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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 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.

1. 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 use 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 [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

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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 altering maternal hormones and growth factors that encourage rapid fetal growth [26,27]; both of which are 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.

2. Methods

2.1. 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 to 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 at < 28 days of life and those with Down syndrome listed on their birth certificate (57 cases and 24 controls) were excluded.

2.2. 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– < 2500, 2500– < 3000, 3000– < 3500, 3500– < 4000, ≥4000), 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).

2.3. 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 Fig. 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 ($\beta_{indirect} = \beta_{total} - \beta_{direct}$). 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.

3. Results

Compared to controls, cases were more likely to be male (cases 54.8%; controls 51.7%, of higher birthweight (≥3,500 g: 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 g at birth (males 53.4%; females 43.3%).

Differences in the risk of childhood cancer by sex were apparent when comparing crude and multivariable adjusted ORs for childhood cancer overall and by cancer type (Fig. 1). ORs > 1 indicate tumor types associated with male sex, whereas ORs < 1 represent 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