Cancer Risk in Children with Overgrowth Features and Syndromes: A Population-Based Assessment among 7-Million Births

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BACKGROUND

While overgrowth syndromes, such as Beckwith-Wiedemann syndrome (BWS), are associated with an increased risk of pediatric cancer,[1] there are few population-based estimates of risk, and there are limited studies describing associations between overgrowth features (e.g. hemihypertrophy) and pediatric cancer among children without diagnosed syndromes.

PURPOSE

We evaluated cancer risk among children with overgrowth features and overgrowth syndromes using data from population-based registries.

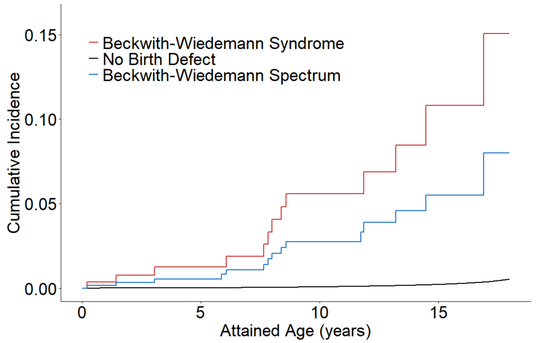
METHODS

- Data from the Texas Birth Defects Registry, one the world's largest population-based birth defects registries, was used to determine overgrowth features (k=18) and syndromes (k=14) among children born in Texas for the period 1999-2017.
- Records for children with and without overgrowth features/syndromes were linked to the Texas Cancer Registry to determine the incidence of cancer up to 18 years among these groups.
- Cox regression models were used to generate a hazard ratio (HR) and 95% confidence interval (CI) for the association between each overgrowth feature/syndrome and cancer adjusting for infant sex and maternal age.

Table 1. Demographic characteristics of eligible GOBACK birth cohort (n=6,997,422)

	Live Birth Status	
	No Birth Defects (n=6,976,215)	Overgrowth Syndromes or Features (n=21,207)
Sex, n(%)		
Male	3,536,160 (50.7)	9,684 (45.7)
Female	3,440,055 (49.3)	11,523 (54.3)
Maternal Education, n(%)		
Less than High School	1,861,251 (26.7)	5,739 (27.1)
High School Diploma	1,953,927 (28.0)	6,133 (28.9)
More than High School	3,118,646 (44.7)	9,191 (43.3)
Unknown	42,391 (0.6)	144 (0.7)
Maternal Race, n(%)		
American Indian or Alaska Native	19,261 (0.3)	54 (0.3)
Asian	294,186 (4.2)	634 (3.0)
Hispanic	3,368,978 (48.3)	11,287 (53.2)
Non-Hispanic Black	801,146 (11.5)	1,968 (9.3)
Non-Hispanic White	2,453,574 (35.2)	7,153 (33.7)
Other	31,042 (0.4)	90 (0.4)
Unknown	7,002 (0.1)	18 (0.1)
Missing	1,026	3
Cancer Status, n(%)		
No Childhood Cancer Diagnosis	6,966,824 (99.9)	21,101 (99.5)
Any Childhood Cancer Diagnosis	9,391 (0.1)	106 (0.5)
Birth Weight, grams (SD)	3,261 (559)	2,896 (1,002)
Gestational Age, weeks (SD)	38 (2)	36 (4)
Maternal Age, years (SD)	27 (6)	28 (6)

Figure 1. Cumulative incidence of childhood cancer by Beckwith-Wiedemann status



Definition:
Beckwith-Wiedemann spectrum: cases of Beckwith-Wiedemann syndrome *and/or* hemihypertrophy

Table 2. Multivariable* cox proportional hazards regression models evaluating the association between overgrowth features/syndromes and childhood cancer.

	Hazard Ratio	95% CI Lower Bound	95% CI Upper Bound	p-value
Overgrowth Syndrome				
Beckwith-Wiedemann Syndrome	41.69	24.20	71.83	3.63E-41
Beckwith-Wiedemann Spectrum	23.16	13.96	38.44	5.01E-34
Overgrowth Feature				
Any Feature	4.70	3.83	5.77	2.44E-49
Cardiomegaly	4.64	3.02	7.12	2.19E-12
Hemangioma	3.33	2.30	4.83	2.08E-10
Hepatomegaly	8.90	6.10	12.98	8.10E-30
Hepatosplenomegaly	23.04	13.37	39.69	1.27E-29
Macroglossia	11.18	6.35	19.70	6.34E-17
Nephromegaly	6.87	3.43	13.74	5.10E-08

* Model adjusted for sex and maternal age.

Table 3. Percent of children with overgrowth syndromes and features diagnosed with cancer over time.

	Attained Age (years)	Cumulative Number of Cases Diagnosed	Number at Risk	% of Children Diagnosed with Cancer	95% CI[1] Lower Bound	95% CI[1] Upper Bound
Overgrowth Syndrome						
Beckwith-Wiedemann Syndrome	5	3	175	1.24	0.00	2.64
	10	9	104	5.58	1.85	9.16
	15	12	31	10.81	3.65	17.44
Beckwith-Wiedemann Spectrum	5	3	397	0.54	0.00	1.15
	10	10	229	2.75	1.00	4.47
	15	14	84	5.51	2.24	8.67
Overgrowth Feature						
Any Feature	5	17	13532	0.11	0.06	0.16
	10	46	7237	0.38	0.27	0.49
	15	75	2474	1.02	0.75	1.29
Cardiomegaly	5	5	3767	0.11	0.01	0.21
	10	12	1741	0.36	0.15	0.58
	15	17	491	0.88	0.35	1.41
Hemangioma	5	3	6180	0.04	0.00	0.09
	10	11	3205	0.20	0.08	0.33
	15	23	1032	0.80	0.43	1.17
Hepatomegaly	5	6	1630	0.30	0.06	0.54
	10	15	1085	0.96	0.47	1.46
	15	23	421	2.17	1.18	3.16
Hepatosplenomegaly	5	2	293	0.56	0.00	1.33
	10	7	189	2.50	0.63	4.33
	15	10	87	4.82	1.50	8.02
Macroglossia	5	3	669	0.41	0.00	0.88
	10	7	397	1.11	0.28	1.93
	15	9	143	1.94	0.45	3.41
Nephromegaly	5	2	579	0.33	0.00	0.78
	10	5	367	0.99	0.11	1.87
	15	7	174	1.68	0.38	2.96

[1] CI; confidence interval

RESULTS

- In the overall birth cohort (n=6,997,422), 6,976,215 children had no reported birth defect; 21,207 children had an overgrowth feature or syndrome.
- In those without birth defects, 0.1% (n=9,391) of children were diagnosed with cancer compared to 0.5% (n=106) of children with an overgrowth feature or syndrome (p-value < 0.001) (Table 1).
- In children without overgrowth syndrome diagnoses, the presence of any isolated overgrowth feature was associated with increased cancer risk (Table 2).
- Among overgrowth features, associations were strongest for hepatosplenomegaly and macroglossia (Table 2).
- Children with BWS were 42-times more likely to develop pediatric cancer (Table 2) with hepatoblastoma (n=8) and Wilm's tumor (n=5) being the most common.
- The percentage of children diagnosed with cancer at 5, 10, and 15 years were highest among children with BWS and Beckwith-Wiedemann spectrum (Figure 1, Table 3).

CONCLUSION

We demonstrated that children with overgrowth features in the absence of a recorded syndrome were more likely to develop cancer compared to children without birth defects, although these may represent undiagnosed disorders. BWS was associated with the greatest increase in cancer risk among analyzed syndromes, supporting current tumor screening guidelines. Our study may inform future research in cancer etiology and disease progression in children with overgrowth features or syndromes.

REFERENCES

1. Lapunzina P. Risk of tumorigenesis in overgrowth syndromes: a comprehensive review. *Am J Med Genet C Semin Med Genet.* 2005;137C(1):53-71. doi:10.1002/ajmg.c.30064