

RISK OF CANCER AMONG OFFSPRING OF CHILDHOOD-CANCER SURVIVORS

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ABSTRACT

Background Increasing numbers of children with cancer survive and reach reproductive age. However, the risk of cancer (other than retinoblastoma) in the offspring of survivors of childhood and adolescent cancer is uncertain.

Methods Using data from national cancer and birth registries, we assessed the risk of cancer among 5847 offspring of 14,652 survivors of cancer in childhood or adolescence diagnosed since the 1940s and 1950s in Denmark, Finland, Iceland, Norway, and Sweden. The offspring were followed up for a diagnosis of cancer for 86,780 person-years, and standardized incidence ratios were calculated.

Results Among the 5847 offspring, 44 malignant neoplasms were diagnosed (standardized incidence ratio, 2.6; 95 percent confidence interval, 1.9 to 3.5). There were 17 retinoblastomas, yielding a standardized incidence ratio of 37. There were 27 neoplasms other than retinoblastoma (standardized incidence ratio, 1.6; 95 percent confidence interval, 1.1 to 2.4). The second most common primary site of cancer among the offspring was the brain and nervous system, in which eight tumors were observed (standardized incidence ratio, 2.0; 95 percent confidence interval, 0.9 to 3.9). There were between zero and four apparently sporadic cases of cancer in other primary sites among the offspring. Excluding 4 likely cases of hereditary cancer and 2 subsequent cancers among the offspring with hereditary retinoblastoma, there were 22 sporadic cancers, for a standardized incidence ratio of 1.3 (95 percent confidence interval, 0.8 to 2.0).

Conclusions There is no evidence of a significantly increased risk of nonhereditary cancer among the offspring of survivors of cancer in childhood. (N Engl J Med 1998;338:1339-44.)

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INCREASING numbers of children with cancer survive and reach reproductive age. In Denmark, between 1983 and 1987, the mean five-year cumulative survival rate was 64 percent for patients who were under the age of 20 when cancer was diagnosed,¹ and in Finland, between 1985 and 1989, the cumulative survival rate was 76 percent for patients under the age of 15.² Estimating the risk of malignant neoplasms among the offspring of these patients has been difficult, because of the rarity of childhood cancer.³⁻⁵

In this collaborative study from five countries —

Denmark, Finland, Iceland, Norway, and Sweden — we assessed the incidence of cancer in large population-based cohorts of offspring of survivors of cancer in childhood or adolescence and compared it with the relevant rates of cancer in the general population.

METHODS

The primary patient population consisted of 14,652 men and women in whom cancer was diagnosed when they were less than 20 years old and who survived until they reached reproductive age (defined as 15 years old). The data were obtained from cancer registries, which had been initiated in 1943 (Denmark), 1953 (Finland and Norway), 1955 (Iceland), and 1958 (Sweden). All the patients who were registered between those years and December 31, 1991 (1987 in Sweden), were included in the study. Patients who died before reaching 15 years of age or before the year in which national computerized registration of offspring began (Iceland, 1955; Norway, 1960; Sweden, 1961; Finland, 1967; and Denmark, 1968) were not eligible. The personal identification number, type of malignant neoplasm, and date of diagnosis of the survivors were extracted from the files of the five nationwide population-based cancer registries. The personal identification number, which is unique to every Scandinavian citizen, incorporates sex (except in Iceland) and the date of birth and permits accurate linkage of information between registries. The malignant neoplasms of the survivors were classified according to a scheme for childhood cancer prepared by the International Agency for Research on Cancer.⁶

The unique personal identification numbers allowed a computerized search of the central population registries (national birth registry in Sweden) for all offspring born to the 14,652 survivors of childhood cancer. As of December 31, 1991, 5847 offspring of these survivors had been identified. In Sweden, the birth registry contained data on the offspring of all female survivors but only on the offspring of the male survivors who were married at the time of the birth of their offspring.

The personal identification numbers of the 5847 offspring were linked with the files of the national cancer registries. The follow-up for cancer among these children started on the date of birth or the date of the introduction of national personal identification numbers in each country, whichever was later (Table 1). The follow-up ended on the date of death or emigration or the closing date of the study — December 31, 1994, or December 31, 1995 (Table 1).

The malignant neoplasms of the offspring were classified according to the *International Classification of Diseases, 7th Revision*.

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TABLE 1. NUMBERS OF SURVIVORS OF CHILDHOOD AND ADOLESCENT CANCER AND THEIR OFFSPRING AND CALENDAR YEARS AND PERSON-YEARS OF FOLLOW-UP FOR CANCER IN THE OFFSPRING.

COUNTRY	No. OF SURVIVORS	No. OF OFFSPRING	FOLLOW-UP OF OFFSPRING	
			CALENDAR YEARS	NO. OF PERSON-YEARS
Denmark	3,649	1810	1968–1994	30,463
Finland	3,389	1449	1967–1995	21,834
Iceland	211	110	1955–1995	1,552
Norway	2,856	1289	1955–1994	17,842
Sweden	4,547	1189*	1961–1994	15,089
Total	14,652	5847		86,780

*Value includes the offspring of all the mothers but those of the married fathers only.

tion (ICD-7).⁷ Multiple primary neoplasms present in one child were considered separate cancers. The registration and coding practices of the five cancer registries have been described elsewhere.⁸ The clinical details about the cancers of the survivor parents and of the offspring were based on the cancer-registry data only. Hospital records were not searched.

The expected numbers of cancers among the offspring were calculated by multiplying the number of person-years of follow-up by the cancer incidence rates for the respective national populations in five-year age groups and calendar periods of observation. Standardized incidence ratios were calculated by dividing the observed numbers of cancers (specific for sex, age, and calendar year) by the respective expected ones. Ninety-five percent confidence intervals were calculated on the basis of the assumption that the observed numbers of cancers followed a Poisson distribution.

RESULTS

Of the 14,652 survivors of cancer in childhood and adolescence (8032 men and 6620 women; male-to-female ratio, 55:45), 3369 (23 percent) had children during the follow-up period (Table 2). The proportion of parents was lowest among the survivors of leukemia (6 percent) and highest among the survivors of carcinomas (43 percent) (Table 2). The mean numbers of offspring per survivor ranged from 1.6 to 1.8, depending on the type of cancer, except for survivors of leukemia, for whom it was 1.3 (Table 2).

The 5847 offspring (2983 male and 2864 female; male-to-female ratio, 51:49) were followed up for a diagnosis of cancer for 86,780 person-years. The median age at the end of follow-up was 14 years (range, 0 to 43 years). The distribution of person-years of follow-up according to age group is shown in Table 3. Forty-four malignant neoplasms were diagnosed among the offspring, yielding a standardized incidence ratio of 2.6 (95 percent confidence interval, 1.9 to 3.5). Approximately half of these neoplasms occurred among the male offspring (23 observed; standardized incidence ratio, 2.5; 95 percent confi-

dence interval, 1.6 to 3.8) and half among the female offspring (21 observed; standardized incidence ratio, 2.7; 95 percent confidence interval, 1.7 to 4.1). There were 17 cases of retinoblastoma among the offspring, yielding a standardized incidence ratio of 37 (95 percent confidence interval, 22 to 60), whereas 27 cases of all the other types of neoplasms combined (nonretinoblastoma) were diagnosed, with 16.5 expected (standardized incidence ratio, 1.6; 95 percent confidence interval, 1.1 to 2.4) (Table 3). When calculated according to the year of birth of the offspring, the standardized incidence ratio for nonretinoblastoma neoplasms remained relatively stable; it was 1.3 (95 percent confidence interval, 0.6 to 2.5) for those born before 1970 and 1.8 for those born from 1970 through 1979 (95 percent confidence interval, 0.9 to 3.4) and from 1980 through 1991 (95 percent confidence interval, 0.8 to 3.6). The overall standardized incidence ratio for nonretinoblastoma neoplasms was slightly higher for those 5 to 9 and 10 to 19 years of age than for those in the youngest (0 to 4 years) and oldest (20 years or older) age groups (Table 3).

The most common primary site of neoplasms other than retinoblastoma was the brain and other parts of the nervous system, with eight tumors observed (standardized incidence ratio, 2.0; 95 percent confidence interval, 0.9 to 3.9) (Table 4). Two of these tumors were neuroblastomas; the primary site of a third neuroblastoma was coded as "endocrine glands." Of the six brain tumors, one was an ependymoma in a child of a woman who had had osteosarcoma and bilateral breast cancer at an early age — circumstances suggestive of Li-Fraumeni syndrome (pair 15, Table 5). Another was a meningioma in a 3-year-old child whose father had had a meningioma at 17 years of age, which raises the possibility of neurofibromatosis (pair 7, Table 5).

One other survivor-offspring pair had features of Li-Fraumeni syndrome: a mother with osteosarcoma, breast cancer, and astrocytoma, whose child had sclerotic fibrous histiocytoma at the age of 17 years (pair 16, Table 5). One family had definitive von Hippel-Lindau disease; the father had had adenocarcinoma of the epididymis, cerebellar hemangioma, and renal carcinoma, and the son had cerebellar hemangioma (pair 26, Table 5).

The risk of cancer among the subgroups of offspring was not significantly increased when analyzed according to the primary site of the cancer in the parent, except for retinoblastoma. No neoplasms were observed among the children of survivors of leukemia, neuroblastoma, or hepatic tumors. The overall standardized incidence ratio for nonretinoblastoma neoplasms was 3.9 (95 percent confidence interval, 2.1 to 6.7) for offspring whose parents were less than 10 years of age at the time of diagnosis, and it was 1.1 (95 percent confidence interval, 0.6 to

TABLE 2. NUMBERS OF SURVIVORS OF CHILDHOOD CANCER, SURVIVORS WHO WERE PARENTS, AND OFFSPRING, ACCORDING TO THE PRIMARY CANCER OF THE SURVIVORS.

PRIMARY CANCER OF SURVIVOR (IARC CODE)*	NO. OF SURVIVORS	NO. WHO WERE PARENTS	NO. OF OFFSPRING	RATIO OF SURVIVOR PARENTS TO ALL SURVIVORS	MEAN NO. OF OFFSPRING/SURVIVOR PARENT
Leukemia (010)	2,232	136	181	0.06	1.3
Lymphomas (020)	2,252	541	924	0.24	1.7
Central nervous system cancers (030)	3,348	664	1137	0.20	1.7
Sympathetic nervous system cancers (040)	331	64	101	0.19	1.6
Retinoblastoma (050)	398	134	218	0.34	1.6
Renal tumors (060)	518	117	188	0.23	1.6
Hepatic tumors (070)	81	6	11	0.07	1.8
Bone tumors (080)	1,095	229	422	0.21	1.8
Soft-tissue tumors (090)	1,090	335	612	0.31	1.8
Germ-cell, gonadal tumors (100)	1,152	243	418	0.21	1.7
Carcinomas (110)	1,927	833	1523	0.43	1.8
Other or unspecified cancers (120)	228	67	112	0.29	1.7
All cancers	14,652	3369	5847	0.23	1.7

*Sites and types of cancers are given according to the classification system of Birch and Marsden.⁶ IARC denotes International Agency for Research on Cancer.

TABLE 3. STANDARDIZED INCIDENCE RATIOS (SIRs) FOR MALIGNANT NEOPLASMS AMONG 5847 OFFSPRING OF SURVIVORS OF CHILDHOOD CANCER, ACCORDING TO SEX AND AGE AT DIAGNOSIS.*

SEX AND AGE OF OFFSPRING AT DIAGNOSIS	NO. OF PERSON-YEARS	RETINOBLASTOMA			ALL OTHER PRIMARY CANCER SITES		
		NO. OBSERVED	NO. EXPECTED	SIR (95% CI)	NO. OBSERVED	NO. EXPECTED	SIR (95% CI)
Sex							
Male	44,322	9	0.2	37 (17-71)	14	8.8	1.6 (0.9-2.7)
Female	42,458	8	0.2	37 (16-74)	13	7.7	1.7 (0.9-2.9)
Age (yr)							
0-4	26,213	17	0.4	45 (26-72)	6	5.0	1.2 (0.4-2.6)
5-9	21,624	0	0.03	—	6	2.5	2.4 (0.8-5.2)
10-19	27,458	0	0.02	—	9	4.0	2.3 (1.0-4.3)
20-43	11,485	0	0.02	—	6	5.0	1.2 (0.4-2.6)
Total	86,780	17	0.5	37 (22-60)	27	16.5	1.6 (1.1-2.4)

*CI denotes confidence interval.

1.8) among the offspring of survivors who were 10 or older at the time of diagnosis. All the offspring with cancer were born at least eight years after cancer was diagnosed in their mothers except one (pair 25, Table 5).

The risk of retinoblastoma among the offspring of retinoblastoma survivors was extremely high: of the 17 offspring with retinoblastoma, 16 each had a parent who had had the disease (standardized incidence ratio, 950; 95 percent confidence interval, 540 to

1500). Only one parent with retinoblastoma had two children with retinoblastoma. Two subsequent nonretinoblastoma tumors occurred among the 16 offspring with hereditary retinoblastoma. One was a sebaceous carcinoma in the eyelid (pair 10, Table 5); the other was a rhabdomyosarcoma in the temporal region (pair 13, Table 5). Both tumors occurred in areas that were probably irradiated during treatment of the retinoblastoma. Among the offspring, there were no retinoblastomas diagnosed before the 1970s;

TABLE 4. STANDARDIZED INCIDENCE RATIOS (SIRs) FOR MALIGNANT NEOPLASMS AMONG 5847 OFFSPRING OF SURVIVORS OF CHILDHOOD CANCER, ACCORDING TO PRIMARY CANCER.

PRIMARY CANCER OF OFFSPRING*	No. OBSERVED	No. EXPECTED	SIR (95% CI)†
Retinoblastoma	17	0.5	37 (22–60)
Brain and nervous system	8	4.0	2.0 (0.9–3.9)
Connective tissue	4	0.5	8.6 (2.3–22)
Non-Hodgkin's lymphoma	3	1.0	3.1 (0.6–9.2)
Leukemia	3	3.5	0.9 (0.2–2.5)
Kidney	2	0.7	2.8 (0.3–10)
Melanoma of skin	2	0.9	2.4 (0.3–8.5)
Stomach	1	0.0	20 (0.3–110)
Ovary	1	0.3	3.5 (0.1–19)
Testis	1	1.2	0.8 (0–4.6)
Other skin	1	0.4	2.2 (0–12)
Endocrine glands	1	0.3	3.9 (0.1–22)
All other sites	0	3.7	0 (0–1.0)

*Two neuroblastomas were included under “brain and nervous system” and one under “endocrine glands” because of different coding practices.

†CI denotes confidence interval.

for offspring born in the 1970s, the overall standardized incidence ratio for retinoblastoma was 37 on the basis of 5 cases, and for those born in 1980 to 1991, the standardized incidence ratio was 49 on the basis of 12 cases.

To assess only the risk of sporadic cancer among the offspring, we excluded the four offspring in whom there were features of hereditary cancer syndromes and the two patients with hereditary retinoblastoma who had solid tumors that probably arose in external-radiotherapy fields. By limiting the analysis to the 22 offspring with apparently sporadic tumors (including the 1 with sporadic retinoblastoma), we found that the standardized incidence ratio decreased from 1.6 to 1.3 (95 percent confidence interval, 0.8 to 2.0).

DISCUSSION

In our large population-based series, the overall standardized incidence ratio for nonretinoblastoma cancers among the offspring of survivors of nonretinoblastoma cancer in childhood or adolescence was 1.6 (95 percent confidence interval, 1.1 to 2.4) on the basis of 27 observed and 16.5 expected cases — a small but statistically significant increase. However, when we limited the analysis to the 22 apparently sporadic tumors, the standardized incidence ratio was only 1.3 (95 percent confidence interval, 0.8 to 2.0). We think that this figure is more relevant to clinical practice than the overall ratio. Our study found that there was less than 1 excess case of cancer per 1000 offspring, whereas in previous, smaller stud-

ies, the numbers of observed cancers were too small to allow reliable estimates of risk.³⁻⁵

There were four instances in which hereditary syndromes other than retinoblastoma were likely. However, our data were limited to two generations, and for this reason we could not construct large pedigrees. These cases included two survivor-offspring pairs with features suggestive of Li-Fraumeni syndrome, one pair with von Hippel-Lindau disease, and one pair with neurofibromatosis type 1 or 2. There were no apparent hereditary cases of neuroblastoma or Wilms' tumor among the offspring, but we did not collect data on the bilateralism of Wilms' tumor among the survivors. The two survivor-offspring pairs in which both parent and offspring had soft-tissue sarcomas (pairs 20 and 21, Table 5) yielded a high standardized incidence ratio of 38, but whether this was due to a hereditary component or a chance finding could not be determined.

Among the offspring, there were no cases of Hodgkin's disease (0.8 was expected) or of malignant tumors in bone (0.5), the thyroid (0.4), the cervix uteri (0.4, in situ not included), colorectum (0.3), the liver (0.2), the breast (0.3), or the lung (0.1). Since the hereditary forms of cancer of the colorectum and breast are almost never diagnosed before the age of 20, these diseases were not encountered among the parents.

In one case, the interval from the diagnosis of the cancer in the survivor mother to the birth of the affected child was three years; the mother had had a mixed tumor of the parotid gland at the age of 19, and her daughter had mucocellular carcinoma of the stomach at the age of 33. In all other cases not involving retinoblastoma, the interval from the mother's diagnosis to the birth of the affected child was between 8 and 23 years, making a direct effect of the mother's cancer treatment on the fetus unlikely.

There was a slight trend toward increased risk with younger survivor parents' ages at the time of diagnosis. The standardized incidence ratio for nonretinoblastoma neoplasms was 3.9 for offspring of survivors whose cancers were diagnosed when they were less than 10 years of age and 1.1 for offspring of survivors whose cancers were diagnosed when they were 10 to 19 years of age. However, the cancer pattern among the offspring of survivors who were given diagnoses when they were less than 10 years old was quite heterogeneous, impeding further conclusions.

The Swedish birth-registry data did not contain information on the offspring of male survivors who were not married when the child was born. However, this limitation should not have caused a selection bias that might have affected the estimate of cancer incidence among the identified offspring in the Swedish data. For purposes of quality control, the offspring of the Swedish male survivors were identi-

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TABLE 5. CLINICAL DETAILS ABOUT SURVIVOR-OFFSPRING PAIRS WITH MALIGNANT NEOPLASMS OTHER THAN HEREDITARY RETINOBLASTOMA.*

PAIR No.	PARENT			INTERVAL FROM DIAGNOSIS OF PARENT TO BIRTH OF OFFSPRING (YR)	OFFSPRING			COMMENTS
	SEX	AGE AT DIAGNOSIS (YR)	PRIMARY SITE OR TYPE AND MORPHOLOGY		SEX	AGE AT DIAGNOSIS (YR)	PRIMARY SITE OR TYPE AND MORPHOLOGY	
1	M	17	Hodgkin's disease	12	M	3	Kidney, Wilms' tumor	
2	M	19	Hodgkin's disease	3	M	12	Cerebellum, medulloblastoma	
3	M	19	Neck, reticulosarcoma	7	M	15	Retroperitoneum, malignant histiocytosis	
4	M	10	Hodgkin's disease	8	M	22	B-cell leukemia	
5	M	10	Cerebellum, astrocytoma	17	F	2	Kidney, Wilms' tumor	
6	M	1	Cranial nerve, astrocytoma	32	M	2	Retinoblastoma, bilateral	
7	M	17	Malignant meningioma	18	M	3	Meningioma	Neurofibromatosis?
8	F	8	Optical nerve, undefined malignant tumor	10	F	5	Neuroblastoma	
9	F	10	Cerebellum, spongioblastoma	8	M	25	Non-Hodgkin's lymphoma	
10	M	3	Retinoblastoma, unilateral	25	M	0	I: Retinoblastoma, bilateral II: Eyelid, sebaceous carcinoma	In radiotherapy field?
11	F	6	Retinoblastoma, unilateral	15	M	17	Cranial nerve, neurofibrosarcoma	
12	F	3	Retinoblastoma, unilateral	20	F	7	Optical nerve, astrocytoma	
13	F	0	Retinoblastoma, bilateral	23	M	0	I: Retinoblastoma, bilateral II: Temporal region, rhabdomyosarcoma	Sister with bilateral retinoblastoma In radiotherapy field?
14	F	5	Kidney, Wilms' tumor	12	M	28	Testis, seminoma	
15	F	12	I: Leg, osteosarcoma	12	M	4	Brain, ependymoma	Li-Fraumeni syndrome?
		35	II: Left breast, carcinoma					
		36	III: Right breast, carcinoma					
16	F	15	I: Leg, osteosarcoma	15	F	17	Fibrous histiocytoma	Li-Fraumeni syndrome?
		33	II: Right breast, carcinoma					
		34	III: Brain, astrocytoma					
17	M	8	Leg, malignant giant-cell tumor of bone	14	M	22	Non-Hodgkin's lymphoma	
18	F	17	Leg, osteosarcoma	14	F	6	Acute lymphatic leukemia	
19	M	9	Leg, synovial sarcoma	19	F	15	Ovary, malignant dysgerminoma	
20	F	1	Leg, neurofibrosarcoma	19	F	17	Pelvis, synovial sarcoma	
21	M	7	Spinal canal, fibrosarcoma	19	F	13	Orbita, mesenchymoma of bone	
22	M	14	Testis, embryonal carcinoma	6	F	19	Arm, melanoma of skin	
23	F	9	Ovary, dysgerminoma	13	F	0	Brain, astrocytoma	
24	M	0	Testis, teratoma	26	F	2	Adrenal gland, neuroblastoma	
25	F	19	Parotid gland, mixed tumor	3	F	33	Stomach, carcinoma	
26	M	15	I: Epididymis, carcinoma II: Cerebellum, hemangioblastoma III: Kidney, carcinoma	14	M	22	Cerebellum, hemangioma	von Hippel-Lindau disease
27	M	14	Nasopharynx, anaplastic malignant tumor (fibrosarcoma?)	8	M	8	Acute lymphatic leukemia	
28	F	16	Placenta, undefined tumor	14	F	19	Leg, melanoma of skin	

*I denotes first neoplasm, II second neoplasm, and III third neoplasm.

fied through the use of another registry, with data on live offspring in 1992. We found that the sex ratio of the survivors resembled that in the other countries, but we could not use the data, because the offspring who had died before 1992 were missing.

We conclude that in this series of patients the risk of cancer among the offspring of survivors of childhood cancer (excluding retinoblastoma and other hereditary cancer syndromes) was small and limited to children of survivors whose cancers were diagnosed when they were less than 10 years of age. Our confidence in concluding that the excess number of nonretinoblastoma cancers was very small is bolstered by the fact that our data represent all the cases of cancer diagnosed in a population of about 20 million people during a 25-to-35-year period. These results imply that fear of cancer in their offspring is no reason to discourage the survivors of sporadic childhood cancer from having children, and efforts to screen for cancer in offspring of the survivors of sporadic cancer in childhood or adolescence are not warranted.

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