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Original Contribution

Are Children With Birth Defects at Higher Risk of Childhood Cancers?

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Birth defects may influence the risk of childhood cancer development through a variety of mechanisms. The rarity of both birth defects and childhood cancers makes it challenging to study these associations, particularly for the very rare instances of each. To address this limitation, the authors conducted a record linkage-based cohort study among Texas children born between 1996 and 2005. Birth defects in the cohort were identified through the Texas Birth Defects Registry, and children who developed cancer were identified by using record linkage with Texas Cancer Registry data. Over 3 million birth records were included; 115,686 subjects had birth defects, and there were 2,351 cancer cases. Overall, children with a birth defect had a 3-fold increased risk of developing cancer (incidence rate ratio (IRR) = 3.05, 95% confidence interval (CI): 2.65, 3.50), with germ cell tumors (IRR = 5.19, 95% CI: 2.67, 9.41), retinoblastomas (IRR = 2.34, 95% CI: 1.21, 4.16), soft-tissue sarcomas (IRR = 2.12, 95% CI: 1.09, 3.79), and leukemias (IRR = 1.39, 95% CI: 1.09, 1.75) having statistically significant elevated point estimates. All birth defect groups except for musculoskeletal had increased cancer incidence. Untangling the strong relation between birth defects and childhood cancers could lead to a better understanding of the genetic and environmental factors that affect both conditions.

birth defects; childhood cancers; congenital anomalies

Abbreviations: CDC, Centers for Disease Control and Prevention; CI, confidence interval; ICCC-3, *International Classification of Childhood Cancer*, Third Edition; IRR, incidence rate ratio.

Studies have consistently shown that children born with certain types of birth defects are at increased risk of developing cancer during childhood (1–7). There are a variety of ways by which the presence of birth defects may influence risk of childhood cancer development, including through shared genetic and/or environmental factors, through changes in organ structure or function, or through lifestyle adaptations related to the malformation. Established birth defect-childhood cancer associations include Down syndrome and specific leukemias, autosomal deletion of 13q14 and retinoblastoma, and Beckwith-Weideman syndrome and Wilms' tumor (8). The magnitude of the association can be quite strong, with studies reporting that Down syndrome children have a 10–50-fold increased risk of developing acute lymphoblastic leukemia or acute myeloid leukemia compared with non-Down syndrome children (9).

In addition to genetic factors, there are indications that environmental exposures may mediate risk of cancer among children with birth defects. In Down syndrome children, some factors have been found to be protective against leukemias (e.g., maternal vitamin use (10)), while others appear to increase risk (e.g., maternal exposure to pesticides (11), maternal infertility (12)). An intriguing aspect of Down syndrome cancer risk is the finding that Down syndrome children and adults actually have a lower incidence of solid tumors than the non-Down syndrome population (13).

The reports of increased risk of childhood cancers among children with birth defects may be an indication that these children constitute a high-risk population. As such, study of this population could help to improve our understanding of certain etiologies of childhood cancers and to identify the genetic and environmental factors driving carcinogenesis in children in the general population. The rarity of both birth defects and childhood cancers makes it challenging, however, to study the association between meaningful groups of birth defects and specific cancers, particularly for the very

rare instances of each. To mitigate this limitation, we conducted a record linkage-based cohort study among children born over a 10-year period in Texas, the second most populous state in the United States. With more than 400,000 births currently recorded annually in Texas, this birth cohort was deemed likely to provide sufficient numbers to allow for evaluation of the association of specific birth defects with specific childhood cancers.

MATERIALS AND METHODS

The birth cohort identified for the study consisted of children born to Texas residents between January 1, 1996, and December 31, 2005 ($n = 3{,}186{,}911$ livebirths). Birth certificate data files for the cohort were provided by the Vital Statistics Unit/Center for Health Statistics of the Texas Department of State Health Services.

Children with and without identified birth defects constituted the 2 comparison groups in the birth cohort. Children with birth defects were identified through the Texas Birth Defects Registry, an active surveillance system. Registry staff routinely visit all delivery and pediatric hospitals in Texas, as well as birth centers and midwife facilities. A *case* is defined as an infant/fetus with any major structural or chromosomal anomaly, whose mother is resident in the Registry coverage area at the time of delivery (based on the birth certificate or, if absent, the medical record). The Texas Birth Defects Registry includes all cases of structural or chromosomal birth defects that are diagnosed by a physician and recorded in medical records. However, the Registry is limited by the sometimes short descriptions found there. Diagnoses with qualifiers such as ''suggests'' or ''rule out'' are typically excluded from statistical analyses and studies. Birth defects associated with prematurity (e.g., patent ductus arteriosus) are not abstracted if a child is born preterm. Defects that are not likely to have a significant impact on the child's life, health, or functioning are recorded only if they co-occur with one that is. Information is abstracted from medical records into a Web-based system where it undergoes extensive quality checks. That includes review by clinical geneticists of roughly 60% of the Registry records (selected on the basis of criteria to find the cases most likely to be problematic).

The Texas Birth Defects Registry started in South Texas and the Houston/Galveston area and gradually expanded so that, by January 1999, it covered the entire state. Birth defects are coded by using a 6-digit system (sometimes referred to as ''BPA codes'') based on the 1979 *British Paediatric Association Classification of Diseases* and the World Health Organization's 1979 *International Classification of Diseases*, Ninth Revision, Clinical Modification, as modified by the US Centers for Disease Control and Prevention (CDC) and the Texas Department of State Health Services. Each birth defect is assigned diagnostic certainty; roughly 96.7% are definite and 3.3% are possible/probable. All pregnancy outcomes are included (livebirths, spontaneous fetal deaths, and pregnancy terminations). Registry cases are linked with birth certificate data first by deterministic matching (based on exact matches) by a variety of combinations of individual identifiers (date of birth, names, and so on). Cases that are not matched are then subjected to human clerical review for further matching. Over 96.2% of Texas Birth Defects Registry cases are linked to a birth certificate by use of this approach.

In the present study, 115,686 liveborn children were identified by the Texas Birth Defects Registry as having one or more definitely diagnosed birth defects and constituted the birth defects comparison group. Individual birth defects were grouped into categories routinely presented by the Registry in their annual reports and to the CDC. Those liveborn children not registered with the Texas Birth Defects Registry as having either a definite or possible/probable birth defect constituted the non-birth defects comparison group in the cohort. All children in this study had a birth certificate.

Children diagnosed with cancer before age 15 years were identified through linkage of birth certificate data with the database of the Texas Cancer Registry, a statewide population-based registry that collects data on incident cases of cancer occurring among Texas residents. The Texas Cancer Registry meets high-quality data standards set by the CDC and is ''Gold-Certified'' by the North American Association of Central Cancer Registries. The Texas Cancer Registry data included cancer diagnoses made between 1996 and 2005 (the latest data year available at the time of the study). Cancer cases were coded according to the *International Classification of Childhood Cancer,* Third Edition (ICCC-3), which categorizes childhood cancers into 12 major groups (14).

The linkage between the Texas Cancer Registry and birth certificate data was conducted by using Link Plus, version 2.0, software developed by the CDC (Atlanta, Georgia). The software matches records using both deterministic and probabilistic methods. The linkage included all records that matched exactly by the infant's first name, last name, date of birth, and sex. In addition, records that did not match exactly because of data entry errors, missing data, or use of alternate names were identified through probabilistic methods, which weighted and scored the likelihood of a match based on the information that did correspond. Possible matches were manually reviewed and included address fields from the birth certificate and Texas Cancer Registry data to help determine true matches.

Data on potential confounders of birth defect-childhood cancer associations were captured from the birth certificate data file. Each subject contributed person-years of observation from the time of birth to either diagnosis with cancer or December 31, 2005, whichever came first. Records for study subjects with multiple birth defects were consolidated when total birth defects were the unit of analysis; each individual defect contributed to the person-time for the analyses evaluating specific defects or groups of defects. The associations between the child's baseline characteristics and birth defects status and the diagnosis of cancers before age 15 years were estimated by using incidence rate ratios and their corresponding 95% confidence intervals. The child's gender, birth weight, plurality, and birth order, as well as the mother's age, race/ethnicity, and education, were all evaluated as potential confounders through Cox proportional hazards regression

analyses (15) and showed no effect (i.e., less than 10% change in point estimates) on the main analysis of birth defects and childhood cancers, so only unadjusted incidence rate ratios are presented.

RESULTS

A total of 115,686 children in the birth cohort of 3,186,911 (3.6%) were identified as having one or more birth defects. The distribution of maternal race/ethnicity and educational attainment was similar among children with and without birth defects, but slightly more mothers of children with birth defects were aged 35 years or older at the time of the child's birth (Table 1). Slightly more males were born with birth defects than females. As indicated by both birth weight and gestational age, children with birth defects were smaller at birth than children without birth defects, and more multiple births occurred among children with birth defects.

A total of 2,351 cancer cases were identified in this birth cohort; 239 cases had one or more birth defects (Table 2). Children with any birth defect had a 3-fold increased risk of developing a childhood cancer when compared with children without birth defects (incidence rate ratio (IRR) = 3.05, 95% confidence interval (CI): 2.65, 3.50) (Table 3). Every major ICCC-3 cancer group had at least 1 child who also had a birth defect, and there were statistically significant elevated risk ratios for leukemia (IRR = 1.39, 95% CI: 1.09, 1.75), retinoblastoma (IRR = 2.34, 95% CI: 1.21, 4.16), soft-tissue sarcomas (IRR = 2.12, 95% CI: 1.09, 3.79), and germ cell tumors (IRR = 5.19, 95% CI: 2.67, 9.41). By age, the association between any birth defect and total childhood cancers was more pronounced among children diagnosed with cancer before age 1 year (IRR = 1.53, 95% CI: 1.23, 1.89) (data not shown). The most common cancers in these youngest children were leukemias, but cancers from every major ICCC-3 group were reported (data not shown).

When the risk of any childhood cancer by specific birth defects grouping was considered, risk ratios for total childhood cancers were elevated for every birth defects group except musculoskeletal defects, with most achieving statistical significance and incidence rate ratios ranging from approximately 2-fold to over 15-fold (Table 4). The strongest association was seen for chromosomal defects (IRR = 15.52, 95% CI: 11.66, 20.27), which reflected leukemia incidence among Down syndrome children (51 of 55 trisomy cancer cases were Down syndrome children with leukemia diagnoses).

Leukemia consistently accounted for the highest percentage of cancers among the different birth defects groups examined (Table 5). Cardiac and circulatory defects were the most frequent type of birth defects to also have a cancer diagnosis, and 50% of these children were diagnosed with leukemia (76/153). Although there were only 5 children with respiratory defects who developed cancer, 4 of the 5 were diagnosed with leukemia. After leukemia, central nervous system neoplasms and neuroblastoma were the next most common cancers diagnosed among children with birth defects. For most birth defects, however, there was an array of cancer types reported among the cases.

DISCUSSION

This analysis indicates that children with birth defects are at increased risk of developing some form of cancer when compared with children without birth defects. Leukemias, retinoblastomas, soft-tissue sarcomas, and germ cell tumors appear to be the cancers this population is most at risk of developing, and children with birth defects who are under the age of 1 year showed a higher risk of developing a cancer than older children. With the exception of musculoskeletal/reduction defects, every category of birth defect evaluated was associated with cancer development in this population, with most categories showing between 2-fold and 4-fold increased risk when compared with children without birth defects.

Earlier studies have consistently found an increased risk of cancer development in children with birth defects (1–7), and all have confirmed, as this study did, a very strong association between Down syndrome and childhood leukemias. Working from the hypothesis that the chromosomal defect in Down syndrome children is a necessary but not sufficient causal factor for leukemia in these children, a series of studies from the Children's Oncology Group have investigated whether environmental exposures that have shown some association with leukemia in non-Down syndrome children might have a similar or more pronounced role in the Down syndrome population. These studies did not confirm an association with medical test irradiation (16), maternal health conditions during pregnancy (17), most reproductive history factors and infertility treatment (12), or other congenital abnormalities (18), but they did find that some household chemical exposures may play a role (11). There is also some evidence from this study population of a protective effect with maternal vitamin use (10) and infections in early life (19). To investigate the influence of chromosomal defects on the overall study results, we excluded subjects with any chromosomal defect from the analyses, which resulted in a lowered incidence rate ratio for leukemia as well as for total cancers. For all other cancer categories, however, the point estimates either increased (neuroblastoma, retinoblastoma, hepatic tumors) or were unchanged, and estimates were less precise. The overall pattern of results was similar to that based on the models that included these children (data not shown). In addition to children with chromosomal defects, there was an overall increased risk of leukemia among children with birth defects. Among children with cardiac and circulatory defects, the group which had the most total cancer diagnoses, there was also some indication that leukemia was the most common cancer type.

Most, but not all (3, 4), epidemiologic studies of birth defects and childhood cancers have reported some evidence of increased risk of retinoblastoma, with the magnitude of risk ranging from a 2-fold to a 15-fold increase (1, 2, 5–7). As with the results presented here, these studies generally found that, rather than a concentration of a specific class of birth defect, various types of birth defects were found among the retinoblastoma cases.

Studies have generally reported a non-statistically significant increased risk of soft-tissue sarcomas with magnitudes similar to the 2-fold risk seen in this study (3, 5, 6). Rankin

Table 1. Birth Characteristics by Presence/Absence of Reported Birth Defects Among Texas Children Born During 1996–2005

Birth Characteristics	Children With Birth Defects		Children Without Birth Defects		Total	
	No.	%	No.	%	No.	%
Maternal age at child's birth, years						
≤20	16,597	14.4	453,462	14.77	470,059	14.8
21–24	30,704	26.5	869,348	28.31	900,052	28.3
25–29	29,832	25.8	820,618	26.72	850,450	26.7
30–34	23,317	20.2	608,401	19.81	631,718	19.8
35–39	12,079	10.4	265,574	8.65	277,653	8.7
≥40	3,152	2.7	53,415	1.74	56,567	1.8
Total	115,681	100.0	3,070,818	100	3,186,499	100.0
Maternal race/ethnicity						
White non-Hispanic	46,297	40.1	1,146,335	37.38	1,192,632	37.5
Black non-Hispanic	12,144	10.5	334,690	10.91	346,834	10.9
Hispanic	53,731	46.5	1,480,474	48.27	1,534,205	48.2
Other non-Hispanic	3,348	2.9	105,567	3.44	108,915	3.4
Total	115,520	100.0	3,067,066	100	3,182,586	100.0
Maternal educational attainment						
Less than high school	36,571	32.1	999,935	33.02	1,036,506	33.0
High school	34,664	30.4	924,558	30.53	959,222	30.5
More than high school	42,627	37.4	1,103,541	36.44	1,146,168	36.5
Total	113,862	100.0	3,028,034	100	3,141,896	100.0
Child's sex						
Male	68,268	59.0	1,560,583	50.81	1,628,851	51.1
Female	47,419	41.0	1,510,652	49.19	1,558,071	48.9
Total	115,687	100.0	3,071,235	100	3,186,922	100.0
Birth weight, g						
<1,500	7,725	6.7	34,937	1.14	42,662	1.3
1,500–1,999	5,858	5.1	42,153	1.37	48,011	1.5
2,000–2,499	10,380	9.0	142,919	4.66	153,299	4.8
≥2,500	91,560	79.3	2,849,110	92.83	2,940,670	92.3
Total	115,523	100.0	3,069,119	100	3,184,642	100.0
Gestational age, weeks						
<32	8,041	7.1	43,309	1.43	51,350	1.6
32–36	18,108	15.9	249,243	8.22	267,351	8.5
≥37	87,596	77.0	2,737,893	90.35	2,825,489	89.9
Total	113,745	100.0	3,030,445	100	3,144,190	100.0
Plurality						
Singleton	109,809	94.9	2,988,224	97.3	3,098,033	97.2
Multiple	5,869	5.1	82,777	2.7	88,646	2.8
Total	115,678	100.0	3,071,001	100	3,186,679	100.0
Birth order						
First	80,333	71.8	2,099,915	70.76	2,180,248	70.8
Second	18,872	16.9	530,656	17.88	549,528	17.9
Third	7,646	6.8	210,486	7.09	218,132	7.1
Fourth	2,946	2.6	75,965	2.56	78,911	2.6
Fifth or higher	2,043	1.8	50,431	1.7	52,474	1.7
Total	111,840	100.0	2,967,453	100	3,079,293	100.0

Table 2. Distribution of Birth Defect Cases by ICCC-3 Cancer Groups Among Texas Children Born During 1996–2005

ICCC-3 Group	With Birth Defect		Without Birth Defect		Total	
	No.	%	No.	%	No.	%
Leukemias	84	35.2	742	35.1	826	35.1
Lymphomas	8	3.4	137	6.5	145	6.2
Central nervous system	35	14.6	394	18.7	429	18.3
Neuroblastoma	31	13.0	274	13.0	305	13.0
Retinoblastoma	13	5.4	125	5.9	138	5.9
Renal tumors	14	5.9	172	8.1	186	7.9
Hepatic tumors	16	6.7	45	2.1	61	2.6
Malignant bone tumors	1	0.4	19	0.9	20	0.9
Soft tissue sarcomas	15	6.3	102	4.8	117	5.0
Germ cell tumors	17	7.1	60	2.8	77	3.3
Other epithelial	2	0.8	19	0.9	21	0.9
Other and unspecified	1	0.4	11	0.5	12	0.5
Total	239		2,112		2,351	

Abbreviation: ICCC-3, *International Classification of Childhood Cancer*, Third Edition.

et al. (7) found an increased risk of 2.98 for rhabdomyosarcoma specifically, but this increase was not statistically significant.

In a study from the Children's Oncology Group, Johnson et al. (20) reported a 2.5-fold increased risk of germ cell tumors for males with any congenital abnormality, with risk increasing for children with multiple abnormalities. The association found in this study was essentially due to cryptorchidism (undescended testicle). This population also had increased risk of extragonadal germ cell tumors associated with mental retardation, congenital heart defects, and skeletal defects. Other studies have also reported associations between skeletal and congenital heart defects and germ cell tumors (4, 6).

Table 3. Risk Ratios by ICCC-3 Cancer Group for Any Birth Defect Versus No Birth Defect Among Texas Children Born During 1996–2005

ICCC3 Cancer Group	IRR	95% CI
Leukemias	1.39	1.09, 1.75
Lymphomas	1.80	0.76, 3.64
Central nervous system	1.11	0.76, 1.57
Neuroblastoma	1.43	0.94, 2.10
Retinoblastoma	2.34	1.21, 4.16
Renal tumors	1.11	0.59, 1.91
Hepatic tumors	1.00	0.52, 1.83
Malignant bone tumors	0.63	0.02, 3.99
Soft tissue sarcomas	2.12	1.09, 3.79
Germ cell tumors	5.19	2.67, 9.41
Other epithelial	2.98	0.34, 12.34
Other and unspecified	5.05	0.12, 34.75
Total cancers	3.05	2.65, 3.50

Abbreviations: CI, confidence interval; ICCC-3, *International Classification of Childhood Cancer*, Third Edition; IRR, incidence rate ratio.

The differences in study results may be due to variations in inclusion criteria for birth defects or in case ascertainment (both for birth defects and childhood cancers). One of the strengths of this study is that the data were derived from high-quality, population-based registries for both birth defects and cancers. In addition, this study had a relatively large number of childhood cancer cases available for analysis. Small numbers in previous studies may also be an explanation for inconsistencies in point estimates for specific birth defects and cancer types. Most studies had approximately 55 or fewer total cancers among their birth defects children (1–3, 5, 7), severely restricting their ability to investigate the relations among the less common cancers and birth defects. One study limitation to note is the lack of death certificate linkage in the study cohort to allow for adjustment of person-year contributions for children who had died before the study end date. Additionally, the maximum amount of follow-up time was 10 years, so cancers that develop more commonly in late childhood, such as thyroid and bone cancers, would be underrepresented in these data. Also, some minor structural birth defects, particularly septal defects, may go undiagnosed in otherwise healthy children but may be more likely to be diagnosed in children with serious illnesses like cancer. This study did not include review of individual birth defects records by a clinical geneticist or dysmorphologist to allow for exclusion of birth defects diagnoses, such as minor septal defects, which were identified as a consequence of a cancer diagnosis. Because diagnoses of birth defects are accepted by the Texas Birth Defects Registry only up to the first birthday of the child, however, we were able to evaluate the potential impact of septal defects that may have been diagnosed solely as a result of cancer diagnosis by excluding cases whose cancer was diagnosed before age 1 year. Point estimates

Table 4. Risk of Any Childhood Cancer for Birth Defect Groups and Selected Defects Among Texas Children Born During 1996–2005

Birth Defects Group	No. of Cases With Birth Defects[a]	IRR	95% CI
Central nervous system	17	3.61	2.10, 5.79
Neural tube	4	3.03	0.83, 7.78
Eye and ear	6	3.47	1.27, 7.56
Anophthalmia/ microphthalmia	5	6.91	2.24, 16.14
Cardiac and circulatory	91	3.50	2.81, 4.31
Conotruncal	7	3.14	1.26, 6.47
Septal	60	3.05	2.32, 3.94
Left ventricular outflow tract	54	4.22	3.16, 5.53
Respiratory	5	3.58	1.16, 8.36
Oral clefts	11	2.69	1.34, 4.82
Gastrointestinal	13	1.69	0.90, 2.89
Gastrointestinal atresia/stenosis	5	2.56	0.83, 5.97
Genitourinary	34	2.37	1.64, 3.32
Musculoskeletal	5	0.88	0.29, 2.06
Limb reduction defects	1	0.80	0.02, 4.49
Abdominal wall defects	3	2.26	0.47, 6.62
Chromosomal[b]	55	15.52	11.66, 20.27
Any monitored defect	234	2.86	2.49, 3.28

Abbreviations: CI, confidence interval; IRR, incidence rate ratio.
[a] Duplicates within each defects group have been removed; that is, a child is counted only once.
[b] This group includes trisomy 21 (Down syndrome), trisomy 13 (Patau syndrome), and trisomy 18 (Edwards syndrome).

were slightly lower and less precise, but the overall pattern of results was similar to that based on the models that included these children (data not shown). Another limitation is that the analyses in this paper did not stratify infants with isolated versus multiple defects. Such analyses can be relevant, because the cases with a birth defect with or without co-occurring defects may be different etiologically (21, 22). Because of this, we intend to address this in future analyses with more cases of birth defects to allow stratification with sufficient statistical power.

There are several ways to consider the underlying mechanisms at work in the complex relations between birth defects and childhood cancers. As Mili et al. (2) noted, it is possible that 1) a birth defect can act to increase the risk of childhood cancers; 2) a cancer can predispose a child to developing a birth defect; and/or 3) birth defects and cancers occur concurrently through some set of common underlying factors. The patterns seen in the results of this study engender several questions. For example, the analysis revealed a wide range of birth defects related to a wide range of cancers. Narod et al. (4) speculated that this may indicate mutations in developmental genes early in embryogenesis leading to tissue mosaicism, such that the range of tissues involved in the mosaicism may

Table 5. Distribution of Birth Defects Groups by Cancer Types Among Texas Children Born During 1996–2005

Birth Defect	ICCC-3 Group																											
	Leukemia		Lymphoma		Central Nervous System		Neuro-blastoma		Retino-blastoma		Renal		Hepatic		Malignant Bone		Soft-Tissue Sarcomas		Germ Cell		Other Epithelial		Other		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Central nervous system	5	29	0	0	6	35	1	6	0	0	0	0	0	0	0	0	1	6	3	18	0	0	1	6	17	100
Eye and ear	3	50	0	0	0	0	1	17	1	17	0	0	0	0	0	0	0	0	1	17	0	0	0	0	6	100
Cardiac and circulatory	76	50	4	3	23	15	16	10	2	1	3	2	18	12	0	0	7	5	4	3	0	0	0	0	153	100
Respiratory	4	80	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	1	20	0	0	0	0	5	100
Oral clefts	3	27	0	0	2	18	2	18	1	9	1	9	1	9	0	0	0	0	1	9	0	0	0	0	11	100
Gastrointestinal	6	46	2	8	4	31	1	8	0	0	0	0	0	0	0	0	0	0	1	8	0	0	0	0	13	100
Genitourinary	5	14	7	6	7	19	5	14	1	3	6	17	4	11	1	3	4	11	1	3	0	0	0	0	36	100
Musculoskeletal	2	40	0	0	0	0	0	0	1	20	0	0	2	40	0	0	0	0	0	0	0	0	0	0	5	100
Chromosomal	51	93	0	0	0	0	1	2	1	2	0	0	2	4	0	0	0	0	0	0	0	0	0	0	55	100
Infants and fetuses with any monitored defect	84		7		35		30		13		13		16		1		13		17		2		1		234	

Abbreviation: ICCC-3, *International Classification of Childhood Cancer*, Third Edition.

be predictive of cancer type or birth defect or both. Along with others, this study also found that there was a higher magnitude of risk for solid tumors among children with birth defects than for leukemias or lymphomas, indicating that perhaps these tumors are related to mutations expressed early in development, in contrast to mutations later in development when cells are forming blood and lymphatic constituents (4). This is supported in part by studies showing that developmental genes that have a role in body plan formation during embryogenesis are also involved in cancer development (e.g., Gorlin and Rubinstein-Taybi syndromes) (23).

Genetics figures prominently in the etiology of specific birth defects, as well as specific childhood cancers. Studies of cancer patterns in parents and siblings of individuals with birth defects, however, do not point to a common inherited genetic pattern that links birth defects and cancers (24, 25). Instead, it may be that birth defects confer a genetic susceptibility such that environmental exposures are less well tolerated in this high-risk population. As the studies in Down syndrome children indicate, there is likely to be a role for specific environmental toxins and dietary factors in the initiation and/or promotion of carcinogenesis in children with birth defects. In considering these results within the Knudson "two hit hypothesis" for some childhood cancers (26), children with birth defects may be described as candidates already having the first genetic "hit" and, hence, may have increased susceptibility to cancer from birth or earlier. If this is the case, further study of the complex relation between these 2 rare events may lead to not only a better understanding of the etiology of both but also possible prevention strategies.

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