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Gestational risk factors and childhood cancers: a cohort study in Taiwan

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Novelty and Impact: There are few epidemiologic studies of childhood cancers from Asian countries. Taiwan has unique risk factors, including a low prevalence of high birth weight by international standards, which may impact associations with cancer. Here we observed variation in associations with some fetal growth metrics in relation to childhood cancer risk compared to studies in Western countries, providing insights into causes and risk factors of childhood cancer in Taiwan.

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Abbreviations:

ALL	Acute Lymphoblastic Leukemia
AML	Acute Myeloid Leukemia
CI	Confidence Interval
CNS	Central Nervous System
HR	Hazard Ratio
ICCC	International Classification of Childhood Cancer
ICD	International Classification of Diseases
NHL	Non-Hodgkin Lymphoma

Abstract

Gestational risk factors such as birth weight, gestational age, and parity have been repeatedly found to be related to pediatric cancers, but few reports have emerged from Asian countries. Here we report on demographic and gestational factors in a Taiwanese cohort. This study included all children born in Taiwan 2004-2014 for whom there was a birth record (N=2 079 037), of which 1900 children had been diagnosed with cancer prior to age 12. We conducted multivariable hazard regression to examine associations between demographic and gestational factors with cancer. Greater parity (family with 2+ older children) was related to acute myeloid leukemia [Hazard ratio (HR)=2.15, 95% confidence interval (CI): 1.31, 3.55], central nervous system tumors (HR=1.67, CI: 1.13, 2.48) and neuroblastoma (HR=1.67, CI: 1.07, 2.63). Hepatoblastoma cases had a higher risk of low birth weight (<2500g; HR=3.01, CI: 1.85, 4.91), very preterm birth (<33 weeks gestation; HR=13.71, CI: 7.45, 25.23), plural pregnancies (HR=2.37, CI: 1.10, 5.14), and both small (HR=2.13, CI: 1.23, 3.67) and large (HR=1.83, CI: 1.01, 3.32) for gestational age. Germ cell tumors were more common among children born in rural areas (HR=1.63, CI: 1.02, 2.60). Despite that Taiwan has lower rates of both high and low birthweight compared to other developed nations, we observed several similar associations to those reported in Western Countries. Further research should examine unique exposures in Taiwan that may be contributing to higher incidence of certain cancer types.

Introduction

In Taiwan, cancer is the second leading cause of death among children younger than 15 years, and a consistent increase in the incidence of most types of childhood cancer was observed from 1980 to 2006.¹ While this is likely due in part to increased healthcare utilization after the initiation of a National Health Insurance program in 1995 as well as improvements in cancer reporting,² it is also possible that environmental factors may be in part responsible. The incidence of childhood hepatic and germ cell tumors is higher than that reported in other developed nations, while the incidence of lymphomas, renal tumors, and central nervous system cancers is lower.²

Studies of pediatric cancers have suggested associations with a number of perinatal characteristics. Cancers have been related to both low (<2500g) birth weight [hepatoblastoma, acute myeloid leukemia (AML), neuroblastoma] and high (4000g+) birth weight [acute lymphoblastic leukemia (ALL), AML, medulloblastoma, neuroblastoma].³⁻⁷ The prevalence of high birth weight in Taiwan is low by international standards (1.96% of births in 2004-2011),⁸ which raises the question as to whether these risk factors are as important predictors of cancer in this population. Other gestational risk factors have been linked to childhood cancers, including preterm birth, small or large size for gestational age, parity, family size, and/or birth order, or multiple birth pregnancies,^{7, 9-19} the latter of which may be in part due to the use of assisted reproduction technologies.^{7, 20}

Taiwan has unique risk cancer factors, including much higher male than female smoking,²¹ the use of betel quid, particularly in aboriginal communities,²² endemic hepatitis (decreasing over time due to prevention and education efforts),²³ and lower overweight and obesity among women of childbearing age as compared

with Western nations.²⁴ Despite varying cancer incidence in Asian nations compared with the West,² there are only a small number of epidemiologic studies from Asian countries examining gestational factors and childhood cancer (a selection is cited here²⁵⁻²⁹). The goal of this study is to examine pediatric cancer risk associated with gestational characteristics, and is, to the best of our knowledge, among the first papers on this topic from an Asian country to use a nationwide cohort.

Methods

This population-based cohort study retrospectively included all live births in Taiwan from January 1, 2004 to December 31, 2014. We used several population-based data sources in Taiwan to obtain data for this study. The Taiwan Maternal and Child Health Database (data available for births 2004-2014) links parents to their children, and it additionally links to the Taiwanese Birth Registry, the Death Registry, and the Registry for Beneficiaries of the National Health Insurance Program.³⁰

In Taiwan, the National Health Insurance Program began operations in March 1995 and it covers 99.9% of residents, including both citizens and non-citizens.³¹ According to Taiwanese law, hospitals or clinics are obligated to report a birth, including all relevant pregnancy, labor, and birth information, to the local health department within 10 days of a baby's delivery. The Birth Registry data on each pregnancy and delivery is completed by obstetricians, and information for the newborn is filled out by pediatricians. Validation studies have reported a strong concordance with birth records, for example birth weight and birth order had 94% agreement with the medical record.³² We retrieved demographic and gestational information from the Taiwan Birth Registry files.

We included all children born in Taiwan during the time period of interest that are listed in the Maternal and Child Health database, that is, children for whom a birth registry record could be identified and who could be linked to their parents. A flowchart illustrating patient inclusion is shown in Figure 1. Children were linked to their birth parents, regardless of whether they are later adopted. We excluded children with missing data on maternal ID (N=1057, 0.05%), age at cancer diagnosis (N=32, 0.001%), and those with missing (N=91,639, 4.2%) or duplicate (N=28, 0.001%) registration records. Using the linked databases, we identified 2 079 037 eligible children born between 2004 and 2014 and their parent IDs. Cancer incidence by tumor type, sex, and age are shown in Supplementary Table 1.

We linked this database with the Taiwan Cancer Registry (established 1979; diagnoses available through 2016). The Registry classifies tumors according to the International Classification of Diseases (ICD-9) and the International Classification of Diseases for Oncology, Version 3 (ICD-O-3). For this study we have additionally converted diagnoses into the International Classification of Childhood Cancer (ICCC-3). Approvals for this study were received from the Institutional Review Board of the Taipei City Hospital, Taiwan, and the University of California, Los Angeles.

Size for gestational age was categorized into lowest 10% percentile, middle 80% percentile, and highest 10% percentile of the sex-specific birth weight standards for a given gestational age by using a method previously described.³³ Urbanization level at birth was categorized into high, moderate, and low level, based on the classification scheme proposed by Liu. Parental cancer history was defined as ever diagnosed with cancer between the establishment of the Cancer Registry in 1979 until the end of 2014; parental cancer diagnoses were obtained from the cancer registry. Monthly household income was categorized into quartiles

(<NT\$40,680, 40680-55199, 55200-79399, and $\geq$ 79400); these estimates were based on health insurance costs, as insurance cost per family is dependent on family income. As we could not ascertain marital status or living arrangements, the mother's and father's incomes were combined whether or not the family lived together. When children were missing data for a father's ID, the income was defined as missing.

Here we report on cancer types for which there were at least 100 cases. We conducted multivariable Cox proportional hazard analysis to examine associations between demographic and gestational factors with cancer. Selection of covariates for adjustment was based on the literature^{10, 34, 35} as well as associations observed in our data. Final models adjusted for mother's age, father's age, family income, and the urbanization level of residence at birth. We examined the correlation between maternal and paternal age to consider issues of collinearity, but found agreement between parents' ages to be low to moderate ($\kappa=0.42$). All analyses were performed with SAS 9.4 (SAS Institute, Cary, US). We additionally stratified analyses by child sex and age.

This study was approved by human subjects protection boards of the Taipei City Hospital Research Ethics Committee and the University of California, Los Angeles.

Data Availability. The data that support the findings of this study are available from the Taiwan National Health Insurance Database.³¹ Restrictions apply to the availability of these data, which were used under license for this study. The National Health Insurance Database restricts use of their data to Taiwanese citizens.

Results

Parental demographic characteristics for cases and non-cases are shown in Table 1. For non-Hodgkin Lymphoma (NHL), retinoblastoma, and neuroblastoma, a slightly larger proportion of parents were older than 40 years. Maternal history of cancer was more common for children with AML, retinoblastoma, hepatoblastoma, and germ cell tumors. With regards to maternal foreign-born status, an examination of the country of birth of the mothers of cancer cases born outside Taiwan showed the largest proportion were born in China (53%) followed by Vietnam (32%), with small numbers from other nations.

Child and gestational characteristics are shown in Table 2. Both lower and higher birth weights were more common in several types of cancer, as were both large and small for gestational age. Plural pregnancies and greater parity were more common in several of the cancers.

Associations with parental characteristics using crude and multivariable Cox proportional regression are shown in Table 3. Several cancer types had a higher effect estimate with either having either a teenage or older (40 years+) parents. Central nervous system (CNS) tumors more often occurred among children residing in suburban locations, while hepatoblastoma and germ cell tumors were more common among families residing in rural areas. We observed little to no associations between cancer incidence and family socioeconomic status after adjustment for demographic factors.

Regression results for child and gestational characteristics are shown in Table 4. Hepatoblastoma was more common in children born very low birth weight, preterm birth, small and large size for gestational age, Cesarean section birth, and for plural pregnancies. Stratification by birth weight indicated that the relation with plural pregnancies was not explained by birthweight: among children of low

birthweight (<2500g), the risk of hepatoblastoma (adjusted HR=1.37, 95% CI 0.47-4.01) was similar to that among children of normal birthweight (2500-3999g; adjusted HR=1.67, 95% CI 0.41-6.83). For low birth weight, we observed a decreased risk for ALL (adjusted HR=0.61, 95% CI 0.39-0.94) and an increased risk with retinoblastoma. CNS tumors, neuroblastoma, and germ cell tumors were more likely to be born to mothers with higher parity.

Comments

This is among the first nationwide studies in an Asian population to describe pediatric cancer risk in relation to demographic and gestational factors. The younger age of the children in this study (ages ≤ 11 years at diagnosis) was likely to impact our results, as cancers diagnosed at earlier ages may reasonably be expected to have a stronger relationship to perinatal factors. For several cancer types, sample sizes were small leading to wide confidence intervals. As other studies have reported, we observed little to no associations between cancers and family socioeconomic status after adjustment for demographic factors.³⁶

In Taiwan, the incidence of childhood cancers has been steadily increasing across the last four decades. This is in part due to increased reporting in the years after the Cancer Registry began in 1979, improved access to care after the National Health Insurance plan after its initiation in 1995, and in 2002, changing cancer classifications.^{1, 2} Yet the incidence of childhood hematopoietic, some CNS cancers, germ cell tumors, retinoblastoma, and hepatoblastoma have continued to increase since 2002.³⁷⁻⁴⁰ Concurrent trends in Taiwan which may possibly be related to pediatric cancer risk include increasing maternal age, decreasing proportions of

foreign-born mothers, and increasing prevalence of pregnancy anemia, diabetes mellitus, and hypertension.⁴¹

Our findings with regards to gestational factors are mostly in line with reports from other nations, with notable exceptions. In contrast to most other studies which have shown a null relation between ALL and low birth weight, we observed a decreased risk for birth weight <2500g.³ Yet low birth weight and very low birth weight (<1500g) increased in Taiwan across the study period, at the same time that ALL incidence has been rising,¹ suggesting no causal relationship. Both trends however have been attributed to increasing parental age and increased use of assisted reproduction technologies.^{8, 42} With regards to risk of cancer with high birth weight, we observed similar point estimates as reported in a previous meta-analysis of ALL and AML.³ Even though our sample size was too small to allow stratification by CNS tumor subtype, our point estimate for risk with high birth weight was higher than what has been reported for astrocytoma and medulloblastoma.⁵ In our population there were no increased risks for neuroblastoma with both high and low birth weight in contrast to was reported in a meta-analysis.⁶ In addition, small size for gestational age has not been reported as a risk factor for CNS tumors,^{12, 13, 43} although other altered fetal growth metrics have been associated with brain tumor risk.^{44, 45}

As we observed, greater parity was previously reported to increase risk for neuroblastoma and some types of CNS tumors.¹⁴ Associations between pediatric cancers and parity have been attributed to increased risk of infectious conditions from having older siblings, or alternatively, variation in hormone levels between first and subsequent pregnancies.⁴⁶ Further, second-born and subsequent babies have higher birth weights than first-borns perhaps due to pregnancy-induced uterine

vascular remodeling leading to increased placental size in second pregnancies,⁴⁷ and placenta size may also predict risk of some pediatric cancers.⁴⁸

Increased risk for ALL was seen with Cesarean section birth, although records did not allow us to determine the type of Cesarean (planned or emergency). This association was previously reported with prelabor Cesarean delivery,⁴⁹ with the hypothesis that the elevated cortisol levels which occur with labor may eliminate preleukemic and leukemic cells (the “adrenal hypothesis”⁵⁰). Alternatively, microbiome variation related to vaginal delivery may impact healthy immune system development.⁵¹

We observed a higher incidence of germ cell tumors in rural areas. An earlier analysis of germ cell tumors diagnosed to 2009 reported a particularly high incidence in Hualien County, a rural area on the eastern coast.³⁹ Hualien County has among the highest proportion of indigenous residents of any county in Taiwan (27% of residents, vs 2% nationwide). Indigenous women in Taiwan have a higher prevalence of smoking, alcohol consumption, and betel nut chewing compared with Chinese Taiwanese women.⁵² While evidence has not been convincing for any association between maternal smoking and germ cell tumors, research on alcohol and betel consumption is very limited.^{53, 54}

As with studies of other rare diseases, we are limited by sample size for some cancer types. We lacked information on some lifestyle factors unavailable on national records which might be associated with some cancer types, such as breastfeeding and paternal smoking, which might be associated with some cancers.⁵⁵ However, there are few established causes of childhood cancers, limiting potential uncontrolled confounding. A further limitation was the multiple comparisons, however most associations observed in this study support those

previously reported in the literature. Strengths of the study include its population-based nature and nationwide scope, and the reliance on objective, prospectively collected data, with no concerns for recall or participation biases.

In this large cohort of Taiwanese children, in which high birth weight is rare and maternal smoking prevalence in pregnancy was expected to be low,²¹ we observed similar associations to what other studies have reported with a number of gestational factors. Our study provides further evidence that determinants of tumorigenesis arise in the perinatal period, suggesting that the promotion of healthy pregnancies and labor and delivery, including promotion of vaginal birth over Cesarean, may decrease offspring cancer risk.⁴⁹ The associations with parity suggest possible relations with infectious or hormonal factors. Our observations continue to support the role of the perinatal period in childhood cancer. Further studies should investigate the risk factors unique to Taiwan to examine associations with cancer risk.

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Authors have no conflict of interest to report.

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Table 1: Parental characteristics of study cohort subjects and cancer cases in Taiwan, 2004-2014

	Non-cases (N=2,077,137) N (%)	ALL (N=527) N (%)	AML (N=137) N (%)	NHL (N=346) N (%)	CNS tumors (N=260) N (%)	Neuroblastoma (N=207) N (%)	Retinoblastoma (N=119) N (%)	Hepatoblastoma (N=105) N (%)	Germ cell tumors (N=183) N (%)
Mother's age at child's birth (years)									
Mean (SD)	30.2 (4.8)	29.6 (4.9)	29.9 (4.5)	30.1 (4.9)	29.5 (5.0)	30.4 (4.9)	30.9 (4.6)	31.1 (4.9)	30.0 (4.7)
<20	31,047 (1.5)	11 (2.1)	a	6 (1.7)	7 (2.7)	3 (1.4)	a	a	3 (1.6)
20-29	863,730 (41.6)	253 (48.0)	62 (45.3)	156 (45.1)	119 (45.8)	87 (42.0)	43 (36.1)	40 (38.1)	77 (42.1)
30-34	798,102 (38.4)	182 (34.5)	57 (41.6)	121 (35.0)	93 (35.8)	77 (37.2)	53 (44.5)	39 (37.1)	74 (40.4)
35-39	331,330 (16.0)	65 (12.3)	14 (10.2)	50 (14.5)	35 (13.5)	32 (15.5)	18 (15.1)	23 (21.9)	25 (13.7)
40+	52,928 (2.5)	16 (3.0)	4 (2.9)	13 (3.8)	6 (2.3)	8 (3.9)	5 (4.2)	3 (2.9)	4 (2.2)
Maternal history of cancer, up to 2014									
Yes	27,012 (1.3)	5 (1.0)	3 (2.2)	b	3 (1.2)	b	3 (2.5)	3 (2.9)	8 (4.4)
Father's age at child's birth (years)									
Mean (SD)	33.3 (5.3)	32.6 (5.4)	33.5 (5.3)	33.2 (5.3)	32.7 (5.1)	33.7 (4.6)	34.1 (5.5)	33.5 (5.8)	32.9 (5.6)
<20	3,485 (0.2)	a	0 (0.0)	a	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
20-29	454,416 (23.3)	133 (27.0)	26 (20.0)	80 (24.8)	69 (29.0)	40 (20.6)	22 (19.6)	26 (26.5)	47 (28.0)
30-34	760,729 (39.0)	204 (41.5)	54 (41.5)	128 (39.6)	80 (33.6)	79 (40.7)	46 (41.1)	33 (33.7)	68 (40.5)
35-39	511,778 (26.2)	104 (21.1)	37 (28.5)	75 (23.2)	65 (27.3)	51 (26.3)	28 (25.0)	25 (25.5)	32 (19.0)
40+	220,433 (11.3)	51 (10.4)	13 (10.0)	40 (12.4)	24 (10.1)	24 (12.4)	16 (14.3)	14 (14.3)	21 (12.5)
Missing	126,296	35	7	23	22	13	7	7	15
Paternal history of cancer, up to 2014									
Yes	19,744 (1.0)	4 (0.8)	b	4 (1.2)	b	b	b	0 (0.0)	3 (1.6)
Family Income, yearly									
<40680	492,431 (24.7)	141 (28.0)	34 (26.2)	82 (24.8)	73 (29.6)	50 (25.3)	26 (22.6)	24 (24.0)	47 (26.9)
40680-55200	500,894 (25.1)	142 (28.2)	34 (26.2)	97 (29.4)	66 (26.7)	49 (24.7)	33 (28.7)	22 (22.0)	56 (32.0)
55200-79400	502,068 (25.2)	106 (21.1)	27 (20.8)	75 (22.7)	63 (25.5)	54 (27.3)	27 (23.5)	24 (24.0)	34 (19.4)

≥79400	499,447 (25)	114 (22.7)	35 (26.9)	76 (23.0)	45 (18.2)	45 (22.7)	29 (25.2)	30 (30.0)	38 (21.7)
Missing	82,297	24	7	16	13	9	4	5	8
Mother's birthplace									
Taiwan	1,400,687 (91.4)	296 (90.8)	72 (81.8)	205 (91.9)	142 (89.3)	134 (90.5)	78 (89.7)	64 (95.5)	106 (87.6)
Foreign born	132,186 (8.6)	30 (9.2)	16 (18.2)	18 (8.1)	17 (10.7)	14 (9.5)	9 (10.3)	3 (4.5)	15 (12.4)
Missing	544,264	201	49	123	101	59	32	38	62
Urbanization level of inhabited area									
High	1,102,804 (53.1)	273 (51.8)	74 (54.0)	176 (50.9)	117 (45.0)	115 (55.6)	61 (51.3)	47 (44.8)	90 (49.2)
Middle	781,704 (37.6)	212 (40.2)	54 (39.4)	144 (41.6)	118 (45.4)	77 (37.2)	48 (40.3)	44 (41.9)	67 (36.6)
Low	192,629 (9.3)	42 (8.0)	9 (6.6)	26 (7.5)	25 (9.6)	15 (7.2)	10 (8.4)	14 (13.3)	26 (14.2)

a: The exact number is below 3, thus we combined the number into the adjacent cell.

b: The exact number below 3 is not specified, in accordance with Taiwanese privacy regulations.

Table 2: Child and gestational characteristics of case and non-case children in Taiwan, 2004-2014

	Non-cases	ALL	AML	NHL	CNS tumors	Neuroblastoma	Retinoblastoma	Hepatoblastoma	Germ cell tumors
	N=2,077,137	(N=527)	(N=137)	(N=346)	(N=260)	(N=207)	(N=119)	(N=105)	(N=183)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Sex									
Male	1,079,206 (52.0)	285 (54.1)	73 (53.3)	188 (54.3)	140 (53.8)	124 (59.9)	67 (56.3)	62 (59.0)	99 (54.1)
Female	997,831 (48.0)	242 (45.9)	64 (46.7)	158 (45.7)	120 (46.2)	83 (40.1)	52 (43.7)	43 (41.0)	84 (45.9)
Missing	100	0	0	0	0	0	0	0	0
Birth weight (g)									
Mean(SD)	3,078.1(449.6)	3,117.5(415.7)	3,032.3(454.8)	3,094.0(447.7)	3,059.0(487.0)	3,099.6(432.1)	3,077.2(455.3)	2,863.6(829.5)	3,080.6(423.7)
<2500	156,549(7.5)	25(4.7)	16(11.7)	21(6.1)	25(9.6)	12(5.8)	14(11.8)	20(19.1)	12(6.6)
2500-3999	1,882,903(90.7)	490(93.0)	117(85.4)	319(92.2)	226 (86.9)	192(82.8)	101 (84.9)	82 (78.1)	168 (91.8)
≥4000	37,685 (1.8)	12 (2.3)	4 (2.9)	6 (1.7)	9 (3.5)	3(1.5)	4 (3.4)	3 (2.9)	3 (1.6)
Gestational age (weeks)									
Mean(SD)	38.3 (1.7)	38.3 (1.7)	38.2 (1.7)	38.2 (1.8)	38.2 (1.5)	38.3 (1.5)	38.2 (1.6)	36.9 (3.8)	38.1 (1.9)
Very preterm(<33)	23,060 (1.1)	5 (1.0)	a	7 (2.0)	a	a	0 (0.0)	15 (14.3)	5 (2.7)
Preterm(33-36)	160,465 (7.7)	43 (8.2)	19 (13.9)	28 (8.1)	24 (9.2)	18 (8.7)	13 (10.9)	8 (7.6)	18 (9.8)
Term(≥37)	1,893,612 (91.2)	479 (90.9)	118 (86.1)	311 (89.9)	236 (90.8)	189 (91.3)	106 (89.1)	82 (78.1)	160 (87.4)
Size for gestational age									
Lowest 10%	196,012(9.4)	35(6.6)	13 (9.5)	25(7.2)	34(13.1)	16(7.7)	12 (10.1)	17(16.2)	13(7.1)
Middle 80%	1,712,616(82.5)	438(83.1)	115 (83.9)	293(84.7)	202(77.7)	175(84.5)	99 (83.2)	74(70.5)	152(83.1)
Highest 10%	168,509(8.1)	54(10.3)	9 (6.6)	28 (8.1)	24 (9.2)	16(7.7)	8 (6.7)	14 (13.3)	18 (9.8)
Method of delivery									
Vaginal	1332153 (64.1)	324 (61.5)	93 (67.9)	212 (61.3)	176 (67.7)	136 (65.7)	74 (62.2)	54 (51.4)	104 (56.8)
Cesarean section	744984 (35.9)	203 (38.5)	44 (32.1)	134 (38.7)	84 (32.3)	71 (34.3)	45 (37.8)	51 (48.6)	79 (43.2)
Multiple birth									
Singleton	2,015,286 (97.0)	513 (97.3)	134 (97.8)	335 (96.8)	253 (97.3)	201 (97.1)	b	98 (93.3)	176 (96.2)
Twin or more	61,851 (3.0)	14 (2.7)	3 (2.2)	11 (3.2)	7 (2.7)	6 (2.9)	b	7 (6.7)	7 (3.8)
Parity									
1	807,623 (38.9)	197 (37.4)	51 (37.2)	126 (36.4)	96 (36.9)	71 (34.3)	43 (36.1)	44 (41.9)	63 (34.4)
2	1,044,150 (50.3)	258 (49.0)	61 (44.5)	174 (50.3)	116 (44.6)	107 (51.7)	60 (50.4)	46 (43.8)	94 (51.4)

3 or more	225,364 (10.9)	72 (13.7)	25 (18.3)	46 (13.3)	48 (18.5)	29 (14.0)	16 (13.4)	15 (14.3)	26 (14.2)
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a: The exact number is below 3 and we combined the number into the adjacent cell.

b: The exact number below 3 is not specified, in accordance with Taiwanese privacy regulations.

Table 3: Hazard ratios and 95% confidence intervals showing relation between parental characteristics and cancers

	ALL		AML		NHL		CNS tumors	
	Crude HR [95%CI]	Adjusted HR [95%CI] ^a	Crude HR [95%CI]	Adjusted HR [95%CI] ^a	Crude HR [95%CI]	Adjusted HR [95%CI] ^a	Crude HR [95%CI]	Adjusted HR [95%CI] ^a
Mother's age [years]								
<20	1.19(0.65-2.17)	1.34(0.61-2.95)	0.45(0.06-3.26)	□	1.04(0.46-2.35)	0.84(0.24-2.95)	1.59(0.74-3.41)	0.41(0.06-2.91)
20-29	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
30-34	0.91(0.75-1.10)	0.92(0.74-1.16)	1.11(0.78-1.60)	0.91(0.60-1.39)	1.01(0.80-1.29)	1.01(0.76-1.34)	1.00(0.76-1.31)	1.16(0.84-1.61)
35-39	0.86(0.65-1.13)	0.89(0.63-1.25)	0.70(0.39-1.25)	0.47(0.23-0.94)	1.12(0.82-1.54)	1.07(0.71-1.60)	0.99(0.68-1.44)	0.95(0.59-1.55)
40+	1.36(0.82-2.25)	1.54(0.85-2.78)	1.26(0.46-3.47)	0.81(0.23-2.88)	1.87(1.06-3.30)	1.83(0.93-3.61)	1.08(0.48-2.45)	0.87(0.30-2.55)
With each 1-year increase	1.00(0.98-1.01)	1.00(0.98-1.03)	1.00(0.96-1.03)	0.96(0.92-1.01)	1.02(1.00-1.04)	1.02(0.99-1.06)	0.99(0.97-1.02)	1.00(0.96-1.03)
Maternal history of cancer, up to 2014								
Yes	0.61(0.25-1.47)	0.53(0.20-1.43)	1.52(0.48-4.77)	1.67(0.53-5.26)	0.36(0.09-1.44)	0.37(0.09-1.50)	0.74(0.24-2.03)	0.83(0.27-2.59)
Father's age [years]								
<20	1.03(0.14-7.36)	0.83(0.11-6.47)	□	□	1.72(0.24-12.35)	2.03(0.24-17.42)	□	□
20-29	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
30-34	1.03(0.82-1.28)	1.09(0.85-1.38)	1.32(0.83-2.11)	1.36(0.82-2.26)	1.10(0.83-1.46)	1.08(0.79-1.48)	0.77(0.56-1.07)	0.76(0.53-1.09)
35-39	0.82(0.64-1.07)	0.89(0.66-1.20)	1.40(0.85-2.31)	1.67(0.94-2.98)	1.02(0.75-1.40)	0.99(0.68-1.44)	0.99(0.71-1.39)	1.02(0.68-1.54)
40+	0.97(0.70-1.33)	0.96(0.65-1.41)	1.16(0.60-2.26)	1.50(0.70-3.20)	1.31(0.90-1.92)	1.16(0.73-1.85)	0.87(0.55-1.39)	0.95(0.55-1.64)
With each 1-year increase	0.99(0.97-1.01)	0.99(0.97-1.01)	1.02(0.99-1.05)	1.03(1.00-1.07)	1.01(0.99-1.03)	1.01(0.98-1.03)	0.99(0.97-1.02)	0.99(0.96-1.02)
Paternal history of cancer, up to 2014								
Yes	0.66(0.25-1.76)	0.69(0.26-1.85)	0.68(0.10-4.83)	0.66(0.09-4.76)	0.97(0.36-2.59)	0.98(0.37-2.64)	0.66(0.16-2.65)	0.68(0.17-2.76)
Family income, yearly								
<40680	1.00(0.78-1.28)	0.96(0.73-1.25)	0.85(0.53-1.37)	0.93(0.56-1.54)	0.83(0.61-1.14)	0.84(0.60-1.18)	1.30(0.89-1.88)	1.16(0.77-1.74)
40680-55200	1.15(0.90-1.48)	1.12(0.86-1.45)	0.93(0.58-1.48)	0.97(0.59-1.59)	1.17(0.87-1.58)	1.22(0.89-1.68)	1.37(0.94-2.00)	1.30(0.87-1.94)
55200-79400	0.86(0.66-1.12)	0.82(0.63-1.08)	0.73(0.44-1.21)	0.73(0.44-1.21)	0.90(0.65-1.23)	0.91(0.66-1.27)	1.29(0.88-1.89)	1.26(0.85-1.86)

≥79400	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Mother's birthplace								
Taiwan born	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Foreign born	0.88(0.61-1.29)	0.84(0.55-1.28)	2.11(1.23-3.63)	2.07(1.07-4.00)	0.74(0.46-1.20)	0.79(0.46-1.35)	1.04(0.63-1.72)	0.99(0.56-1.77)
Urbanization level of inhabited area								
High	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Middle	1.08(0.90-1.29)	1.06(0.87-1.28)	1.02(0.72-1.45)	1.03(0.72-1.49)	1.13(0.91-1.41)	1.14(0.90-1.43)	1.40(1.08-1.80)	1.39(1.06-1.82)
Low	0.83(0.60-1.15)	0.77(0.54-1.09)	0.67(0.34-1.34)	0.74(0.37-1.50)	0.79(0.52-1.19)	0.71(0.45-1.12)	1.15(0.75-1.77)	1.11(0.70-1.78)

^a Models adjust for mother's age, father's age, family income, and urbanization level of residence at birth. The adjusted model not shown when the N of exposed cases in a category is <5.

Mother's birthplace								
Taiwan born	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Foreign born	1.01(0.58-1.76)	0.92(0.49-1.71)	1.13(0.57-2.25)	1.33(0.59-3.01)	0.46(0.14-1.46)	0.51(0.15-1.77)	1.33(0.78-2.29)	1.49(0.78-2.83)
Urbanization level of inhabited area								
High	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Middle	0.94(0.70-1.25)	0.96(0.71-1.30)	1.10(0.75-1.61)	1.16(0.78-1.71)	1.31(0.87-1.98)	1.37(0.88-2.11)	1.04(0.76-1.42)	1.07(0.77-1.50)
Low	0.73(0.42-1.24)	0.70(0.39-1.26)	0.92(0.47-1.79)	0.62(0.26-1.45)	1.67(0.92-3.03)	1.90(1.00-3.59)	1.59(1.03-2.46)	1.63(1.02-2.60)

^a Models adjust for mother's age, father's age, family income, and urbanization level of residence at birth. The adjusted model not shown when the N of exposed cases in a category is <5.

Table 4: Hazard ratios and 95% confidence intervals showing relation between child and gestational characteristics and cancers

	ALL		AML		NHL		CNS tumors	
	Crude HR [95%CI]	Adjusted HR [95%CI] ^a	Crude HR [95%CI]	Adjusted HR [95%CI] ^a	Crude HR [95%CI]	Adjusted HR [95%CI] ^a	Crude HR [95%CI]	Adjusted HR [95%CI] ^a
Sex								
Female	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Male	1.08(0.91- 1.29)	1.07(0.90- 1.28)	1.05(0.75- 1.47)	1.11(0.79- 1.57)	1.09(0.88- 1.35)	1.10(0.88- 1.37)	1.07(0.84- 1.37)	1.09(0.84- 1.40)
Birth weight [g]								
<2500	0.64(0.43- 0.96)	0.61(0.39- 0.94)	1.70(1.01- 2.87)	1.79(1.05- 3.07)	0.84(0.54- 1.30)	0.75(0.46- 1.23)	1.40(0.92- 2.11)	1.26(0.80- 1.99)
2500-3999	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
≥4000	1.13(0.64- 2.00)	1.21(0.68- 2.15)	1.62(0.60- 4.39)	1.71(0.63- 4.63)	0.85(0.38- 1.91)	0.88(0.39- 1.98)	1.83(0.94- 3.56)	1.73(0.85- 3.51)
Gestational age [weeks]								
Very preterm [<33]	0.94(0.39- 2.27)	0.66(0.21- 2.04)	0.75(0.11- 5.38)	0.87(0.12- 6.26)	2.04(0.96- 4.31)	1.31(0.49- 3.50)	0.76(0.19- 3.06)	0.90(0.22- 3.61)
Preterm [33-36]	1.07(0.78- 1.46)	1.13(0.82- 1.56)	1.81(1.10- 2.97)	1.89(1.14- 3.15)	1.07(0.73- 1.58)	1.08(0.73- 1.62)	1.11(0.72- 1.72)	1.13(0.72- 1.79)
Term [≥37]	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Size for gestational age								
Lowest 10%	0.71(0.50- 1.00)	0.69(0.48- 1.00)	1.00(0.56- 1.77)	1.01(0.56- 1.83)	0.76(0.50- 1.14)	0.71(0.46- 1.11)	1.49(1.03- 2.14)	1.54(1.05- 2.26)
Middle 80%	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Highest 10%	1.20(0.90- 1.59)	1.27(0.96- 1.70)	0.77(0.39- 1.52)	0.72(0.35- 1.47)	0.92(0.63- 1.36)	0.96(0.65- 1.42)	1.15(0.76- 1.76)	1.20(0.78- 1.85)
Method of delivery								
Vaginal	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Cesarean section	1.14(0.96- 1.36)	1.18(0.98- 1.42)	0.86(0.60- 1.22)	0.79(0.54- 1.15)	1.16(0.93- 1.43)	1.16(0.93- 1.46)	0.87(0.67- 1.13)	0.94(0.72- 1.24)
Multiple birth								
Singleton	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Twin or more	0.94(0.55- 1.60)	1.00(0.59- 1.70)	0.75(0.24- 2.37)	0.77(0.25- 2.43)	1.14(0.62- 2.08)	1.17(0.64- 2.13)	0.95(0.45- 2.02)	1.02(0.48- 2.17)
Parity								
1	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
2	1.06(0.88- 1.28)	1.03(0.84- 1.25)	0.94(0.65- 1.36)	1.01(0.68- 1.50)	1.17(0.93- 1.48)	1.22(0.95- 1.56)	1.03(0.78- 1.35)	1.01(0.76- 1.35)
3 or more	1.33(1.02- 1.75)	1.26(0.94- 1.69)	1.76(1.09- 2.84)	2.15(1.31- 3.55)	1.39(0.99- 1.95)	1.50(1.04- 2.17)	1.92(1.36- 2.72)	1.67(1.13- 2.48)

^a Models adjust for mother's age, father's age, family income, and urbanization level of residence at birth. The adjusted model not shown when the N of exposed cases in a category is <5.

Table 4 [cont.]: Hazard ratios and 95% confidence intervals showing relation between child and gestational characteristics and cancers

	Neuroblastoma		Retinoblastoma		Hepatoblastoma		Germ cell tumors	
	Crude HR [95%CI]	Adjusted HR [95%CI] ^a	Crude HR [95%CI]	Adjusted HR [95%CI] ^a	Crude HR [95%CI]	Adjusted HR [95%CI] ^a	Crude HR [95%CI]	Adjusted HR [95%CI] ^a
Sex								
Female	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Male	1.38(1.04-1.82)	1.37(1.03-1.83)	1.19(0.83-1.71)	1.32(0.91-1.93)	1.33(0.90-1.96)	1.46(0.97-2.19)	1.09(0.81-1.45)	1.04(0.77-1.40)
Birth weight [g]								
<2500	0.77(0.43-1.39)	0.79(0.42-1.45)	1.72(0.98-3.00)	1.77(0.99-3.15)	3.01(1.85-4.91)	2.56(1.50-4.39)	0.89(0.49-1.59)	0.84(0.44-1.59)
2500-3999	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
≥4000	0.75(0.24-2.34)	0.77(0.25-2.42)	1.91(0.70-5.18)	1.95(0.72-5.30)	1.77(0.56-5.59)	1.81(0.57-5.74)	0.85(0.27-2.65)	0.91(0.29-2.85)
Gestational age [weeks]								
Very preterm [<33]	0.94(0.23-3.76)	1.05(0.26-4.22)	□	□	16.13(9.30-27.96)	13.71(7.45-25.23)	2.76(1.13-6.72)	3.20(1.31-7.80)
Preterm [33-36]	1.00(0.60-1.67)	1.10(0.66-1.83)	1.45(0.82-2.58)	1.44(0.79-2.63)	1.16(0.56-2.39)	0.89(0.39-2.05)	1.33(0.82-2.17)	1.24(0.73-2.10)
Term [≥37]	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Size for gestational age								
Lowest 10%	0.81(0.48-1.35)	0.79(0.46-1.36)	1.07(0.59-1.95)	1.11(0.59-2.07)	2.02(1.19-3.43)	2.13(1.23-3.67)	0.75(0.43-1.33)	0.85(0.48-1.51)
Middle 80%	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Highest 10%	0.91(0.54-1.52)	0.94(0.56-1.57)	0.81(0.39-1.65)	0.82(0.40-1.70)	1.89(1.07-3.34)	1.83(1.01-3.32)	1.17(0.72-1.91)	1.21(0.73-2.00)
Method of delivery								
Vaginal	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Cesarean section	0.94(0.71-1.25)	0.90(0.67-1.21)	1.09(0.76-1.58)	1.08(0.73-1.58)	1.70(1.16-2.49)	1.70(1.14-2.54)	1.37(1.03-1.84)	1.33(0.98-1.81)
Multiple birth								
Singleton	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
Twin or more	1.00(0.44-2.25)	1.02(0.45-2.30)	0.57(0.14-2.31)	0.57(0.14-2.30)	2.38(1.11-5.13)	2.37(1.10-5.14)	1.34(0.63-2.85)	1.02(0.42-2.47)
Parity								
1	Reference	Reference	Reference	Reference	Reference	Reference	Reference	Reference
2	1.15(0.85-1.55)	1.18(0.86-1.63)	1.04(0.70-1.54)	1.13(0.74-1.71)	0.79(0.52-1.19)	0.83(0.53-1.28)	1.20(0.87-1.66)	1.28(0.91-1.81)
3 or more	1.43(0.93-2.20)	1.67(1.07-2.63)	1.28(0.72-2.27)	1.51(0.83-2.78)	1.19(0.66-2.13)	1.14(0.60-2.16)	1.52(0.97-2.41)	1.53(0.93-2.52)

^a Models adjust for mother's age, father's age, family income, and urbanization level of residence at birth. Results not shown when the N of exposed cases in a category is <5.

Figure 1. Flowchart of study inclusion.

Supplementary Table 1. Cancer incidence by tumor type, age at diagnosis, and sex.

Year of diagnosis	By cancer type									By age				By sex	
	All cancer cases	ALL	AML	NHL	CNS tumors	Neuroblastoma	Retinoblastoma	Hepatoblastoma	Germ cell tumors	<1	1-4	5-9	10-14	Male	Female
2004	31	5	≤3	≤3	4	≤3	≤3	≤3	≤3	31	--	--	--	10	21
2005	73	8	8	≤3	8	4	7	5	16	33	40	--	--	37	36
2006	105	15	10	≤3	16	18	8	5	18	32	73	--	--	63	42
2007	150	47	19	≤3	13	17	13	6	13	27	123	--	--	90	60
2008	171	45	12	6	20	27	10	18	17	32	139	--	--	99	72
2009	179	54	12	6	21	22	9	10	12	15	141	23	--	99	80
2010	195	58	8	38	29	15	18	14	15	20	139	36	--	111	84
2011	228	68	21	56	27	29	13	8	16	19	147	62	--	140	88
2012	240	67	16	68	41	22	8	14	23	28	143	69	--	113	127
2013	258	78	21	80	35	26	17	12	24	25	143	90	--	137	121
2014	270	82	7	89	46	24	13	10	25	27	132	91	20	151	119