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Wilms tumor and congenital anomalies in a population-based cohort study in Denmark

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Wilms tumor and congenital anomalies in a population-based cohort study in Denmark

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ABSTRACT OF THE THESIS

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a population-based cohort study in Denmark

by

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Master of Science in Epidemiology

University of California, Los Angeles, 2017

Professor Beate R. Ritz, Chair

Cancer is the primary cause of death from disease in children past infancy in the United States, but little is known about its etiology. Studies have demonstrated an increased occurrence of congenital anomalies in children with Wilms tumor. Data from a population-based cohort study in Denmark between 1968 and 2014 were utilized to investigate the relationship between congenital anomalies and Wilms tumor cases. We ascertained 202 Wilms tumor cases and 4,040 controls. Odds ratios were computed using unconditional logistic regression. The data suggests potential increased odds of cryptorchidism (OR=3.0, 95% CI 1.4, 6.3) and hernias (OR= 2.3, 95% CI 1.2, 4.4) in Wilms cases in our study cohort. The odds of cryptorchidism increased when adjusted on maternal age (OR= 11.3, 95% CI .94, 135.2). We also observed increased odds of hernia after adjusting for maternal age and maternal smoking during pregnancy (OR= 2.0, 95% CI 0.7, 5.8). This study supports the association between congenital anomalies and Wilms tumor and suggests that environmental factors also contribute to solid pediatric cancers.

The thesis of Kyasha Moore is approved.

Julia E Heck

Niklas Krause

Ondine S. von Ehrenstein

Beate R Ritz, Committee Chair

University of California, Los Angeles

2018

Dedication

I dedicate this thesis to my loving family, supportive colleagues, and the many people who work to improve the health of others as an act of social justice.

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Background

Cancer is the primary cause of death from disease in children past infancy in the United States. In 2017, it was estimated that 10,270 cases of cancer will be diagnosed in children aged 0-14 years old (1). Due to their rarity, little is known about pediatric solid tumors such as Wilms tumor (nephroblastoma), which has an incidence of 100 per million before the age of 15 years (2). Renal tumors account for 4% of childhood cancers, and Wilms tumor makes up more than 90% of these tumors (3). The incidence of Wilms is most common in children under the age of 5 years old, with a 5-year survival rate of 88% (2). The etiology of pediatric cancers remains largely unknown, with several established risk factors, including chemotherapeutic agents, diethylstilbestrol, parental smoking, ionizing radiation, and congenital anomalies, accounting for a small proportion of cases (4–6).

Congenital anomalies are recognized to occur with childhood cancer (7). Among the most well-recognized associations is an increase in acute leukemia among children with Down syndrome (Trisomy 21) (8), cardiac defects with neurofibromatosis (NF1), which is related to pediatric gliomas (9–12), and Wilms tumor, aniridia, genitourinary anomalies, and mental retardation (WAGR) syndrome and Wilms tumor (*WT1* gene) (13,14). These associations suggest a common cause of both the congenital malformation and the malignancy, whether genetic or environmental. Establishing additional associations between congenital defects and childhood malignancies is of great importance, as more than 7.9 million infants in the world are born annually with birth defects (15). Elucidating this association can result in a better understanding of the genetic and environmental factors that influence cancer pathogenesis.

This study seeks to describe the relationship between congenital anomalies and malignancies in childhood. Earlier studies have found it difficult to investigate this association due to a lack of power, as both pathologies are rare (16). Hospital-based studies have had greater detail regarding anomalies but have been limited by smaller sample sizes. Register-based studies which relied on the International Codes of Disease Ninth Edition (ICD-9) codes had poorer specificity to identify specific anomalies and syndromes compared to ICD-10. Our study will utilize linked data between the Danish Cancer Registry, the Danish Medical Births Registry, and the Danish National Patient Register to identify specific

congenital anomalies. Denmark began using ICD-10 in 1994, which was an earlier uptake then some other nations (17). This will allow us to better characterize ICD coding, as we can rely upon a longer time period to identify anomalies.

Methods

This study is a population-based case-control study which included cancer cases identified in the Danish Cancer Registry from Danish children born from 1968 to 2014. Our methods have been previously described (18). Briefly, twenty controls were selected at random from the Danish Central Population Registry and matched by sex, birth year, and plurality. Information from multiple databases was linked using the unique personal identification number, which is assigned by the national Central Population Registry and given to each person living in Denmark (19).

Childhood cancer diagnosis was reported using the International Classification of Childhood Cancer (ICCC). ICCC-1 was based on the original notifications forms consistent with the International Classification of Disease for Oncology (ICD-O). ICD-O-1 codes were used from 1978 until 2007, and ICCC-3 based on ICD-O-3 codes after 2003 (20,21). The Danish Cancer Registry contains all malignancies diagnosed from 1943, with an estimated inclusion of 95-98% of cases (22). The Danish Cancer Registry documents the type of cancer using histological samples and links to death certificates annually. Parental ages and other demographic information were obtained from the Central Population Registry. Study inclusion criteria were that children had to have been born in Denmark, in order to have more complete information on birth and parent-related factors.

The Danish Medical Birth Registry collects data about each birth within Denmark, with files computerized in 1973. The gestational factors that are collected included maternal smoking during pregnancy, maternal pregnancy history, birthweight, gestational age, congenital malformations recognized at birth (using the customized Danish ICD-10, as explained below) and other variables. Validation studies have established agreement between the registry and medical records (23).

Not all congenital anomalies are initially detected at birth, such as in gonadal dysgenesis (24). As such, we also collected data about congenital anomalies from the National Patient Registry in order to

capture later diagnoses. The Danish National Patient Registry recorded diagnoses from inpatient visits from 1977 and outpatient visits from 1995 (25). Children were diagnosed in accordance with an extended Danish version of the International Classification of Diseases (ICD-10) from 1994 to present day. Before adopting ICD-10, an extended Danish version of ICD-8 was used to report congenital anomalies.

Here we report upon congenital anomalies (ICD-8 74099-75999; ICD-10 Q00-Q99) found in cases, as well as conditions known to co-occur with Wilms tumor, based upon the literature. The following congenital anomalies and disorders have been described in patients with Wilms tumor, but they were not found in our cases: agenesis of the ovary, aortic stenosis, bilateral renal cyst, congenital hemihypertrophy, congenital malformations in ovaries, fallopian tubes and uterus ligaments Denys-Drash syndrome, Down syndrome, Fanconi anemia, Fragile X, horseshoe kidney, Li Fraumeni syndrome, Marfan syndrome, Meckel's diverticulum, mental retardation, microcephaly, Mulibrey Nanism, nystagmus, Patau syndrome, Perlman syndrome, Sotos syndrome, spina bifida, transposition of the great vessels, and Turner syndrome (26–31).

This study did not require direct contact with study participants, so it was deemed exempt from the informed consent requirement. This study was approved by the human internal review board of the University of California, Los Angeles, and the Danish Data Protection Agency.

The parent study contained 223 cases of Wilms tumor and 4,040 matched controls. Exclusion criteria for the current analysis included those who died before 1994 or emigrated from Denmark before 1994, which was the year of initial uptake of ICD-10. This eliminated 21 cases and their 420 controls from our study population. The final analysis included 4,242 participants with 202 cases and 4,040 controls.

We estimated risk of Wilms tumor using unconditional logistic regression. Despite the matched case-control study design, we decided to break the matches and include all possible controls in each regression, increasing the likelihood of having any control with each of these rare conditions, which allowed us to calculate a point estimate for the associations of interest.

All models adjusted for the matching factors, birth year, sex, and plurality. After reviewing the literature, we considered adjusting for the following potential confounders and effect measure modifiers: maternal age at birth (categorical variable), paternal age at birth (categorical variable), maternal smoking (yes vs. no), social status (High (1)- Low (5)), birthweight (categorical), and gestational age (≤36 weeks, ≥37-40 weeks, >40 weeks) (18,32–34,34–36). Gestational age was measured from the date of the last reported menstruation with imputation for missing information, as described previously (18). After analyzing the impact of each covariate, we adjusted cryptorchidism on maternal age, and hernia on maternal age and maternal smoking.

Results

The cases and controls were quite similar demographically. However, maternal smoking was 29% among Wilms cases and 24.8 % for controls (Table 1). Our results indicate a difference in congenital anomalies among cases and controls (Table 2). Hernias were the most common congenital anomaly in our study, with 172 controls having a hernia and 21 cases having a hernia. The second most common congenital anomaly was cryptorchidism, with an odds ratio of 7.5. Aniridia occurred in 2.5% of cases. Auras alatae was diagnosed in 12 patients, constituting 0.3% of controls. Children with Wilms are 1.7 times more likely to have a ventral septal defect than controls.

Discussion

This study provides a thorough description of congenital anomalies in Wilms tumor cases in Denmark, using a validated population-based registry from 1968-2015. In our study population, hernias and cryptorchidism were most frequently seen, and these have also been reported previously with Wilms tumor. Case reports have been published reporting on rare anomalies that have occurred with Wilms (37–40) and our group made efforts to search for such cases, as well as those more frequently reported, in order to characterize the prevalence within this population-based cohort. As such, this study strengthens our understanding of congenital anomalies found in Wilms tumor.

It has been established that specific mutations contribute to Wilms tumor. One such mutation is in the *WT1* gene with deletions in 11p13. This site is involved with cell growth, differentiation, and

apoptosis in the kidney and is associated with 4% of cases (41). The *WT2* gene is another gene that has been associated with Wilms and Beckwith-Wiedemann syndrome, due to a deletion at 11p15 (42). Mutations in *WT1* are associated with congenital nephrotic syndrome, Denys-Drash, Frasier syndrome, in addition to Wilms (43).

There were two cases of a "congenital anomaly of the tongue." Although we had no way to determine the type of tongue anomaly, it is in keeping with descriptions in the literature of Beckwith-Wiedemann syndrome, which includes macroglossia (44). The children with the tongue anomaly were not also the children with Beckwith-Wiedemann. While it is possible that tongue anomalies could occur in the absence of Beckwith-Wiedemann, there is also a possibility that Beckwith-Wiedemann is underrepresented in medical records. The prevalence of Beckwith-Wiedemann in our Wilms study was 0.05%, compared to a percent of 1.1% among Wilms Tumor Study Group.

Wilms tumor is well-recognized to occur with high birthweight (≥ 4000 grams) and overgrowth syndromes. It is hypothesized that Wilms is associated with an excess level of growth factor(45). The association of congenital hemihypertrophy (asymmetrical overgrowth) (46) and Beckwith-Wiedemann syndrome (macroglossia, visceromegaly and hypoglycemia) (44) support this notion. However, in our study, the low birthweight children had 1.4-time increased odds of Wilms as compared to normal birthweight children. Those with a high birthweight had reduced odds of Wilms with an odds ratio of 0.7 as compared to the normal birthweight children. Schuz et al. also found that children with lower birthweights had a 1.1 times increased odds of Wilms tumor(47), but the high birthweight children in their study had a 1.43 times increased odds of Wilms. Perhaps this increase in birthweight among Wilms cases is more pronounced in congenital hemihypertrophy and Beckwith-Wiedemann syndrome, however our cohort only had one Wilms case with Beckwith-Wiedemann and no cases of congenital hemihypertrophy.

Other studies have reported associations between Wilms tumor and Down syndrome (48). No Wilms cases in our study were diagnosed with Down syndrome. This anomaly is likely underrepresented in the Danish population. In 2004, Denmark issued national guidelines that recommended that all

pregnant women have access to information about prenatal screening and a first trimester screening that tests for Down Syndrome (Trisomy 21), Edwards syndrome (Trisomy 18), and Patau syndrome (Trisomy 13) (49,50). Since that time, there has been a decrease in Down syndrome incidence of 50% (51), thus we were not able to estimate the risk of Down syndrome among Wilms tumor cases.

Our results found an increased risk of Wilms tumor in fathers older than 40 years old with 2.0 times increased odds for Wilms cases as compared to controls. It is hypothesized that fathers accumulate more *de novo* mutations due to the increased number of cell divisions that occurs in spermatogonial cells as compared to oogonial cells (18). Deletions are found in the DNA of sperm of older fathers (52). These mutations may contribute to the development of Wilms tumor, as it is deletions in *WT1* that are most frequently reported in WAGR syndrome.

The extant literature demonstrates many congenital anomalies that are associated with Wilms tumor, not all of which we were able to observe in our study due to the sample size, however our population- based approach provides the prevalence of the most commonly reported mutations. The strengths of this study include the ability to retain all subjects due to linkage via the unique identifiers. Furthermore, there was no differential recruitment of study participants as the study used register-based data.

Limitations of the study include possible differential misclassification of congenital abnormalities among children with cancer. This could occur if children with cancer are examined more frequently and thoroughly by clinicians, which increases the likelihood of diagnosing additional congenital abnormalities which may normally go undetected. This misclassification would positively bias the point estimate away from the null and overestimate the true association between congenital abnormalities and malignancies. Yet, high uptake of prenatal screening (more than 90% of mothers in Denmark undergo the first-trimester risk assessment(53) and free and universal access to health care in Denmark would simultaneously increase the observation and reporting of anomalies in controls. Universal health care access in Denmark was initiated in 1970, thus during forty-seven of the forty-nine years of the study period (53). Danish children have regular well-child visits at five weeks, five months, and then yearly until the age of five

(54). While this differs substantially from the well-child visit in the United States (before five years of age, eleven visits are recommended (55)), nonetheless we expect that all children in the study would have had the opportunity for regular medical surveillance. Our choice to break the matches and use unconditional logistic regression may have led to less robust findings, however it allowed us to calculate odds ratios for rare conditions (56).

Future research might include genetic and non-genetic epidemiologic studies to better understand shared risk factors for congenital anomalies and Wilms tumor. A better understanding of these associations can help inform genomic studies, and provide targeted recommendations for screening among children living with congenital malformations.

Table 1. Demographic characteristics of Wilms tumor cases and controls, 1968-2014

	Case (N)	Case (%)	Mean (SD)	Control (N)	Control (%)	Mean (SD)	Crude Odds Ratio (95% CI)	Lower CL	Upper CL
Characteristic									
Age			9.0 (6.4)			9.0 (6.4)			
Sex									
Male	103	51.0		2060	51.0		1.0	0.8	1.3
Female	99	49.0		1980	49.0		Referent	-----	-----
Gestational Age									
Preterm	19	9.4		214	5.3		1.9	1.2	3.2
Term	183	90.6		3804	94.2		Referent	-----	-----
Late term	0	0.0		22	0.5		-------	-----	-----
Birth Weight (grams)			3393.3 (618.9)			3402.5 (601.1)			
Low birthweight	14	7.0		197	4.9		1.4	0.8	2.4
Normal birthweight	163	81.1		3146	78.1		Referent	-----	-----
High birthweight	24	11.9		686	17.0		0.7	0.4	1.0
Family SES									
1 (Low)	22	10.9		350	8.7		Referent	-----	-----
2	19	9.4		557	13.8		0.5	0.3	0.9
3	24	11.9		566	14.0		0.7	0.4	-----
4	58	28.7		1066	26.4		0.8	0.5	1.4
5 (High)	24	11.9		512	12.7		0.7	0.4	1.3
Missing	55	27.2		989	24.5		-----	-----	-----
Maternal Age			28.2 (24.4)			28.0 (4.9)			
<24	49	24.3		949	23.5		0.9	0.6	1.3
25-29	86	42.6		1552	38.4		Referent	-----	-----
30-34	50	24.8		1085	26.9		0.9	0.6	1.2
35-39	15	7.4		390	9.7		0.7	0.4	1.3

	Case (N)	Case (%)	Mean (SD)	Control (N)	Control (%)	Mean (SD)	Crude Odds Ratio (95% CI)	Lower CL	Upper CL
40+	2	1.0		64	1.6		0.6	0.2	2.6
Paternal Age			31.0 (28)			28.0 (16.1)			
<24	55	27.2		1448	36.4		0.3	0.2	0.5
25-29	69	34.2		643	16.2		Referent	-----	-----
30-34	37	18.3		475	11.9		0.7	0.5	1.1
35-39	18	8.9		331	8.3		0.5	0.3	0.9
40+	23	11.4		1085	27.3		0.2	0.1	0.3
Maternal Smoking*	18	29.0		374	24.8		1.3	0.7	2.2
Multiple Birth‡	0	0.0		10	1.0		-----	-----	-----

*Available 1991+

‡ Available 1997+

Table 2. Association between Wilms tumor and congenital anomalies, 1968-2014

Congenital Anomaly	Cases (N)	Cases (%)	Controls (N)	Controls (%)	Odds Ratio[a]	Odds Ratio[a] 95% CI	Odds Ratio	Odds Ratio 95% CI
Cardiovascular System								
Congenital Heart Valve Disease	1	.50	3	.07	7.3	(0.7, 70.5)	-	-
Ventral Septal Defect	2	.99	24	.59	1.7	(0.41, 7.4)	-	-
Chromosomal Abnormality							-	
Edward Syndrome (Trisomy 18)	1	.50	0	0	-	-	-	-
Endocrine System								
Hyperparathyroidism-jaw tumor syndrome	1	.50	0	0	-	-	-	-
Nervous System								
Other congenital malformations of the brain	1	.50	2	.05	11.1	(.9, 123.8)	-	-
Reproductive System								
Cryptorchidism	10	5.0	57	1.4	3.0	(1.4, 6.3)	11.3[b]	(0.9, 135.2)
Bilateral cryptorchidism	4	2.0	14	.35	4.9	(1.6, 15.1)	-	-
Unilateral cryptorchidism	6	3.0	43	1.1	2.6	(1.1, 5.8)	-	-
Hypospadias	1	.50	4	.10	5.1	(0.6, 46.3)	-	-
Testicular Aplasia	1	.50	0	0	-	-	-	-
Testicular Retention	1	.50	0	0	-	-	-	-
Sensory Anomaly								
Aniridia	5	2.5	0	0	-	-	-	-
Congenital Cataracts	3	1.5	4	.10	17.3	(3.8, 78.6)	-	-
Structural Anomaly								
Aures alatae	1	.50	33	.82	0.6	(0.08, 4.6)	-	-
Beckwith-Wiedemann Syndrome	1	.50	0	0	-	-	-	-
Congenital malformation of the tongue	2	.99	3	.07	15.	(2.5, 91.1)		-
Hernia	11	5.5	172	2.4	2.3	(1.2, 4.4)	2.0[c]	(0.7, 5.8)
Systemic Anomaly								
Congenital syndromes affecting multiple systems	1	.50	0	0	-	-	-	-
Tuberous sclerosis	1	.50	1	.02	22.3	(1.4, 360.9)	-	-

a Adjusted on matching variables: sex, birth year, plurality
b Adjusted on maternal age
c Adjusted on maternal age and maternal smoking

Supplementary Table 1. Danish extended version of ICD-8 and ICD-10: Codes used to identify congenital anomalies associated with Wilms tumor

Cardiovascular System	**ICD-10**	**ICD-8**
Congenital Heart Valve Disease	-	74699
Ventral Septal Defect	Q210	74639
Chromosomal Abnormality		
Edward Syndrome (Trisomy 18)	Q910, Q911, Q912, Q913, Q913A	75940
Endocrine System		
Hyperparathyroidism-jaw tumor syndrome	-	E210, E210A, E210B
Nervous System		
Other congenital malformations of the brain	Q15	74329
Reproductive System		
Bilateral cryptorchidism	Q532	75211
Hypospadias	Q54	75220
Testicular Aplasia	Q550B	75280
Testicular Retention	Q532	75219
Unilateral cryptorchidism	Q531	75210
Sensory Anomaly		
Aniridia	Q131	74459
Congenital Cataracts	Q120	74439
Structural Anomaly		
Aures alatae	Q175	74520
Beckwith-Wiedemann syndrome	Q873, Q873A, Q873B, 873C	-
Congenital malformation of the tongue	Q383	75009
Hernia	H430, J985C, K40, K400, K401, K401, K402A, K403, K403A, K403B, K404, K409, K41, K410, K411, K412, K412A, K413, K413A, K413B, K414, K419, K42, K420, K420A, K420B, K421, K429, K43, K430, K431, K432, K433, K434, K435, K435A, K435B, K435C, K435D, K436, K436A, K436B,	12950, 40540, 40549, 40560, 40569, 40570, 40579, 40580, 40600, 40620, 40621, 40640, 40660, 40680, 40740, 40760, 40800, 40801, 40840, 40900, 40940, 42000, 42100, 42400, 42500, 42600, 42700, 42710, 42900

	K437, K439, K44, K440, K440A, K440B, K441, K449, K450D, K450E, K450F, K450H, K450I, K450J, K450K, K450L, K450M, K451D, K451E, K451F, K451H, K451I, K451J, K451K, K451L, K451M, K458D, K458E, K458F, K458H, K458I, K458J, K458K, K458L, K458M, M628A, N816A, N834A, Q401, 647H, Q790	
Systemic Anomaly		
Congenital syndromes affecting multiple systems	-	75999
Tuberous sclerosis	Q851	75969

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