Cancer Risk in Children with Birth Defects and in Their Families: A Population Based Cohort Study of 5.2 Million Children from Norway and Sweden

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Abstract

Background: **Cancer and birth defects may share factors that influence risk. A malformation may involve physiologic changes or changes in lifestyle that might affect cancer risks.**

Methods: **In Norway and Sweden, the population-based medical birth and cancer registries were linked to identify subsequent cancer occurrence in children with birth defects and among their parents and siblings. Altogether, 5.2 million children and their families were included. The standardized incidence ratio (SIR) served as a measure of relative risk.**

Results: **There was an increased overall cancer risk in individuals with birth defects in the two countries [SIR, 1.7; 95% confidence interval (95% CI), 1.6-1.9], and the increased risk remained into early adulthood. Individuals with malformations in the nervous system were at increased risk of developing cancer in the brain/nervous system (Norway: SIR, 58; 95% CI, 41-80; Sweden: SIR, 8.3; 95% CI, 4.0-15), individuals with Down syndrome were at an increased risk of leukemia (Norway: SIR, 36; 95% CI, 26-48; Sweden: SIR, 36; 95% CI, 28-46), and there was an increased overall cancer risk for individuals with multiple birth defects (Norway: SIR, 5.5; 95% CI, 3.3-8.7; Sweden: SIR, 3.6; 95% CI, 2.2-5.4). There was no increased overall cancer risk among mothers (SIR, 1.0; 95% CI, 1.0-1.0), fathers (SIR, 1.0; 95% CI, 0.9-1.0), and siblings (SIR, 1.0; 95% CI, 0.9-1.1) of children with birth defects.**

Conclusions: **We observed an increased overall cancer risk in individuals with birth defects. The highest risks were seen for individuals with malformations in the nervous system, Down syndrome, and multiple defects. No increased overall cancer risk was seen among their parents or siblings.** (Cancer Epidemiol Biomarkers Prev 2008;17(3):500–6)

Introduction

Cancer and birth defects may share factors that influence risk, being of genetic and/or environmental origin. Furthermore, a malformation may involve physiologic changes or changes in lifestyle that might in turn affect cancer risk (1).

Previously, population-based studies have found an excess risk of cancer in children with congenital malformations (2-5). In particular, children with Down syndrome and children with central nervous system defects are at increased risk of developing leukemia and central nervous system tumors, respectively. A recent population- and registry-based Danish study found no evidence that individuals born with oral clefts had an increased overall cancer risk, although increased risks were found for certain subsites (breast, brain, and lung cancer; ref. 1).

If cancer and birth defects share a common etiology, parents or siblings of children with malformations may be at increased risk of cancer. A relatively recent population-based case-control study found no increased overall risk of cancer in parents after the birth of their first live-born child with congenital malformations (6). However, increased risks of lymphomas [odds ratio, 4.2; 95% confidence interval (95% CI), 1.3-13.5] and leukemia (odds ratio, 8.1; 95% CI, 2.0-34) were found in parents whose firstborn child had cleft lip/palate. Birth defects have increased recurrence in families, but recurrence appears to be mostly for a similar type of defect (7-9). Studies that have explored the cancer risk in siblings of childhood cancer patients have given inconsistent results (10, 11). We are unaware of any studies that investigate the cancer risk in siblings of children with birth defects.

Very large cohorts are needed to include a sufficient number of malformed children to allow estimates of cancer risks. The cohorts also need to be followed systematically several years after birth to follow the incidence of cancer. We took advantage of the opportunity to cross-link the population-based medical birth registries with the cancer registries in Norway and Sweden. The aim was to estimate the overall and site-specific cancer risk among individuals with birth defects and to estimate the risk of cancer among their parents and siblings.

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Table 1. Number of subjects with registered birth defects in Norway (1967-2004) and Sweden (1973-2004)

Malformation	*ICD-8**	*ICD-9* †	*ICD-10* ‡	Norway	Sweden
Nervous system	*740-43*	*740-42*	*Q00-07*	1,058	1,943
Eye, ear, face, and neck	*744-45 (excluding 7451)*	*743-44 (excluding 744B)*	*Q10-18 (excluding Q17.0)*	1,388	2,657
Heart and blood vessels	*746-47*	*745-47*	*Q20-28*	6,045	23,268
Respiratory organs	*748*	*748*	*Q30-34*	1,017	1,372
Lip/palate	*749*	*749*	*Q35-37*	3,465	4,340
Digestive system	*750-51*	*750-51*	*Q38-45*	1,463	2,869
Genitalia	*752 (excluding 7521, 7524)*	*752 (excluding 752F)*	*Q50-56 (excluding Q53)*	3,416	6,328
Urinary organs	*753*	*753*	*Q60-64*	1,377	2,309
Musculoskeletal system	*754-56, 5511-14 (excluding 7556)*	*754-56 (excluding 754D)*	*Q65-79 (excluding Q65.0-6)*	20,770	20,582
Down syndrome	*7593*	*758A*	*Q90*	2,108	3,201
Other chromosomal abnormalities	*7594-95*	*758 (excluding 758A)*	*Q91-99*	161	480
Other and unspecified	*757-58, 7590-92, 7596, 7598-99 (excluding 7571)*	*757, 759*	*Q80-89 (excluding Q82.5)*	1,803	2,938
Multiple defects§				1,604	3,766
Total				45,675	76,053

*Norway 1967-1998 and Sweden 1973-1986.
† Sweden 1987-1996.
‡ Norway 1999- and Sweden 1997-.
§Defects included in more than one of the main categories listed above.

Materials and Methods

Data Sources. The Medical Birth Registry of Norway and the Swedish Medical Birth Register are population-based registries that contain information on all births in Norway and Sweden since 1967 and 1973, respectively (12-14). The registries include a unique identification number assigned to all live-born children as well as the parents. Reporting of cancer cases is compulsory in the two countries, and the Cancer Registry of Norway and the Swedish Cancer Registry cover the whole populations from 1953 and 1958, respectively (15, 16).

Classification of Birth Defects. The Medical Birth Registry of Norway records births defects that have been diagnosed at the time of delivery or during the initial hospitalization (13). After the introduction of a modified notification form in 1999, also prenatal diagnoses and diagnoses obtained at the pediatric departments are reported separately. In the Swedish Medical Birth Register, information on malformations is obtained from codes given to the newborn at the pediatric examination or from neonatal units (15).

In this study, data on birth defects included the *International Classification of Diseases, Eighth Edition* (*ICD-8*) codes 740-759 in addition to 5511-5514, the *ICD-9* codes 740-759, and the *ICD-10* codes Q00-Q99, and the defects were grouped by organ system (Table 1). We excluded diagnoses of accessory auricle, hydrocele, undescended testicle, hip dislocation/subluxation, and nevus from the main analyses because of large variations in diagnosing these malformations. However, subanalyses were done for subjects with undescended testicle and hypospadias.

Cases with Down syndrome were not included in other categories of birth defects although they were registered with several defects. In some subanalyses, Down syndrome and other chromosomal abnormalities were excluded as they represent genetic syndromes rather than birth defects per se. Cases with other multiple defects (defects included in more than one of the main categories listed in Table 1) were pooled in a separate category. In the analyses, individuals with multiple defects were only included in this category and in the ''Total''.

Study Subjects. All live infants delivered in Norway and Sweden during 1967/1973 to 2004 and their parents were defined as our study cohort. However, twins, triplets, and quadruplets were excluded from the analyses. In our study, siblings denote full siblings only.

The personal identification number was used to link with the cancer registries to identify cancers at different sites as outlined in Table 2.

Only histologically verified malignant tumors were included, except for benign lesions of the central nervous system and not histologically verified tumors at this site. Noninvasive urothelial tumors were included. For each individual, only the first cancer diagnosis was used.

Statistical Analyses. We compared the cancer incidence among children with and without a birth defect. The follow-up of children was from birth until cancer diagnosis, emigration, death, or December 2004. Similarly, children with and without a sibling with a birth defect were compared. The siblings were counted in the category ''no siblings with birth defects'' until they had a sibling with a defect. Thereafter, they changed category and were counted among ''siblings with birth defects''.

We compared the cancer incidence in parents of children with and without birth defects. For the parents, follow-up started at the time of the first birth in women/men ages ≥20 years and at 20 years if the birth occurred before that age. Parents were counted in the category ''parents with children without birth defects'' until they had a child with a defect. Thereafter, they were counted in the category ''parents with children with birth defects.'' Follow-up ended at the date of cancer diagnosis, age 75 years, emigration, death, or December 2004.

The cancer incidence in exposed and unexposed groups was compared by calculation of the standardized incidence ratio (SIR) as described by Andersen et al. (17).

Table 2. SIRs of cancer occurrence in 121,728 patients with birth defects during follow-up in Norway (1967-2004) and Sweden (1973-2004)

*ICD-7**	Cancer site	Norway		Sweden	
		Observed	SIR (95% CI)	Observed	SIR (95% CI)
140-141, 143-148, 160-161	Head and neck	1	0.7 (0.0-4.0)	2	1.2 (0.1-4.4)
142	Salivary glands	1	1.8 (0.0-9.9)	1	1.3 (0.0-7.1)
150-154 †	Gastrointestinal tract	6	2.4 (0.9-5.2)	2	0.7 (0.1-2.6)
155-157 †*/155, 157* ‡	Liver/gallbladder/pancreas	3	1.8 (0.4-5.4)	5	2.3 (0.8-5.4)
158	Peritoneum	2	4.4 (0.5-16)	1	9.7 (0.2-54)
162-163	Lung/pleura	0	0.0 (0.0-4.3)	1	1.2 (0.0-6.5)
164	Mediastinum/thymus/heart	0	0.0 (0.0-19)	1	2.0 (0.1-11)
170	Breast	1	0.3 (0.0-1.9)	1	0.6 (0.0-3.4)
171	Uterine cervix	2	0.5 (0.1-1.6)	3	1.1 (0.2-3.3)
175	Ovary	3	1.4 (0.3-4.1)	10	4.0 (1.9-7.4)
172-174, 176	Other female genital organs	1	1.6 (0.0-9.2)	1	3.5 (0.1-20)
178	Testis	32	1.5 (1.0-2.1)	27	1.9 (1.3-2.8)
177, 179	Other male genital organs	1	5.7 (0.1-32)	1	4.5 (0.1-25)
180.0 †*/180.0, 180.9* ‡	Kidney	7	1.7 (0.7-3.4)	16	1.8 (1.0-3.0)
180.1-9, 181 †*/180.1-8, 181* ‡	Urinary bladder/organs	0	0.0 (0.0-3.9)	0	0.0 (0.0-4.5)
190	Melanoma of skin	11	0.9 (0.4-1.6)	7	0.7 (0.3-1.4)
191	Other skin	5	2.5 (0.8-5.9)	0	0.0 (0.0-2.7)
192	Eye	6	2.0 (0.7-4.3)	5	0.8 (0.3-1.9)
193	Brain/nervous system	82	2.5 (2.0-3.1)	69	1.3 (1.0-1.6)
194	Thyroid gland	9	2.3 (1.0-4.3)	7	1.4 (0.6-3.0)
195	Other endocrine organs	8	3.3 (1.4-6.5)	9	3.3 (1.5-6.3)
196	Bone	2	0.4 (0.0-1.5)	9	1.2 (0.5-2.2)
197	Connective tissue	3	1.0 (0.2-2.8)	12	1.5 (0.8-2.6)
206 †*/200-202* ‡	Lymphoma	12	0.7 (0.3-1.2)	32	1.2 (0.8-1.7)
Hist§*/203* ‡	Multiple myeloma/plasmocytoma	0	0.0 (0.0-36)	0	-
207 †*/204-207* ‡	Leukaemia	66	2.5 (1.9-3.2)	130	2.8 (2.4-3.4)
199 †*/156, 199* ‡	Other and unspecified sites	2	2.5 (0.3-9.0)	4	2.4 (0.7-6.3)
	Total	266	1.7 (1.5-1.9)	356	1.7 (1.5-1.9)

*Modified version of *ICD-7*.
† Norway.
‡ Sweden.
§Based on histology/morphology codes in Norway.

The study period 1967 to 2004 was divided into seven periods (1967-1972, 1973-1977, . . ., 1993-1997, and 1998-2004). The number of cancer cases was further calculated in both sexes and in different age groups for children (0, 1-4, 5-9, . . ., 35-39) and parents (20-24, . . ., 70-74).

We calculated estimates separately for the Norwegian and Swedish data, allowing ourselves to look for direct replication of associations between the two populations. We first estimated SIRs for 27 different categories of cancer for all birth defects combined and then the overall SIR of cancer for 14 different categories of defects. After this, we investigated associations between specific malformation categories and risk of cancer at specific sites.

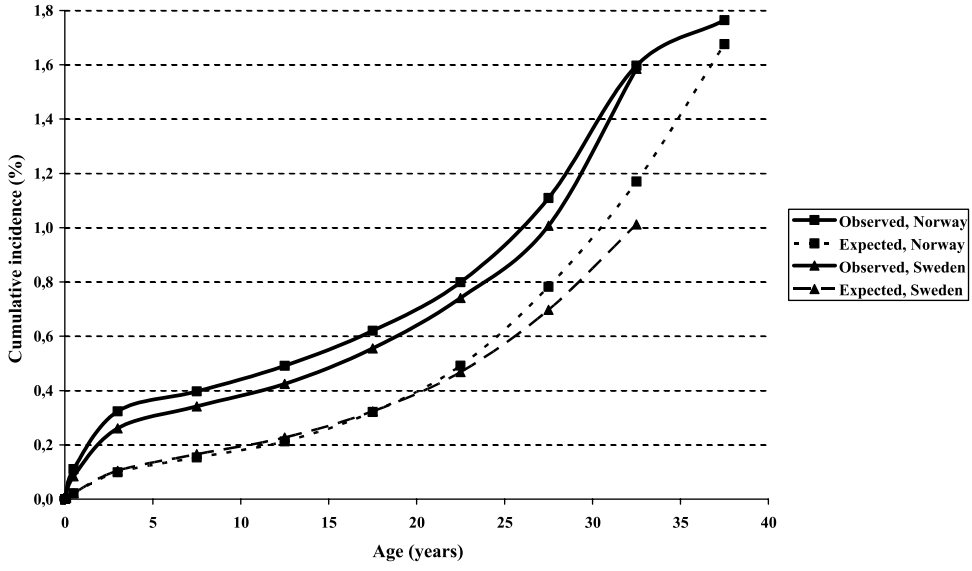

Figure 1. Cumulative incidence of cancer overall in children with birth defects in Norway (1967-2004) and Sweden (1973-2004).

Table 3. SIRs of overall cancer occurrence in patients with different birth defects

Malformation	Norway		Sweden	
	Observed	SIR (95% CI)	Observed	SIR (95% CI)
Nervous system	41	13 (9.7-18)	22	4.7 (2.9-7.1)
Eye, ear, face, and neck	8	1.9 (0.8-3.8)	11	1.8 (0.9-3.3)
Heart and blood vessels	14	1.2 (0.7-2.0)	74	1.2 (1.0-1.6)
Respiratory organs	4	1.7 (0.5-4.3)	1	0.2 (0.0-1.2)
Lip and palate	17	1.1 (0.6-1.7)	16	1.2 (0.7-1.9)
Digestive system	5	1.2 (0.4-2.7)	8	1.0 (0.4-2.0)
Genitalia	11	0.9 (0.4-1.6)	25	1.3 (0.9-1.9)
Urinary organs	4	1.7 (0.5-4.3)	11	2.7 (1.4-4.9)
Musculoskeletal system	79	1.0 (0.8-1.2)	87	1.3 (1.0-1.6)
Down syndrome	51	7.2 (5.3-9.4)	71	8.7 (6.8-11)
Other chromosomal abnormalities	0	0.0 (0.0-14)	0	0.0 (0.0-6.6)
Other and unspecified	14	2.2 (1.2-3.7)	8	1.5 (0.7-3.0)
Multiple defects*	18	5.5 (3.3-8.7)	22	3.6 (2.2-5.4)
Total/overall	266	1.7 (1.5-1.9)	356	1.7 (1.5-1.9)

*Defects included in more than one of the main categories listed above.

We estimated the cumulative incidence (CumInc) of cancer by

$$\mathrm{CumInc} = 1 - \exp(-\sum_i \mathrm{IR}_i * \mathrm{w}_i)$$

where IR_i and w_i are the incidence rate and width of the age interval i, respectively (18).

Ethics. The study was approved by the Regional Committee for Medical Research Ethics of Western Norway.

Results

Cancer Risk in Individuals with Birth Defects. Among 2,127,452 and 3,111,080 registered live births in Norway (since 1967) and Sweden (since 1973), respectively, 45,675 and 76,053 had birth defects (Table 1). About 56% of the defects occurred in males. The 5,238,532 newborns were followed for on average 17 years. Among these, a total of 19,174 cancer cases were registered, and 622 were in individuals with birth defects.

Overall, the risk of cancer in individuals with birth defects was increased in the two countries (combined SIR, 1.7; 95% CI, 1.6-1.9). The increase in observed and expected cumulative overall cancer incidence with age in children with defects is illustrated in Fig. 1. During the first year of life, the cancer risk in children with birth defects was more than five times the risk for those without defects in Norway and about four times in Sweden. The SIR decreased with age, but in both countries the excess cancer risk in individuals with birth defects remained into early adulthood. For example, in children with birth defects compared with children without birth defects, the cumulative incidence was doubled in Norway and Sweden at 10 years of age, whereas at 20 years the cumulative incidence was >50% increased. When excluding children with Down syndrome and other chromosomal abnormalities, the SIRs (95% CIs) for overall cancer risk were 1.5 (1.3-1.7) and 1.4 (1.3-1.6) in Norway and Sweden, respectively.

The SIRs were elevated for cancers of the testis, brain/nervous system, other endocrine organs, and leukemia in both countries (Table 2). In Norway, the SIR was also elevated for cancer of the thyroid gland, whereas in

Table 4. SIRs of cancer occurrence (selected sites) in patients with specific birth defects

Malformation	Cancer site	Norway		Sweden	
		Observed	SIR (95% CI)	Observed	SIR (95% CI)
Nervous system	Brain/nervous system	37	58 (41-80)	10	8.3 (4.0-15)
	Other and unspecified sites	2	118 (14-425)	0	NS*
	Other endocrine organs	0	NS*	2	33 (4.1-121)
Down syndrome	Leukemia	42	36 (26-48)	66	36 (28-46)
	Acute myeloid leukemia	23	115 (73-173)	35	141 (98-196)
	Acute lymphoid leukemia	12	15 (7.5-25)	25	18 (11-26)
	Testicular cancer	5	5.5 (1.8-13)	2	NS*
Urinary organs	Kidney	2	21 (2.5-74)	2	9.1 (1.1-33)
	Other endocrine organs	1	NS*	2	28 (3.4-100)
Oral clefts	Brain/nervous system	4	NS*	9	2.6 (1.2-5.0)
Multiple defects	Brain/nervous system	9	12 (5.4-22)	5	3.1 (1.0-7.3)
	Bone	2	20 (2.4-71)	0	NS*
	Kidney	1	NS*	5	18 (6.0-43)
	Eye	0	NS*	2	10 (1.2-37)

*Not significantly increased SIRs of cancer occurrence.

Sweden the SIRs were elevated for cancers of the ovary and kidney.

Elevations in SIR for overall cancer occurrence were seen for malformations in the nervous system, Down syndrome, and multiple defects in the two countries (Table 3). Elevated SIRs were also seen for other and unspecified malformations in Norway and for malformations in the urinary organs and the musculoskeletal system in Sweden.

Next, we wanted to investigate associations between specific categories of malformations and risk of cancer in more detail. Individuals with malformations in the nervous system were at increased risk of developing cancer in the brain/nervous system (Table 4). The highest SIRs were seen in the first year of life in the two countries, but in Norway the risk remained elevated through the ages 0 to 19 years (data not shown). Individuals with malformations in the nervous system were also at an increased risk of cancer at other and unspecified sites in Norway and other endocrine organs in Sweden.

The risk of cancer in individuals with Down syndrome was increased in both Norway and Sweden (Table 4). In this group, the risk of acute myeloid leukemia was strongly elevated, and all cases occurred before age 5 years. The risk of acute lymphoid leukemia was elevated as well, but at a lower level. In Norway, the risk of testicular cancer was elevated in males with Down syndrome.

Individuals with malformations in the urinary organs had an increased risk of cancers of the kidney in both Norway and Sweden. In Sweden, the risk of cancer in other endocrine organs was also elevated. In Sweden, individuals with undescended testicle and hypospadias had an overall increased cancer risk (SIR, 1.5; 95% CI, 1.2-1.8) and increased risks for testicular (SIR, 2.7; 95% CI, 1.6-4.3) and kidney (SIR, 5.4; 95% CI, 2.7-9.7) cancers.

In individuals with oral clefts (cleft lip and palate), there was no increased overall cancer risk. However, in Sweden, there was an increased risk of cancers of the brain/nervous system. No association was revealed between cleft palate and cancer risk (data not shown).

In individuals with multiple defects, there was an increased overall cancer risk, most pronounced during the first years of life. In both countries, the risk was elevated for cancer of the brain/nervous system. In Norway, the risk was also elevated for cancer of bone, and in Sweden, the risks were also elevated for cancers of the kidney and eye.

Cancer Risk in Parents and Siblings. In the total study cohort, there were 148,679, 128,818, and 18,403 cancer cases among mothers, fathers, and siblings, respectively. The mean ages at the end of follow-up were 46 years in Norway and 44 years in Sweden for the mothers, 49 years in Norway and 47 years in Sweden for the fathers, and 19 years in Norway and 16 years in Sweden for the siblings.

There was no increased overall cancer risk among mothers (Norway: SIR, 1.0; 95% CI, 1.0-1.0; $n_{observed}$ = 2,745; Sweden: SIR, 1.0; 95% CI, 1.0-1.1; $n_{observed}$ = 2,350) and fathers (Norway: SIR, 1.0; 95% CI, 0.9-1.0; $n_{observed}$ = 2,349; Sweden: SIR, 1.0; 95% CI, 0.9-1.0; $n_{observed}$ = 1,743) of children with birth defects. Among the parents, however, SIRs were elevated for cancers of other endocrine organs (mothers and fathers) and bone (mothers) in Norway and of the eye (mothers) in Sweden. There was no increased overall cancer risk among siblings (Norway: SIR, 1.0; 95% CI, 0.9-1.2; $n_{observed}$ = 180; Sweden: SIR, 1.0; 95% CI, 0.8-1.1; $n_{observed}$ = 195).

Discussion

Analyses of cancer occurrence in families of children with birth defects revealed an increased cancer risk in the individuals with birth defects. The highest risks were seen for those with malformations in the nervous system, with Down syndrome, and with multiple defects. No increased overall cancer risk was seen among their parents or siblings.

Strengths and Limitations. We used large health registries, covering the entire populations in Norway and Sweden, to get reliable data on birth defects and cancer occurrence and in this way created the largest cohort study to date on the relation between congenital malformations and cancer risk overall and at specific sites. As far as we know, our study is one of the first to examine the relation between children with congenital malformations and cancer risk among parents and the first study to examine the relation between children with congenital malformations and cancer risk among siblings. Although the reporting and notification of malformations and cancer cases are quite similar in Norway and Sweden, there are also differences between the two countries. Nevertheless, country-specific analyses yielded a high degree of consistency of the results.

Reporting of cancer cases to the national cancer registries has been compulsory in the two countries since the 1950s, and the reporting has been almost complete and of high quality (19). Although the birth registries are of high quality, they do not contain data on all birth defects, like other registries based on routine medical birth records (20). Some defects are under-registered at birth and some are ascertained too late to be captured by the registries. There have also been changes in reporting of defects over time. Further, ascertainment is related to type and severity of malformation. In the Medical Birth Registry of Norway (1967-98), 94% of all cleft lip and palate are ascertained (21), 83% for cleft lip alone and 82% of all children with Down syndrome (2001-5).[5] Problems related to registration of severe malformations in Sweden mainly concern underreporting.

Malformations such as accessory auricle, hydrocele, undescended testicle, hip dislocation/subluxation, and nevus were excluded from the main analyses. These are often considered to be minor malformations. In addition, there were large variations in frequencies between the two countries. For malformations in the heart and blood vessels, there were also large variations in the frequencies. We grouped the congenital malformations by organ system to get a larger number of individuals in each category and did not focus on specific malformations.

The occurrence of congenital malformation and childhood/early adult cancer is rare, and some of the risk estimates are based on few observations. Numerous comparisons in this study also made the risk of

[5] Unpublished data.

false-positive results substantial. However, the consistency of the results between the two populations made it less likely that the results are random findings.

Comparison with Other Studies. Associations between birth defects and cancer were first recognized in clinical series (22). Previous registry-based studies have reported on an increased cancer risk in children with congenital anomalies (3-5, 18, 23). Also, more recent studies have reported similar findings (24, 25). Our study, with follow-up of 121,730 Norwegian and Swedish children with birth defects for an average of 15 years, confirms that children with defects are at an increased risk of various malignancies and suggests that carcinogenesis and teratogenesis may have a common basis, at least for some cancer sites.

Although being the most common solid tumor in children below 15 years, childhood brain tumors, which comprise many histologic types, are of largely unknown etiology. However, a few genetic syndromes (neurofibromatosis, Li-Fraumeni syndrome, Gorlin's syndrome, Turcot syndrome, and ataxia telangiectasia) and ionizing radiation are established risk factors (26).

The brain is composed of two main types of cells (neurons and glia) arising in early development from the primitive neuroectoderm. The human brain is actively developing for a much longer period than the other major organs, beginning early in gestation and continuing 2 to 3 years after birth (27). Earlier studies have shown an increased risk of central nervous system tumors in children with central nervous system defects (3, 5), and it is possible that childhood cancer represents a continuum of abnormal development. In the early 1990s, it was shown that periconceptional supplementation with folate prevented most cases of neural tube defects, a serious congenital malformation of the central nervous system (28). The literature on childhood brain tumor etiology has also suggested a potential protective role of maternal vitamins (29, 30).

A recent Norwegian registry-based study found head circumference to be positively associated with brain cancer in childhood up to 10 years of age (31). The authors stated that increased head circumference was unlikely to be the direct cause of cancer but might be an associated feature of underlying causes. In our study, we found an elevated risk of developing cancer in the brain/nervous system in subjects with nervous system defects. Altogether, 32% of the cases had congenital hydrocephalus, which might be a consequence of tumoral influence on circulation of the cerebrospinal fluid.

The magnitude of the risk estimate for cancer overall and for cancer of the brain/nervous system among individuals with nervous system malformations differed between Norway and Sweden. Differences in reporting and coding practices in the two countries might be part of the explanation.

Numerous studies have reported on the high relative risk of leukemia, especially acute myeloid leukemia, in individuals with Down syndrome (32). More than 90% of those with Down syndrome have a full trisomy 21 (33), and the increased leukemia risk is most likely related to an additional copy of RUNX1, a hematopoietic transcription factor. The risk of leukemia is found to be very high in early childhood but decreases with age (34-36). Individuals with Down syndrome may also have a predisposition to testicular cancer (37, 38), but the risk of other solid tumors is low. We found a strongly increased risk of acute myeloid leukemia in individuals with Down syndrome as well, and all the cases we found occurred before age 5 years. The risk of testicular cancer was also elevated in males with Down syndrome (Norway).

About 10% of Wilms' tumor/nephroblastoma develop in association with dysmorphic syndromes. Patients with WAGR syndrome (Wilms' tumor, aniridia, genitourinary malformations, and mental retardation), resulting from deletion of chromosome 11, including the WT1 gene, carries a 30% risk of developing nephroblastoma (39-41). Wilms' tumor/nephroblastoma has also been reported previously to be associated with a high rate of congenital anomalies, such as genitourinary malformations, in registry-based studies (4). In our study, individuals with malformations in urinary organs and males with undescended testicle and hypospadias (Sweden) were at increased risks for cancer of the kidney.

Constitutional molecular defects can give rise to both congenital anomalies and cancer. In a recent Dutch study of 1,073 children with cancer, a high incidence of malformation syndromes was seen (42). An increased risk of childhood cancer with increasing number of congenital malformations was also reported in an Australian population-based case-control study (3). We found an increased overall cancer risk in individuals who had defects in more than one organ system.

Children with congenital abnormalities have been shown to have a higher cancer risk particularly during the early years of life (2). The risk has, however, remained higher during the first 10 to 15 years of life in children with abnormalities but at a lower level (2, 18). In our study, the excess risk in individuals with birth defects was most pronounced during the first 5 years of life but remained elevated into early adulthood.

It has been suggested that birth defects and parental cancer might be correlated if common heritable causes are operating, if environmental exposures are acting as both carcinogens and teratogens, or if parental preclinical cancer at the time of conception leads to physiologic changes leading to malformations in the offspring (6). In accordance with earlier studies (6, 43), however, we found no increased overall cancer risk among parents of children with birth defects nor among the siblings of such children, suggesting that the etiologies do not have an obvious inherited component.

Conclusion

We observed an increased overall cancer risk in individuals with birth defects. The highest risks were seen for individuals with malformations in the nervous system, with Down syndrome, and with multiple defects. However, no increased overall cancer risk was seen among their parents or siblings. Although cancer and birth defects do not appear to share a common genetic predisposition, cancer may be a complication of some birth defects.

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