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Maternal Preeclampsia and Odds of Childhood Cancers in Offspring — A California Statewide Case-Control Study

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Abstract

Background: Preeclampsia is a major cause of adverse effects on fetal health. We examined associations between fetal exposure to preeclampsia and subsequent odds of childhood cancers.

Methods: We obtained childhood cancer cases (n=13,669) diagnosed at five years old or younger between 1988 and 2012 from the California Cancer Registry and linked them to birth certificates. Controls (n=271,383) were randomly selected from all California births and frequency matched to cases by birth year. We obtained data regarding preeclampsia during pregnancy, labour, and delivery from the medical worksheet of the electronic birth record. We used unconditional logistic regression models with stabilised inverse probability weights to estimate the effect of preeclampsia on each subtype of childhood cancer, taking into account potential confounding by pregnancy characteristics. Marginal structural models were fitted to assess the controlled direct effects of preeclampsia, independent of preterm delivery and NICU admission.

Results: Although a null association was observed for all cancer subtypes combined (odds ratio (OR) 1.0, 95% confidence interval (CI) 0.9, 1.2), preeclampsia was found to be associated with increased odds of two histologic subtypes of germ cell tumours: seminomas (OR 8.6, 95% CI 1.9, 38.4) and teratoma (OR 3.0, 95% CI 1.7, 5.4), but not yolk sac tumours in children. Odds remained elevated after adjusting for preterm delivery and NICU admission. Increases in odds were also observed for hepatoblastoma, however this association was attenuated in marginal structural models after accounting for NICU admission.

Conclusions: These findings suggest that maternal preeclampsia is associated with higher odds of some rare childhood cancers and may shed light on new aetiologic factors for these cancers.

Key Words: Preeclampsia, Childhood cancer epidemiology, Germ cell tumours, Hepatoblastoma, risk factors, hypertension; Marginal Structural models; Controlled direct effect

Introduction

Preeclampsia, a subtype of hypertensive disorders during pregnancy, is a complex pregnancy-induced syndrome that occurs after the 20th week of gestation. Preeclampsia or eclampsia account for one third of severe maternal morbidities, 10%-15% of maternal deaths in low to middle- income countries and 30%-35% of preterm births worldwide.[1, 2] Preeclampsia is thought to be the consequence of reduced placental perfusion, and endothelial cell dysfunction, processes that causes persistent placental hypoxia, and subsequent release of antiangiogenic factors into the maternal system. These adaptive changes can alter placental development and even contribute to adverse health outcomes in offspring in the long run.[3]

By comparing placenta specimens from preeclampsia-complicated pregnancies with those from normotensive pregnancies, detrimental cellular signalling markers have been found to be overexpressed in umbilical cords from preeclamptic pregnancies and have been connected to chronic adverse health effects in offspring.[4] Whether placental transmission of detrimental factors can have tumorigenic effects on the fetus remains unknown.

Cancer is the second leading cause of mortality among children in the US, with very few well-established preventable causes. Since childhood cancers are diagnosed at an early age, it has been hypothesized that its pathogenesis is initiated during fetal development and possibly fueled by fetal growth. Indeed, population-based studies have linked various perinatal factors with childhood cancers.[5-9] Low birthweight and preterm delivery, both common consequences of preeclampsia, have been shown to be associated with increased childhood cancer risk.[5, 7, 10]

Because of the rarity of cancers in young children, only a small number of previous registry-based studies have evaluated the association between preeclampsia and some types of paediatric cancers with little discussion of potential biologic mechanisms. Some but not all studies have found positive associations.[6, 7, 10-12]

We hypothesise that preeclampsia may affect cancer risk in the offspring either indirectly through adverse neonatal outcomes or directly as a consequence of an altered maternal-fetal circulation resulting from poor perfusion and conducted a large, population-based case control study to examine the association between preeclampsia and various childhood cancers including some rare subtypes.

Methods

Childhood cancer cases (n = 13,677) who were born 1983-2011 and diagnosed at five years of age and younger between 1988-2012 were identified from the California Cancer Registry, as previously described.[5] Each case was matched to a California birth certificate by first and last name, date of birth, and social security number when available, using a probabilistic record linkage program with a successful linkage rate of 89%.[7] Given prior reports of rates of residential mobility in early childhood among California children, the remaining 11% of cases were likely born out of state.[13] Controls were randomly selected from among all California birth records during this period, frequency matching them by birth year (20:1 matching rate). All controls were alive and without a cancer diagnosis in California by age 5 according to CA statedeath files. As this was a record-linkage study, informed consent from each individual

subject was not feasible. We excluded children whose mothers had unknown or unreported preeclampsia/eclampsia status (n = 188), controls who died before reaching age six (n = 1,792), and controls who were likely not viable (n = 130 gestational age < 20 weeks and n = 65 birth weight < 500g), resulting in 13,669 cases and 271,383 controls for the final analyses.

We obtained maternal demographic and socioeconomic information, pregnancy history, pregnancy characteristics, and newborn abnormal conditions or clinical procedures from California birth certificates. Preeclampsia and eclampsia during pregnancy, labour, and delivery were based on the VS-10A medical data supplemental worksheet, an additional form attached to the live birth registry record, which is completed by hospital clerks based upon the medical record. Exposure to preeclampsia or eclampsia was first treated as a binary variable. Furthermore, we assessed the effect of preeclampsia/eclampsia according to the severity of the condition. When preeclampsia is worsening, the decision to induce birth will be made even if the baby is very premature. Thus, in mothers with preeclampsia we used preterm delivery as a marker of more severe preeclampsia. Mothers with preeclampsia and preterm delivery together with mothers who had eclampsia were classified as having “severe preeclampsia/eclampsia”. Otherwise mothers with preeclampsia were considered having “mild preeclampsia”.

Selection of potential confounding variables was based upon associations observed in our data as well as our review of the literature. As adjusting for post-exposure events in the causal pathway between exposures and outcome would block part of the total effect of preeclampsia

on childhood cancers (i.e., act as an intermediate), any related condition occurring after preeclampsia onset such as delivery method, complications in labour and delivery, and adverse birth outcomes, could not be controlled when estimating the odds of cancer due to preeclampsia. Since the birth certificate stopped recording the child's race/ethnicity in 1998, we used maternal race/ethnicity instead. Gestational age was recorded as the number of weeks since the last menstrual period. An obstetric estimate of gestational age at delivery (in completed weeks) is estimated by a physician after a 20th-week ultrasound and was recorded only from 2007 onward. For subjects with missing gestational age information after 2006, we used the obstetric estimate to replace the missing value. Maternal education and primary payment method for prenatal care were used as proxies for maternal socioeconomic status, as described previously.[6] Other potential confounders such as multiple gestations, parity, and previous preterm births were recorded during the entire study period.

Maternal demographics, reproductive histories and perinatal characteristics of the index pregnancy were compared for childhood cancer cases and controls. We restricted our analysis to cancer subtypes with five or more exposed cases. Unconditional logistic regression analysis with stabilized inverse probability weights[14] was used to calculate odds ratios and 95% confidence intervals (CI) for each type of childhood cancer, accounting for the matching variable, birth year. Considering the heterogeneous aetiology of cancer subtypes, separate weights were generated for each subtype of cancer by generating the inverse probability weight for the foetus being exposed to preeclampsia based on various sets of covariates. Common variables used to generate the weights include maternal age at pregnancy,

race/ethnicity and maternal birth place, which our group previously observed to be risk factors for childhood cancer[6, 15] and are previously reported risk factors for preeclampsia.[1, 16-18] Additional factors examined as potential confounders and effect modifiers include previous history of preterm birth, previous miscarriages, multiparity, principal payment method for prenatal care, and the number of prenatal care visits; they were retained in the model if effect estimates changed by 10% or more. Since childhood cancers are very rare, odds ratios are good estimates of incidence rate ratios for childhood cancer.

To assess if preeclampsia has an adverse effect on childhood cancer odds beyond being mediated through preterm delivery, we applied a marginal structural model to estimate controlled direct effects[19] of preeclampsia on childhood cancers independent of preterm birth. Logistic regression with inverse probability weights was used, handling both confounding of the "preeclampsia—cancer" association and confounding of the "mediator—cancer" association. A directed acyclic graph showing the hypothesized underlying causal relationships is given in **Supplement Figure 1**. A similar approach was applied to estimate effects of preeclampsia on childhood cancers independent of NICU admission. Cases that were diagnosed within five days after birth were further excluded from the mediation analysis to prevent possible reverse causation of NICU attendance.

The coding for hypertensive conditions during pregnancy changed across the study period: in mothers whose children were born 1983-2005, chronic hypertension and preeclampsia/eclampsia were recorded separately; from 2006-2011, only one of the following

hypertensive conditions during pregnancy was recorded: pre-existing hypertension, pregnancy-induced hypertension, and eclampsia. We used pregnancy-induced hypertension as a proxy for preeclampsia in 2006-2011. We separately analyzed the subset of children born before 2006 to evaluate the possibility of misclassification bias due to the changes in recording methods.

Results

The study population consisted of a majority of Hispanics (45%), nulliparous pregnancies (40%), and women with at least 12 years of education (74%). Most women had at least more than five prenatal care visits (95%). Childhood cancer was more common among children born to mothers with advanced age at pregnancy, White non-Hispanic mothers, mothers with 16 or more years of education, mothers with less frequent prenatal care visits, and mothers whose prenatal care was paid by private insurance (Tables 1 and 2). Associations between demographic factors and specific cancer subtypes have been described previously.[5-7, 20, 21] Mothers of children with any type of childhood cancer and controls were similar in terms of parity and birth type (singleton vs. multiple gestation), but distributions varied by cancer subtype. Table 2 shows that case children had pregnancy characteristics and delivery outcomes distinct from control children. Consistent with previous reports,[8] cancer in all subtypes were more common in male children. Children with cancer had a higher propensity to be delivered preterm, had lower birth weight, and were more often transferred to the NICU after delivery.

Fetal exposure to preeclampsia was associated with a nearly two-fold increase in odds of germ cell tumours and hepatoblastoma, but no increased odds was observed for all cancer types

combined (OR 1.04, 95% CI 0.92, 1.18). Both germ cell tumor odds and hepatoblastoma odds were further elevated with fetal exposure to severe preeclampsia (Table 3).

As shown in stratified analyses presented in Table 4, the associations between preeclampsia and germ cell tumours were not uniform across histologic nor morphological subtypes. Preeclampsia was strongly associated with seminomas and less so with non-seminomas. Only one subtype of non-seminomas, teratoma, displayed an increased odds after preeclampsia exposure, while none of the 211 children who had yolk sac tumours were exposed to preeclampsia during gestation. Maternal preeclampsia doubled the odds of having an offspring with extracranial and extragonadal germ cell tumour even after restricting to children with a term birth. The direct effect of preeclampsia on teratoma after controlling for the intermediate effects of preterm delivery and NICU admission is nearly as strong as the total effect (Table 5). The controlled direct effect of preeclampsia on seminomas remained similar after controlling for preterm delivery, but strengthened further after the adjustment for NICU admission. The increased odds of hepatoblastoma, however, was attenuated after controlling for preterm delivery and NICU admission.

Comment

This study suggests that maternal preeclampsia during pregnancy is associated with increased odds of germ cell tumours and hepatoblastoma in offspring, while no increased odds for all paediatric tumours combined was observed. The association between preeclampsia exposure and germ cell tumours differed across histologic subtypes, with the strongest association

observed in seminomas. Maternal preeclampsia did not increase the odds of germ cell tumours in a specific site except for extracranial and extragonadal germ cell tumours. These findings may point to different possible aetiologies of germ cell tumours and hepatoblastoma.

The increased odds of hepatoblastoma in children born to mothers who had severe preeclampsia/eclampsia during pregnancy was previously reported in the United Kingdom Childhood Cancer Study (UKCCS), in which both preeclampsia and cancer diagnoses were abstracted from medical records.[11] The possible connection between preeclampsia and hepatoblastoma may have been supported by the finding of a lower level of apolipoprotein A-1 (Apo A-I) protein expression in the umbilical cord blood from pre-eclamptic pregnancies also identified in children with hepatoblastoma and this protein has been suggested as a serum biomarker for early diagnosis of hepatoblastoma.[22, 23]As reflected by our controlled direct effect estimates from a marginal structural model, the association between maternal preeclampsia and hepatoblastoma can be partly explained by mediation by NICU attendance and the intensive medical care associated with it. A previous investigation identified di-(2-ethylhexyl) phthalate (DEHP), a commonly applied plasticizer in medical devices and tubing, as a rodent hepatocarcinogen.[24, 25] Infants going through intensive and long-term medical interventions such as mechanical ventilation and oxygen therapy are more likely to be exposed to high cumulative doses of DEHP which have tumorigenic effects on the immature liver.[25]

Most epidemiologic research has focused on adult rather than childhood germ cell tumours due to their much higher incidence; only a limited number of previous studies were designed to

223 investigate the effect of perinatal factors on paediatric germ cell tumours. Different from our
224 results, a null association between preeclampsia and paediatric testicular germ cell tumours
225 was previously observed in a record linkage study in Nordic countries,[10] but the studies are
226 difficult to compare since the Nordic study was restricted to boys only and included cases up to
227 age 18; thus, the histologic types of cancer also differed due to the case ages as did the
228 ethnic/racial composition of the two populations (our study included 45% Hispanics).
229
230 Germ cell tumours are presumed to arise from pluripotent primordial germ cells and show a
231 broad range of possible histologies.[26] Both biologic features and clinical presentation differ by
232 histologic subtype of germ cell tumours, which implies distinct aetiologies and necessitates
233 subgroup analysis. Differential epigenetic changes, microRNA expression and signalling pathway
234 activation were observed in certain subtypes of germ cell tumours, which provided potential
235 biological evidence for distinct preeclampsia—germ cell tumor associations in epidemiologic
236 studies. Interestingly, miR-182, that functions by downregulating immune response and
237 antiapoptosis genes,[27] was found to be overexpressed in preeclamptic placentas and, was also
238 suggested to be specifically linked to seminomas in contrast to other germ cell tumour
239 subtypes.[28] This might partly explain the striking elevated odds for seminomas in preeclampsia
240 patients observed in our study.
241
242 One typical pathophysiologic change in preeclampsia is placental hypoxia resulting from
243 abnormal trophoblastic implantation,[3] which could lead to increased hypoxia-inducible factor
244 (HIF)-1α and HIF-2α level in the placenta circulation as an adaptive response to the hypoxic

environment. The controlled direct effect of preeclampsia on increased teratoma odds is possibly driven by HIF-2α's tumour promoting effect by altering stem cell differentiation through the activation of Oct-4, as proposed by Covello et al.[29]

Consistent with another case control study on haematological malignancies nested within the UKCCS study population,[12] no elevated odds were seen for ALL or AML. UKCCS also reported a doubling in odds for non-Hodgkin's lymphoma, for which the incidence in children peaks after the age of 10, outside the age range of our study population.

Strengths of the study

Our population-based study had a sufficient number of cases for many cancer subtypes. By using a record-linkage design, we did not rely upon interview-collected data for pregnancy characteristics and avoided recall bias. Furthermore, important confounding variables related to maternal demographic characteristics, perinatal characteristics and pregnancy history based on the birth certificate are reliably recorded on birth records lowering the chance of residual confounding.[30, 31] The novel findings for germ cell tumour subtypes provide the first epidemiologic evidence for distinct aetiologies of these cancers.

Limitations of the data

The results from our study should be interpreted with caution due to the following limitations. Firstly, our study is subject to misclassification bias. Underreporting of preeclampsia on the birth certificate was confirmed in our data. The rate of preeclampsia/eclampsia among controls

was 2.2%, which is lower than the rate in California reported in a health plan database (4.5% in 2010-2012) [32] and in hospital records (3.1% in 2001-2006).[33] The sensitivity of preeclampsia exposure ascertainment thus is reduced with severe preeclampsia more likely to be recorded on the birth certificate.[34] Additionally, the change in recording of hypertensive conditions during pregnancy since 2006 attenuated estimates due to non-differential, independent under-reporting as shown in the restricted analysis in **Supplemental Table 1**. Secondly, the birth certificate does not record the date of onset of pregnancy complications. Researchers have suggested that the pathological mechanism differs for early and late onset of preeclampsia, but we were unable to consider timing of disease onset to assess potential effect measure modification.[35] Nor were we able to consider the effect of antihypertensives used to control the development of preeclampsia. Moreover, maternal smoking and maternal BMI were only available after 2006, which prevented us from adjusting for these two factors in the analysis and this may have caused residual confounding. An inherent problem of birth outcomes research other than neonatal death is that we can only assess the outcomes among live births. Since severe preeclampsia significantly increases the risk of fetal demise[2], the competing risk of death prevents some children from developing childhood cancer. Otherwise, stronger associations might have been observed.

We found a strong association between paediatric seminomas and fetal exposure to preeclampsia, a three-fold increased odds of teratomas in children born to mothers who experienced preeclampsia, and our findings support a direct effect of preeclampsia on these germ cell tumours. The observation of distinct associations by histologic subtype of germ cell

tumours provides epidemiologic evidence suggesting heterogeneous pathogenesis. The additional finding of elevated odds of hepatoblastoma in relation to severe preeclampsia exposure seemed to be due to an indirect effect through preeclampsia-associated preterm delivery and intensive neonatal medical care as well as having a direct effect. These findings underscore the importance of effective interventions targeting modifiable risk factors of maternal preeclampsia and close monitoring of high-risk women through antenatal health care to prevent the long-term health effects of in utero exposure to preeclampsia in children.

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Table1. Demographic Characteristics in Relation to Childhood Cancers, California Cancer Registry, Birth year 1983-2011 (n=285,052)

Characteristic	Controls n (%)	All Cancers n (%)
Total	271383 (100%)	13669 (100%)
Maternal Age		
<20	28661 (10.6%)	1299 (9.5%)
20-29	140767 (51.9%)	6826 (49.9%)
30-34	63232 (23.3%)	3355 (24.5%)
>35	38681 (14.3%)	2187 (16.0%)
Missing	42 (0%)	2 (0%)
Maternal Race/Ethnicity		
White non-Hispanic	94945 (35.0%)	5231 (38.3%)
Hispanic	124636 (45.9%)	6125 (44.8%)
Black	18041 (6.6%)	703 (5.1%)
Asian/ PI	26518 (9.8%)	1246 (9.1%)
Other	7243 (2.7%)	364 (2.7%)
Maternal Birth Place		
US	68556 (25.3%)	3236 (23.7%)
Mexico	153381 (56.5%)	8068 (59.0%)
Other Foreign	49185 (18.1%)	2357 (17.2%)
Missing	261 (0.1%)	8 (0.1%)
Maternal Education (years) [a]		
8 or less	29392 (12.4%)	1355 (11.3%)
9-11	43020 (18.1%)	1995 (16.7%)
12	66092 (27.8%)	3456 (28.9%)
13-15	47429 (19.9%)	2355 (19.7%)
16 or more	47330 (19.9%)	2579 (21.5%)
Missing	4417 (1.9%)	229 (1.9%)
Principal method of payment for prenatal care [a]		
Government program/self	117782 (49.5%)	5370 (44.9%)
Private	117233 (49.3%)	6509 (54.4%)
Missing	2665 (1.1%)	90 (0.7%)
Parity		
0	106713 (39.3%)	5328 (39%)
1	84935 (31.3%)	4307 (31.5%)
>=2	79557 (29.3%)	4028 (29.5%)
Missing	178 (0.1%)	6 (0%)
Prior Miscarriages		
Yes	46811 (17.2%)	2468 (18.1%)
No	224318 (82.7%)	11191 (81.9%)
Missing	254 (0.1%)	10 (0.1%)

[a] This variable was not collected on birth certificates until 1989, therefore n(%) was based on data in existing years.

Table2. Characteristics of Index Pregnancies and Deliveries in Relation to Childhood Cancers, California Cancer Registry, Birth year 1983-2011 (n=285,052)

Characteristic	Controls n (%)	All Cases n (%)
Total	271383 (100%)	13669 (100%)
Child's Sex		
Male	138527 (51.0%)	7543 (55.2%)
Female	132853 (49.0%)	6126 (44.8%)
Unknown	3 (0%)	0 (0%)
Birth Type		
Single	264363 (97.4%)	13313 (97.4%)
Multiple	7020 (2.6%)	356 (2.6%)
No. of Prenatal Care Visit [a]		
5 times or fewer	13502 (5.7%)	567 (4.7%)
6 to 10 times	71341 (30.0%)	3520 (29.4%)
11 to 15 times	122999 (51.7%)	6275 (52.4%)
16 times or more	24277 (10.2%)	1330 (11.1%)
Missing	5560 (2.3%)	277 (2.3%)
Preeclampsia		
Yes	5686 (2.1%)	304 (2.2%)
No	265696 (97.9%)	13365 (97.8%)
Chronic hypertension		
Yes	902 (0.3%)	62 (0.5%)
No	270449 (99.7%)	13605 (99.5%)
Missing	32 (0%)	2 (0%)
Length of gestation		
≤ 37 weeks	26410 (9.7%)	1532 (11.2%)
38-42 weeks	222398 (81.9%)	11043 (80.8%)
≥ 42 weeks	9842 (3.6%)	477 (3.5%)
Missing	12733 (4.7%)	617 (4.5%)
Birthweight		
≤ 1499 g	2162 (0.8%)	172 (1.3%)
1500 - 2499 g	13885 (5.1%)	689 (5.0%)
2500 - 3999 g	227140 (83.7%)	11155 (81.6%)
≥ 4000 g	27968 (10.3%)	1637 (12.0%)
Missing	228 (0.1%)	16 (0.1%)
Size for gestational age		
Small	27301 (10.1%)	1272 (9.3%)
Normal	205747 (75.8%)	10260 (75.1%)
Large	38107 (14.0%)	2121 (15.5%)
Missing	228 (0.1%)	16 (0.1%)
NICU attendance [a]		
Yes	7951 (3.3%)	644 (5.4%)
No	229729 (96.6%)	11325 (94.6%)

[a] This variable was not collected on birth certificates until 1989, therefore n (%) was based on data in existing years.

Table3. Maternal Preeclampsia During Pregnancy and the Odds of Childhood Cancers by Severity of Preeclampsia

Cancer Type	N	Preeclampsia Severity					
		All diagnoses		Mild Preeclampsia		Severe Preeclampsia	
		n	Adjusted [a] OR (95% CI)	n	Adjusted [a] OR (95% CI)	n	Adjusted [a] OR (95% CI)
All childhood cancers	13669	304	1.0 (0.9, 1.2)	206	1.0 (0.9, 1.2)	87	1.1 (0.9, 1.4)
ALL	4133	87	1.1 (0.9, 1.4)	66	1.1 (0.8, 1.4)	21	0.9 (0.6, 1.5)
AML	740	19	1.3 (0.8, 2.1)	13	1.2 (0.7, 2.0)	6	1.8 (0.9, 3.8)
Lymphoma	620	7	0.7 (0.3, 1.4)	5	0.5 (0.2, 1.3)	2	NA [b]
CNS tumor	2378	42	0.8 (0.6, 1.1)	31	1.0 (0.7, 1.4)	9	0.7 (0.4, 1.3)
Neuroblastoma and ganglioneuroblastoma	1385	37	1.2 (0.9, 1.8)	26	1.3 (0.9, 2.0)	11	1.3 (0.7, 2.4)
Retinoblastoma	746	16	1.1 (0.6, 1.7)	11	0.9 (0.5, 1.8)	5	1.2 (0.5, 2.9)
Wilms	1056	22	1.0 (0.7, 1.6)	14	1.0 (0.4, 2.2)	8	1.0 (0.6, 1.6)
Hepatoblastoma	346	13	1.7 (1.0, 3.0)	6	0.7 (0.3, 2.0)	7	4.9 (2.5, 9.5)
Soft tissue sarcomas	705	17	1.0 (0.6, 1.8)	14	1.2 (0.7, 2.1)	3	NA [b]
Germ Cell tumors	451	16	1.8 (1.1, 3.0)	9	1.3 (0.7, 2.6)	7	4.2 (2.2, 7.9)
Controls	271383	265697	1.0 (reference)	3987	1.0 (reference)	1468	1.0 (reference)

[a] For each type of childhood cancer we adjusted for a unique set of covariates.

[b] Not applicable due to less than five exposed cases.

Table4. Maternal Preeclampsia During Pregnancy and the Odds of Germ Cell Tumors by Histologic and Morphological Subtypes

		Cases	Adjusted OR[a] (95% CI)
Germ Cell Tumors		451	1.8 (1.1, 3.0)
Stratified by Histological Types	**Seminomas**	16	8.6 (1.9, 38.4)
	Non-Seminomas[b]	431	1.7 (1.0, 2.8)
	Teratoma	211	3.0 (1.7, 5.4)
	Yolk sac tumor	181	NA [c]
	Other rare types	4	NA [c]
Stratified by Morphological Sites	**CNS germ cell tumor**	43	2.5 (0.6, 10.5)
	Extracranial germ cell tumor	408	1.8 (1.0, 3.0)
	Malignant gonadal tumor	192	0.9 (0.3, 2.7)
	Extracranial and extragonadal germ cell tumor	216	2.5 (1.3, 4.5)

[a] Adjusted for maternal age, race/ethnicity, maternal birth place, parity, birth type (multiple vs. single birth) and birth year

[b] Only more common subtypes were listed

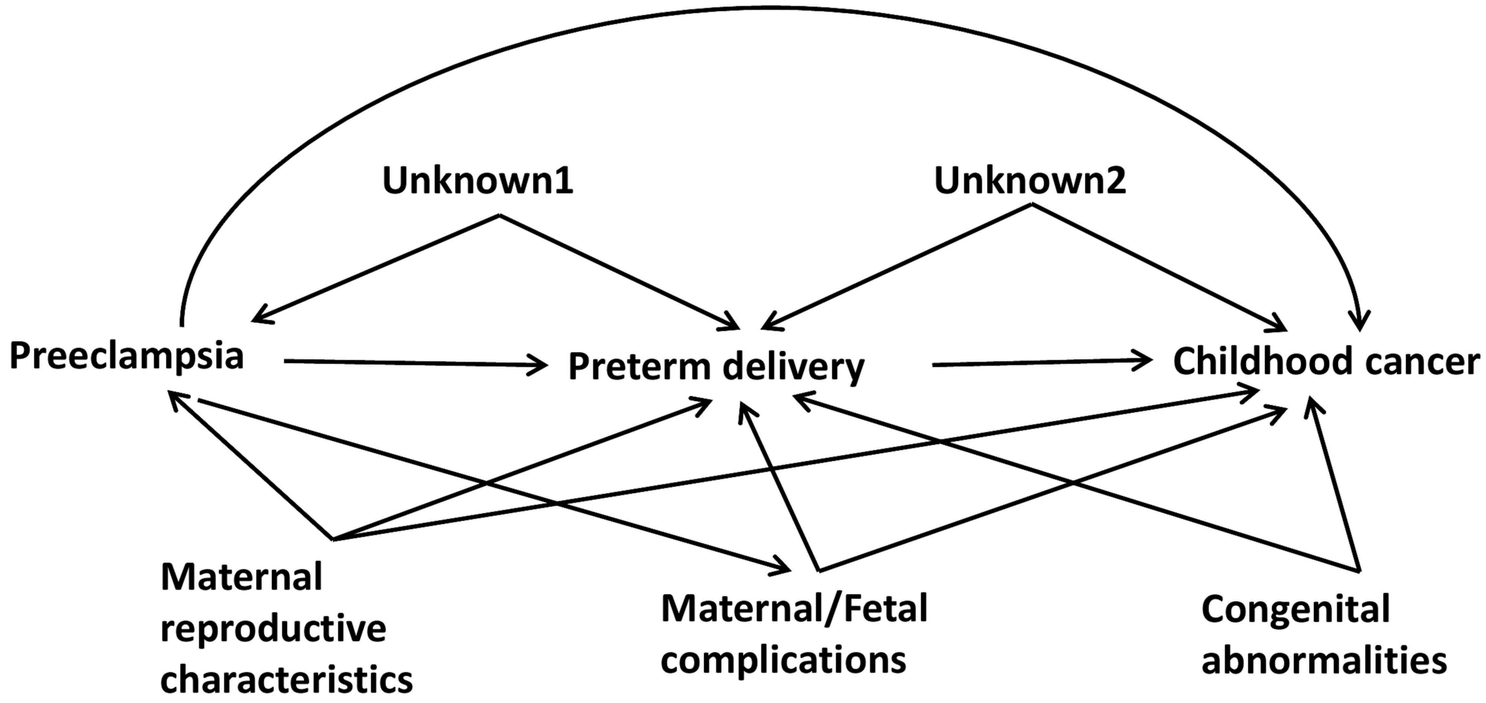
[c] Not applicable due to less than five exposed cases

Table 5. Controlled Direct Effects of Maternal Preeclampsia During Pregnancy and the Odds of Childhood Cancers Accounting for Mediation by Preterm Delivery and Neonatal NICU Admission

	Total Effects	Controlled direct effect accounting for preterm birth[1]	Controlled direct effect accounting for NICU admission[2]
	OR (95% CI)	OR (95% CI)	OR (95% CI)
Hepatoblastoma	2.1 (1.2, 3.6)	1.8 (1.0, 3.2)	1.5 (0.8, 3.0)
Germ cell tumors			
Seminomas	7.2 (1.6, 31.6)	7.2 (1.7, 29.4)	10.2 (2.2, 46.6)
Teratoma	3.2 (1.6, 6.6)	3.2 (1.5, 6.9)	3.2 (1.5, 6.7)

[1] Marginal structural models were applied; adjusted for maternal age, race/ethnicity, parity, birth type, birth year, and congenital abnormalities using inverse probability weighting

[2] Marginal structural models were applied; adjusted for maternal age, race/ethnicity, parity, birth type, birth year, preterm delivery, congenital abnormalities, low birthweight using inverse probability weighting



Supplemental Figure1. Directed Acyclic Graph (DAG)

Notes: Hypothetical maternal reproductive characteristics that may confound preeclampsia—cancer association or preeclampsia—preterm birth association include: maternal age, race/ethnicity, maternal birth place, birth type, parity, principal method of payment for prenatal care, previous history of preterm birth, previous miscarriages and number of prenatal care visit; hypothetical factors confound preterm birth—cancer association include: maternal infections, congenital abnormalities, fetal distress and placental abruption.

Supplemental Table1. Maternal Preeclampsia During Pregnancy and the Odds of Germ Cell Tumors by Histologic and Morphological Subtypes, a Subset of Data of Birth year before 2006

		Cases	Adjusted [a] OR (95% CI)
Germ Cell Tumors		355	2.2 (1.3, 3.7)
Stratified by HistologicTypes	Seminomas	15	9.4 (2.1, 42.4)
	Non-Seminomas[b]	337	2.0 (1.1, 3.4)
	Teratoma	168	3.5 (1.9, 6.3)
	Yolk sac tumor	141	NA [c]
	Other rare types	4	NA [c]
Stratified by Morphological Sites	CNS germ cell tumor	36	3.2 (0.7, 13.3)
	Extracranial germ cell tumor	319	2.1 (1.2, 3.7)
	Malignant gonadal tumor	142	1.2 (0.4, 3.9)
	Extracranial and extragonadal germ cell tumor	177	2.7 (1.4, 5.1)

[a]Adjusted for maternal age, race/ethnicity, maternal birth place, parity, birth type and birth year

[b] Only more common subtypes were listed

[c] Not applicable due to less than five exposed cases

Supplemental Table 2. Maternal Preeclampsia During Pregnancy and the Odds of Childhood Cancers by Calendar Years

	Birthyear 1983 to 2005[a]		Birthyear 2006 to 2011[b]	
	N	OR (95% CI)	N	OR (95% CI)
All childhood cancers	10997	1.0 (0.9, 1.2)	2672	1.0 (0.8, 1.3)
ALL	3690	1.1 (0.8, 1.3)	443	1.3 (0.8, 2.4)
AML	562	1.5 (0.9, 2.5)	178	NA [c]
Lymphoma	540	0.8 (0.4, 1.7)	80	NA [c]
CNS tumor	1965	0.8 (0.5, 1.2)	413	0.7 (0.3, 1.6)
Neuroblastoma and ganglioneuroblastoma	1083	1.2 (0.8, 1.7)	302	1.1 (0.5, 2.3)
Retinoblastoma	582	0.9 (0.5, 1.7)	164	1.5 (0.6, 3.6)
Wilms' tumor	859	1.0 (0.6, 1.7)	197	1.2 (0.5, 2.9)
Hepatoblastoma	245	1.8 (1.0, 3.4)	101	NA [c]
Soft tissue sarcomas	572	0.8 (0.4, 1.7)	133	1.8 (0.7, 4.4)
Germ Cell tumors	355	2.2 (1.3, 3.7)	96	NA [c]
Controls	218244	1.0 Reference	53139	1.0 Reference

[a] Exposure was preeclampsia or eclampsia during pregnancy

[b] Exposure was hypertension during pregnancy (including pregnancy-induced hypertension and preeclampsia) or eclampsia

[c] Not applicable due to less than five exposed cases