Male sex and the risk of childhood cancer: the mediating effect of birth defects

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Abstract: 250
Words: 3000

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Abstract

**Background:** There is a persistent, unexplained disparity in sex ratio among childhood cancer cases, whereby males are more likely to develop most cancers. This male predominance is also seen for most birth defects, which are strongly associated with risk of childhood cancer. We conducted mediation analysis to estimate whether the increased risk of cancer among males is partially explained by birth defect status.

**Methods:** We used a population-based birth cohort with linked data from birth certificates, birth defects registries, and cancer registries from Arkansas, Michigan, North Carolina, and Texas. We conducted counterfactual mediation analysis to estimate the natural direct and indirect effects of sex on cancer risk, modeling birth defect status as mediator. State, birth year, plurality, and maternal race/ethnicity, age, and education were considered confounders. We conducted separate analyses limited to cancers diagnosed at age <1 year.

**Results:** Our dataset included 10,181,074 children: 15,110 diagnosed with cancer, 539,567 diagnosed with birth defects, and 2,124 co-occurring cases. Birth defect status mediated 38% of the association between sex and cancer overall. The proportion mediated varied by cancer type, including acute myeloid leukemia (93%), neuroblastoma (35%), and non-Hodgkin lymphoma (6%). Among children <1 year of age at cancer diagnosis, the proportion mediated was substantially higher (82%).

**Conclusions:** Our results suggest birth defects mediate a statistically significant proportion of the relationship between sex and childhood cancer. The proportion mediated varied by cancer type and diagnosis age. These findings improve our understanding of the causal pathway underlying male sex as risk factor for childhood cancer.
It is well established that males have a higher risk of childhood cancer compared to females[1]. This male excess in incidence is observed for most major tumor types and the overall male-to-female incidence rate ratio for all childhood cancers is 1.19 (95% confidence interval [CI]: 1.18, 1.20)[1], with a range for specific cancers from 1.13 (astrocytoma and neuroblastoma) to 4.62 (Burkitt lymphoma). The tumors with a female preponderance are nephroblastoma (Wilms tumor), extracranial and extragonadal germ cell tumors, and thyroid carcinoma. The causal pathways underlying the association between male sex and childhood cancer are unknown.

Birth defects have emerged as another important risk factor for childhood cancer[2-8]. Increased risk for childhood cancers have been observed for children with chromosomal anomalies and monogenic syndromes, and those with non-syndromic birth defects. This association is consistent across nearly every major tumor type, which was confirmed in a recent analysis which utilized the dataset described herein[2].

These associations are notable, as there is evidence that males are also more likely to be born with a birth defect. A report from the National Birth Defects Prevention Study described an male to female sex ratio of 1.18 (95% CI: 1.13 to 1.24) among 25,952 clinically reviewed infants with a documented birth defect[9]. Anomalies with a high male preponderance included craniosynostosis (sex ratio = 2.05, 95% CI = 1.81 to 2.32), left ventricular outflow tract defects (sex ratio = 2.20, 95% CI = 1.94 to 2.49), and bilateral renal agenesis or hypoplasia (sex ratio = 1.95, 95% CI = 1.38 to 2.76). Notably, each of these anomalies is also associated with childhood cancer risk (hazard ratio = 2.6, 95% CI = 2.1 to 3.2 for craniosynostosis; hazard ratio = 2.5, 95% CI = 1.7 to 3.7 for left ventricular outflow tract defects; and hazard ratio = 3.5, 95% CI = 2.3 to 5.2 for bilateral renal agenesis or hypoplasia)[2].

Although both sex and birth defect status have been individually evaluated as risk factors for childhood cancer, the extent to which the male excess in childhood cancer incidence may be
attributable to the male excess in the birth prevalence of birth defects is unknown. As sex determination occurs at the moment of conception and onset of most major birth defects occurs during organogenesis in weeks three through sixteen of gestation[10, 11], birth defect status may be a mediator in the sex-childhood cancer relationship. Here we conduct a mediation analysis utilizing a population-based study of over 10,000,000 live births to quantify the proportion of the association between male sex and childhood cancer that is mediated by birth defects.

Methods

Study Design

The GOBACK study was designed using population-based state registries to evaluate the association between birth defects and childhood cancer[2]. This analysis utilizes the GOBACK data which are described briefly below; further details are published elsewhere[2].

Birth Certificate Data

The study included all recorded live births in Texas from 1999-2013, Arkansas from 1995-2011, Michigan from 1992-2011, and North Carolina from 2003-2012; differences in study years reflect data availability from state-specific registries (Supplementary Table 1). Demographic and birth data were obtained from birth certificates.

Birth Defects Ascertainment

Birth defects surveillance systems in Texas, Arkansas, and North Carolina employ active ascertainment methods; passive ascertainment methods are used in Michigan[6, 12-16]. Specific birth defects included were “major” defects[14, 15] included as part of the National Birth Defects Prevention Network’s annual surveillance report[12] or the National Birth Defects Prevention Study case definitions[14].

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**Childhood Cancer Ascertainment**

Data on cancer site, morphology, behavior, and age at diagnosis were obtained from the population-based cancer registries of each state. All participating cancer registries follow the standards of the National Program of Cancer Registries and are certified by the North American Association of Central Cancer Registries[17].

The childhood cancer cases were coded into groups according to the International Classification of Childhood Cancer, Third Edition. Children diagnosed <18 years of age are included. In the subset of children with more than one cancer diagnosis (N=235), we included only the first primary cancer.

**Record Linkage**

Within each state, birth defects and cancer registries were linked to birth certificates. Individual records in the assembled birth cohort were linked across data sources using deterministic and probabilistic linkage. Over 95% of birth defect cases and >70% of childhood cancer cases across the cohort were matched to birth certificates[6, 16, 18]. Linked data were de-identified and systematically cleaned, harmonized, and coded across states.

**Statistical Analysis**

We conducted counterfactual mediation analysis[19] to estimate the direct and indirect effects of sex on risk of childhood cancer, modeling sex as the exposure (male/female), birth defect status as the mediator (any/none), and cancer type as the outcome (cancer overall and by subtype). The counterfactual mediation analysis provides a framework whereby the total effect of an exposure on an outcome can be decomposed into a natural direct effect and natural indirect effect. In this analysis, the natural direct effect is defined as $NDE_{a,a^*}(a^*) = E[T_{aMa^*}]/E[T_{a*Ma^*}]$ and the natural indirect effect is defined as $NIE_{a,a^*}(a) = E[T_{aM_a}]/E[T_{aMa^*}]$, where $T_a$ and $M_a$ denote the values of the time-to-event cancer...
outcome and birth defect mediator that would have been observed if the exposure $A$ had been set to level $a$. $T_{am}$ is the value of the time-to-event cancer outcome that would have been observed if the exposure $A$ and mediator $M$ had been set to levels $a$ and $m$ respectively. We have included a directed acyclic graph of our model in Supplementary Figure 1. The natural direct effect captures the influence of infant sex on childhood cancer risk if the link between infant sex and the mediator (birth defect status) was prevented or removed hypothetically. This simulates a scenario wherein the sample distributions of the mediator are no longer dependent on infant sex. By contrast, the natural indirect effect captures the effect of infant sex on childhood cancer risk that operates through birth defects status. Consistent with previous analyses\cite{12, 20}, we assessed the effect of sex on birth defects status using logistic regression models and the effect of both sex and birth defects status on childhood cancer risk using Cox proportional hazards models. Person-years were calculated as time from birth to death, cancer diagnosis, or end of study period (December 31, 2011 in Arkansas and Michigan, December 31, 2012 in North Carolina, and December 31, 2013 in Texas). We estimated standard errors of the hazard ratios (HR) through the delta method. The proportion mediated was reported only if the hazard ratios for the direct and indirect effects were in the same direction\cite{19, 21}.

Counterfactual mediation analyses assume that, conditional on the covariates, there is no confounding of 1) the exposure-outcome relationship, 2) the mediator-outcome relationship, 3) the exposure-mediator relationship, and that 4) there is no effect of the exposure that itself confounds the mediator-outcome relationship. Assumptions 1 and 3 are likely to hold when the main exposure variable is infant sex. Birth year, state, maternal race/ethnicity (non-Hispanic white, non-Hispanic black, other), maternal education (less than high school, high school, more than high school), maternal age (continuous), and plurality (singleton vs. multiple) were identified a priori as potential mediator-outcome confounders to address assumption 2. Finally, there are no known effects of infant sex which
may confound the birth defect-childhood cancer relationship. Therefore we do not believe that assumption 4 is violated.

Due to lower success rates of linkage to birth records among adolescent cancer cases, we conducted a subgroup analysis limiting to cancers diagnosed at age <5 years. Additionally, due to observations that the association between birth defects and cancer is strongest for those diagnosed with cancer at the youngest ages\[3, 7\], we conducted analyses restricting to children diagnosed with cancer before 1 year of age. We conducted analyses for only those cancers with at least five cases diagnosed among each age group. Because of the documented association between certain childhood cancers and chromosomal anomalies or single gene disorders, which are generally independent of sex \[9, 22-24\], we conducted subgroup analyses excluding children with chromosomal anomalies (N=22,420), or single gene disorders (neurofibromatosis type I and tuberous sclerosis) (N=2,972). This was done to quantify the mediation effect of non-syndromic birth defects alone. Finally, to account for multiple comparisons, we corrected the p-values for the natural indirect effects using the Benjamini-Hochberg method of the False Discovery Rate (FDR), setting α=0.05. Statistical analyses were performed in SAS 9.4. All statistical tests were two-sided.

**Results**

Our dataset included 10,181,074 children (5,208,379 males; 4,972,695 females), including 15,110 with cancer diagnoses (8,044 males; 7,066 females), 539,567 children with birth defects diagnoses (320,666 males; 218,901 females), and 2,124 co-occurring cases (children with both cancer and one or more birth defect diagnoses: 1,186 males; 938 females). Table 1 shows demographic characteristics of the study population. Males were more likely to be diagnosed with any childhood cancer (HR = 1.09, 95% CI = 1.05 to 1.12) and were more likely to have a birth defect (odds ratio = 1.42, 95% CI = 1.41 to 1.43). The associations between sex and childhood cancer are presented in
Supplementary Table 2 and those between sex and birth defects status are presented in Supplementary Table 3.

Figure 1 shows the proportion mediated for all cancers combined and by major diagnostic category, for all children and within subgroups by age at diagnosis. Among cancer categories where we could compute a proportion mediated for more than one age group, we generally observed that the proportion mediated increased with decreasing age. We observed statistically significant mediation of the association between sex and childhood cancer by birth defect status among children age <18 years (proportion mediated [PM] = 38%; Table 2). In analyses of specific cancer types, we observed variation of the estimated proportion mediated among several cancers, including acute myeloid leukemia (PM = 93%), neuroblastoma (PM = 35%), hepatoblastoma (PM = 33%), non-Hodgkin lymphoma (PM = 6%) and soft tissue sarcomas (PM = 24%). The indirect effects for most cancers were statistically significant, albeit with modest effect sizes (<1.05). The largest indirect effects we observed were for hepatoblastoma (HR_{NIE} = 1.11, 95% CI = 1.09 to 1.13) and extracranial and extragonadal germ cell tumors (HR_{NIE} = 1.14, 95% CI = 1.11 to 1.18).

In analyses of children age <5 years at cancer diagnosis, we observed similar results (Supplementary Table 4). The proportion of the effect of sex on cancer risk among children age <5 years mediated by birth defects status was 42%. In analyses of children age <1 year at cancer diagnosis, we observed stronger indirect effects, and the proportion of the sex-childhood cancer association mediated by birth defects status among infants was 82% (Table 3). The proportion mediated in infants was moderate to high in nearly every cancer type where this statistic could be calculated, including ependymoma (28%), medulloblastoma (44%), neuroblastoma (35%), retinoblastoma (31%), hepatoblastoma (42%), and non-rhabdomyosarcoma soft tissue sarcomas (60%), with the only exception being gonadal germ cell tumors (5%). Figure 2 shows cancer-specific results for selected leukemias, central nervous system tumors, and embryonal tumors.
In analyses restricted to non-syndromic birth defects (Supplementary Table 5), we observed a weakened indirect effect for acute lymphoblastic leukemia and acute myeloid leukemia (PM = 4% and 29%, respectively). However, associations for solid tumors remained largely consistent with those observed when considering all anomaly types (chromosomal, single gene, and non-syndromic).

Discussion

In this population-based analysis of over 10,000,000 live births, we observed that birth defects status is likely to explain a substantial proportion of the sex ratio disparity in childhood cancer. The proportion mediated varied considerably by cancer type and age at diagnosis; notably, we estimate that 82% of the male excess in childhood cancer incidence among infants is mediated by birth defects status.

The increased risk of cancer among adult males compared to adult females is well established[25] and differences in risk are at least partially attributable to differences in risk behaviors such as alcohol and tobacco use[26, 27]. By contrast, there is a paucity of published data on the possible causal pathways underlying the sex disparity in childhood cancer incidence. In one study[28], the authors conducted a mediation analysis to examine whether the sex-childhood cancer relationship is mediated by birth weight. They reported modest mediation for all cancers combined and for acute lymphoblastic leukemia. However, birth weight did not explain a large proportion of the sex-cancer relationships examined.

We observed strong mediation effects for the embryonal tumors neuroblastoma and hepatoblastoma. Notably, these tumors were the two most commonly associated with non-chromosomal birth defects in our recent assessment. We also observed nearly complete mediation of the sex association with acute myeloid leukemia among children of all ages (proportion mediated: 93%). Birth defects did not mediate a large proportion of the sex effect on medulloblastoma for all children or
children diagnosed <5 years old, but we did observe a larger mediation effect among infants (proportion mediated: 44%).

We observed a wide range of proportion mediated. Each childhood cancer subtype has different associations with child sex, thus the sex-specific incidence of each cancer type is one factor driving these results. Additionally, GOBACK data showed that birth defects are more strongly associated with some childhood cancer types than others[2]. Thus cancers which are strongly associated with birth defects, such as hepatoblastoma, are more likely to have a strong mediation effect.

For some cancers, we observed age-dependent variation in our results when comparing analyses of the entire study population to subgroup analyses among children <5 years and <1 year of age. It is well-established that the sex-ratio among childhood cancer cases differs by age[1]. Analyses of the birth defect-cancer associations have also seen age-dependent results, with stronger effect estimates for younger age at cancer onset[3, 7]. Finally, evidence suggests that there are age-dependent biologically distinct subtypes of a single cancer (i.e. acute lymphoblastic leukemia) based on the differing etiology and molecular subtypes that vary by age at diagnosis[29, 30]. We believe these factors are driving the differences we observed by age at diagnosis.

There were some cancer types for which we observed positive, statistically significant, natural indirect effects with natural direct effects below the null. These results indicate that the pathway through birth defects is driving the male incidence for that particular cancer type up, while male sex has an inverse association with that particular cancer through all other pathways. For example, there was a strong natural indirect effect for extracranial germ cell tumors (HR_{NIE} = 1.14, 95% CI = 1.11 to 1.18) while the natural direct effect showed a strong inverse association (HR_{NDE} = 0.45, 95% CI = 0.33 to 0.62). These results indicate that, in the absence of an effect of birth defects, the female excess in extracranial germ
cell tumor incidence would be even more pronounced than currently observed. We observed similar patterns for acute myeloid leukemia among children <5 years and <1 year of age at diagnosis.

When we conducted analyses of non-syndromic birth defects only, we observed a decrease in the proportion mediated for acute lymphoblastic leukemia and acute myeloid leukemia, while most other results remained unchanged (Supplementary Table 5). Risk of both acute lymphoblastic leukemia and acute myeloid leukemia are increased among children with Down syndrome[23, 31, 32]. Furthermore, results from our data (Supplementary Table 3) and other analyses have shown a male excess among infants born with Down syndrome[9, 33]. Thus the exclusion of Down syndrome in this subgroup analysis is likely driving these results.

There are limitations to consider when interpreting these results. Due to linkage procedures, children who migrated away from their birth state would be lost to follow-up, therefore would not be identified if they subsequently developed cancer. Our linkage success rates among children age 0-5 years, 6-10 years, and 11+ years of age at cancer diagnosis were 74%, 66%, and 60%, respectively. These rates are similar to those observed in previous studies[18, 30] and were not differential by child’s sex in any age group. Additionally, there is evidence which suggests out-of-state migration is non-differential according to birth defect status[34], which limits the possibility of differential misclassification. We observed unexpected sex ratios of some tumor types (Supplementary Table 2), most notably osteosarcoma and Ewing sarcoma. The unexpected sex ratios are likely due to the lower linkage success rates of older cancer cases. In osteosarcoma and Ewing sarcoma occurring <18 years of age, the male excess is due almost entirely to adolescent cases; there is nearly no difference in sex ratio among younger cases[1]. Despite this limitation, we do not expect that early life migration is differential by birth defects status or child sex, as noted above. Therefore it is unlikely that results were influenced by lower linkage success of older cases. There may be limitations in birth defect ascertainment if the presence of cancer caused the appearance of a birth defect that was in fact a structural displacement.
due to cancerous growth. However we have previously shown that birth defect-cancer associations for which this is a concern (i.e., hydrocephaly secondary to central nervous system tumors) remained statistically significant after exclusion of cases with these combinations diagnosed in infancy[2]. Due to small sample size of minority populations in this dataset (Table 1)[2], we categorized Hispanic, Asian, American Indian/Alaskan Native, and other/unknown mothers into the ‘Other’ racial/ethnic category. Finally, although there are some factors such as birth weight which are associated with infant sex, the sex determination of the fetus nearly always precedes these factors and therefore they would not confound the sex-birth defect relationship or the sex-cancer relationship. However, it is possible that unmeasured confounders exist for the mediator-outcome relationship. The underlying causes of the strong association between birth defects and childhood cancer risk are unknown and may be due to shared environmental risk factors, unidentified developmental disorders or genetic syndromes.

In conclusion, we evaluated mediation of the sex-childhood cancer relationship by birth defects utilizing a population-based study design with a very large sample size. Our results suggest that birth defects mediate a substantial proportion of the overall relationship between sex and childhood cancer, particularly among younger children. While approximately 60% of the male excess in childhood cancer incidence among children age <18 years remains unexplained, these findings add to our understanding of the causal pathway of male sex as a risk factor for childhood cancer. These results may assist in refinement of risk stratifications and surveillance strategies among children with birth defects as we develop an increased understanding of the pathways involved in carcinogenesis in this population. Other possible mechanisms underlying the male excess include sex-specific genetic factors or immune response[35-37]. Additional studies are underway to characterize the biology underlying these observations.
Funding

This work was supported by the Cancer Prevention & Research Institute of Texas (CPRIT RP140258, RP170071, RP160097, and RP160283), National Cancer Institute at the National Institutes of Health (CA125123), Arkansas Biosciences Institute, Alex’s Lemonade Stand Foundation, and the Children’s Cancer Research Fund.

Notes

Role of the funders: The funders had no role in the design of the study; the collection, analysis, and interpretation of the data; the writing of the manuscript; and the decision to submit the manuscript for publication.

Disclosures: The authors have no disclosures.

Acknowledgements: We would like to acknowledge the various state agencies that made this work possible, including the Texas Birth Defects Registry, Texas Cancer Registry, Texas Center for Health Statistics, Texas Department of State Health Services, Arkansas Reproductive Health Monitoring System, Arkansas Cancer Registry, Michigan Department of Health and Human Services, North Carolina Central Cancer Registry, North Carolina Birth Defects Monitoring Program, North Carolina State Center for Health Statistics, and the North Carolina Division of Public Health.
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Table 1. Infant and maternal characteristics of children included in this analysis

| Category                  | Non-cancer births, No. (%) | Childhood cancer births, No. (%) |
|---------------------------|-----------------------------|---------------------------------|
|                           | Male                        | Female                         | Total                  | Male                        | Female                         | Total                  |
| Total                     | 5,200,335 (51.2)            | 4,965,629 (48.8)               | 10,165,964 (100)       | 8,044 (53.2)               | 7,066 (46.8)                  | 15,110 (100)           |
| Any birth defect          | 319,480 (6.1)               | 217,963 (4.4)                  | 537,442 (5.3)          | 1,186 (14.7)               | 938 (13.3)                    | 2,124 (14.1)          |
| Chromosomal anomaly       | 11,013 (0.2)                | 10,915 (0.2)                   | 21,928 (0.2)           | 166 (2.4)                  | 172 (2.7)                     | 338 (2.2)             |
| Genetic anomaly           | 12,736 (0.3)                | 12,308 (0.3)                   | 25,044 (0.2)           | 190 (2.7)                  | 193 (3.1)                     | 383 (2.5)             |
| Non-syndromic birth defect| 306,744 (5.9)               | 205,655 (4.2)                  | 512,399 (5.0)          | 996 (12.7)                 | 745 (10.8)                    | 1,741 (11.5)          |
| Maternal race/ethnicity   |                             |                                |                       |                            |                                |                       |
| Non-Hispanic White        | 3,314,406 (63.7)            | 3,152,974 (63.5)               | 6,467,380 (63.6)       | 5,313 (66.1)               | 4,619 (65.4)                  | 9,932 (65.7)          |
| Non-Hispanic Black        | 778,429 (15.0)              | 752,815 (15.2)                 | 1,531,244 (15.1)       | 890 (11.1)                 | 827 (11.7)                    | 1,717 (11.4)          |
| Other                     | 1,107,500 (21.3)            | 1,059,840 (21.3)               | 2,167,340 (21.3)       | 1,841 (22.8)               | 1,620 (22.9)                  | 3,461 (22.9)          |
| Maternal education        |                             |                                |                       |                            |                                |                       |
| Less than high school     | 1,140,726 (21.9)            | 1,096,149 (22.1)               | 2,236,875 (22.0)       | 1,714 (21.3)               | 1,597 (22.6)                  | 3,311 (21.9)          |
| High School               | 1,484,689 (28.6)            | 1,418,830 (28.6)               | 2,903,519 (28.6)       | 2,369 (29.5)               | 2,037 (28.8)                  | 4,406 (29.2)          |
| Greater than high school  | 2,239,554 (42.9)            | 2,130,883 (42.9)               | 4,370,437 (43.0)       | 3,500 (43.5)               | 3,049 (43.2)                  | 6,549 (43.3)          |
| missing                   | 335,366 (6.5)               | 319,767 (6.4)                  | 655,133 (6.4)          | 461 (5.7)                  | 383 (5.4)                     | 844 (5.6)             |
| Birth weight              |                             |                                |                       |                            |                                |                       |
| Low birth weight (<2500g) | 387,058 (7.4)               | 427,651 (8.6)                  | 814,709 (8.0)          | 614 (7.6)                  | 591 (8.4)                     | 1,205 (8.0)           |
| Normal birth weight (2500-3999g) | 4,129,384 (79.4) | 4,077,298 (82.1)               | 8,206,682 (80.7)       | 6,166 (76.7)               | 5,645 (79.9)                  | 11,811 (78.2)         |
| High birth weight (≥4000g) | 500,295 (9.6)               | 285,463 (5.7)                  | 785,758 (7.7)          | 908 (11.3)                 | 512 (7.3)                     | 1,420 (9.4)           |
| missing                   | 183,598 (3.5)               | 175,217 (3.5)                  | 358,815 (3.5)          | 356 (4.4)                  | 318 (4.5)                     | 674 (4.5)             |
| Gestational age           |                             |                                |                       |                            |                                |                       |
| < 28 weeks                | 34,615 (0.7)                | 30,553 (0.6)                   | 65168 (0.6)            | 66 (0.8)                   | 40 (0.6)                      | 106 (0.7)             |
| 28 to 37 weeks            | 984,916 (18.9)              | 889,045 (17.9)                 | 1,873,961 (18.4)       | 1,625 (20.2)               | 1,378 (19.5)                  | 3,003 (19.9)          |
| ≥ 38 weeks                | 4,148,337 (79.8)            | 4,016,498 (80.9)               | 8,164,835 (80.3)       | 6,293 (78.2)               | 5,603 (79.3)                  | 11,896 (78.7)         |
| missing                   | 32,467 (0.6)                | 29,533 (0.6)                   | 62,000 (0.6)           | 60 (0.7)                   | 45 (0.6)                      | 105 (0.7)             |
| Plurality                 |                             |                                |                       |                            |                                |                       |
| Singleton                 | 5,040,061 (96.9)            | 4,807,125 (96.8)               | 9,847,186 (96.9)       | 7,800 (97.0)               | 6,871 (97.3)                  | 14,671 (97.1)         |
| Multiple                  | 159,353 (3.1)               | 157,685 (3.2)                  | 317,038 (3.1)          | 244 (3.0)                  | 193 (2.7)                     | 437 (2.9)             |
| State          | missing | 921 (0.0) | 819 (0.0) | 1740 (0.0) | 0 (0.0) | 2 (0.0) | 2 (0.0) |
|---------------|---------|-----------|-----------|------------|--------|--------|--------|
| Arkansas      | 321,638 (6.2) | 306,411 (6.2) | 628,049 (6.2) | 562 (7.0) | 475 (6.7) | 1,037 (6.9) |
| Michigan      | 1,314,886 (25.3) | 1,251,418 (25.2) | 2,566,304 (25.2) | 2,166 (26.9) | 1,933 (27.4) | 4,099 (27.1) |
| North Carolina| 633,709 (12.2) | 604,544 (12.2) | 1,238,253 (12.2) | 719 (8.9) | 606 (8.6) | 1,325 (8.8) |
| Texas         | 2,930,102 (56.3) | 2,803,256 (56.5) | 5,733,358 (56.4) | 4,597 (57.2) | 4,052 (57.4) | 8,649 (57.2) |
Table 2. Hazard ratios (HR) from the mediation analysis for the association between sex and childhood cancer mediated by birth defects status*

| Cancer                                | Natural indirect effect HR (95%CI) | Natural direct effect HR (95%CI) | Total HR (95%CI) | Proportion mediated, % | FDR-adjusted p-value for the natural indirect effect |
|----------------------------------------|------------------------------------|----------------------------------|------------------|------------------------|------------------------------------------------------|
| Any cancer                             | 1.03 (1.02 to 1.03)                | 1.05 (1.02 to 1.09)              | 1.08 (1.05 to 1.12) | 38                     | <0.001                                               |
| Leukemia                               | 1.03 (1.02 to 1.03)                | 1.09 (1.03 to 1.16)              | 1.12 (1.06 1.19)  | 26                     | <0.001                                               |
| Acute lymphoblastic leukemia           | 1.02 (1.01 to 1.02)                | 1.14 (1.07 to 1.22)              | 1.16 (1.08 to 1.24) | 11                     | <0.001                                               |
| Acute myeloid leukemia                 | 1.07 (1.06 to 1.08)                | 1.01 (0.86 to 1.18)              | 1.08 (0.92 to 1.26) | 93                     | <0.001                                               |
| Other leukemia                         | 1.08 (1.06 to 1.09)                | 0.88 (0.73 to 1.06)              | 0.95 (0.79 to 1.14) | --                     | <0.001                                               |
| Lymphoma                               | 1.02 (1.01 to 1.02)                | 1.52 (1.36 to 1.70)              | 1.54 (1.38 to 1.72) | 4                      | <0.001                                               |
| Hodgkin lymphoma                       | 1.00 (0.99 to 1.00)                | 1.50 (1.21 to 1.86)              | 1.49 (1.20 to 1.85) | --                     | <0.001                                               |
| Non-Hodgkin lymphoma                   | 1.02 (1.01 to 1.03)                | 1.44 (1.20 to 1.74)              | 1.47 (1.22 to 1.77) | 6                      | <0.001                                               |
| Other lymphoma                         | 1.02 (1.01 to 1.03)                | 1.61 (1.35 to 1.92)              | 1.65 (1.39 to 1.96) | 6                      | <0.001                                               |
| Central Nervous System                 | 1.03 (1.02 to 1.03)                | 1.05 (0.98 to 1.12)              | 1.08 (1.01 to 1.16) | 37                     | <0.001                                               |
| Ependymoma                             | 1.01 (1.00 to 1.03)                | 1.33 (1.04 to 1.69)              | 1.35 (1.06 to 1.71) | 6                      | 0.16                                                 |
| Medulloblastoma                        | 1.03 (1.02 to 1.05)                | 1.59 (1.30 to 1.94)              | 1.64 (1.35 to 2.00) | 8                      | <0.001                                               |
| Astrocytoma                            | 1.03 (1.03 to 1.04)                | 0.95 (0.86 to 1.06)              | 0.98 (0.88 to 1.10) | --                     | <0.001                                               |
| Primitive neuroectodermal tumor        | 1.02 (1.00 to 1.04)                | 0.86 (0.59 to 1.26)              | 0.88 (0.60 to 1.29) | --                     | <0.001                                               |
| Other central nervous system           | 1.03 (1.02 to 1.03)                | 1.00 (0.90 to 1.12)              | 1.03 (0.93 to 1.15) | 84                     | <0.001                                               |
| Peripheral Nervous System              | 1.04 (1.03 to 1.05)                | 1.10 (0.98 to 1.22)              | 1.14 (1.02 to 1.27) | 32                     | <0.001                                               |
| Neuroblastoma                          | 1.04 (1.03 to 1.05)                | 1.08 (0.97 to 1.21)              | 1.12 (1.01 to 1.25) | 35                     | <0.001                                               |
| Other peripheral nervous system        | 1.09 (1.00 to 1.20)                | 5.79 (1.30 to 25.7)              | 6.32 (1.43 to 28.0) | 10                     | 0.06                                                 |
| Retinoblastoma                         | 1.02 (1.01 to 1.03)                | 0.98 (0.83 to 1.17)              | 1.01 (0.85 to 1.20) | --                     | <0.001                                               |
| Renal                                  | 1.03 (1.02 to 1.04)                | 0.78 (0.69 to 0.89)              | 0.81 (0.71 to 0.92) | --                     | <0.001                                               |
| Nephroblastoma                         | 1.03 (1.02 to 1.04)                | 0.76 (0.67 to 0.88)              | 0.79 (0.69 to 0.90) | --                     | <0.001                                               |
| Other renal                            | 1.04 (1.01 to 1.06)                | 0.99 (0.64 to 1.51)              | 1.02 (0.67 to 1.56) | --                     | 0.01                                                 |
| Hepatic                                | 1.11 (1.09 to 1.13)                | 1.27 (1.00 to 1.60)              | 1.41 (1.11 to 1.78) | 35                     | <0.001                                               |
| Hepatoblastoma                         | 1.11 (1.09 to 1.13)                | 1.30 (1.01 to 1.67)              | 1.44 (1.12 to 1.85) | 33                     | <0.001                                               |
| Other hepatic                          | 1.14 (1.07 to 1.22)                | 1.02 (0.50 to 2.08)              | 1.17 (0.58 to 2.37) | 86                     | <0.001                                               |
| Bone                                   | 1.01 (1.00 to 1.02)                | 1.00 (0.81 to 1.23)              | 1.00 (0.81 to 1.23) | --                     | 0.99                                                 |
| Osteosarcoma                           | 1.00 (0.99 to 1.01)                | 0.99 (0.74 to 1.33)              | 1.00 (0.74 to 1.34) | --                     | 0.99                                                 |
| Tumor Type                     | Hazard Ratio (CI)                  | OR (CI)          | P-Value |
|-------------------------------|-----------------------------------|------------------|---------|
| Ewing sarcoma                 | 1.00 (0.99 to 1.01)               | 1.03 (0.72 to 1.47) | 1.03 (0.72 to 1.47) | -- | 0.90 |
| Other bone                    | 1.04 (1.00 to 1.07)               | 0.92 (0.55 to 1.56) | 0.95 (0.57 to 1.61) | -- | 0.06 |
| Soft tissue                   | 1.03 (1.02 to 1.03)               | 1.10 (0.98 to 1.24) | 1.13 (1.01 to 1.27) | 24 | <0.001 |
| Any rhabdomyosarcoma          | 1.01 (1.00 to 1.02)               | 1.28 (1.06 to 1.56) | 1.30 (1.07 to 1.57) | 5 | 0.02 |
| Other rhabdomyosarcoma        | 1.02 (1.00 to 1.04)               | 1.34 (0.89 to 2.02) | 1.37 (0.91 to 2.06) | 6 | 0.10 |
| Alveolar rhabdomyosarcoma     | 1.01 (0.99 to 1.03)               | 1.01 (0.66 to 1.56) | 1.02 (0.67 to 1.57) | 39 | 0.39 |
| Embryonal rhabdomyosarcoma    | 1.01 (1.00 to 1.02)               | 1.37 (1.06 to 1.77) | 1.38 (1.07 to 1.79) | 3 | 0.15 |
| Other soft tissue             | 1.04 (1.03 to 1.05)               | 1.00 (0.87 to 1.16) | 1.04 (0.90 to 1.21) | 91 | <0.001 |
| Germ cell tumor               | 1.07 (1.05 to 1.08)               | 0.83 (0.70 to 0.99) | 0.89 (0.74 to 1.06) | -- | <0.001 |
| Extracranial germ cell tumor  | 1.14 (1.11 to 1.18)               | 0.45 (0.33 to 0.62) | 0.52 (0.37 to 0.71) | -- | <0.001 |
| Gonadal germ cell tumor       | 1.02 (1.01 to 1.04)               | 1.15 (0.88 to 1.49) | 1.17 (0.90 to 1.52) | 16 | 0.002 |
| Intracranial germ cell tumor  | 1.05 (1.02 to 1.08)               | 1.03 (0.70 to 1.50) | 1.08 (0.74 to 1.57) | 64 | <0.001 |
| Epithelial                    | 1.01 (1.00 to 1.02)               | 0.54 (0.45 to 0.64) | 0.55 (0.46 to 0.65) | -- | 0.03 |
| Any other                     | 1.02 (1.00 to 1.05)               | 1.18 (0.80 to 1.73) | 1.20 (0.82 to 1.77) | 13 | 0.05 |

*Analyses are adjusted for birth year, state, maternal race/ethnicity, maternal education, maternal age, plurality.
†Empty cells are present when the proportion mediated is not estimable because the natural direct and indirect effects are in opposite directions.
Table 3. Hazard ratios (HRs) from the mediation analysis for the association between sex and childhood cancer mediated by birth defect status; restricted to children age <1 year*

| Cancer                   | Natural indirect effect HR (95%CI) | Natural direct effect HR (95%CI) | Total HR (95%CI) | Proportion mediated, % | FDR-adjusted p-value for the natural indirect effect |
|--------------------------|-----------------------------------|---------------------------------|-----------------|------------------------|-------------------------------------------------------|
| Any cancer               | 1.08 (1.07 to 1.09)               | 1.02 (0.95 to 1.09)             | 1.10 (1.02 to 1.18) | 82                     | <0.001                                                |
| Leukemia                 | 1.08 (1.07 to 1.09)               | 0.88 (0.75 to 1.02)             | 0.95 (0.81 to 1.11) | --                     | <0.001                                                |
| Acute lymphoblastic leukemia | 1.03 (1.02 to 1.05)             | 0.97 (0.77 to 1.23)             | 1.00 (0.79 to 1.27) | --                     | <0.001                                                |
| Acute myeloid leukemia   | 1.12 (1.09 to 1.15)               | 0.70 (0.53 to 0.92)             | 0.78 (0.59 to 1.03) | --                     | <0.001                                                |
| Other leukemia           | 1.13 (1.10 to 1.16)               | 0.98 (0.72 to 1.33)             | 1.10 (0.81 to 1.49) | --                     | <0.001                                                |
| Lymphoma                 | 1.07 (1.04 to 1.10)               | 1.08 (0.76 to 1.55)             | 1.16 (0.81 to 1.66) | 47                     | <0.001                                                |
| Hodgkin lymphoma         | --                                | --                              | --              | --                     | --                                                   |
| Non-Hodgkin lymphoma     | --                                | --                              | --              | --                     | --                                                   |
| Other lymphoma           | 1.07 (1.04 to 1.10)               | 1.11 (0.75 to 1.65)             | 1.19 (0.80 to 1.77) | 42                     | <0.001                                                |
| Central Nervous System   | 1.09 (1.07 to 1.11)               | 0.99 (0.83 to 1.20)             | 1.09 (0.91 to 1.30) | --                     | <0.001                                                |
| Ependymoma               | 1.06 (1.02 to 1.10)               | 1.17 (0.64 to 2.13)             | 1.24 (0.68 to 2.25) | 28                     | 0.01                                                  |
| Medulloblastoma          | 1.12 (1.07 to 1.18)               | 1.18 (0.66 to 2.10)             | 1.32 (0.74 to 2.35) | 44                     | <0.001                                                |
| Astrocytoma              | 1.08 (1.05 to 1.11)               | 0.95 (0.69 to 1.31)             | 1.02 (0.74 to 1.41) | --                     | <0.001                                                |
| Primitive neuroectodermal tumor | --                        | --                              | --              | --                     | --                                                   |
| Other central nervous system | 1.10 (1.07 to 1.13)            | 0.98 (0.75 to 1.28)             | 1.08 (0.83 to 1.41) | --                     | <0.001                                                |
| Peripheral Nervous System | 1.07 (1.06 to 1.08)             | 1.16 (0.99 to 1.35)             | 1.24 (1.06 to 1.45) | 34                     | <0.001                                                |
| Neuroblastoma            | 1.07 (1.06 to 1.08)               | 1.15 (0.98 to 1.34)             | 1.23 (1.05 to 1.44) | 35                     | <0.001                                                |
| Other peripheral nervous system | --                      | --                              | --              | --                     | --                                                   |
| Retinoblastoma           | 1.04 (1.03 to 1.06)               | 1.10 (0.87 to 1.40)             | 1.15 (0.91 to 1.46) | 31                     | <0.001                                                |
| Renal                    | 1.07 (1.05 to 1.09)               | 1.00 (0.77 to 1.31)             | 1.07 (0.82 to 1.39) | 99                     | <0.001                                                |
| Nephroblastoma           | 1.07 (1.05 to 1.10)               | 0.95 (0.72 to 1.27)             | 1.02 (0.77 to 1.36) | --                     | <0.001                                                |
| Other renal              | --                                | --                              | --              | --                     | --                                                   |
| Hepatic                  | 1.15 (1.11 to 1.18)               | 1.27 (0.90 to 1.80)             | 1.46 (1.03 to 2.07) | 42                     | <0.001                                                |
| Hepatoblastoma           | 1.14 (1.11 to 1.18)               | 1.26 (0.88 to 1.79)             | 1.43 (1.00 to 2.04) | 42                     | <0.001                                                |
| Other hepatic            | --                                | --                              | --              | --                     | --                                                   |
| Bone                     | --                                | --                              | --              | --                     | --                                                   |
| Osteosarcoma             | --                                | --                              | --              | --                     | --                                                   |
| Outcome Category                               | Ratio Estimate (95% CI) | Prop Ratio Estimate (95% CI) | P-value |
|-----------------------------------------------|-------------------------|------------------------------|---------|
| **Ewing sarcoma**                             | --                      | --                           | --      |
| **Other bone**                                | --                      | --                           | --      |
| **Soft tissue**                               | 1.07 (1.05 to 1.09)     | 1.00 (0.78 to 1.30)          | 1.08 (0.83 to 1.39) | 95 | <0.001 |
| **Any rhabdomyosarcoma**                      | 1.03 (1.00 to 1.06)     | 0.87 (0.54 to 1.39)          | 0.89 (0.56 to 1.43) | -- | 0.04   |
| **Other rhabdomyosarcoma**                    | --                      | --                           | --      |
| **Alveolar rhabdomyosarcoma**                 | --                      | --                           | --      |
| **Embryonal rhabdomyosarcoma**                | 1.04 (1.00 to 1.09)     | 0.59 (0.31 to 1.13)          | 0.62 (0.32 to 1.18) | -- | 0.05   |
| **Other soft tissue**                         | 1.10 (1.07 to 1.12)     | 1.07 (0.79 to 1.45)          | 1.17 (0.86 to 1.59) | 60 | <0.001 |
| **Germ cell tumor**                           | 1.13 (1.10 to 1.16)     | 0.95 (0.72 to 1.26)          | 1.08 (0.82 to 1.42) | -- | <0.001 |
| **Extracranial germ cell tumor**              | 1.18 (1.14 to 1.22)     | 0.38 (0.26 to 0.55)          | 0.44 (0.30 to 0.65) | -- | <0.001 |
| **Gonadal germ cell tumor**                   | 1.05 (1.01 to 1.08)     | 17.9 (5.61 to 57.2)          | 18.8 (5.88 to 59.8) | 5  | 0.01   |
| **Intracranial germ cell tumor**              | 1.13 (1.05 to 1.22)     | 0.91 (0.39 to 2.16)          | 1.03 (0.44 to 2.43) | -- | 0.002  |
| **Epithelial**                                | --                      | --                           | --      |
| **Any other**                                 | 1.05 (1.00 to 1.10)     | 1.03 (0.50 to 2.12)          | 1.08 (0.53 to 2.22) | 62 | 0.06   |

* Analyses are adjusted for birth year, state, maternal race/ethnicity, maternal education, maternal age, plurality.
† Empty cells are present when there were fewer of five cancer cases in the category.
‡ Empty cells are present when the proportion mediated is not estimable because the natural direct and indirect effects are in opposite directions.
Figures titles and legends

Figure 1. Proportion of the sex-cancer association mediated by birth defects status for major tumor types, by age at diagnosis.

Figure 2. Proportion of the sex-cancer association mediated by birth defects status for selected leukemias, central nervous system tumors, and embryonal tumors, by age at diagnosis.
Figure 1. Proportion of the sex-cancer association mediated by birth defects status for major tumor types, by age at diagnosis.
Figure 2. Proportion of the sex-cancer association mediated by birth defects status for selected leukemias, central nervous system tumors, and embryonal tumors, by age at diagnosis.