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Author manuscript

*Cancer Epidemiol.* Author manuscript; available in PMC 2019 December 01.

Published in final edited form as:

*Cancer Epidemiol.* 2018 December ; 57: 7–12. doi:10.1016/j.canep.2018.09.002.

## The association between sex and most childhood cancers is not mediated by birthweight

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### Abstract

**Background**—Male sex is associated with an increased risk of childhood cancer as is high birthweight. Given that sex determination precedes birthweight we conducted a mediation analysis to estimate the direct effect of sex in association with childhood cancer tumor type with birthweight as the mediator.

**Methods**—Cases (n=12,632) and controls (n=64,439) (ages 0–14 years) were identified from population-based cancer and birth registries in Minnesota, New York, and Washington states (1970–2014). An inverse odds weighting (IOW) mediation analysis was used to estimate odds ratios (OR) and 95% confidence intervals (95% CI) as the measure of association between sex and cancer.

**Results**—A significant indirect effect was observed for sex and lymphoid leukemia, mediated by birthweight (indirectOR: 1.03; 95% CI: 1.02–1.04). We observed significant direct effects for male

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All authors approve of the final version.

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Declarations of interest: none.

\*Cancer types for which the models failed to produce adjusted ORs are excluded.

sex and lymphoid leukemia (directOR: 1.16; 95% CI: 1.08–1.25), Hodgkin lymphoma (directOR: 1.48; 95% CI: 1.22–1.81), Burkitt lymphoma (directOR: 5.02; 95% CI: 3.40–7.42), other non-Hodgkin lymphoma (directOR: 1.42; 95% CI: 1.18–1.70), intracranial embryonal tumors (directOR: 1.49; 95% CI: 1.26–1.76), hepatoblastoma (directOR: 1.90; 95% CI: 1.40–2.59), and rhabdomyosarcoma (directOR: 1.47; 95% CI: 1.19–1.81). There were also inverse associations for extracranial GCTs (directOR: 0.41; 95% CI: 0.26–0.63) and thyroid carcinoma (directOR: 0.35; 95% CI: 0.25–0.50).

**Conclusion**—Significant direct effects for sex and numerous childhood cancer types suggests sex-specific factors such as differences in gene expression from the autosomes or the X chromosome, rather than birthweight, may underlie sex differences in tumor risk.

### Keywords

childhood cancer; sex-disparity; birthweight; mediation analysis

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### Introduction

The scientific evidence showing an increased risk of cancer among males relative to females over the life course is well established[1–5]. Differences in risk between the sexes in adulthood are attributable in part to risk factor differences for behaviors such as alcohol and tobacco intake between males and females[6,7]. In studies of the US population, males have a higher incidence rate of childhood cancer in general and by tumor type for acute lymphoblastic leukemia, Non-Hodgkin lymphoma, medulloblastoma, hepatic tumors, osteosarcoma, and germ cell tumors compared with females[5]. However, unlike adult cancers the mechanisms underlying the differences in childhood cancer incidence by sex are largely unknown[8]. Compared to females, male children are often of higher birthweight[9], experience a higher number of childhood infections[10–13], have an accelerated pubertal growth rate[14], and experience a different hormonal milieu over the childhood and adolescent periods[15]; therefore, these differences in risk factors may contribute to the observed sex disparity in childhood cancer incidence.

Although both sex and birthweight have been examined in association with childhood cancer, there has been no formal mediation analysis to quantify the direct effect of sex on childhood cancer risk. Male infants generally have higher birthweights than females[9] of the same gestational age[16–18] by approximately 100–200 grams[9,18]. Increasing birthweight is an established risk factor for childhood malignancy[19] including leukemia[19–22] and central nervous system (CNS) tumors[19,20,23–25], the two most common classes of childhood cancers. High birthweight may increase the risk of childhood cancer by increasing the number of mitotic events and thus the frequency of somatic mutations in larger babies[20], or by alterations in maternal hormones and growth factors that encourage rapid fetal growth [26,27]; factors that may ultimately impact cancer occurrence.

Since sex determination precedes birthweight, we conducted a mediation analysis using an inverse odds weighting (IOW) method to estimate the indirect, direct, and total effects of sex on childhood cancer risk while treating birthweight as the mediator. A benefit of a using

mediation analysis is that we can examine the direct effect of sex on the risk of childhood cancer while also determining the degree to which this association operates through birthweight. Quantifying the direct effect of sex on childhood cancer risk may guide future studies to uncover the biologic mechanisms contributing to the observed sex-disparity in the incidence of most childhood cancer types. We carried out the IOW mediation analysis using a pooled study of 12,632 cases and 64,439 controls from population-based cancer registries and birth registries in Minnesota, New York, and Washington states with cancer diagnoses captured from 1970–2014.

## Methods

### Study population.

The present analysis includes 12,632 cases and 64,439 controls from 3 of the 5 states included in an earlier childhood cancer study [19,28–32], including incident cancer cases diagnosed in children aged 0–14 years identified from population-based cancer registries in Minnesota (MN), California (CA), New York (NY [excluding New York City]), Texas (TX), and Washington (WA) state. CA and TX individually matched cases and controls on sex and were therefore excluded from the present analysis. The current analysis is restricted to data from MN, NY, and WA, which did not match on sex and therefore could be used to estimate its association with cancer. For MN, NY, and WA, cases and controls were frequency matched on birth year (MN:1976–2004; NY: 1970–2001; WA: 1980–2004)[28]. The MN data also arose from a linkage between the Department of Health (MN DOH) Minnesota Cancer Surveillance System and the Minnesota birth registry for all cancers diagnosed from 1989–2014 as described previously[33] where cases and controls were frequency matched on birth year (1989–2010). Approval for the study was obtained from each state’s respective department of health and from Institutional Review Boards at all participating institutions and informed consent was waived.

Cancer type was classified using the International Classification of Childhood Cancer, Third Edition (ICCC-3)[34]. Tumor types with fewer than 20 cases in either males or females in the fully adjusted models or types labeled as “other” or “miscellaneous” were excluded from the cancer type-specific analyses (case counts for included tumor types are presented in Supplemental Table 1). Excluded tumor types were leukemia, not otherwise specified (NOS); myelodysplastic syndrome; lymphoma, NOS; miscellaneous lymphoma; CNS, NOS; other gliomas; other intracranial, chondrosarcoma; soft tissue sarcomas (STS), NOS; other STS; adrenocortical carcinoma and other, unspecified carcinomas. Data was harmonized across the studies for maternal and birth characteristics as previously described[28–30]. Children diagnosed with cancer <28 days of life and those with Down syndrome listed on their birth certificate (57 cases and 24 controls) were excluded.

### Variables of interest.

Covariates were selected *a priori* for inclusion based on established associations with sex and childhood cancer[19,28,31,35] and in consideration of the study design (state and birth year). Final models included birthweight category (grams) (>350–<2,500, 2,500–<3,000, 3,000–<3,500, 3,500–<4,000, 4,000), gestational age (weeks) continuous (18–46), maternal

race/ethnicity (Non-Hispanic white, Hispanic, other), maternal age (continuous) (13–54 years), maternal education (high school graduate, some college, college graduate), state of birth (MN, NY, WA), and birth year category (1970–1984, 1985–1990, 1991–1996, 1997–2010).

### Statistical analysis.

We used a semiparametric, inverse odds weighting (IOW) method described by Nguyen et al. (2014)[36] and others[37,38] to test for mediation of the association between sex and childhood cancer by birthweight for tumor types with a significant total effect (IOW code is available in Nguyen et al. (2014)[36]). The advantage of the IOW method is that the generation of the IOW renders the mediator, birthweight, and the exposure, sex, independent. IOW first leg results where the exposure, sex, was regressed onto the mediator, birthweight, while adjusting for gestational age, maternal race/ethnicity, maternal education, and state and year of birth are presented in Supplemental Table 2.

The IOW method was used to estimate the direct effect of sex on cancer risk (Supplemental Figure 1), independent of birthweight, through the use of a weighted logistic model accounting for the IOW generated for each subject from the multivariate logistic regression model for birthweight in association with sex and adjusted for the additional covariates mentioned above. The weight, defined by the inverse of the odds from the aforementioned model was assigned to males. Females, the referent category, were assigned a weight value of 1. To estimate the indirect effect of sex on childhood cancer operating through birthweight, the beta from the logistic model for the direct effect was subtracted from the beta for the total effect, which was estimated from a standard logistic regression model without the IOW specification ( $\beta_{\text{indirect}} = \beta_{\text{total}} - \beta_{\text{direct}}$ ). For the total, direct, and indirect effects, the resulting odds ratios (OR) and bootstrapped standard errors (1000 replications) were used to estimate the 95% confidence intervals (95% CI). The statistical significance of an indirect effect is interpreted as evidence of mediation by birthweight on the sex-childhood cancer association. We also quantified the degree of mediation by calculating the percent change from the total effect to the direct effect such that a larger percent change indicated a stronger mediation effect. ORs and 95% CIs were estimated using Stata 15.0 (College Station, Texas) for the IOW analysis and SAS version 9.4 (Cary, North Carolina) for multivariable logistic regression models. Cases and controls with missing data for any of the covariates were excluded from the relevant adjusted models. P-values for tests of statistical significance were generated for two-sided hypotheses tests with alpha equal to 0.05.

## Results

Compared to controls, cases were more likely to be male (cases 54.8%; controls 51.7%), of higher birthweight (< 3,500 grams: cases 48.8%; controls 45.1%), born at gestational age of 40 weeks (cases 75.2%; controls 72.1%), born to non-Hispanic, white mothers (cases 87.7%; controls 84.5%), and were more likely to have mothers with some college education (cases 52.5%; controls 50.6%) (Table 1). Compared to females, male cases were more likely to weigh < 3,500 grams at birth (males 53.4%; females 43.3%).

Differences in the risk of childhood cancer by sex are apparent when comparing crude and multivariable adjusted ORs for childhood cancer overall and by cancer type (Figure 1). ORs >1 indicate tumor types associated with male sex, whereas ORs<1 represents tumor types associated with female sex. The ORs from multivariable logistic regression correspond to the total effects estimates presented in Table 2.

Male sex was significantly associated with childhood cancer overall (adjusted OR [adjOR]: 1.11; 95% confidence interval [95% CI]: 1.06–1.16) as well as lymphoid leukemia (adjOR: 1.19; 95% CI: 1.09–1.30), Hodgkin lymphoma (adjOR: 1.51; 95% CI: 1.20–1.90), Burkitt lymphoma (adjOR: 5.39; 95% CI: 3.49–8.34), other non-Hodgkin lymphoma (adjOR: 1.42; 95% CI: 1.16–1.75), intracranial embryonal tumors (adjOR: 1.49; 95% CI: 1.23–1.80), hepatoblastoma (adjOR: 1.63; 95% CI: 1.16–2.30), and rhabdomyosarcoma (adjOR: 1.42; 95% CI: 1.13–1.79) (Figure 1). Conversely, male sex displayed a significant, inverse association with extracranial germ cell tumors (GCTs) (adjOR: 0.44; 95% CI: 0.27–0.70) and thyroid carcinoma (adjOR: 0.38; 95% CI: 0.26–0.56). Adjustment for gestational age, maternal age, maternal education, state and year of birth did not substantially alter results (Figure 1). The largest amount of missing data arose from maternal education (27% controls, 19% cases). Estimates from models excluding maternal education (results not shown) were similar in direction and magnitude to those observed in our fully adjusted model.

IOW analysis first leg results are presented in Supplemental Table 2 where high birthweight (> 4,000g), relative to normal birthweight (2,500–<4,000g), is generally positively associated with male sex for each tumor type. We did not observe a significant total effect for sex and the following tumor types: acute myeloid leukemia, chronic myelodysplastic diseases, ependymoma, astrocytoma, neuroblastoma, retinoblastoma, Wilms tumor, osteosarcoma, Ewing sarcoma, intracranial germ cell tumor (GCT), gonadal GCT, or melanoma. In the IOW mediation analysis among tumor types where a significant total effect was observed (Table 2), birthweight showed a modest, but significant mediation effect on the association between male sex and all cancer types combined (indirectOR: 1.02; 95% CI: 1.01–1.03) and among lymphoid leukemia (indirectOR: 1.03; 95% CI: 1.02–1.05).

When we examined the direct effect of sex on childhood cancer overall and by tumor type (Table 2), the ORs mirror those observed for the total effects, suggesting that birthweight does not have a strong mediating effect on the association between sex and childhood cancer overall and among many tumor types, which is also represented in the small values for the percent change from total to direct effect. We found significant direct effects for male sex and all childhood cancers combined (directOR: 1.12; 95% CI: 1.08–1.17) along with lymphoid leukemia (directOR: 1.16; 95% CI: 1.08–1.25), Hodgkin lymphoma (directOR: 1.48; 95% CI: 1.22–1.81), Burkitt lymphoma (directOR: 5.02; 95% CI: 3.40–7.42), other non-Hodgkin lymphoma (directOR: 1.42; 95% CI: 1.18–1.70), intracranial embryonal tumors (directOR: 1.49; 95% CI: 1.26–1.76), hepatoblastoma (directOR: 1.90; 95% CI: 1.40–2.59), and rhabdomyosarcoma (directOR: 1.47; 95% CI: 1.19–1.81). We also observed inverse associations between male sex and extracranial GCTs (directOR: 0.41; 95% CI: 0.26–0.63) and thyroid carcinoma (directOR: 0.35; 95% CI: 0.25–0.50). The estimates from the fully adjusted IOW mediation analysis (Supplemental Table 3) were similar to those from the crude model (Table 2) in both direction and magnitude.

## Discussion

In our pooled analysis from population-based case-control data of the association between sex and risk of childhood cancer, we observed evidence of a modest, but significant mediation effect by birthweight for childhood cancer overall and for lymphoid leukemia. However, the direct effect of male sex was significant and much stronger than that of birthweight for several tumor types. Among children, we and others have reported that males are at greater risk of, or were more frequently diagnosed with acute lymphoblastic leukemia (ALL)[39,40], but not acute myeloid leukemia (AML)[2,41], intracranial embryonal tumors (assumed to be predominantly medulloblastomas)[2,42–44], lymphomas[2,39,41], hepatoblastoma[41], and rhabdomyosarcoma[2,39,45]. We observed an increased, marginally significant ( $p=0.05$ ) risk of neuroblastoma among males as observed elsewhere[41]. We observed a significant inverse association between male sex and extracranial germ cell tumors (GCTs), consistent with SEER data showing an increased risk of GCTs among females aged 0–14 years[46,47], and an increased incidence rate of extragonadal tumors among females aged 0–9 years[48]. We also observed an inverse association between male sex and thyroid carcinoma, consistent with numerous reports based on subjects of all ages[1,4,45,49–51].

The American Cancer Society reports that males aged 0–14 years have an overall cancer incidence rate of 178.0 per 1,000,000 while females have a rate of 160.1 cases per 1,000,000[2], corresponding to a crude incidence rate ratio for childhood cancer of 1.11 for male versus female sex in relation to childhood cancer. Analyses of sex disparities in childhood cancer incidence are limited with few earlier focused studies[39]. Many childhood cancer studies match cases to controls on sex, which precludes analysis of this relationship. However, consistent with one prior study[39], there are several tumor types associated strongly with male sex including hematologic malignancies, embryonal tumors, and sarcomas; therefore, these tumor types may be especially sensitive to the sex-specific biologic differences in childhood. Our results indicate these associations are independent of birthweight, suggesting that other biologic factors may be responsible for increased cancer diagnoses among boys.

The increased risk of childhood cancer among males may have a genetic basis, as the differences in male and female hormones during childhood are minimal compared to the differences observed between adults[10]. Although sex differences in tissue-specific gene expression have been observed during development in animal models[52], there are few studies of sex differences in gene expression during development available for humans. Among adults, genes on the X chromosome have shown more variation in expression between the sexes than is observed for autosomal genes and this may depend on sex-differences in chromatin accessibility[53].

Other possible genetic mechanisms may depend on acquiring somatic mutations on the X chromosome. This may differentially impact males and females as skewing toward one X over the other can occur with aging such that mutations on the X chromosome could be preferentially confined to the inactivated copy due to selective pressures[52], whereas the expression of any X- mutation in males is obligate over the life course and may be more

likely to have an impact on gene expression and carcinogenesis[54]. The X chromosome may contain multiple tumor suppressors and genes that promote cell growth[54]; therefore, it is plausible that the X chromosome plays an important role in the observed sex disparity in a childhood cancer[10]. The Y chromosome, which contains less than 100 genes[55], may also play a role in the increased risk of cancer among males. To date the Y chromosome has largely been viewed as responsible for sex determination and germ cell differentiation and is usually not investigated in association with cancer; however, work in adult hepatocellular carcinoma, which is more frequent in males, suggests genes on the Y chromosome, particularly TSPY, may in fact play a role in carcinogenesis[56–58]. The contribution of Y chromosome genes to the observed male excess in childhood cancers should be explored.

Further, there is some evidence that the difference in cancer risk for boys and girls may lie in the immune response to tumor development. Males have lower innate and adaptive immune responses than females as demonstrated by higher rates of infectious diseases in males and greater levels of autoimmune diseases in females[10–13]. The X chromosome houses a large number of immune-related genes and differential expression of such genes [10,59], which may underlie the observed differences in immunity between males and females. Sex differences in immunity could also be due to X mosaicism in females[52], for whom the increased genetic diversity may result in a more comprehensive immune response; conversely, males rely upon the single X chromosome of maternal origin leading to less diversity in their immune response[10,12]. Evaluating tissue-specific germline and somatic differences in the X chromosome for DNA mutations, DNA methylation, and gene expression between boys and girls with childhood cancer will be critical for understanding the role of the X chromosome in carcinogenesis in children and adolescents.

Our study should be interpreted in light of some limitations. Even though we have accounted for known reliably measured risk factors for childhood cancer in our adjusted models such as birthweight, gestational age and maternal age, we may be missing other confounders of the association between sex and cancer risk; however, we do not expect there to be tremendous residual confounding as there are few strong risk factors for childhood cancer in children aged 0–14 years that we have not accounted for herein. We cannot rule out misclassification of disease status among controls, but the misclassification bias is likely to be negligible as Johnson et al. have described in detail[28]. Limitations to the IOW method, as suggested by Nguyen et al. [36], arise from larger variances than what might be observed in other mediation analysis techniques, which may hinder the discovery of smaller indirect effects. Concerning missing data, we do not expect the values of the missing data to differ between cases and controls as the maternal characteristic data were derived from birth registries, which collected the data prospectively.

## Conclusions

Our findings suggest that the association between sex and childhood cancer may operate to a small degree through birthweight for lymphoid leukemia. For most tumors, though, there was little evidence of mediation by birthweight on the association between sex and childhood cancer suggesting that factors associated with sex other than birthweight, play a critical biologic role in carcinogenesis among children. Suspected biological mechanisms

may be rooted in differences in sex chromosome gene expression or methylation or may be due to differences in immune function between males and females during infancy and childhood. Characterization of genomic differences on the X chromosome between males and females during prenatal development and childhood will be important for discovering the underlying biologic mechanisms responsible for the observed sex differences in childhood cancer risk.

## Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

## Acknowledgments

### Funding

This work was supported by the National Institutes of Health (grant numbers T32 CA099936 to LAW (MN); N01 CN05230 to WA); Children's Cancer Research Fund, Minneapolis, MN; Fred Hutchinson Cancer Research Center; Centers for Disease Control and Prevention's National Program of Cancer Registries by cooperative agreement (U58 DP000783-01 to NY).

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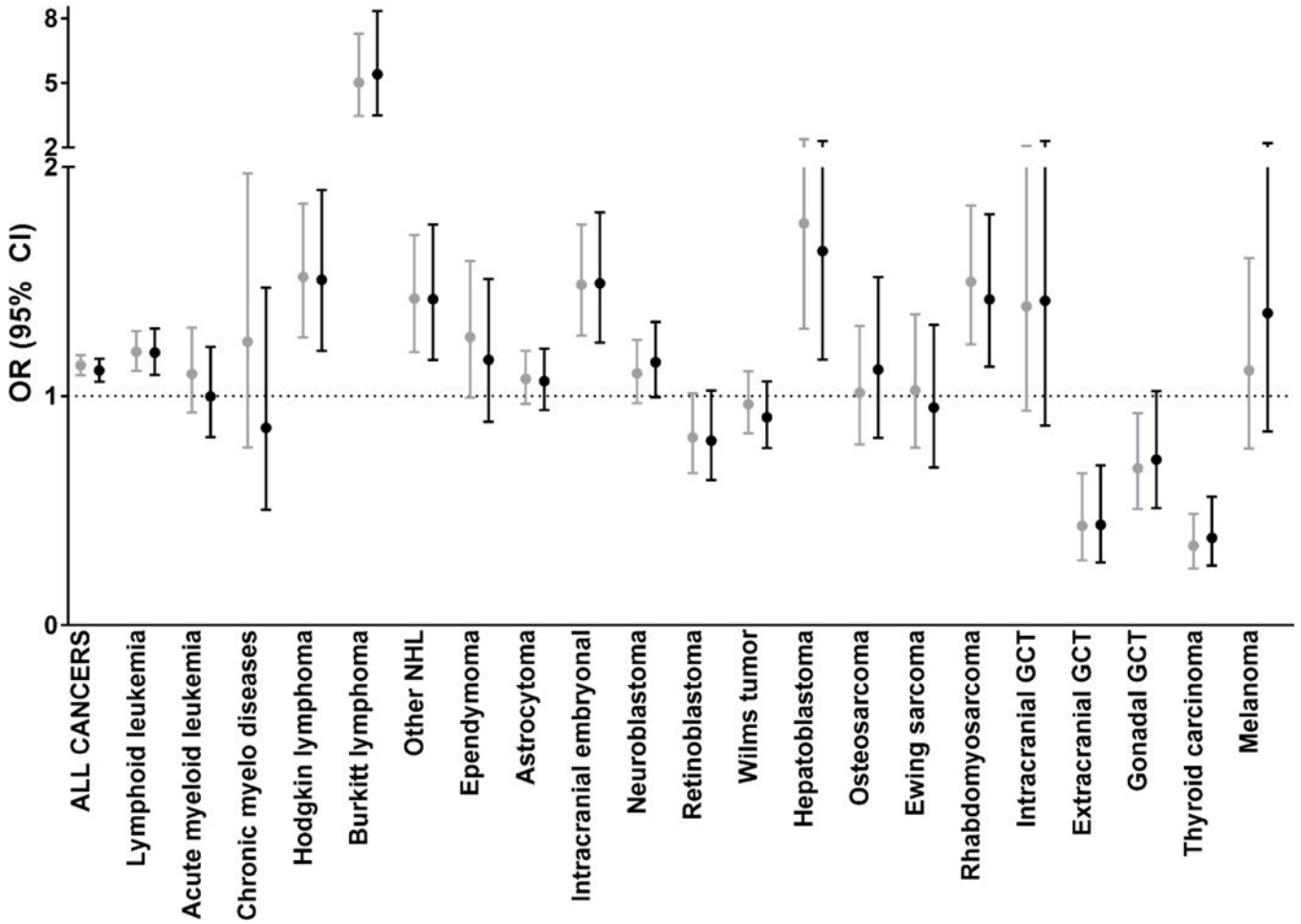
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### Highlights

- Males have a higher childhood cancer incidence than females, but little work has focused on biologic mechanisms explaining this phenomenon
- Male sex is associated with an increased risk of a number of childhood cancer types, these associations are not mediated by birthweight, and are independent of other perinatal risk factors
- Biologic mechanisms underlying the increased risk of childhood cancer among males may be due to genomic differences between the sexes



**Figure 1.** Relationship between crude and adjusted<sup>a</sup> odds ratios (OR) and 95% confidence intervals (95% CI) for male sex by childhood cancer type, 3-state pooled analysis (1970–2014)

<sup>a</sup>Models adjusted for gestational age, maternal race/ethnicity, maternal age, maternal education, state of birth, and birth year

**Table 1.**

Infant and maternal characteristics of children in the 3-state analyses (1970–2014)

	Controls			Cases		
	Males N = 33,295	Females N = 31,144	Total N = 64,439	Males N = 6,924	Females N = 5,708	Total N = 12,632
<b>Birthweight (grams)</b>						
mean (standard deviation)	3,477	3,350	3,416	3,504	3,386	3,450
>350 – <2,500	1,663	1,877	3,540	352	341 (6.0)	693
2,500 – <3,000	3,850	4,881	8,731	770	820	1,590
3,000 – <3,500	10,886	12,124	23,010	2,096	2,067	4,163
3,500 – <4,000	11,439	9,090	20,529	2,484	1,822	4,306
4000	5,350	3,068	8,418	1,203	640	1,843
<i>Missing</i>	107	104	211	19	18	37
<b>Gestational age (weeks)</b>						
mean (standard deviation)	39.3	39.4	39.4	39.2	39.3	39.2
<37	2,651	2,182	4,833	574	448 (8.3)	1,022
37–38	5,816	5,078	10,894	1,265	999	2,264
39–40	14,416	13,975	28,391	3,141	2,592	5,733
41	5,061	4,747	9,808	946	808	1,754
42	3,636	3,612	7,248	651	579	1,230
<i>Missing</i>	1,715	1,550	3,265	347	282	629
<b>Maternal Race</b>						
Non-Hispanic, white	27,817	26,024	53,841	6,002	4,988	10,990
Hispanic	1,488	1,358	2,846	283	204 (3.6)	487
Other	3,618	3,395	7,013	597	461 (8.2)	1,058
<i>Missing</i>	372	367	739	42	55	97
<b>Maternal Education</b>						
High school	12,097	11,175	23,272	2,614	2,222	4,836
Some college	6,051	5,812	11,863	1,491	1,136	2,627
College graduate	6,181	5,800	11,981	1,506	1,223	2,729
<i>Missing</i>	8,966	8,357	17,323	1,313	1,127	2,440
<b>Birth year</b>						
1970–1984	7,796	7,172	14,968	1,624	1,347	2,971
1985–1990	8,719	8,174	16,893	1,997	1,640	3,637
1991–1996	8,806	8,235	17,041	1,659	1,428	3,087
1997–2010	7,974	7,563	15,537	1,644	1,293	2,937
<b>State</b>						
Minnesota	14,674	13,999	28,673	3,316	2,638	5,954
New York	6,280	5,759	12,039	2,393	1,964	4,357
Washington	12,341	11,386	23,727	1,215	1,106	2,321

**Table 2.**

Odds ratios (OR) and 95% confidence intervals (95% CI) from the mediation analysis for the crude association between sex and childhood cancer risk mediated by birthweight<sup>a</sup>, 3-state pooled analysis (1970–2014)

	Indirect			Direct			Total			% Change from total to direct
	OR	(95% CI)	p-	OR	(95% CI)	p-	OR	(95% CI)	p-	
All cancers combined	1.01	(1.01-	<0.001	1.12	(1.08-	<0.001	1.13	(1.09-	<0.001	11
Lymphoid leukemia	1.03	(1.02-	<0.001	1.16	(1.08-	<0.001	1.19	(1.11-	<0.001	16
Hodgkin lymphoma	1.01	(0.98-	0.4	1.48	(1.22-	<0.001	1.50	(1.24-	<0.001	3
Burkitt lymphoma	1.00	(0.96-	0.9	5.02	(3.40-	<0.001	5.02	(3.42-	<0.001	2
Other non-Hodgkin	1.01	(0.98-	0.7	1.42	(1.18-	<0.001	1.43	(1.20-	<0.001	0
Intracranial embryonal	0.99	(0.97-	0.6	1.49	(1.26-	<0.001	1.48	(1.26-	<0.001	-2
Hepatoblastoma	0.92	(0.88-	<0.001	1.90	(1.40-	<0.001	1.75	(1.29-	<0.001	-15
Rhabdomyosarcoma	1.01	(0.98-	0.5	1.47	(1.19-	<0.001	1.49	(1.21-	<0.001	3
Extracranial GCT	1.06	(0.97-	0.2	0.41	(0.26-	<0.001	0.43	(0.28-	<0.001	-7
Thyroid carcinoma	0.99	(0.94-	0.8	0.35	(0.25-	<0.001	0.35	(0.25-	<0.001	1

<sup>a</sup>Percent change from total to direct effect  $((\beta_{\text{total}} - \beta_{\text{direct}}) / \beta_{\text{total}}) * 100$