	1.01 (0.92–1.10)	1.00 (0.95–1.05)	0.92 (0.77–1.10)	1.10 (1.01–1.20)

* Hazard ratio for type of birth defect versus no birth defect, adjusted for maternal age at first delivery, total parity, multiple birth, comorbidity, material deprivation, and period at first delivery. Dashes are due to no cancer events in the exposed. Sample sizes are shown in Table S4.

consistent association with other forms of cancer. Heart defects also tended to be more strongly associated with cancer, but again not consistently. Given the large sample size and absence of persistently elevated associations across types of cancer and birth defects, it is possible that the positive results for specific subgroups of women are spurious. Overall, we found no evidence of an association between birth defects and some of the more common cancer types but cannot confirm the absence of association with rare cancers due to limited power.

The link between birth defects and maternal cancer has been investigated in previous research, but conclusive data are lacking. In a Danish study of mortality, having an infant with a major birth defect was associated with 1.11 times the risk of death from cancer [10]. The study could not confirm whether birth defects were associated with occurrence of cancer in addition to cancer mortality. Moreover, specific causes of cancer mortality could not be investigated. Risks also appeared to be greater for cardiovascular mortality [10]; a finding that aligns with recent evidence that women who have infants with heart defects have a higher incidence of cardiovascular morbidity [23].

Studies of birth defects and maternal cancer incidence all lack of consistency. Associations have been found between specific birth defects and various cancers [11–14]; but findings are not comparable from study to study. Infant oral clefts were associated with maternal hemolymphopoietic cancer in one analysis [12]; whereas a separate study found that infant heart or central nervous system defects were associated with the risk of respiratory and digestive cancers [11]. The wide variation in study findings suggests that most results are due to chance, owing to comparisons of a many types of birth defects and cancers. Moreover, one study found that having an infant with birth defects was associated with the risk of maternal cancer before or during pregnancy rather than after pregnancy [14]. This finding raises the possibility that cancer treatment may have caused birth defects and induced spurious associations in previous studies that did not exclude prepregnancy cancers [13, 15].

In addition, there is little support for an association between birth defects and risk of cancer in fathers or siblings. Three cohort studies report no consistent association between birth defects and paternal cancer [11, 12, 15]; and two sibling studies found no link between birth defects and the risk of breast cancer or cancers overall [13, 15]. These findings contrast with various studies suggesting that birth defects are associated with the risk of cancer in affected infants, a relationship that is thought to reflect a genetic predisposition [5, 6]. However, it is not clear why a similar genetic predisposition for cancer would not be present in close relatives, including parents and siblings who share 50% of genes. It may be that the link between birth defects and future childhood cancer is not genetic, but rather due to other exposures. Low-grade radiation is a possibility, as many infants with birth defects undergo diagnostic imaging. Some researchers have postulated that radiation exposures from X-rays or other

Table 4
Number of infants with birth defects and future risk of maternal cancer*

Cancer site	Women with only one pregnancy				Women with two or more pregnancies			
	No infant with anomaly		One infant with anomaly		One infant with anomaly		Two or more infants with anomalies	
	n	Hazard ratio (95% CI)	*n*	Hazard ratio (95% CI)	*n*	Hazard ratio (95% CI)	*n*	Hazard ratio (95% CI)
Breast	7157	0.98 (0.95–1.02)	427	1.00 (0.90–1.10)	834	1.00 (0.93–1.07)	62	1.06 (0.82–1.36)
Lung	1687	1.57 (1.43–1.71)	97	1.56 (1.26–1.93)	106	0.98 (0.80–1.19)	5	0.66 (0.27–1.58)
Colorectal	1190	1.13 (1.03–1.24)	92	1.49 (1.20–1.85)	120	1.03 (0.85–1.25)	8	0.97 (0.49–1.95)
Head and neck	315	1.14 (0.96–1.35)	17	1.05 (0.64–1.73)	39	1.11 (0.79–1.55)	2	0.78 (0.20–3.16)
Thyroid	1690	0.79 (0.74–0.84)	97	0.74 (0.60–0.90)	340	1.01 (0.90–1.13)	27	1.12 (0.77–1.64)
Upper gastrointestinal tract	194	1.23 (0.97–1.55)	12	1.28 (0.71–2.32)	17	0.88 (0.53–1.46)	<5	1.48 (0.37–5.95)
Cervical	827	1.31 (1.19–1.46)	61	1.62 (1.25–2.11)	117	1.00 (0.82–1.21)	10	1.12 (0.60–2.08)
Uterus	765	1.50 (1.32–1.71)	44	1.49 (1.09–2.04)	45	0.83 (0.61–1.13)	7	1.83 (0.87–3.86)
Placenta	13	0.90 (0.44–1.83)	<5	3.21 (0.93–11.03)	6	1.96 (0.79–4.86)	0	—
Ovarian	615	1.32 (1.16–1.50)	48	1.75 (1.30–2.36)	59	1.00 (0.76–1.31)	5	1.17 (0.49–2.82)
Other reproductive	144	0.95 (0.74–1.24)	8	0.90 (0.44–1.85)	19	1.14 (0.71–1.85)	<5	0.84 (0.12–6.01)
Badder	159	1.18 (0.91–1.54)	8	1.02 (0.49–2.13)	13	0.89 (0.50–1.57)	0	—
Kidney and ureter	357	0.95 (0.81–1.12)	18	0.81 (0.50–1.30)	42	0.92 (0.66–1.26)	5	1.50 (0.62–3.62)
Hepatobiliary	122	1.14 (0.85–1.52)	9	1.41 (0.70–2.83)	14	1.19 (0.68–2.09)	0	—
Pancreas	202	1.44 (1.13–1.84)	10	1.18 (0.61–2.27)	23	1.39 (0.89–2.17)	0	—
Melanoma	568	1.00 (0.89–1.12)	35	1.03 (0.73–1.45)	94	1.07 (0.86–1.32)	11	1.71 (0.94–3.11)
Eye, brain, and central nervous system	356	1.12 (0.96–1.30)	17	0.89 (0.54–1.45)	51	0.99 (0.74–1.32)	<5	0.52 (0.13–2.08)
Heart and thorax	24	1.47 (0.79–2.74)	<5	3.06 (0.92–10.23)	<5	0.75 (0.18–3.21)	0	—
Bone	81	1.17 (0.84–1.64)	<5	0.74 (0.24–2.35)	8	0.78 (0.38–1.62)	<5	1.33 (0.19–9.42)
Connective and soft tissue	126	0.95 (0.73–1.22)	9	1.10 (0.55–2.19)	14	0.70 (0.41–1.22)	<5	1.36 (0.34–5.51)
Hemolymphopoietic	1150	1.15 (1.05–1.26)	77	1.28 (1.02–1.62)	129	0.87 (0.72–1.04)	12	1.09 (0.62–1.92)
Leukemia	260	1.14 (0.95–1.38)	24	1.74 (1.14–2.67)	41	1.22 (0.88–1.70)	<5	0.79 (0.20–3.20)
Lymphoid leukemia	79	1.19 (0.85–1.67)	10	2.51 (1.30–4.86)	13	1.36 (0.75–2.46)	<5	1.41 (0.20–10.22)
Myeloid leukemia	176	1.17 (0.93–1.47)	14	1.54 (0.88–2.70)	27	1.17 (0.78–1.76)	<5	0.58 (0.08–4.14)
Other leukemia	25	0.81 (0.46–1.43)	<5	0.52 (0.07–3.91)	<5	0.94 (0.33–2.69)	0	—
Multiple myeloma	86	0.69 (0.50–0.96)	<5	0.27 (0.07–1.10)	6	0.55 (0.24–1.26)	<5	1.36 (0.19–9.76)
Lymphoma	657	1.14 (1.01–1.28)	41	1.19 (0.87–1.63)	67	0.73 (0.57–0.94)	7	1.03 (0.49–2.16)
Hodgkin's	217	1.29 (1.06–1.56)	12	1.16 (0.65–2.09)	26	0.73 (0.49–1.09)	<5	1.49 (0.55–3.99)
Non-Hodgkin's	455	1.07 (0.92–1.23)	30	1.19 (0.83–1.72)	42	0.72 (0.53–0.99)	<5	0.71 (0.23–2.20)
Other hemopoietic	204	1.48 (1.18–1.85)	12	1.44 (0.79–2.61)	19	0.99 (0.61–1.60)	<5	1.41 (0.35–5.70)
Other or ill-defined	1778	1.23 (1.06–1.43)	96	1.26 (0.85–1.85)	215	1.13 (0.84–1.52)	15	0.63 (0.16–2.53)
Any cancer	18,305	1.07 (1.04–1.09)	1113	1.10 (1.04–1.18)	2213	1.00 (0.96–1.05)	172	1.09 (0.93–1.27)

* All hazard ratios are relative to women with more than one pregnancy and no birth defects, adjusted for maternal age at first delivery, multiple birth, comorbidity, material deprivation, and period at first delivery. Dashes are due to no cancer events in the exposed.

diagnostic imaging techniques may be linked with the future risk of cancer in childhood [24].

The absence of a shared genetic mechanism is supported by our own findings. Our data showed that infant chromosomal anomalies, which have a genetic etiology, were not associated with the risk of maternal cancer [4]. Only heart defects, where a genetic component is less well established, were associated with maternal cancer. Although we suspect that this finding is incidental, it is also possible that lifestyle-related factors are involved. Heart defects are serious congenital anomalies [25]. Caring for a child with a major heart defects can lead to stress and lifestyle changes that impact maternal health [9]; including the risk of cancer [26]. However, this mechanism is uncertain as we found no association with central nervous system defects, which are also a burden on parents [27].

We found that infant birth defects were associated with a higher risk of leukemia and placental cancer. This association may also be incidental, as these two forms of cancer to our knowledge do not have similar pathophysiology. Leukemia stems from blood-forming tissues that have an immunologic component [19]; whereas the pathways leading to placental cancer relate to the trophoblastic epithelium [28]. A common relation between leukemia and placental cancer is not immediately evident. There is however some evidence that placental cancer is associated with molar pregnancies, especially partial molar pregnancies that frequently are chromosomally abnormal [28]. In our study, there were no cases of placental cancer in women whose infants had chromosomal anomalies; however, we cannot rule out the possibility that confined placental mosaicism may have increased the risk of cancer in rare cases. Also, birth defects share common risk factors with both leukemia and placental cancer. Radiation, for example, is a risk factor for both birth defects and maternal leukemia [4, 19]. Smoking is another possibility, as tobacco exposure is associated with birth defects [4], leukemia, and placental cancer [28, 29]. However, the extent to which smoking contributes to the findings is unclear, as we found no association with lung cancer. Smoking accounts for 90% of lung cancers [7].

This longitudinal study of more than 1.2 million women has a number of limitations. Birth defects could only be diagnosed in infants who were born alive, and we lacked data on defects for miscarriages, stillbirths, and terminations. We did not have information on defects that were missed at birth and detected only later in childhood. These limitations may have resulted in non-differential misclassification of the exposure. Because women were the unit of analysis, the proportion whose infants had birth defects is not comparable to the prevalence in infants at birth. We could only identify cancers among women who were hospitalized in Quebec, not those treated outside the province. We also had a low number of cases for some cancer sites, such as placental cancer, which may have limited the statistical power of the analysis. We did not have information on diet, ethnicity, assisted conception, and accessibility to cancer-screening programs. Moreover, our cohort includes relatively young women, many of whom may not

have reached menopause before the end of study. Longer follow-up may be needed to determine if infant birth defects are associated with late-onset cancers. Finally, our findings may not generalize to populations where the prevalence of birth defects or cancer differs substantially from the prevalence in our study.

Conclusions

We did not find substantial evidence of an association between having an infant with a birth defect and the risk of early cancers in women. The associations we found for leukemia and placental cancer, and for heart defects with various cancers, may reflect type I error. However, we cannot rule out the possibility of an association with cancer much later in life. Mothers of children with birth defects may be reassured that birth defects are not markers of future risk of early-onset cancer in women.

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Appendix

Table S1
Diagnostic and procedure codes for congenital anomalies and maternal comorbidity

Variable	Diagnostic codes – International Classification of Diseases 9th/10th revisions	Procedure codes – Canadian Classification of Diagnostic, Therapeutic, and Surgical Procedures/ Canadian Classification of Health Interventions
Congenital anomalies		
Central nervous system	740-742/Q00-Q07	15.31–15.43, 16.42, 16.59/1.AC.52-1.AC.54, 1.AW.72, 1.AX.73
Heart*	745-746, 747.1–747.4, 759.3/Q20-Q24, Q25.1-Q26.4, Q26.8, Q26.9, Q89.3	47.52–47.55, 47.62–47.64, 47.72–47.74, 47.81–47.83/ 1.HN.80, 1.HP.87, 1.HR.80, 1.IN.84, 1.LA.84, 1.LC.84, 1.LD.84
Genitourinary	752.6, 752.7, 753/Q54, Q56-Q64	—
Musculoskeletal	754.3, 754.5–754.7, 755.0–756.0, 756.9/Q65, Q66, Q68.1-Q75.2, Q75.8-Q75.9	95.75, 98.71/1.UF.84, 1.UI.71, 1.UJ.71, 1.WE.72, 1.WL.71
Chromosomal	758, 759.8/Q87, Q90-Q99	—
Other anomaly	—	—
Orofacial cleft	749.0–749.2/Q35-Q37	39.49, 39.52–39.59/1.FB.86, 1.YE.80
Respiratory	748.2–748.9/Q31-Q34	—
Digestive	750.1–751/Q38.0, Q38.2-Q45	—
Sensory	366.0, 743, 744.0–744.3, 748.0, 748.1/H26.0, Q10-Q17, Q30	27.61, 27.62, 27.72/1.CL.59, 1.CL.89
Abdominal wall	756.6, 756.72, 756.73/Q79.0-Q79.3	66.63/1.SY.84
Maternal comorbidity	249-250, 278.0, 291, 292, 303–305, 357.5, 357.6, 425.5, 535.3, 571.0–571.3, 577.0, 577.9, 649.0, 649.1, 655.4, 655.5, 790.3, 965.0, 967.0, 967.4, 969.1–969.9, 970.8, 980.0, 989.84, V11.3, V15.82, V65.42, V79.1/E10-E14, E66, F10-F19, K292, K70, K852, K860, K869, O354, O355, R781-R785, T40, T510, T652, X42, X45, X62, X65, Y12, Y15, Z502, Z508, Z587, Z714-Z716, Z720-Z722, Z864	—

* We included patent ductus arteriosus and atrial septal defect at term because these defects may be physiological preterm.

Table S2
Topography and morphology codes for cancer outcomes

Cancer site	International Classification of Diseases for Oncology 1st, 2nd, and 3rd revisions	
	Topography	Morphology
Breast	174/C50	All morphology codes*
Lung	162/C33, C34	All morphology codes*
Colorectal	153-154/C18-C21	All morphology codes*
Head and neck	140-149, 160–161/C00-C14, C30-C32	All morphology codes*
Thyroid	193/C73	All morphology codes*
Upper gastrointestinal tract	150-152/C15-C17	All morphology codes*
Cervical	180/C53	All morphology codes*
Uterus	179, 182/C54-C55	All morphology codes*
Placenta	181/C58	All morphology codes*
Ovarian	183.0/C56	All morphology codes*
Other reproductive	183.2–184/C51, C52, C57	All morphology codes*
Bladder	188/C67	All morphology codes*
Kidney and ureter	189/C64-C66, C68	All morphology codes*
Hepatobiliary	155-156/C22-C24	All morphology codes*
Pancreas	157/C25	All morphology codes*
Melanoma	173/C44	8720–8790
Eye, brain and central nervous system	190-192/C69-C72	All morphology codes*
Heart and thorax	163-165/C37-C39	All morphology codes*
Bone	170/C40-C41	All morphology codes*
Connective and soft tissue	171, 176/C47, C49	All morphology codes*
Hemolymphopoietic	—	9590–9992
Leukemia	—	9733, 9742, 9800–9948, 9963-9964
Lymphoid leukemia	—	9811–9837
Myeloid leukemia	—	9840–9948
Other leukemia	—	9733, 9742, 9800–9809, 9963-9964
Multiple myeloma	—	9731-9732, 9734
Lymphoma	—	9590-9729, 9735-9738
Hodgkin's	—	9650–9667
Non-Hodgkin's	—	9590-9597, 9670–9729, 9735-9738
Other hemopoietic	—	9740-9741, 9750–9769, 9950–9962, 9965-9992
Other or ill-defined	158-159, 194–195, 199, 209/C26, C48, C74-C76, C80	All morphology codes*

* Excluding 9050–9055, 9140, 9590-9992.

Table S3
Association of other birth defects with future risk of maternal cancer*

Cancer site	Hazard ratio (95% confidence interval)					
	Orofacial cleft, $n = 2427$	Respiratory defect, $n = 2577$	Digestive defect, $n = 6634$	Sensory defect, $n = 11,475$	Abdominal wall defect, $n = 1199$	Multiple defect, $n = 7187$
Breast	0.91 (0.62–1.35)	0.94 (0.64–1.39)	1.00 (0.80–1.25)	1.07 (0.89–1.29)	1.23 (0.68–2.21)	0.93 (0.74–1.17)
Lung	0.85 (0.32–2.27)	0.23 (0.03–1.59)	1.73 (1.13–2.63)	1.28 (0.82–1.99)	—	0.99 (0.57–1.70)
Colorectal	2.16 (1.12–4.16)	1.69 (0.81–3.56)	1.22 (0.72–2.06)	1.04 (0.63–1.70)	1.48 (0.37–5.91)	0.93 (0.51–1.68)
Head and neck	0.82 (0.11–5.82)	2.48 (0.80–7.73)	2.38 (1.18–4.77)	0.88 (0.33–2.34)	—	2.05 (0.97–4.33)
Thyroid	0.93 (0.49–1.80)	1.55 (0.95–2.54)	1.21 (0.86–1.70)	0.94 (0.69–1.29)	0.26 (0.04–1.83)	1.15 (0.82–1.62)
Upper gastrointestinal tract	—	—	0.52 (0.07–3.73)	0.38 (0.05–2.71)	—	—
Cervical	1.07 (0.40–2.86)	1.63 (0.73–3.61)	0.88 (0.46–1.69)	1.53 (1.01–2.31)	—	1.17 (0.66–2.06)
Uterus	0.89 (0.22–3.56)	1.38 (0.44–4.30)	1.14 (0.54–2.40)	0.65 (0.27–1.58)	3.00 (0.75–12.03)	1.59 (0.85–2.98)
Placenta	12.19 (1.58–94.39)	—	—	4.89 (1.20–19.91)	—	—
Ovarian	0.47 (0.07–3.37)	2.90 (1.30–6.49)	1.71 (0.92–3.19)	1.53 (0.87–2.70)	2.98 (0.75–11.84)	1.87 (1.03–3.39)
Other reproductive	—	3.25 (0.80–13.14)	0.60 (0.09–4.28)	1.85 (0.69–4.95)	—	0.58 (0.08–4.14)
Bladder	—	—	0.68 (0.10–4.83)	1.61 (0.52–4.99)	—	2.68 (0.99–7.22)
Kidney and ureter	0.65 (0.09–4.64)	0.64 (0.09–4.56)	1.19 (0.49–2.88)	0.90 (0.37–2.17)	1.96 (0.28–14.01)	0.91 (0.34–2.45)
Hepatobiliary	2.20 (0.31–15.84)	—	0.80 (0.11–5.77)	1.95 (0.62–6.14)	—	0.74 (0.11–5.25)
Pancreas	—	3.01 (0.74–12.20)	0.56 (0.08–3.97)	1.72 (0.64–4.61)	—	—
Melanoma	0.38 (0.05–2.71)	0.38 (0.05–2.66)	0.95 (0.45–2.00)	1.75 (1.11–2.75)	1.09 (0.15–7.73)	1.08 (0.54–2.16)
Eye, brain, and central nervous system	1.24 (0.31–4.96)	—	1.12 (0.46–2.68)	1.88 (1.06–3.34)	1.75 (0.25–12.41)	1.77 (0.88–3.56)
Heart and thorax	11.25 (1.49–84.71)	—	—	—	—	4.02 (0.52–30.85)
Bone	—	—	—	0.76 (0.11–5.42)	—	1.12 (0.16–8.11)
Connective and soft tissue	1.70 (0.24–12.21)	—	0.61 (0.08–4.34)	0.41 (0.06–2.96)	—	1.17 (0.29–4.72)
Hemolymphopoietic	1.02 (0.43–2.45)	1.00 (0.42–2.41)	0.59 (0.30–1.19)	1.15 (0.76–1.76)	1.15 (0.29–4.59)	0.43 (0.19–0.96)
Leukemia	0.90 (0.13–6.41)	2.63 (0.84–8.19)	0.99 (0.32–3.09)	1.18 (0.49–2.85)	—	0.31 (0.04–2.22)
Lymphoid leukemia	—	5.54 (1.36–22.48)	2.16 (0.52–8.91)	1.58 (0.39–6.45)	—	—
Myeloid leukemia	1.37 (0.19–9.74)	1.34 (0.19–9.55)	0.49 (0.07–3.53)	0.70 (0.17–2.80)	—	0.48 (0.07–3.42)
Other leukemia	—	7.43 (1.05–52.62)	—	2.07 (0.29–14.64)	—	—
Multiple myeloma	—	2.68 (0.38–18.85)	0.98 (0.14–6.92)	1.58 (0.39–6.40)	—	1.83 (0.46–7.35)
Lymphoma	1.02 (0.33–3.17)	0.34 (0.05–2.39)	0.37 (0.12–1.16)	0.68 (0.34–1.37)	1.86 (0.47–7.43)	0.37 (0.12–1.14)
Hodgkin's	1.79 (0.45–7.15)	—	0.33 (0.05–2.33)	0.42 (0.10–1.68)	2.09 (0.30–14.75)	—
Non-Hodgkin's	0.53 (0.08–3.78)	0.54 (0.08–3.82)	0.39 (0.10–1.55)	0.97 (0.46–2.05)	1.58 (0.22–11.18)	0.57 (0.18–1.79)
Other hemopoietic	1.35 (0.19–9.64)	1.31 (0.18–9.35)	1.00 (0.25–4.01)	2.63 (1.24–5.61)	—	0.46 (0.07–3.32)
Other or ill-defined	1.81 (0.58–5.63)	1.86 (0.60–3.00)	1.69 (0.91–3.16)	1.92 (0.27–13.61)	1.72 (0.85–3.46)	1.72 (0.85–3.46)
Any cancer	0.96 (0.75–1.22)	1.13 (0.90–1.41)	1.07 (0.93–1.23)	1.16 (1.04–1.30)	0.95 (0.63–1.44)	1.02 (0.89–1.18)

* Hazard ratio for type of birth defect versus no birth defect, adjusted for maternal age at first delivery, total parity, multiple birth, comorbidity, material deprivation, and period at first delivery. Dashes are due to no cancer events in the exposed. Sample sizes are shown in Table S4.

Table S4
Number of women whose infants had birth defects and who subsequently developed cancer

Cancer site	No. women with infant birth defect										
	Central nervous system	Heart	Genitourinary	Musculoskeletal	Chromosomal	Orofacial cleft	Respiratory	Digestive	Sensory	Abdominal wall	Multiple defect
Breast	43	239	202	653	58	25	26	77	114	11	73
Lung	8	30	28	108	8	<5	<5	22	20	0	13
Colorectal	<5	37	35	104	9	9	7	14	16	<5	11
Head and neck	<5	7	10	29	<5	<5	<5	8	<5	0	7
Thyroid	16	83	78	236	12	9	16	33	40	<5	33
Upper gastrointestinal tract	<5	8	8	11	<5	0	0	<5	<5	0	0
Cervical	7	39	32	88	5	<5	6	9	23	0	12
Uterus	7	25	11	44	<5	<5	<5	7	5	<5	10
Placenta	0	<5	<5	<5	0	<5	0	0	<5	0	0
Ovarian	5	18	17	55	5	<5	6	10	12	<5	11
Other reproductive	<5	<5	<5	14	<5	0	<5	<5	<5	0	<5
Bladder	<5	5	<5	12	0	0	0	<5	<5	0	<5
Kidney and ureter	<5	14	8	32	<5	<5	<5	5	5	<5	<5
Hepatobiliary	<5	9	<5	<5	<5	<5	0	<5	<5	0	<5
Pancreas	0	6	6	14	0	0	<5	<5	<5	0	0
Melanoma	6	20	26	70	5	<5	<5	7	19	<5	8
Eye, brain, and central nervous system	5	14	7	31	<5	<5	0	5	12	<5	8
Heart and thorax	<5	0	0	<5	0	<5	0	0	0	0	<5
Bone	<5	<5	<5	8	0	0	0	0	<5	0	<5
Connective and soft tissue	<5	<5	<5	14	0	<5	0	<5	<5	0	<5
Hemolymphopoietic	8	36	39	102	7	5	5	8	22	<5	6
Leukemia	<5	15	11	28	<5	<5	<5	<5	5	0	<5
Lymphoid leukemia	<5	6	<5	8	0	0	<5	<5	<5	0	0
Myeloid leukemia	<5	9	8	20	<5	<5	<5	<5	<5	0	<5
Other leukemia	0	<5	0	<5	0	0	<5	0	<5	0	0
Multiple myeloma	<5	<5	<5	<5	0	0	<5	<5	<5	0	<5
Lymphoma	<5	18	21	62	5	<5	<5	<5	8	<5	<5
Hodgkin's	0	7	9	22	<5	<5	0	<5	<5	<5	0
Non-Hodgkin's	<5	12	12	40	<5	<5	<5	<5	7	<5	<5
Other hemopoietic	<5	<5	5	12	<5	<5	<5	<5	7	0	<5
Other or ill-defined	<5	14	8	43	<5	<5	<5	6	10	<5	8
Any cancer	121	592	510	1596	122	65	77	202	305	22	198