Risk of cancer during the first four years of life in children from The Beckwith-Wiedemann Syndrome Registry

Michael R. DeBaun, MD, MPH, and Margaret A. Tucker, MD

To determine the incidence and relative risk (RR) of cancer in children with Beckwith-Wiedemann syndrome (BWS), children with BWS were followed up from birth until death, diagnosis of cancer, fourth birthday, or last day of follow-up. A total of 183 children with BWS were followed up for 482 person-years. The end points were incidence of cancer, RR of cancer, and RR associated with specific BWS phenotypic features. Thirteen children were identified with cancers before the fourth year of life in comparison with fewer than one cancer expected in this group on the basis of general population rates over the same period. The average annual incidence of cancer in the first 4 years of life was 0.027 cancer per person-year. The RR of Wilms tumor (RR = 816; 95% confidence interval [CI], 359-1156), neuroblastoma (RR = 197; 95% CI, 22-711), and hepatoblastoma (RR = 2280; 95% CI, 928-11,656) were statistically significant. Asymmetry of the limbs (hemihypertrophy) was the only clinical feature associated with an increased RR of cancer (RR = 4.6; 95% CI, 1.5-14.2). Given the high incidence of cancer in infancy and early childhood of patients with BWS, a prospective study is warranted to address the utility of screening for cancer. (J Pediatr 1998;132:398-400)

See related articles, p. 377, p. 389, and p. 401.

Beckwith-Wiedemann syndrome is an overgrowth syndrome associated with embryonal cancer in infants and children.[1] Classically, children with BWS are identified at birth by macroglossia, omphalocele, and macrosomia. Additionally, children with BWS may have some or all of the following features: ear pits or creases, asymmetry of the limbs (hemihypertrophy), neonatal hypoglycemia, and organomegaly.[2]

The association between cancer and BWS is well documented.[1,3] The cancers most commonly associated with BWS are embryonal tumors of childhood, including Wilms tumor, hepatoblastoma, adrenal cortical carcinoma, neuroblastoma, and rhabdomyosarcoma.[1,3] The frequency of cancer in children with BWS, as with any rare cancer syndrome, is commonly described from cross-sectional[2] or retrospective analyses.[1,3] No such studies have been able to describe the incidence rates of cancer in children with BWS because such incidence rates require a group of children with BWS without cancer to be followed up for a designated period. The frequency of a cancer in children with BWS only tells how often an event may occur and not when the event is most likely to occur. For a fully informed decision to be made regarding efficient patient care management decisions, the age-specific incidence of cancer in infancy or early childhood is required.[4] To estimate the incidence and relative risk of cancer and to better understand the natural history of BWS we created The Beckwith-Wiedemann Syndrome Registry.

BWS	Beckwith-Wiedemann syndrome
CI	Confidence interval
RR	Relative risk
WT	Wilms tumor

METHODS

Between April 1989 and January 1994, 192 patients with BWS were registered in the BWS parent support group. Parents contacted the support group for a variety of reasons including seeking information on BWS, identifying other families with a child who has BWS, and seeking referrals to pediatric specialists. As part of the initial

From Genetic Epidemiology Branch, National Cancer Institute, National Institutes of Health, Bethesda, Maryland; and Division of Pediatric Hematology-Oncology, Department of Pediatrics, Washington University School of Medicine, St. Louis, Missouri.

Dr. DeBaun is currently funded by the Robert Woods Johnson Minority Faculty Development Award.

Submitted for publication Dec. 17, 1996; accepted Aug. 20, 1997.

Reprint requests: Michael R. DeBaun, EPN 400, Genetic Epidemiology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892-7372.

0022-3476/98/$5.00 + 0 **9/21/85587**

Table I. Age at diagnosis and diagnosis for the 13 patients in the cohort who had cancer

Age at diagnosis (mo)	Diagnosis
2	WT
4	WT
6	WT
8	WT
16	WT
20	WT
4	Hepatoblastoma
5	Hepatoblastoma
6	Hepatoblastoma
7	Hepatoblastoma
19	Hepatoblastoma
7	Neuroblastoma
17	Neuroblastoma

Table II. Relative risk of cancer in the first 4 years of life for 186 children with BWS followed up for 482 person-years

Cancer	Observed events	RR	95% CI
WT	6	816	359-1156
Hepato-blastoma	5	2280	928-1165
Neuro-blastoma	2	197	22-711
All cancers	13	676	60-1157

registration for the support group, parents were interviewed and asked a series of questions regarding the cardinal features of BWS.[5] With regard to informed consent, each parent was contacted on two separate occasions with a written letter requesting permission for access to the initial information collected. For those families who agreed to participate, informed consent and medical information release documents were mailed. In this group two children had cancer before ascertainment, and six children had incomplete information; all eight children were excluded from the analysis. The remaining 183 children with BWS who joined the BWS support group before the development of cancer comprise the cohort used in the analysis.

In January 1994, a parent or legal guardian of each proband was interviewed by phone to confirm participation and to determine whether cancer had developed since registration in the BWS Support Network. For purposes of this study, we defined a patient as having BWS if a clinical diagnosis of BWS had been made by a physician and the patient had at least two of the five most common features of BWS[5]: (1) macroglossia, (2) birth weight greater than the 90th percentile, (3) hypoglycemia in the first month of life, (4) ear creases or ear pits, and (5) abdominal wall defect (omphalocele, diastasis recti, umbilical hernia). If a cancer was reported, the diagnosis was confirmed by review of the final pathology report and medical records. The average annual incidence of cancer was determined by dividing the total number of cancers by the total number of patient-years in the cohort. For estimating the risk of developing cancer, person-years were accumulated from birth until death, fourth-year birthday, diagnosis of a cancer, or the last month of contact for each patient (January 1994). The expected number of WTs, hepatoblastomas, and neuroblastomas were obtained from the Surveillance Epidemiology and End Results Program by multiplying age-specific and calendar year–specific incidence rates for each cancer by the accumulated person-years. The estimated RR, defined as the ratio of observed-to-expected cancers and 95% confidence intervals were based on the assumption that the observed cancers have a Poisson distribution.[6] The estimated RR was considered to be significantly increased when the observed-to-expected ratio was greater than 1.0 and the 95% CIs did not include 1.0.

We used a univariate logistic regression model to detect the RR for each selected clinical characteristic and laboratory value. The following parameters were assessed: sex (female or male), macrosomia (birth weight >90th percentile), macroglossia (present or absent), ear pits or ear creases (present or absent), abdominal wall defect (omphalocele, diastasis recti, or umbilical hernia present or absent), asymmetry of the limbs (present or absent), and hypoglycemia (present or absent).

Table III. Frequency of clinical features with RR of cancer associated with BWS

Clinical feature	Frequency of clinical feature (%)	RR	95% CI
Asymmetry of the limbs	25	4.6	1.5-14.2
Macrosomia	62	1.1	0.3-4.0
Ear pits or creases	51	1.8	0.6-5.6
Umbilical hernia	37	1.3	0.4-4.0
Omphalocele	27	1.1	0.3-3.6
Diastasis recti	26	0.7	0.2-2.8
Macroglossia	87	1.2	0.4-4.2
Hypoglycemia	41	1.7	0.6-5.1
Female	41	0.6	0.2-1.9

RESULTS

We followed up 183 patients for 482 patient-years during the first 4 years of life. The mean age of the cohort was 3.7 years, and the mean age at which the patient was signed up for The BWS Network was 1.6 years; 57% were boys. Thirteen children had cancer (six had WT, five had hepatoblastoma, and two had neuroblastoma) within the first 4 years of life. An additional patient, not included in the cohort, was diagnosed at 65 months. The median and mean ages at the time of the cancer diagnosis were 7.0 years (standard deviation, 6.6) and 10.4 years (standard deviation, 6.7) respectively (Table I).

On the basis of Surveillance Epidemiology and End Results data for whites, 0.019 cancers were expected in this cohort during the same period (observed-to-expected ratio of cancer in the first 4 years of life was 676; 95% CI = 60-1157). The mean age at diagnosis of the 13 cancers during the first 4 years of life was 1.2 years. The average annual incidence for the first 4 years of life was estimated to be 0.027 cancers per person-year. When the cohort was extended beyond 4 years to

age 10, an additional 204 patient-years were accumulated. One WT occurred in this age group. If the cancer incidence observed in infancy and early childhood were similar in later childhood, we would have anticipated at least five tumors in this older age group (ages 5 to 9 years).

WT, neuroblastoma, and hepatoblastoma in the first 4 years of life were all significantly increased (Table II). The estimated RRs were high with broad CIs because of the small expected values and relatively small number of events. The RR for the older age group was not estimated because there was only one event.

Table III presents the RRs of all cancers associated with each clinical characteristic of BWS. Only asymmetry of the limbs was associated with a statistically significant increase in the risk of cancer (RR = 4.6; 95% CI = 1.5-14.2).

Discussion

The association of early childhood cancer and BWS is well established, but the magnitude of this risk during infancy and early childhood is not. Previous retrospective analyses of a series of children with BWS focused solely on the frequency of cancer, ranging from 4%[5] to 7.5%.[1] No study has identified a cohort of children with BWS to determine the incidence of cancer. Our results indicate that both the average incidence and RR of cancer in the first 4 years of life are elevated with significant excesses of WT, hepatoblastoma, and neuroblastoma. We did not calculate the incidence and RR in children over 4 years of age because the data were too sparse for the point estimate to be of clinical utility.

Although the association between asymmetry of the limbs and increased risk of cancer in children with BWS has been reported previously,[1,3] the risk was not quantified. Neither study addressed whether other characteristics of BWS were associated with cancer, nor did the investigators quantify the relationship. Children with BWS and clinically obvious limb asymmetries have at least a fourfold greater risk of cancer than children with BWS without asymmetry.

Previous reports have also indicated a relationship between macrosomia and cancer, particularly WT[7,8]; our results, however, do not demonstrate this relationship. The most likely reason for the disparity may be that macrosomia is a proxy for overgrowth syndromes associated with WT such as BWS, Perlman nephroblastomatosis syndrome,[9] and Sotos' syndrome.[10] In addition, the difference in results may reflect the selection criteria of the study participants. In our study some of the patients were selected because they had macrosomia, whereas for the other studies, patients were identified because they had cancer.[7,8]

There are several limitations in our study. The issue of how the probands were ascertained is important for interpretation and extrapolation of the results. The BWS Registry is similar to other registries for rare genetic syndromes, such as those for Fanconi's anemia[11] and ataxia telangiectasia,[12] in that patients are entered into the registry on the basis of some predetermined criteria. The families are either self-referred or referred by physicians, usually from tertiary care centers and therefore may be biased toward more clinically affected individuals. This ascertainment bias probably does not affect the major finding of the very high incidence of cancer in the first 4 years of life.

Because our cohort is still young, cancers identified do not represent the full spectrum of cancers reported in children with BWS or the full age range in this population. Although this is the largest cohort of children with BWS followed up systematically, our sample size is too small to fully describe the spectrum of cancers in this population. In our cohort we only included person-years before the fourth birthday because the majority of cancers in children with BWS occur during infancy or early childhood.[1,13] As our cohort ages, patients may have a wider range of cancer. However, according to published data,[1,3,13] this older group is expected to have a much lower incidence of cancer, decreasing the potential clinical utility of cancer surveillance.

Cancer, more specifically embryonal cancer, is a major complication in children with BWS. Both the incidence and the RR in the first 4 years of life are high enough for consideration of a cancer surveillance program in this population.[14] Formal evaluation of cancer screening is required to determine whether the expense of cancer screening justifies the potential benefit.

We thank the participating families who made the project possible; the staff of the Genetic Epidemiology Branch at the National Cancer Institute for their helpful comments and encouragement; and the staff of Westat Inc. and IMS for their support.

References

1. Sotelo-Avila C, Gonzalez-Crussi F, Fowler JW. Complete and incomplete forms of Beckwith-Wiedemann syndrome: their oncogenic potential. J Pediatr 1980;96:47-50.
2. Elliott M, Bayly R, Cole T, Temple IK, Maher ER. Clinical features and natural history of Beckwith-Wiedemann syndrome: presentation of 74 new cases. Clin Genet 1994;46:168-74.
3. Wiedemann HR. Tumor and hemihypertrophy associated with Wiedemann-Beckwith's syndrome [letter]. Eur J Pediatr 1983; 141:129.
4. Prorok PC, Connor RJ. Screening for the early detection of cancer. Cancer Invest 1986;4:225-38.
5. Pettenati MJ, Haines JL, Higgins RR, Wappner RS, Palmer CG, Weaver DD. Wiedemann-Beckwith syndrome: presentation of clinical and cytogenetic data on 22 new cases and review of the literature. Hum Genet 1986;74:143-54.
6. Bailar JC III, Edere F. Significance factors for the ratio of a Poisson variable to its expectation. Biometrics 1964;20:639-43.
7. Olshan AF. Wilms' tumor, overgrowth, and fetal growth factors: a hypothesis. Cancer Genet Cytogenet 1986;21:303-7.
8. Daling JR, Starzyk P, Olshan AF, Weiss NS. Birth weight and the incidence of childhood cancer. J Natl Cancer Inst 1984; 72:1039-41.
9. Greenberg F, Stein F, Gresik MV, Finegold MJ, Carpenter RJ, Riccardi VM, et al. The Perlman familial nephroblastomatosis syndrome. Am J Med Genet 1986;24:101-10.
10. Cohen MM Jr. A comprehensive and critical assessment of overgrowth and overgrowth syndromes. Adv Hum Genet 1989;18:181-303, 373-6.
11. Butturini A, Gale RP, Verlander PC, Adler-Brecher B, Gillio AP, Auerbach AD. Hematologic abnormalities in Fanconi anemia: an International Fanconi Anemia Registry study. Blood 1994;84:1650-5.
12. Morrell D, Cromartie E, Swift M. Mortality and cancer incidence in 263 patients with ataxia-telangiectasia. J Natl Cancer Inst 1986;77:89-92.
13. Breslow N, Olshan A, Beckwith JB, Green DM. Epidemiology of Wilms' tumor. Med Pediatr Oncol 1993;21:172-81.
14. DeBaun MR, Brown M, Kessler L. Screening for Wilms' tumor in children with high-risk congenital syndromes: consideration for an intervention trial. Med Pediatr Oncol 1996;27:415-21.