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Congenital Anomalies and Childhood Cancer in Great Britain

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Summary

The presence of cancer and a congenital anomaly in the same child may be explained in certain cases by an underlying genetic abnormality. The study of these associations may lead to the identification of genes that are important in both processes. We have examined the records of 20,304 children with cancer in Britain, who were entered into the National Registry of Childhood Tumors (NRCT) during 1971–86, for the presence of congenital anomalies. The frequency of anomalies was much higher among children with solid tumors (4.4%) than among those with leukemia or lymphoma (2.6%; $P < .0001$). The types of cancer with the highest rates of anomalies were Wilms tumor (8.1%), Ewing sarcoma (5.8%), hepatoblastoma (6.4%), and gonadal and germ-cell tumors (6.4%). Cases of spina bifida and abnormalities of the eye, ribs, and spine were more common in children with cancer than among population-based controls. Future studies may be directed toward identifying the developmental pathways and the relevant genes that are involved in the overlap between pediatric cancer and malformation.

Introduction

Several genetic diseases predispose children to both cancer and congenital anomalies. Children with Down syndrome are at increased risk both for cardiac malformations and for acute leukemia (Miller 1963). The association of Wilms tumor with aniridia, growth and gurinary abnormalities, and mental retardation (WAGR) has been linked to a chromosomal deletion in the region of the WT1 gene on chromosome 11p13 (Riccardi et al. 1978), and point mutations in WT1 may be found in children with the Denys-Drash syndrome (Pelletier et al. 1991). There is an excess of embryonal tumors among children with overgrowth syndromes, including hemihypertrophy and the Beckwith-Weidemann syndrome (Weidemann 1983). Children with retinoblastoma may have a deletion in the region of chromosome 13q14, which may lead to developmental and growth delay and a facial abnormality (Motegi et al. 1983).

A few of the known associations are attributable to contiguous-gene syndromes, but the mechanism for most such occurrences is unknown. With the exception of diethylstilbestrol (Herbst et al. 1971), there is little evidence to support the hypothesis that human teratogens also act as transplacental carcinogens. It may be that mutation in genes (or their regulatory elements) that are expressed in development can adversely affect tissue organization and result in preneoplastic lesions. It is hoped that the study of the association of childhood cancer and congenital anomalies will lead to the identification of new genes that are involved in development and cancer. To investigate the association between childhood cancer and congenital anomalies, we have reviewed the records of 20,304 children with cancer, of whom 720 had a congenital anomaly, in the NRCT for England, Scotland, and Wales. The frequency of reported anomalies in these children was then compared with the expected frequency based on a population-based registry of congenital malformations.

Cases and Methods

We have reviewed the 20,304 cases of childhood cancer diagnosed during 1971–86 and reported to the NRCT for the presence of congenital anomalies. The registry receives copies of all notifications for children <15 years of age who are reported to national cancer-registration schemes in England, Scotland, and Wales. Confirmation of diagnosis subsequently is obtained either from the hospitals at which the children are treated, from their family doctors, or from organizers of clinical trials. Included are all malignant neoplasms and benign tumors of the brain and spinal cord, classified according to the Birch and Marsden (1987) scheme with the following modifications: (1) acute megakaryocytic leukemia is included with acute nonlymphocytic leukemia; (2) non-Hodgkin, Burkitt, and unspecified lymphoma are combined; (3) intracranial primitive neuroectodermal tumor is classified with medulloblastoma; (4) "other glioma" and miscellaneous intracranial and intraspinal

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neoplasms are combined; (5) peripheral neuroectodermal tumors are included with other sympathetic-nervous-system tumors; and (6) rhabdoid renal tumor and clear-cell sarcoma of the kidney are classified with Wilms tumor. Incidence rates for the registry, as well as a description of methods, have been published previously (Stiller et al. 1995).

Information on congenital anomalies was obtained at the same time as the confirmation of the diagnosis for all registrations, except for a small proportion of cases registered during 1971–77. Information on congenital anomalies also was obtained through a postal questionnaire that was addressed to the family physicians of children who were diagnosed with cancer during 1971–84 and who were alive at the end of 1988 (including those diagnosed during 1971–77 for whom information had not been obtained previously). This information was collected in the course of a study on childhood-cancer survivors and was incorporated into the existing registry records.

Congenital anomalies were classified according to the International Classification of Diseases, 9th revision (ICD 9), for category XIV, including codes 7400–7599. Three percent of children in the registry are known to have predisposing genetic conditions (Narod et al. 1991). Several genetic conditions, including Down syndrome, neurofibromatosis, and tuberous sclerosis, are known to predispose to both cancer and congenital anomalies. For example, cases of leukemia associated with congenital heart disease may be due to the underlying diagnosis of Down syndrome. Similarly, the majority of cases of aniridia and Wilms tumor are known to be due to chromosome 11p deletions.

Because the purpose of the present study was to identify new associations of malformations and cancer, 275 cases with an established genetic cause were removed, including 167 children with Down syndrome, 23 children with tuberous sclerosis, 16 children with neurofibromatosis, 15 children with the Wilms/aniridia syndrome, and 2 children with immunodeficiency syndromes. Fifty-two additional children were excluded because of a chromosomal defect other than Down syndrome. These exclusions reduce to 20,029 the total number of children with tumors studied. Because chromosome studies were not done for all children, or because the results may not have been reported in all cases, it is unlikely that all children with abnormal karyotypes have been excluded. There were a small number of children for whom genetic conditions were listed and who were not excluded (e.g., those with osteogenesis imperfecta) because the relationship between these conditions and increased cancer risks is not yet established.

The observed number of children with cancer of a specific type and a particular congenital anomaly was compared with the expected number based on one of the following two comparison groups:

1. The expected number was based on the frequency of the anomalies among children in the entire study group.
2. The expected number was based on the frequency of anomalies recorded in the British Columbia Health Surveillance Registry (BC Registry). The BC Registry compiles data on the number and type of all anomalies for children born in British Columbia, according to the ICD 9 classification scheme (Baird 1987). Neoplastic conditions are registered and are classified by anatomic type. Information is derived from >60 types of source record, including the physician's notice of birth, the hospital admission and discharge forms, and death registrations. Although information is recorded for stillbirths, the present analysis is restricted to live-born children. The children used for this comparison were born in British Columbia during 1969–88. There were 48,926 anomalies, 1,049 malignant neoplasms, and 777,158 births registered during this period. There were 122 children listed with both anomalies and cancers. On the basis of British Columbia Provincial data, this number was 1.85 times higher than expected ($P < .01$).

The observed associations were tested for significance by use of two-tailed P values calculated by comparing the proportion of children with anomalies in the case group with the proportion of children in the comparison group. The Fisher exact test, or, where appropriate, its asymptotic approximation, was used. To establish the significance levels for relative risks associated with comparison group (1) defined above, the proportion of cases with a specific anomaly among children with cancer of a particular type was compared with the proportion of children with this anomaly among children who had other types of cancer. For relative risks associated with comparison group (2), the proportions of children with anomalies in the Oxford registry were compared with the proportions of children in British Columbia who had the same anomaly. For sex-specific malformations (e.g., cryptorchidism and uterine abnormality), the denominators were adjusted to include only children of the appropriate sex.

Results

In order to identify novel associations between malformation and neoplasia, the 275 children whose cancers could be attributed to known genetic diseases were excluded from these analyses. This group included 45% of the 223 anomalies found in children with leukemia (and that commonly were associated with Down syndrome). In the remaining children, a total of 832 congenital anomalies were recorded in the NRCT and were distributed among 720 (3.59%) of the 20,029 children. The proportions of patients diagnosed with a congenital anomaly in

Table 1

Proportion of Children with Congenital Anomalies, by Type of Cancer

Type of Cancer (No.)	No. of Children with Anomalies (No. of Anomalies)	Percent of Children with Anomalies
Leukemia (6,588)	160 (174)	2.4
Lymphoma (2,191)	67 (73)	3.1
Brain and spinal cord (4,698)	144 (167)	3.1
Neuroblastoma (1,208)	64 (73)	5.3
Retinoblastoma (549)	27 (36)	4.9
Wilms (1,148)	93 (106)	8.1
Liver (165)	12 (14)	7.3
Osteosarcoma (549)	14 (19)	2.6
Ewing sarcoma (396)	23 (26)	5.8
Soft-tissue sarcoma (1,248)	45 (56)	3.6
Gonadal and germ cell (544)	35 (43)	6.4
Other[a] (745)	36 (45)	4.8
Overall (20,029)	720 (832)	3.6

[a] Includes carcinomas, other sympathetic-nervous-system tumors, chondrosarcomas, and other bone tumors.

relation to specific types of childhood cancer are given in table 1. The highest observed rates of congenital anomalies were observed for Wilms tumor (8.1%), Ewing sarcoma (5.8%), liver tumors (7.3%) (the majority are hepatoblastomas), and gonadal and germ-cell tumors (6.4%). Three categories of anomalies were significantly overrepresented among children with cancer (table 2): neural tube defects, anomalies of the eye, and anomalies of the genitourinary system ($P < .005$ for each). There was a significant deficit of respiratory anomalies among the children with cancer ($P < .001$).

However, the majority of these cases in the BC Registry belonged to ICD 9 category 7485—agenesis, hypoplasia, and dysplasia of the lung—and a high proportion of these are likely to be lethal. The rate of anomalies among the children with leukemia or lymphoma (2.59%) was much less than the rate observed among all children with solid tumors (4.38%; $P < .0001$).

The observed and expected numbers of anomalies in children with solid tumors at specific sites are given in tables 3–8. The overall frequency of anomalies among children with brain tumors was lower than that for most other solid tumors (table 1). Hydrocephalus, spina bifida, and other anomalies of the spine were more common than expected in children with brain tumors than in the British Columbia controls (table 3). Two children with medulloblastoma were diagnosed with the Rubinstein-Taybi syndrome (broad thumbs and a characteristic dysmorphic facies). This syndrome was not reported for any other children with cancer.

An excess of gastrointestinal malformations was seen in children with neuroblastoma, including four cases of pyloric stenosis and two anal abnormalities (one atresia and one stenosis) (table 4). Malformations of the head and neck and of the gastrointestinal and musculoskeletal systems were significantly more common in children with neuroblastoma than in children with other forms of cancer. Abnormalities of the musculoskeletal system in these children were particularly common in the spine and in the lower limb.

The types of anomalies associated with retinoblastoma were similar to those associated with neuroblastoma and included cardiac septal defects, gastrointestinal abnormalities, and musculoskeletal abnormalities (table 5). These were in significant excess when compared with the frequency in the internal controls.

Wilms tumor was associated with the highest rate of congenital anomalies (table 6). Previous associations with genitourinary malformations were confirmed, and other associations were revealed. Three cases of transposition of the great vessels were recorded in the NRCT, two of which occurred in children with Wilms tumor ($P < .01$) (the other case was a neuroblastoma), as did two of the four recorded cases of chondrodystrophy ($P < .01$). Several other malformations—including aortic stenosis, ventricular septal defects, and abnormalities of the spine and lower limb—were seen more frequently in children with Wilms tumor than in the population controls.

There were no excesses of specific types of anomalies among the 165 children with liver tumors or among the 549 children with osteosarcoma (data not shown). High frequencies of anomalies of several types were observed

Table 2

Anomalies Listed in NRCT

Type of Anomaly (No.)	Percent of Anomalies	
	NRCT	BC Registry
Neural tube defects[a] (24)	2.9	.9
Other nervous system[b] (38)	4.6	2.9
Eye[a] (30)	3.6	1.9
Head and neck (25)	3.0	3.2
Cardiac (74)	8.9	10.9
Other circulatory (30)	3.6	9.9
Respiratory (8)	1.0	5.7
Cleft lip and palate (17)	2.0	3.2
Digestive (68)	8.2	8.7
Genitourinary[a] (171)	20.6	16.4
Musculoskeletal (249)	29.9	29.4
Skin (40)	4.8	5.0
Other (58)	7.0	1.9
Total (832)	100.0[c]	100.0[c]

NOTE.—Anomalies for 275 children with known genetic conditions were not included in this table (see Cases and Methods).

[a] Overrepresented, at $P = .005$.

[b] Overrepresented, at $P = .01$.

[c] Because of rounding error, entries do not sum exactly to 100.

Table 3

Anomalies Associated with Brain and Spinal Neoplasms

Anomaly (ICD Code)[a]	No. Observed	No. Expected (RR)	
		NRCT	BC Registry
Spina bifida (741)	8	5.6 (1.4)	2.4 (3.3**)
Hydrocephalus (7423)	10	4.0 (2.5*)	2.5 (4.0***)
Pyloric stenosis (7505)	7	4.9 (1.4)	7.8 (.9)
Skull (7560)	6	4.2 (1.4)	4.2 (1.4)
Spine (7561)	9	9.2 (.98)	.94 (9.6***)
Other	127	167.2 (.76)	277.9 (.46)
Total	167	195.1 (.86)	295.7[a] (.56)

[a] Categories with an ICD code are those for which an excess number of anomalies is observed, as well as selected sites of interest (e.g., spine).
[b] Because of rounding error, entries do not sum exactly to total shown.
* $P < .05$.
** $P < .01$.
*** $P < .001$.

in children with Ewing sarcoma (table 7). Two children with Ewing sarcoma had a diagnosis of osteogenesis imperfecta. A single additional case of osteogenesis imperfecta was recorded in a child with a hepatoblastoma. A child with Klippel-Trenaunay-Weber syndrome had both a rhabdomyosarcoma and a hepatoblastoma, and a child with the Laurence-Moon-Biedl syndrome had a rhabdomyosarcoma.

There was a significant excess of musculoskeletal abnormalities, in particular those involving the spine,

Table 4

Anomalies Associated with Neuroblastoma

Anomaly (ICD Code)	No. Observed	No. Expected (RR)	
		NRCT	BC Registry
Ear, head, and neck (744)	5	1.51 (3.3*)	2.32 (2.2)
Branchial cleft[a] (7444)	2	.24 (8.3*)	.21 (9.5*)
Septal defects (745)	3	2.72 (1.1)	5.25 (.57)
Tetralogy of Fallot[b] (7452)	2	.24 (8.3*)	.53 (3.8)
Pulmonary valve (7460)	2	.36 (5.5)	.51 (3.9)
Other aorta (7472)	2	.30 (6.7)	.017 (118***)
Cleft lip or palate (749)	3	1.02 (2.9)	2.30 (1.3)
Gastrointestinal (750-51)	9	2.90 (3.1**)	3.74 (2.4*)
Pyloric stenosis[c] (7505)	4	1.27 (3.1*)	2.01 (2.0)
Imperforate anus[c] (7512)	2	.54 (3.7)	.43 (4.7)
Genitourinary (752-53)	15	10.0 (1.5)	11.8 (1.3)
Musculoskeletal (754-56)	20	6.63 (3.0***)	13.9 (1.4)
Foot deformity[d] (7545-47)	8	2.42 (3.3**)	5.8 (1.4)
Spinal[d] (7561)	4	2.35 (1.7)	.24 (16.7***)
Other	12	24.8 (.48)	36.3 (.33)
Total	71	50.2[e] (1.4**)	76.1[e] (.93)

[a] Subcategory of "Ear, neck, head"; data shown were not used to calculate "Total" values.
[b] Subcategory of "Septal defects": data shown were not used to calculate "Total" values.
[c] Subcategory of "Gastrointestinal"; data shown were not used to calculate "Total" values.
[d] Subcategory of "Musculoskeletal": data shown were not used to calculate "Total" values.
[e] Because of rounding error, entries do not sum exactly to total shown.
* $P < .05$.
** $P < .01$.
*** $P < .001$.

Table 5

Anomalies Associated with Retinoblastoma

Anomaly (ICD Code)	No. Observed	No. Expected (RR)	
		NRCT	BC Registry
Cataract (7433)	2	.16 (12.5*)	.12 (16.6*)
Ventricular septal defects (7454)	5	.82 (6.1**)	1.11 (4.5*)
Other heart (746)	3	.85 (3.5)	1.17 (2.6)
Gastrointestinal (750-51)	5	1.32 (3.8*)	2.82 (1.8)
Genitourinary (752-53)	5	4.69 (1.1)	5.67 (.88)
Musculoskeletal (754)	8	3.01 (2.7*)	6.31 (1.3)
Other	8	11.96 (.67)	17.30 (.46)
Total	36	22.8*[a] (1.6)	34.50 (1.0)

[a] Because of rounding error, entries do not sum exactly to total shown.
* $P < .05$.
** $P < .01$.

among children with germ-cell tumors, compared with the frequency in children with other tumors (table 8). One child with a mixed germ-cell tumor also was diagnosed with the nail-patella syndrome.

The spectrum of cancers associated with particular classes of abnormalities is given in tables 9–12. Spina bifida and cardiac septal defects were found to be in excess in children with cancer of several types (tables 9 and 10). Genitourinary malformations were common in children with soft-tissue sarcoma as well as Wilms tumor (table 11). A striking excess of spinal and rib malformations was found in children with cancer of almost all types, when compared with children in the BC Registry (table 11). The association was most pronounced for renal carcinoma; 2 of 22 children with renal carcinoma had a spinal abnormality,

Table 6

Anomalies Associated with Wilms Tumor

Anomaly (ICD Code)	No. Observed	No. Expected (RR)	
		NRCT	BC Registry
Spina bifida (741)	3	1.38 (1.4)	.60 (5.0*)
Microcephaly (7421)	2	.63 (3.2)	.35 (5.7)
Transposition of the great vessels (7451)	2	.17 (11.8*)	.45 (4.4)
Ventricular septal defect (7454)	7	1.72 (4.1**)	2.33 (3.0*)
Congenital aortic stenosis (7463)	2	.46 (4.3)	.13 (15.4*)
Pyloric stenosis (7505)	3	1.20 (2.5)	1.91 (1.6)
Ovary (7520)	2	.11 (18.2*)	.08 (25.0**)
Uterus (7523)	2	.17 (11.8**)	.02 (100***)
Cryptorchidism (7525)	8	3.72 (2.2)	2.91 (2.7*)
Hypospadias (7526)	5	1.73 (2.9)	2.61 (1.9)
Urinary system (753)	14	3.78 (3.7***)	.24 (58.3***)
Congenital hip dislocation (7543)	5	2.01 (2.5)	3.61 (1.4)
Lower limb (7556)	3	1.43 (2.1)	.29 (10.3**)
Skull and facial bones (7560)	2	1.03 (1.9)	1.02 (2.0)
Spinal (7561)	3	2.23 (1.3)	.23 (13.0**)
Chondrodystrophy (7564)	2	.23 (8.7*)	.27 (7.4)
Other	41	25.6 (1.6**)	55.3 (.74)
Total	106	47.60 (2.2***)	72.3[a] (1.5***)

[a] Because of rounding error, entries do not sum exactly to total shown.
* $P < .05$.
** $P < .01$.
*** $P < .001$.

Table 7

Anomalies Associated with Ewing Sarcoma

Anomaly (ICD Code)	No. Observed	No. Expected (RR)	
		NRCT	BC Registry
Spina bifida (741)	2	.47 (4.3)	.21 (9.5*)
Cataracts (7433)	2	.14 (14.3*)	.087 (23.0**)
Orbit (7436)	2	.36 (8.3)	.15 (13.3*)
Genitourinary (752-3)	5	3.38 (1.5)	4.09 (1.2)
Musculoskeletal (754-6)	10	4.92 (2.0)	6.92 (1.4)
Spinal[a] (7561)	2	.77 (2.6)	.079 (25.3**)
Osteodystrophy[a] (7565)	2	.059 (33.9**)	.048 (41.7**)
Other	5	7.17 (.70)	13.4 (.37)
Total	26	16.44[b] (1.58)	24.9[b] (1.0)

[a] Subcategory of "Musculoskeletal"; data shown were not used to calculate "Total" values.
[b] Because of rounding error, entries do not sum exactly to total shown.
* $P < .05$.
** $P < .01$.

in contrast to only 8 of 8,779 children with leukemia or lymphoma ($P < .001$).

Discussion

Because congenital anomalies and childhood cancer are both infrequent events, it was necessary to study a large population of children, in order to identify substantial numbers of children with both conditions. Registries such as the NRCT are valuable resources in this respect. Furthermore, by excluding children with a known genetic basis of cancer, we were able to improve the power to detect novel associations of cancer and malformation. We have performed many comparisons, and some statistically significant results may be due to chance; for other results, the P values are sufficiently small to effectively rule out this possibility.

The frequency of abnormalities in children with solid tumors was almost double that observed in children with either leukemia or lymphoma. The overall frequency of abnormalities among children with cancer in the NRCT was not higher than the frequency observed in British Columbia children. This is surprising, given the excess numbers of congenital anomalies observed in children with specific tumors, but it may be due to more complete reporting of anomalies in the BC Registry. The BC Registry obtains and updates information from >60 sources, including death certificates and hospital admission records, for children ≤7 years of age (Baird 1987). For example, registrations for cleft lip are most commonly made from the physician's notice of birth, but registrations for congenital heart defect are more frequently made through the hospital-admission record.

The rates of certain malformations may differ in chil-

Table 8

Anomalies Associated with Gonadal and Germ-Cell Tumors

Anomaly (ICD Code)	No. Observed	No. Expected (RR)	
		NRCT	BC Registry
Other nervous (742)	3	.81 (3.7*)	.94 (3.2)
Septal defects (745)	3	1.17 (2.6)	2.37 (1.3)
Musculoskeletal (754-6)	18	6.76 (2.7***)	9.51 (1.9**)
Spinal[a] (7561)	6	1.06 (5.7***)	.11 (54.5***)
Other	19	13.9 (1.4)	20.5 (.93)
Total	43	22.6[b] (1.9***)	33.4[b] (1.3)

[a] Subcategory of "Musculoskeletal"; data shown were not used to calculate "Total" values.
[b] Because of rounding error, entries do not sum exactly to total shown.
* $P < .05$.
** $P < .01$.
*** $P < .001$.

Table 9

Cancers Associated with Spina Bifida

Neoplasm	No. Observed	No. Expected (RR) NRCT	No. Expected (RR) BC Registry
Leukemias	6	7.90 (.76)	3.42 (1.8)
Brain and spinal	8	5.64 (1.4)	2.47 (3.2**)
Wilms	3	1.38 (2.2)	.60 (5.0*)
Ewing	2	.47 (4.3)	.21 (9.5*)
Hepatoblastoma	2	.99 (2.0)	.43 (4.7)
Neuroblastoma	1	1.45 (.69)	.63 (1.6)
Bone	1	.05 (20.0)	.02 (50.0*)
Gonadal and germ cell	1	.65 (1.5)	.29 (3.5)
Other	0	5.46	2.33
Total	24	24.00[a]	10.40 (2.3***)

[a] Because of rounding error, entries do not sum exactly to total shown.

* $P < .05$.

** $P < .01$.

*** $P < .001$.

dren in the United Kingdom versus children in British Columbia. Several abnormalities, in particular anencephaly and pulmonary atresia, are associated with high rates of infant mortality and are expected to be rare in children who have developed cancer in postinfancy. Differences in specific malformation rates also may be due to variations in coding practices in Canada and the United Kingdom. Because of the possible differences in the baseline congenital anomaly rates in the two countries, we have chosen to use two control groups. Nevertheless, the significantly higher frequency of abnormalities in children with solid tumors than in children with leukemia, which was seen clearly both in British Columbia (relative risk [RR] = 1.83) and in the United Kingdom (RR = 1.72) is compelling evidence that congenital anomalies are associated with some types of childhood cancer. These observations suggest that pediatric solid tumors may result from mutation or inactivation of genes that are expressed early in development, whereas leukemias and lymphomas may be more likely to be due to mutations that occur at later stages of tissue development, in cells committed to form blood and lymphatic elements.

There was no excess of malformations in children with leukemia or lymphoma, in either registry, after children with Down syndrome were excluded. In British Columbia, there were a total of 23 abnormalities observed among children with leukemia, compared with 24.9 abnormalities expected, after cases with abnormalities listed in ICD 9 category 758 (chromosomal abnormalities) were excluded. The possibility of a selection bias may be considered, but there is no reason to believe that the reporting, by physicians in the United Kingdom or by physicians in Canada, of congenital anomalies with leukemias and lymphomas was different from that for children with solid tumors.

With the exception of children with Down syndrome, there are few reports of malformations in children with leukemia. In a previous study, 7 (4.9%) of 142 children with acute lymphocytic leukemia (ALL) had congenital renal anomalies, including duplication of the collecting system (6 cases) and a missing kidney (Robison et al. 1982), but in the present study the rate of genitourinary malformations among children with ALL was only 0.5%, which was not higher than that for other types (table 10).

Several other investigators have also found an overall association between congenital anomalies and cancer. Through parent interviews, Mann et al. (1993) found abnormalities in 60 (10.8%) of 555 children with childhood cancer. Eight of these children had predisposing genetic conditions and would have been excluded under the present criteria, giving an overall frequency of 9.8%, compared with a control frequency of 4.9%. Windham et al. (1985) found the rate of cancer in children with birth defects to be 28.3/100,000/year, approximately double the rate in controls.

We report 10 cases of hydrocephalus in children with brain tumors. Hydrocephalus previously has been associated with childhood brain tumors, possibly as a result of obstruction due to neoplastic disease (Miller 1968; Mili et al. 1993*a*).

Van der Weil (1960) noted the association of gliomas and a family history of neural tube defects. In the study by Windham et al. (1985), children with a defect involving the CNS had an increased risk of both CNS tumors and retinoblastoma. Mann et al. (1993) found 5 (0.9%)

Table 10

Cancers Associated with Cardiac Septal Defects

Neoplasm	No. Observed	No. Expected (RR) NRCT	No. Expected (RR) BC Registry
Leukemia	8	14.8 (.54)	28.7 (.28)
Lymphomas	3	4.94 (.61)	9.53 (.31)
Brain and spinal	6	10.57 (.57)	20.4 (.29)
Neuroblastoma	4	2.71 (1.5)	5.25 (.76)
Retinoblastoma	5	1.23 (4.1*)	2.39 (2.1)
Wilms	10	2.46 (4.1***)	5.03 (2.0)
Germ cell	3	.47 (6.4*)	.91 (3.3)
Ewing sarcoma	1	.89 (1.1)	1.72 (.58)
Rhabdomyosarcoma	2	1.85 (1.1)	3.59 (.56)
Carcinoma	1	1.28 (.78)	2.47 (.40)
Other	0	1.80	7.21
Total	43	43.00	87.20 (.49)

* $P < .05$.

*** $P < .001$.

Table 11

Cancers Associated with Genitourinary Malformations

Neoplasm	No. Observed	No. Expected (RR)	
		NRCT	BC Registry
Leukemia	36	56.2 (.64)	64.1 (.56)
Lymphoma	20	18.7 (1.1)	21.3 (.94)
Brain and spinal	26	40.1 (.65)	45.7 (.57)
Neuroblastoma and other sympathetic	16	10.6 (1.5)	12.1 (1.3)
Retinoblastoma	5	4.68 (1.1)	5.34 (.94)
Wilms	29	9.92 (2.9***)	11.2 (2.6***)
Soft-tissue sarcoma	18	10.7 (1.7*)	12.1 (1.5)
Liver	3	1.41 (2.1)	1.60 (1.9)
Ewing sarcoma	5	3.38 (1.5)	3.85 (1.3)
Osteosarcoma	1	4.68 (.21)	5.34 (.19)
Gonadal and germ cell	6	4.65 (1.3)	5.30 (1.1)
Carcinoma/other	6	5.28 (1.1)	6.02 (1.0)
Total	171	171	194.0[a] (.88)

[a] Because of rounding error, entries do not sum exactly to total shown.
* $P < .05$.
*** $P < .001$.

neural tube defects among 555 cases of childhood cancer but none among 1,110 controls. The frequency of neural tube defects was much less (0.1%) in the present study. The incidence of neural tube defects has been correlated with dietary folate (Mulinare et al. 1988), and insufficient vitamin intake also has been implicated as a possible cause of primitive neuroectodermal tumors (including medulloblastoma) (Bunin et al. 1993). We saw only a single case of medulloblastoma and spina bifida; however, the eight cases of spina bifida seen in all children with brain tumors were more than expected (table 4), consistent with the hypothesis of a common maternal factor.

We observed the striking association of medulloblastoma and the Rubinstein-Taybi syndrome in two children, one of whom was the case reported by Evans et

Table 12

Cancers Associated with Spine and Rib Malformations

Neoplasm	No. Observed	No. Expected (RR)	
		NRCT	BC Registry
Leukemia	6	16.7 (.4)	1.92 (3.1*)
Lymphoma	7	5.4 (1.3)	.64 (10.9**)
Brain and spinal	12	11.7 (1.0)	1.4 (8.6***)
Neuroblastoma	5	3.0 (1.7)	.35 (14.3***)
Retinoblastoma	0	1.4 (.0)	.16 (.0)
Wilms	4	2.9 (1.4)	.33 (12.1***)
Renal carcinoma	2	.054 (37.0**)	.0059 (339***)
Liver	0	.43 (.0)	.05 (.0)
Bone	6	2.5 (2.4)	.27 (22.2***)
Soft-tissue sarcoma	3	3.1 (1.0)	.36 (8.3*)
Gonadal and germ cell	6	1.4 (4.3**)	.16 (37.5***)
Other	1	3.42 (.29)	.20 (.50)
Total	52	52.0[a]	5.85[a] (8.89***)

[a] Because of rounding error, entries do not sum exactly to total shown.
* $P < .05$.
** $P < .01$.
*** $P < .001$.

al. (1993). In a case series of 724 persons with Rubinstein-Taybi syndrome, there were 13 childhood cancers, including 3 cases of ALL, 4 brain tumors, 2 neuroblastomas, 2 rhabdomyosarcomas, 1 leiomyosarcoma, and 1 embryonal carcinoma (Miller and Rubinstein 1995). The gene for Rubinstein-Taybi syndrome maps to chromosome 16p13.3 and recently has been identified (Petrij et al. 1995). The gene CBP codes for a transcription coactivator, CREB-binding protein. It will be of interest if this gene is involved in the pathogenesis of sporadic medulloblastoma. Miller (1968) reported three children with gliomas and tetralogy of Fallot—one similar case was seen in our study. Vieregge et al. (1987) review the association of congenital anomalies and familial brain tumors in adults.

The frequency of cleft lip or palate was higher among children in our study who had either a brain tumor (0.11%), a neuroblastoma (0.25%), or a retinoblastoma (0.18%) than among those with leukemia (0.03%). Baptiste et al. (1989) found a nonsignificant excess of cleft lip and palate among 338 patients with CNS tumors and their siblings, when compared with 676 controls, but observed no overall increase in the frequency of congenital anomalies in this group of children. In a previous study of children who died of cancer in Britain during 1953–73, the overall frequency of cleft palate was not elevated, but 3 of the 17 cases were in children with Wilms tumor (<1 expected) (Blot et al. 1980).

Several studies have documented an excess of congenital anomalies among children with neuroblastoma, including that of Berry et al. (1970), who identified abnormalities in 6 of 144 cases of neuroblastoma, including a child with bilateral pes cavus. In a historical cohort study, 4 of 19,373 children with birth defects developed neuroblastoma (RR = 20.3; $P < .05$) (Mili et al. (1993*a*). Miller et al. (1968) noted congenital heart defects in 6 of 502 children hospitalized with neuroblastoma, compared with 2.8 cases expected. Sy and Edmonsdon (1968) reviewed 26 cases of birth defects and neuroblastoma; a high proportion (~30%) of the abnormalities also involved the cardiovascular system, and there were 2 other cases of clubfoot.

Retinoblastoma has been associated with facial abnormality in association with a constitutional deletion of chromosome 13q14 (Motegi et al. 1983), but, in contrast to Wilms tumor, there are relatively few reports of malformations associated with retinoblastoma in the absence of karyotypic abnormalities. In the study by Mili et al. (1993*a*), children with birth defects were at 4.7 times increased risk for retinoblastoma ($P < .05$). We saw an excess of ventricular septal defect in children with retinoblastoma, and we also confirmed our previous finding of an association between septal defect and Wilms tumor (Stiller et al. 1987). Cases of ventricular septal defect have been reported, by others, in children with these tumor types (Mehes et al. 1985; Bonaiti-Pellié et al. 1992; Mili et al. 1993*a*).

The proportion of children with congenital anomalies in our study was higher for Wilms tumor than for any other cancer type. Wilms tumor classically has been associated with hemihypertrophy, with aniridia, and with genitourinary malformations (Miller et al. 1964). Berry et al. (1970) found 9 abnormalities among 103 children with Wilms tumor, including a case of aortic stenosis. Cich (1993) reported a syndrome of bilateral Wilms tumor in a mother and two daughters with auditory-canal stenosis, cataracts, blepharophimosis, ptosis, microphthalmia, and colobomata. Our report of two children with Wilms tumor and transposition of the great vessels extends the total number of reported cases to four, including those of Miller (1968) and of Lynch and Green (1968). We identified two children with Wilms tumor and chondrodystrophy; Miller (1968) noted a case of chondrodystrophy in a child with Wilms tumor and another case in a child with neuroblastoma.

In our study, a high frequency of abnormalities was seen in children with liver tumors, but, because of the rarity of cancer at this site, few of the subgroup comparisons were significant. Birth defects previously were seen in 4 of 40 children with hepatoblastoma (Berry et al. 1970) and in 9 of 42 children with liver tumors (Mann et al. 1990). Some children in the latter study also are included in our study.

We did not find an excess of congenital anomalies of any type in children with osteosarcoma. Mulvihill et al. (1977) describe a syndrome of osteosarcoma and limb abnormalities (clinodactyly, brachymesophalangy, and radioulnar synostosis) in three siblings in a consanguineous American Indian family. In contrast to the rate for osteosarcoma, there was a high incidence of abnormalities among children with Ewing sarcoma. In a previous study, developmental abnormalities were found in 56 of 154 children with Ewing sarcoma, including 9 genitourinary abnormalities, 8 rib abnormalities, and 7 vertebral defects (McKeen et al. 1983). Our data confirm these associations. Of particular interest are the two children with Ewing sarcoma and osteogenesis imperfecta (type not specified). There was only one other case of osteogenesis imperfecta reported in the NRCT. A possible explanation for these findings is that the bony matrix of children with osteogenesis imperfecta is particularly suited to the growth of malignant cells. Osteosarcoma also has been reported in children with osteogenesis imperfecta (Klenerman and Ockenden 1967), and Ewing sarcoma has been observed to arise at the site of benign bone tumors (McKeen et al. 1983).

In the study by Ruymann et al. (1988), 37 of 115 children dying of rhabdomyosarcoma were found, on autopsy, to have congenital anomalies. PAX3 is an example of a gene that is known to be involved in a devel-

opmental syndrome and in cancer. Germ-line mutation in the DNA-binding domain of the human homologue of PAX3 is the cause of Waardenburg syndrome (Tassabehji et al. 1992), and the gene is rearranged by somatic translocation in alveolar rhabdomyosarcoma (Barr et al. 1993).

We observed congenital anomalies in 6.4% of children with gonadal and germ-cell tumors. Birth defects have been reported elsewhere in 2 (11.8%) of 17 children with gonadal teratomas (Berry et al. 1970), in 7 (17.1%) of 41 children with germ-cell tumors (Mann et al. 1993), and in 48 (13%) of 369 children with germ-cell tumors (Fraumeni et al. 1973). Birch et al. (1982) found an excess of neural tube defects in children with germ-cell tumors (Birch et al. 1982). Elsewhere, sacrococcygeal teratomas have been associated with a high rate of malformations affecting midline structures, including intestinal atresia (Berry et al. 1970).

The most striking excess of malformations was for those seen to involve the spine and ribs. In many cases, these malformations often will have been detected through the use of diagnostic x-rays as part of the investigation of a child with cancer. However, in a previous study the frequency of rib abnormalities was estimated from the chest x-rays of 1,000 children with cancer and of 200 controls (Schumacher et al. 1992). Overall, 21.8% of the children with cancer were found to have minor rib anomalies, compared with 5.5% of the controls. A high frequency of rib anomalies in that study was seen for children with Wilms tumor (23%), neuroblastoma (33%), brain tumors (27.4%), ALL (26.8%), soft-tissue sarcoma (24.5%), and Ewing sarcoma (24.5%). A second study documented an excess of spinal and rib malformations in children with Ewing sarcoma (McKeen et al. 1983). These observations suggest the possibility that genes controlling the development of vertebral segmentation may be involved in carcinogenesis. Recently, germ-line mutations in one of the homeobox genes (HOXa13) have been shown to be associated with an inherited abnormality of limb development in mice (Mortlock et al. 1996). The possibility of germ-line or somatic mutation in (or of errors in the imprinting of) one of the members of the homeobox gene family in children with cancer and spinal malformations is an area for future research.

An excess of cancer in children with pyloric stenosis has been reported recently by Mili et al. (1993*a*). Children with pyloric stenosis registered in the Metropolitan Atlanta Congenital Defects Program developed cancer at a rate 7.5 times greater than expected. Berry et al. (1970) identified both one case of pyloric stenosis in a child with a gonadal germ-cell tumor and another in a child with neuroblastoma. Other cases have been reported by Miller (1963), by Sy and Edmonsdon (1968), and by Atwell and Levick (1981). When the present study is combined with these five reports, the types of cancer that have been described most frequently in children with pyloric stenosis include brain tumors (8 cases reported), Wilms tumor (8 cases), leukemia (8 cases), neuroblastoma (7 cases), lymphoma (4 cases), germ-cell tumors (2 cases), and retinoblastoma (1 case).

Most cases of malformation and cancer are sporadic and are not associated with a family history of disease. It is therefore unlikely that these cases are due to transmissible germ-line mutations, and other disease mechanisms must be considered. These mechanisms include early somatic mutation leading to mosaicism, errors of imprinting, and uniparental isodisomy. Theoretically, if a tumor-suppressor gene is imprinted, then both alleles may be rendered inactive through somatic recombination. If this gene also were involved in development, then somatic recombination early in embryogenesis might predispose a child to both cancer and a congenital anomaly. Because it is believed that imprinting errors are corrected in gametogenesis, such a disorder is unlikely to be familial. Beckwith-Weidemann syndrome is an example of a malformation syndrome that is associated with an increased risk of cancer and that may be the result of uniparental isodisomy of an imprinted region of chromosome 11p (Weksberg et al. 1993). The syndrome is rarely familial.

In several of the initial reports on cancers and congenital abnormalities, associations were due to chromosomal anomalies, including Down syndrome and the WAGR syndrome. Point mutations in specific genes, such as NF1 and the gene for CREB-binding protein, also may lead to both cancer and an anomaly in an individual. In contrast, the present study is remarkable in that wide classes of anomalies (e.g., septal defects, genitourinary malformations, and spine and rib abnormalities) were observed with a range of cancer types. A possible explanation for this is that a mutation in a developmental gene early in embryogenesis will lead to tissue mosaicism; the range of tissues involved in the mosaicism may be predictive of either the type of cancer observed, the particular malformation, or both.

Many dominant adult-cancer syndromes are associated with mutations in tumor-suppressor genes, including the Li-Fraumeni syndrome (p53), hereditary breast/ovarian cancer (BRCA1), neurofibromatosis type 2 (NF2), and the Von Hippel-Lindau syndrome (VHL). In these cases it is believed that somatic mutation of the second suppressor allele gives a predisposed cell a proliferative advantage, leading to clonal expansion and eventually to cancer. It is not necessary to invoke a similar mechanism of cell selection by enhanced growth in childhood cancer. This is because the embryo itself is rapidly growing, and, if a mutation occurs early in embryogenesis, then a clone of mutant cells will be generated that may involve a substantial fraction of the total fetal cell

number. It is possible that there are classes of developmental genes that, when mutated or inactivated, lead to cancer in children but are not associated with malignancy in adults. It is also possible that the location of these genes may be identified by studies of loss of heterozygosity in malignant and nonmalignant tissues from children with both cancer and a congenital abnormality. Chao et al. (1993) observed bilateral loss of heterozygosity of chromosome 11p in children with unilateral Wilms tumor. It will be of interest to see whether this phenomenon is generalizable to other childhood-tumor types.

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References

Atwell JD, Levick P (1981) Congenital hypertrophic pyloric stenosis and associated anomalies in the genitourinary tract. J Pediatr Surg 16:1029–1035

Baird PA (1987) Measuring birth defects and handicapping disorders in the population: the British Columbia Health Surveillance Registry. Can Med Assoc J 36:109–111

Baptiste M, Nasca P, Metzger B, Field N, McCubbi P, Greenwald P, Armbrustmacher V, et al (1989) Neurofibromatosis and other disorders among children with CNS tumors and their families. Neurology 39:487–492

Barr FG, Galili N, Holick J, Biegel JA, Rovera G, Emanuel BS (1993) Rearrangement of the PAX3 paired box gene in the paediatric solid tumour alveolar rhabdomyosarcoma. Nat Genet 3:113–117

Berry CL, Keeling J, Hilton C (1970) Coincidence of congenital malformation and embryonic tumors of childhood. Arch Dis Child 45:229–231

Birch JM, Marsden HB (1987) A classification scheme for childhood cancer. Int J Cancer 40:620–624

Birch JM, Marsden HB, Swindell R (1982) Prenatal factors in the origin of germ cell tumors in childhood. Carcinogenesis 3:75–80

Blot WJ, Stiller CA, Kinnier-Wilson LM (1980) Oral clefts and childhood cancer. Lancet 1:722

Bonaiti-Pellie C, Chompret A, Tournade M-F, Hochez J, Moutou C, Zucker J-M, Steschenko D, et al (1992) Genetics and genetic epidemiology of Wilms' tumour in the French Wilms' Tumour Study. Med Pediatr Oncol 20:284–291

Bunin GR, Kuitjen RR, Buckley JD, Rorke LB, Meadows AT (1993) Relation between maternal diet and subsequent primitive neuroectodermal brain tumors in young children. N Engl J Med 329:536–541

Chao L-Y, Huff V, Tomlinson G, Riccardi VM, Strong LC, Saunders GF (1993) Genetic mosaicism in normal tissue of Wilms tumour patients. Nat Genet 3:127–131

Cich JA (1993) Autosomal dominant inheritance of Wilms tumor and branchial cleft anomalies: a new syndrome? Causes Childhood Cancer Newslett 4(2): 1–2

Evans G, Burnell L, Campbell R, Gattamaneni HR, Birch J (1993) Congenital anomalies and genetic syndromes in 173 cases of medulloblastoma Med Pediatr Oncol 21:433–434

Fraumeni JF, Li FP, Dalager N (1973) Teratomas in children: epidemiologic features. J Natl Cancer Inst 51:1425–1430

Herbst AL, Cole P, Carlton T, Robbay ST, Scully RE (1971) Adenocarcinoma of the vagina: association of maternal stilbestrol therapy with tumor appearance in young women. N Engl J Med 284;878–881

Klenerman L, Ockenden BG, Townsend AC (1967) Osteosarcoma occurring in osteogenesis imperfecta: report of two cases. J Bone Joint Surg 49:314–323

Lynch HT, Green GS (1968) Wilms' tumor and congenital heart disease: report of a case and a family. Am J Dis Child 115:723–726

Mann JR, Dodd HE, Draper GJ, Waterhouse JAH, Birch JM, Cartwright RA, Hartley AL, et al (1993) Congenital abnormalities in children with cancer and their relatives: results from a case-control study (IRESCC). Br J Cancer 357–363

Mann JR, Kasthuri N, Raafat F, Pincott JR, Parkes SE, Muir KR, Ingram LC, et al (1990) Malignant hepatic tumors in children: incidence, clinical features and etiology. Paediatr Perinat Epidemiol 4:276–289

McKeen EA, Hanson MR, Mulvihill JJ, Glaubiger DL (1983) Birth defects with Ewing's sarcoma. N Engl J Med 309: 1522

Mehes K, Signer E, Pluss HJ, Muller HJ, Stalder G (1985) Increased prevalence of minor anomalies in childhood malignancy. Eur J Pediatr 144:243–249

Mili F, Khoury MJ, Flanders WD, Greenberg RS (1993A) Risk of childhood cancer for infants with birth defects. I. A record linkage study, Atlanta, Georgia 1968–1988. Am J Epidemiol 137:629–638

Miller RW (1963) Down's syndrome (mongolism), other congenital malformations and cancers among the sibs of leukemic children. N Engl J Med 268:393–401

——— (1968) Relation between cancer and congenital defects: and epidemiologic evaluation. J Natl Cancer Inst 40:1079–1085

Miller RW, Fraumeni JF, Manning MD (1964) Association of Wilms' tumour with aniridia, hemihypertrophy and other congenital abnormalities. N Engl J Med 207:922–927

Miller RW, Rubinstein JH (1995) Tumors in Rubinstein-Taybi syndrome. Am J Med Genet 56:112–115

Mortlock DP, Post LC, Innis JW (1996) The molecular basis of hypodactyly (Hd): a deletion in HOXa13 leads to arrest of digital arch formation. Nat Genet 13:284–289

Motegi T, Kaga M, Yanagawa Y, Kadowaki H, Watanabe K,

Inove A, Komatsu M, et al (1983) A recognizable pattern of the midface of retinoblastoma patients with interstitial deletion of 13q. Hum Genet 64:160–162

Mulinare J, Cordero JF, Erickson JD, Berry RJ (1988) Periconceptual use of multivitamins and the occurrence of neural tube defects. JAMA 260:3141–3145

Mulvihill JJ, Gralnick HR, Whang-Peng J, Leventhal BG (1977) Multiple childhood osteosarcomas in an American Indian family with erythroid macrocytosis and skeletal anomalies. Cancer 40:3115–3122

Narod SA, Stiller C, Lenoir GM (1991) An estimate of the heritable fraction of childhood cancer. Br J Cancer 63:993–999

Pelletier J, Bruening W, Kashtan CE, Mauer SM, Manivel JC, Striegel JZE, Houghton DC, et al (1991) Germline mutations in the Wilms' tumor suppressor gene are associated with abnormal urogenital development in Denys-Drash syndrome. Cell 87:437–447

Petrij F, Giles R, Dauwerese HG, Saris JJ, Hennekam RCM, Masuno M, Tommerup N, et al (1995) Rubinstein-Taybi syndrome caused by mutations in the transcriptional co-activator CBP. Nature 376:348–351

Riccardi VM, Sujansky E, Smith AC, Francke U (1978) Chromosomal imbalance in the aniridia-Wilms' tumour association: 11p interstitial deletion. Pediatrics 61:604–610

Robison LL, Swanson T, Day D, Ramsay NKC, L'Heureux P, Nesbit ME (1982) Renal anomalies in childhood acute lymphoblastic leukemia. N Engl J Med 307:1086–1087

Ruymann FB, Maddux HR, Ragab A, Soule EH, Palmer N, Beltangady M, Gehan EA, et al (1988) Congenital anomalies associated with rhabdomyosarcoma: an autopsy study of 115 cases: a report from the International Rhabdomyosarcoma Study Committee. Med Pediatr Oncol 16:33–39

Schumacher R, Mai A, Gutjahr P (1992) Association of rib anomalies and malignancy in childhood. Eur J Pediatr 151: 432–434

Stiller CA, Allen MB, Eatock EM (1995) Childhood cancer in Britain: the National Registry of Childhood Tumour and incidence rates, 1978–87. Eur J Cancer Suppl 31A:2028–2034

Stiller CA, Lennox EL, Kinnier-Wilson LM (1987) Incidence of cardiac septal defects in children with Wilms' tumour and other malignant disease. Carcinogenesis 8:129–132

Sy WM, Edmonsdon JH (1968) The developmental defects associated with neuroblastoma-etiologic implications. Cancer 22:234–238

Tassabehji M, Read AP, Newton VE, Harris R, Balling R, Gruss P, Strachan T (1992) Waardenburg syndrome (WS) patients have mutations in the human homologue of the Pax-3 paired box gene. Nature 355:635–636

Van der Wiel HJ (1960) Inheritance of glioma: the genetic aspects of cerebral glioma and its relation to status dysraphicus. Elsevier, Amsterdam

Vieregge P, Gerhard L, Nahser HC (1987) Familial glioma: occurrence within the familial cancer syndrome and systemic malformations. J Neurol 234:220–232

Weksberg R, Teshima I, Williams B, Greenberg C, Pueschel S, Chernos J, Fawlow SB, et al (1993) Molecular characterization of cytogenetic alterations associated with Beckwith-Wiedemann syndrome (BWS) pheontype refines the localisation and suggests the gene for BWS is imprinted. Hum Mol Genet 2:549–556

Wiedemann HR (1983) Tumors and hemihypertrophy associated with Wiedemann-Beckwith syndrome. Eur J Pediatr 141:129

Windham GC, Bjerkedal T, Langmark F (1985) A population-based study of cancer incidence in twins and in children with congenital malformations or low birth weight, Norway, 1967–1980. Am J Epidemiol 121:49–56