




Cancer Risk in Children with Birth Defects: A Population-Based Registry Linkage Study


Texas Children's Cancer and Hematology Centers


Baylor College of Medicine


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Pediatrics


Birth Defects



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Birth Defects

- Structural or functional anomalies present at the time of birth
- “1 in 33 born with a birth defect”
- 5 most common birth defects
 - Congenital heart defects
 - Neural tube defects
 - Hemoglobin disorders
 - Down syndrome
 - Glucose-6-phosphate dehydrogenase deficiency

25% of all birth defects

7,000 birth defects

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Impact of Birth Defects

- Leading cause of death in the 1st year of life
- Overall birth defects are common
 - 1 in 33 births
 - 120,000 babies per year in the U.S.
- Specific birth defects are rare
 - 7,000 birth defects
 - Often difficult to study

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Etiology of Birth Defects

- Chromosomal abnormalities
 - 6% of all birth defects
 - Down syndrome (trisomy 21)

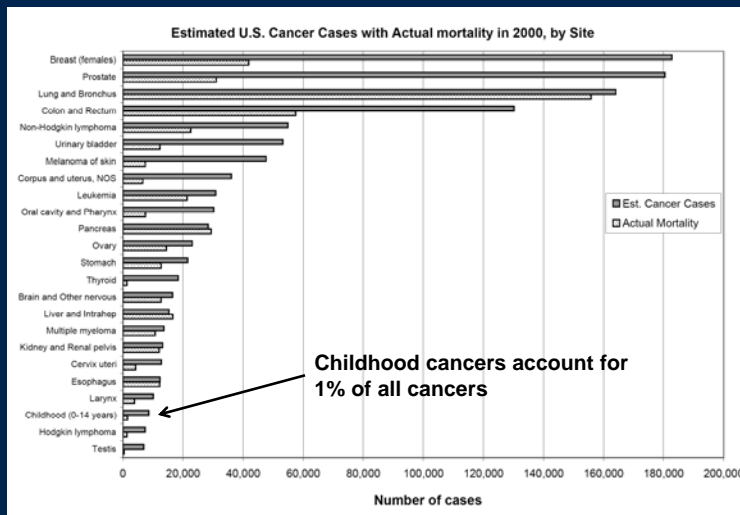
- Single gene defects
 - 7.5% of all birth defects
 - Neurofibromatosis type I

- Multifactorial disorders (non-syndromic)
 - 85% of all birth defects
 - Congenital heart defects

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Childhood Cancer



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Impact of Childhood Cancer

- Leading cause of death among children 1 to 14 years
- Incidence is increasing
- Survival rates are improving
 - 5-year survival is 79.6%
 - "Late effects" are a common and serious problem in survivors
- Specific childhood cancers are rare

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Etiology of Childhood Cancers

- Few established risk factors
 - High levels of ionizing radiation
 - Genetic syndromes
- ***Is having a birth defect a risk factor for childhood cancer?***

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Birth Defects and Childhood Cancer

- Chromosomal abnormalities

- 6% of all birth defects
- Trisomy 21



Acute leukemia

- Single gene defects

- 7.5% of all birth defects
- Neurofibromatosis type I



Rhabdomyosarcoma

- Multifactorial disorders (non-syndromic)

- 85% of all birth defects
- Congenital heart defects



???

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Previous Studies

- Risk of any cancer if born with any birth defect

- *Grouped BD-Grouped CC*

- Risk of specific cancer if born with any birth defect

- *Grouped BD-Specific CC*

- Risk of any cancer if born with specific birth defects

- *Specific BD-Grouped CC*

- What is missing?

- *Specific BD-Specific CC*

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Linkage Studies

First author	Study period	Sample size	Reported Associations		Molecular study
			Grouped BD and/or CC	Specific BD and CC	
Narod	1971-1986	20,304	X	✓	X
Altman	1984-1993	2,850	✓	X	X
Agha	1979-1996	90,400	✓	X	X
Rankin	1985-2001	599,290	✓	X	X
Bjørge	1967-2004	5.2 million	✓	✓	X
Fisher	1988-2004	3.2 million	✓	X	X
Carozza	1996-2005	3.2 million	✓	X	X
Botto	1983-2006	2.8 million	✓	X	X

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Issue


- **Identifying novel** birth defect-childhood cancer (BD-CC) patterns among less common phenotypes
- **What is needed:** Large population-based cohorts with sufficient numbers of birth defects to allow for meaningful estimation of childhood cancer risks

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Establishing Novel Associations


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Texas Linkage Study

- Birth cohort
 - Children born to Texas residents between 1996 and 2009
 - Birth certificates
 - 5,275,792 livebirths
- Comparison groups
 - Those with birth defects
 - Those without birth defects



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Linking Registries

- Texas Birth Defects Registry

- Active surveillance system
- Within 1st year of delivery
- 184,698 cases

- Texas Cancer Registry

- Gold Certified by the North American Association of Central Cancer Registries (NAACCR)
- <15 years of age
- 5,571 cases

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Methods

- Linkage conducted using Link Plus, version 2.0
- Data on potential confounders obtained from birth certificate data
- Statistical analysis: Cox proportional hazards regression
 - Hazard ratio (HR)
 - 95% confidence interval (CI)
- Excluded cases with chromosomal abnormalities

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Grouped BD-Specific CC

Cancer Group	HR	95% CI
Germ cell tumors	3.94	2.07-7.49
Hepatic tumors	9.65	5.66-16.47
Leukemias	1.69	1.29-2.21
Retinoblastoma	1.16	0.48-2.82
CNS tumors	2.26	1.69-3.03
Neuroblastoma	2.53	1.70-3.79
Lymphomas	3.06	1.93-4.85
Renal tumors	1.73	0.85-3.16
Soft-tissue sarcomas	1.72	0.85-3.47
Bone tumors	0.68	0.10-4.91

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Cardiac Defects and Lymphoma Risk

Cardiac Defect	HR	95% CI
Transposition of the great vessels	9.37	1.32-66.56
Atrial septal defects	4.33	1.80-10.41
Aortic valve stenosis	19.45	2.74-138.20
Patent ductus arteriosus	22.12	3.11-157.18
Coarctation of the aorta	5.90	2.64-13.13

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Specific BD-Grouped CC

Birth Defects Group	HR	95% CI
Biliary atresia	13.20	4.95-35.18
Anophthalmia	9.45	1.33-67.13
Microphthalmia	7.33	3.29-16.32
Omphalocele	7.96	3.31-19.13
Patent ductus arteriosus	3.18	2.46-4.12
Atrial septal defect	2.68	2.03-3.53
Coarctation of the aorta	2.47	1.03-5.94
Cleft lip with or without cleft palate	3.03	1.76-5.22
Renal agenesis	2.45	1.02-5.89
Spina bifida	7.59	4.20-13.72

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An/Microphthalmia and Cancer Risk

Cancer Group	HR	95% CI
Leukemias	9.41	3.04-29.24
Lymphomas	16.51	2.32-117.53
Neuroblastoma	20.51	5.11-82.23
Retinoblastoma	23.41	3.28-166.91

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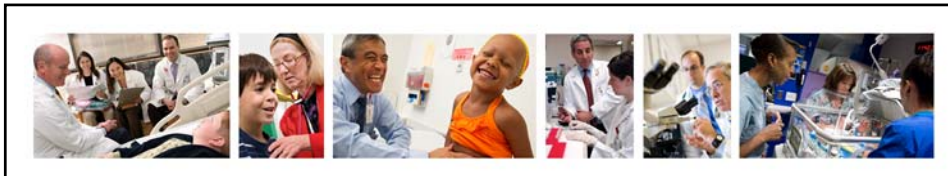
Key Findings

- Overall, children with birth defects were 3-times more likely to be diagnosed with cancer compared to their unaffected contemporaries
- HR=3.07, 95% CI: 2.80-3.37
- A majority (60%) of childhood cancers were significantly associated with having any non-chromosomal birth defects
- The risk of childhood cancer was seen among most (55%) monitored birth defects

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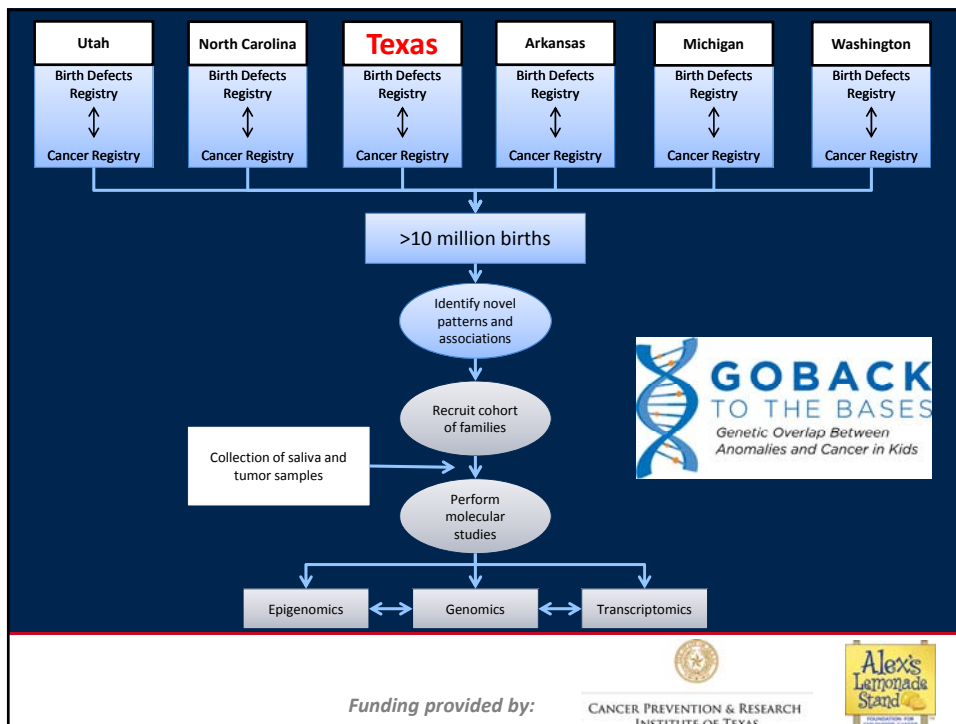
Future Plans

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A Population-Based Birth Cohort

- Identify novel patterns
 - Specific BD-Specific CC combinations
- Collect biological samples
- Discover consistent genomic alterations
 - Genetic
 - Epigenetic

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Conclusions


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Importance

- Children with specific birth defects and/or identified mutations are candidates for prevention and screening clinics
- Novel genes provide insight into:
 - Development
 - Cancer susceptibility
- Improved treatment protocols

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Conclusions

- Birth defects = one of the strongest risk factors for childhood cancer
- >10% of childhood cancer cases
 - Minor and major defects
- Population-based cohorts needed
 - Identify novel patterns
 - Collect biological samples
- Potential for improved surveillance protocols

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Questions



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