

Lifelong Cancer Incidence in 47 697 Patients Treated for Childhood Cancer in the Nordic Countries

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- Background** The pattern of cancer in long-term survivors from childhood cancer has not been investigated comprehensively.
- Methods** We obtained a cohort of 47 697 children and adolescents aged 0–19 years with cancer as defined by the country-wide cancer registries of Denmark, Finland, Iceland, Norway, and Sweden during 1943–2005. Cohort members were followed through age 79 years for subsequent primary cancers notified to the registries, and the age-specific risk pattern of the survivors was compared with that of the national populations using country and sex standardized incidence ratios (SIRs). We used a multiplicative Poisson regression model to estimate relative risk of cancer for attained age, with adjustment for calendar period and age at diagnosis of primary cancer. We also calculated excess absolute risk (EAR) attributable to status as childhood cancer survivor and determined the cumulative incidence of second primary cancer as a function of attained age for three subcohorts defined by period of treatment for childhood cancer.
- Results** A total of 1180 asynchronous second primary cancers were observed in 1088 persons, yielding an overall SIR of 3.3 (95% confidence interval = 3.1 to 3.5). The relative risk was statistically significantly increased in all age groups, even for cohort members approaching 70 years of age. The EAR for second primary cancer among survivors increased gradually from one additional case per 1000 person-years of observation in early life to six additional cases per 1000 person-years in the age group 60–69 years. For children treated in the prechemotherapy era (1943–1959), the cumulative risk for a second primary cancer reached 18%, 34%, and 48% at ages 60, 70, and 80 years, respectively. The age-specific incidence rates were highest for cohort members treated in the era of intensive, multiple-agent chemotherapy (1975–2005).
- Conclusion** Survivors of childhood cancer have a persistent excess risk for a second primary cancer throughout their lives, accompanied by continuous changes in the risk of cancers at specific sites.

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Cancer in children and adolescents aged 0–19 years (referred to as childhood cancer in this article) occurs at a rate of about 18 per 100 000 population per year in the Nordic countries (Denmark, Finland, Iceland, Norway, and Sweden). In general, the cancer rates in this age range have been stable since the start of the Nordic cancer registries in the 1940s and 1950s (1). In contrast, beginning in the 1960s, the overall 5-year survival rate from childhood cancer improved considerably, from approximately 25% in the 1950s to almost 80% around the turn of the century (2,3). Consequently, in the Nordic countries and in other developed parts of the world, a growing proportion of adults have been treated for cancer during childhood with cytostatic drugs or radiation or a combination thereof. Thus, at the end of 2005, more than 24 000 persons in Denmark, Finland, Iceland, Norway, and Sweden combined were survivors of childhood cancer, and they constitute approximately 0.1% of the national populations.

Large studies in Europe and the United States have consistently demonstrated that the risk for a second primary cancer after treat-

ment for cancer in childhood is substantially higher than that in the general population (4–9). In most of these studies, however, the length of follow-up was restricted to one, two, or a few decades,

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and the incidence of cancer in long-term survivors was rarely investigated (10). Here, we present follow-up data on the incidence of second cancer among former childhood cancer patients over the full age range of 0–79 years.

Patients and Methods

The cohort comprised persons in whom a cancer had been diagnosed before the age of 20 who were reported to the cancer registry of Denmark, Finland, Iceland, Norway, or Sweden over a period of up to 61 years (Table 1). All five of these registries are population based, and all of the registries rely on reporting from multiple sources; thus, the registries receive more than one report on each cancer, and close to 100% coverage is achieved (11). The Nordic cancer registries request reports on all cases of carcinoma, sarcoma, leukemia, lymphoma, and multiple myeloma. In addition, notification is requested for the following tumor-like and benign lesions: papillomas of the lower urinary tract (renal pelvis, ureter, urinary bladder, and urethra) and histologically benign tumors of the central nervous system and intracranial meninges. These particular lesions are included in the cancer registries incidence tables under the appropriate site of origin and were included in this survey as well. Nonmelanoma skin cancers were included in this study as defined by the individual cancer registries. In Norway, Sweden, Iceland, and Finland, the group of nonmelanoma skin cancer is composed of squamous cell skin cancer only; in Denmark, this category also includes basal cell skin cancer. All primary cancers reported were registered following the inclusion criteria described above, regardless of the number of cancers per individual. Identification and acceptance of a new report to the cancer registries as a subsequent primary cancer in a patient already known to the registries followed a common set of rules proposed by the International Association of Cancer Registries (IACR) and the International Agency for Research on Cancer (IARC) (12). According to these rules, a new primary cancer is one that originates in a new primary site or tissue and is thus an extension, a recurrence, or a metastasis. Tumors have been classified in all registries according to the *International Classification of Diseases*, seventh revision (ICD-7), although various modifications and additions to this classification have been used in different periods. The methods of data collection and coding at each registry are described in detail elsewhere (11).

The patients in this study were assigned according to the first malignant neoplasm diagnosed in childhood to one of the 12 main diagnostic groups of the International Classification Scheme for Childhood Cancer prepared by the IARC (13). The diagnostic groups are defined mainly in terms of morphology and are based on the *International Classification of Diseases for Oncology* (ICD-O) (14). ICD-O has been used in addition to ICD-7 in cancer registration in Denmark since 1978, in Iceland since 1983 and in Norway and Sweden since 1993. All cases of cancer in childhood that were reported to the Danish and Icelandic registries before 1978 and 1983, respectively, were reevaluated previously on the basis of the initial information given by the clinicians and pathologists, and an ICD-O code was applied. In addition to ICD-7, the Norwegian registry used the *Manual of Tumour Nomenclature and Coding* (MoTNaC) (a system related to the ICD-O morphology coding system) from 1970 to 1992, which allowed for unambiguous

CONTEXT AND CAVEATS

Prior knowledge

The long-term risks of second primary cancers in survivors of childhood malignancies were not known.

Study design

Incidence of second primary cancers was determined based on data from national registries of the Nordic countries. Risk patterns of survivors were compared with the populations of these countries using standardized incidence ratios. Cumulative risks of a second malignancy were calculated separately for those treated in the prechemotherapy era, the first-generation chemotherapy era, and the era of combination chemotherapy.

Contribution

This study quantified long-term temporal patterns of increased risk of cancer at specific sites in survivors of childhood cancer. The results may be useful in the screening and care of these individuals. Cumulative risks in survivors appeared somewhat higher in those treated in the era of intensive multiple-agent chemotherapy.

Implications

Survivors of childhood cancers are at increased risk for second primary malignancies throughout their lives.

Limitations

The registries lacked data on treatment variables that might have allowed the investigators to analyze risks of second cancers associated with different types and doses of treatment.

From the Editors

assignment to diagnostic groups of the International Classification Scheme for Childhood Cancer (15). The MoTNaC classification was also used retrospectively for cancers in patients younger than 20 years and reported during the period 1953–1969. In Sweden before 1993, tumor morphology and tumor behavior were coded by use of the World Health Organization C24 code (16), and in Finland, the 1951 version of MoTNaC was used for coding tumor morphology during the entire reporting period of the registry (17). For the present study, the Swedish and Finnish cancer registries transformed the codes for tumor site and morphology into the IARC classification scheme for childhood cancer.

Statistical Analysis

Data on all members of the study cohort were linked to the central population registers and the death certificate files of the respective Nordic countries for verification of the personal identification number and for information on vital status and migration. The period of follow-up for second primary cancers in the cancer registries started on the date of diagnosis of the first primary cancer and ended on the date of death; the date of emigration; or the closing date of December 31, 2002 (Norway), 2003 (Denmark, Iceland, and Sweden), or 2005 (Finland). All second primary cancers were classified according to ICD-7. The expected numbers of cancers were calculated by multiplying the number of person-years of cohort members by the sex-specific cancer incidence rates for the whole population of each of the five countries in 5-year age groups and calendar periods of observation. The standardized incidence ratio (SIR) was used as a measure of the relative risk, with 95%

confidence intervals (CIs) calculated assuming Poisson-distributed numbers of observed cancers (18). Furthermore, we used a multiplicative Poisson regression model to estimate relative risk for attained age in 10-year age groups, with adjustment for calendar period for first primary cancer using three periods (1943–1959, 1960–1974, and 1975–2005) and age at diagnosis of primary cancer using four age ranges (1–4, 5–9, 10–14, and 15–19 years) (19). The GENMOD procedure in SAS version 9.1 for UNIX (SAS Institute, Cary, NC) was used for statistical analysis, with external reference rates incorporated from the five Nordic cancer registries. We also calculated the cumulative incidence of second primary cancer as a function of attained age for three subcohorts defined by period of treatment for childhood cancer. This estimate was based on the assumption that no other causes of death were in operation (20). The subcohorts were defined as children diagnosed for a first primary cancer during 1943–1959, that is, the prechemotherapy era; children diagnosed in 1960–1974, the first-generation chemotherapy era; and children diagnosed in 1975–2005, the combination chemotherapy era. Finally, excess absolute risks (EARs) attributable to the status as childhood cancer survivor were derived as the difference between the observed and the expected rates expressed per 100 000 person-years at risk. All tests of statistical significance were two-sided, and the threshold for statistical significance was .05. In accordance with current regulations, data on cohort members were received at the analyzing center from each of the Nordic cancer registers without personal identifiers.

Results

During the study period 1943–2005, a first malignant neoplasm was diagnosed in 47 697 children (26 168 boys and 21 529 girls) (Table 1). The main tumor types according to IARC groups were leukemia (26%), central nervous system neoplasm (23%), lymphoma (13%), and malignant epithelial neoplasm (8%), followed by soft tissue sarcomas (6%), malignant bone tumors (6%), gonadal neoplasms (5%), renal tumors (4%), sympathetic nervous system neoplasms (4%), and other or unspecified malignant neoplasms (5%). Cancer was diagnosed in 33% of the cohort members at the age of 0–4 years, in 19% at the age of 5–9 years, in 19% at the age of 10–14 years, and in 29% at the age of 15–19 years. The group was monitored for 476 289 person-years, and 1180 asynchronous second cancers were observed in 1088 persons (1005 persons had

one second primary cancer, 74 had two, and nine had three). A total of 355.7 new cancers would have been expected, yielding an overall SIR for second primary cancers of 3.3 (95% CI = 3.1 to 3.5) for the five participating countries, both sexes, and all age groups combined. Estimates from individual countries ranged from 2.6 (95% CI = 2.1 to 3.1) in Norway to 4.1 (95% CI = 3.6 to 4.6) in Finland (Table 1). The relative risk for second primary cancers in male survivors (3.8 [95% CI = 3.5 to 4.1]) was statistically significantly higher than that in female survivors (3.0 [95% CI = 2.8 to 3.2]). The latter observation was not due to differences in the sex-specific incidence rates of second cancer but was rather a consequence of a substantially higher general cancer incidence in females compared with males among young and middle-aged citizens of the Nordic countries, which is due primarily to early-onset breast cancer. After exclusion from the risk analysis of 85 observed and 22.3 expected second primary cancers classified as nonmelanoma skin cancers, we obtained an overall SIR of second primary cancers of 3.3 (95% CI = 3.1 to 3.5), an estimate identical to that including nonmelanoma skin cancers.

For each age group covered in the follow-up, the observed incidence rate of a new primary cancer was higher than that expected from the national age-, sex-, and calendar time-specific incidence rates of cancer (Figure 1). Correspondingly, Table 2 shows that the relative risks were statistically significantly increased at all ages, even for cohort members approaching 70 years of age; however, the level of increase diminished considerably with increasing age, from 7.0 in the second decade of life to 2.3 in the age range 60–69 years. In contrast, the EAR of second primary cancers increased steadily with age, from approximately 100 extra cancers per 100 000 person-years in early life to more than 600 extra cancers per 100 000 person-years in the age group 60–69 years (Table 2). For the age range 70 years and older, only a few person-years and second primary cancers (four observed and 2.4 expected) were available for analysis; thus, the associated risk estimate was unstable and not included in Figure 1 or Table 2.

We stratified the cohort into children diagnosed for a first primary cancer during 1943–1959 ($n = 5720$; 56 298 person-years), 1960–1974 ($n = 13254$; 155 632 person-years), and 1975–2005 ($n = 28723$; 264 359 person-years). Among survivors, the cumulative risks for a second cancer before the age of 50 were 8.6% in the 1943–1959 subcohort (prechemotherapy era), 12.2% for 1960–1974 subcohort (first-generation chemotherapy era),

Table 1. Childhood cancer incidence (ages 0–19 years) in the Nordic countries and overall standardized incidence ratio of second primary cancer, 1943–2005*

Country or sex	Period	No. of first cancers	IR†	No. of second cancers	SIR	95% CI
Denmark	1943–2003	12 099	17.6	345	2.7	2.5 to 3.0
Finland	1953–2005	11 103	18.3	287	4.1	3.6 to 4.6
Iceland	1955–2003	609	18.3	13	3.6	1.9 to 6.1
Norway	1953–2002	8609	17.5	125	2.6	2.1 to 3.1
Sweden	1958–2003	15 277	17.5	410	3.9	3.5 to 4.2
All Nordic countries	NA	47 697	17.7	1180	3.3	3.1 to 3.5
Boys	NA	26 168	18.6	559	3.8	3.5 to 4.1
Girls	NA	21 529	16.7	621	3.0	2.8 to 3.2

* IR = incidence rate; SIR = standardized incidence ratio; CI = confidence interval; NA = not applicable because follow-up periods in individual countries differed.

† Average annual incidence rate of childhood cancer per 100 000 population (1990–2005).

and 13.3% for 1975–2005 subcohort (combination chemotherapy era; Figure 2). In the 1943–1959 subcohort, the cumulative risk for a second primary cancer reached 18% at age 60, 34% at age 70, and 48% at age 80. For the approximate comparison, the equivalent figures in the Nordic populations combined were 9%, 18%, and 31%, respectively.

Increased relative risk for second cancer was seen at a number of sites or groups of sites (Table 3). Overall, high risks were seen for tumors of the bone, connective tissue, brain, thyroid, and other endocrine glands, with SIRs higher than 5.0. Moderate-to-high risks were observed for tumors of the nonmelanoma skin, urinary system, and digestive organs, with incidence ratios between 3.0 and 4.0. Clearly increased risks were also seen for tumors of the mouth and pharynx, melanocytic skin, bone marrow and lymphatic system, breast, and respiratory tract. The 824 second cancers in excess among survivors (1180 observed cases vs 356 expected) were distributed as follows: 229 (28%) in the brain, 85 (10%) in female breast, 84 (10%) in bone and connective tissue, 84 (10%) in digestive organs, 68 (8%) in the bone marrow and lymphatic system, 63 (8%) in nonmelanoma skin, 42 (5%) as cutaneous malignant melanoma, 42 (5%) in the thyroid, and 127 (16%) at remaining or unspecified sites. The site-specific distribution of the observed excess cancers changed considerably, however, during life (Figure 3). Thus, 83% and 46% of the second primary cancers diagnosed at ages 0–14 and 15–39, respectively, consisted of tumors of the brain, bone, soft tissue, bone marrow, or lymphatic system, but 56% and 84% of those diagnosed at ages 40–59 and 60 years and older, respectively, consisted of cancers of the breast or digestive, respiratory, or genital organs. The relative risk for second brain cancer remained elevated 4- to 10-fold throughout life.

Of the 1180 second cancers seen in the Nordic study cohort, 380 (32%) were diagnosed in the age range 40–74 years. Because there is only limited published data on risk of second cancers in this age range, we calculated SIRs for site-specific second cancers by type of childhood cancer whenever five or more cancers were observed in a category (Table 4). In addition, strong associations were seen for retinoblastoma in childhood and

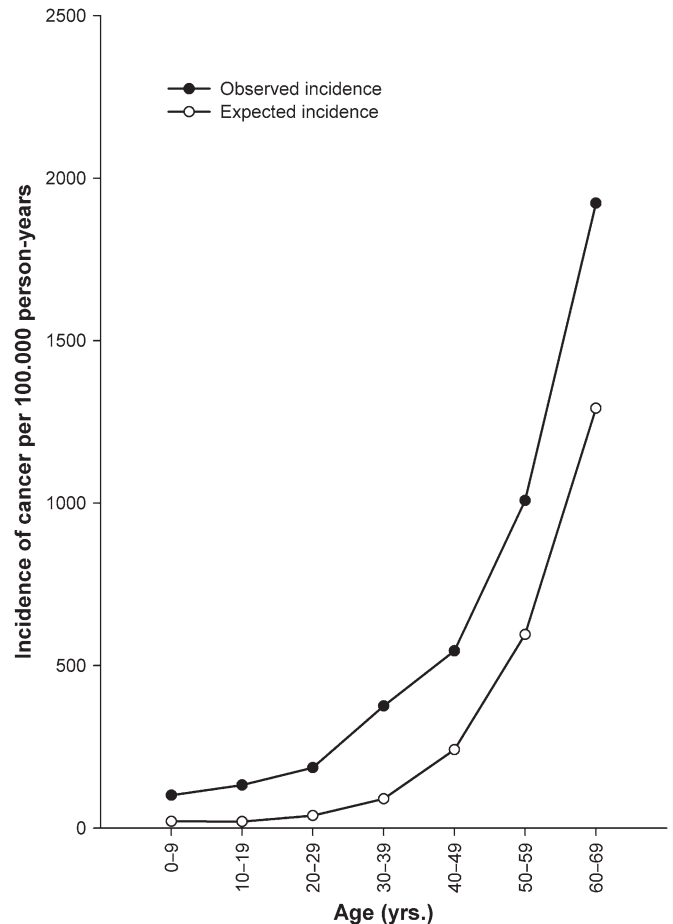


Figure 1. Observed incidence (closed circles) of second primary cancer among former childhood cancer patients by attained age during follow-up and cancer incidence expected from population rates (open circles).

sarcoma (SIR = 75, 95% CI = 8.5 to 272) or sinonasal cancer (SIR = 285, 95% CI = 32 to 1027) in adulthood, although these ratios were based on only two observed outcomes for each cancer combination.

Table 2. Age-specific standardized incidence ratio, adjusted relative risk, and excess absolute risk of second primary cancer among Nordic childhood cancer survivors by attained age during follow-up*

Age, y	No. of survivors†	No. of second cancers	IR‡	SIR	RR§	95% CI	EAR	95% CI
0–9	19317	71	101	6.7	5.4	4.1 to 7.2	86	63 to 109
10–19	30372	180	132	7.8	7.0	5.8 to 8.4	115	96 to 134
20–29	19350	266	186	4.9	4.8	4.2 to 5.5	148	148 to 170
30–39	10358	283	376	4.2	4.5	3.9 to 5.2	286	242 to 330
40–49	5115	195	545	2.3	2.8	2.3 to 3.4	304	227 to 580
50–59	2305	138	1008	1.7	2.3	1.8 to 2.9	412	244 to 580
60–69	574	43	1923	1.5	2.3	1.6 to 3.2	631	56 to 1206
70–79	52	4	163	NA	NA	NA	NA	NA
All ages	47697	1180	248	3.3	3.3	3.1 to 3.5	173	168 to 177

* IR = incidence rate; SIR = standardized incidence ratio; RR = relative risk; CI = confidence interval; EAR = excess absolute risk; NA = not applicable due to small number of second cancers.

† Number of survivors at entrance into age category.

‡ Incidence rate of second primary cancers per 100000 person-years of follow-up.

§ RR adjusted for calendar period and age at diagnosis of first primary cancer.

|| EAR of second primary cancer per 100000 person-years of follow-up.

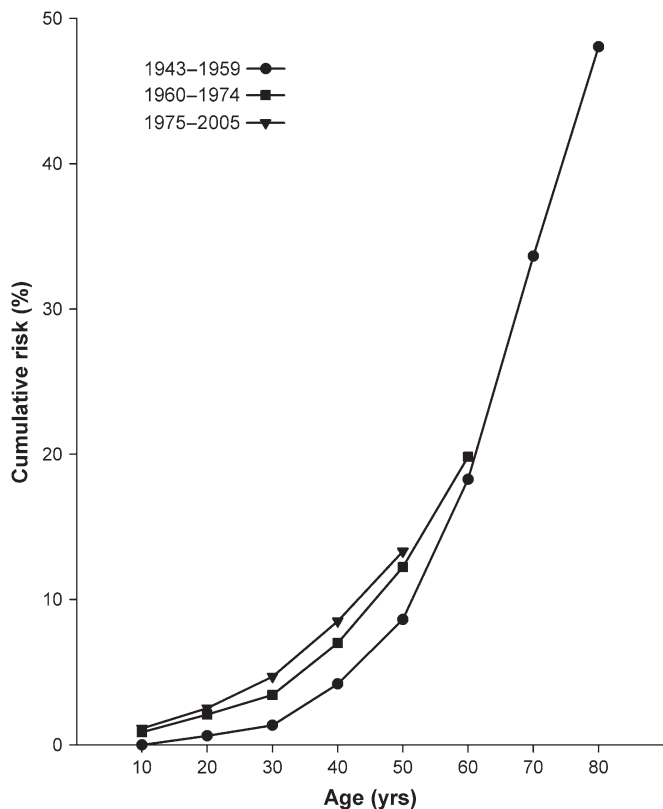


Figure 2. Cumulative risk for second primary cancer among former childhood cancer patients by attained age, with cohort members subgrouped according to period of treatment of first primary cancer (prechemotherapy era 1943–1959, closed circles; first-generation chemotherapy era 1960–1974, rectangles; and combination chemotherapy era 1975–2005, triangles).

Discussion

Our long-term follow-up study of second cancers in more than 47 000 survivors of childhood cancer in the five Nordic countries shows an overall SIR for a second malignant neoplasm of 3.3, on the basis of 1180 asynchronous cancers in 1088 persons. The relative risk for a second cancer remained statistically significantly increased during the age range of 0–69 years, suggesting that the carcinogenic effects of treatment for childhood cancer persist throughout life. The extent of the relative increase diminished as patients became older; however, this reduction appeared to be a consequence of the age-dependent increase in background rates (unrelated to radiation treatment or chemotherapy), rather than a moderation of the carcinogenic effect associated with treatment for childhood cancer. Our estimates of the age-specific EAR attributable to the status of former childhood cancer patient in fact showed an increase throughout life, from approximately one extra cancer case per 1000 person-years of observation in the age range 0–19 years to six extra cases per 1000 person-years in the age range 60–69 years. This strongly indicates, unfortunately, that the number of patients with second cancers after cancer in childhood will continue to increase not only because of a growing number of long-term survivors in the national populations but also because the average age of the childhood cancer survivor population will increase.

This study was conducted in an area of northern Europe with about 24 million inhabitants, which has been covered since the

1940s and 1950s by national cancer registries. Besides the unusually long registration periods, the strengths of our study include a high registration quality in each of the five countries. The latter is supported by the striking similarities in cancer patterns (4) and in overall childhood cancer incidence (Table 1), the similarity of incidence overall to that in other countries or areas with high-quality cancer registration (21), and the stability of the rates over the entire registration period (22). The main determinants of the quality of the data are the availability of personal identification numbers in all the Nordic countries and the multiple sources of information used by each registry (11). The nationwide coverage of the cancer registries and the personal identification number systems of the countries ensured that cohort members were all followed-up to date of death or date of emigration, that is, without any loss of follow-up.

Second primary cancers in survivors of childhood cancer have been recognized as late sequelae of therapy since the 1970s (23). Most of the studies on this topic are, however, limited by the size and composition of the study populations and by the duration and completeness of follow-up. In addition to the Nordic study, two unique sources of patients are available: the Childhood Cancer Survivor Study (CCSS) cohort, consisting of 13 581 5-year survivors treated at 25 Canadian and US institutions between 1970 and 1986, and a large population-based cohort in the United Kingdom, consisting of 16 541 3-year survivors in a national childhood cancer registry. The latter cohort mainly covers patients diagnosed in the period 1962–1987 but is supplemented by 3-year survivors of cancers diagnosed before 1962 from preserved hospital lists. In the study in North America, cohort members were followed up for a second primary cancer until the end of 1999, that is, for 6–29 years from the date of diagnosis of the childhood cancer (6). During that time, 314 second cancers were observed, yielding a highly statistically significant overall relative risk of 6.4. This estimate is compatible with those in our study, which gave relative risk estimates for a second primary cancer of between 4.5 and 7.0 in persons aged 0–39 years during follow-up. During follow-up of survivors of cancers other than retinoblastoma in the British study (5), 201 noncutaneous cancers were registered, yielding a highly statistically significant relative risk of 5.8, which is compatible with the estimates in the Nordic study, in the age range 0–39 years. The British study included a subset of approximately 800 persons who survived 30 years or more, in whom 11 cases of a second primary were seen, resulting in a relative risk of 2.4 (95% CI = 1.2 to 4.9). Although this estimate is unstable, it is compatible with the relative risk estimate of 2.8 in our study for the age range 40–49 years. In yet another, recent follow-up study from the United States of 25 965 two-month survivors of childhood cancer reported to one of nine SEER population-based cancer registries, the overall relative risk of second primary cancer during ages 0–39 was estimated to be 5.9 on the basis of 433 observed cancers (24). This estimate was also close to that observed in the Nordic study for similar age groups and close to the overall estimate derived in the CCSS cohort mentioned above. The recruitment periods used in the CCSS cohort and the recent SEER-based study do indicate, however, the existence of an overlap between the two studies, not further specified in the SEER-based study (24).

Table 3. Standardized incidence ratio of selected sites or group of sites of second cancer among Nordic childhood cancer survivors and overall distribution of excess number of site-specific second cancers in percentage of all second cancers*

Site of second cancer (ICD-7)	No. of second cancers	SIR	95% CI	Cases in excess, No. (%)
All sites combined (140–205)	1180	3.3	3.1 to 3.5	824 (100)
High-risk sites				
Connective tissue (197)	53	12.1	9.1 to 16	49 (6)
Bone (196)	39	10.1	7.2 to 14	35 (4)
Brain (192–193)	262	8.1	7.1 to 9.1	229 (28)
Other endocrine glands (195)	25	6.0	3.9 to 8.9	21 (2)
Thyroid (194)	51	5.4	4.0 to 7.1	42 (5)
Moderate- to high-risk sites				
Nonmelanoma skin (191)	85	3.8	3.0 to 4.7	63 (8)
Urinary system (180–181)	51	3.4	2.5 to 4.4	36 (4)
Digestive organs (150–159)	123	3.2	2.7 to 3.8	84 (10)
Other specified sites				
Malignant melanoma of skin (190)	69	2.6	2.0 to 3.3	42 (5)
Mouth and pharynx (140–148)	21	2.8	1.8 to 4.3	14 (2)
Bone marrow and lymphatic system (200–205)	110	2.6	2.2 to 3.2	68 (8)
Breast (170)	148	2.4	2.0 to 2.8	85 (10)
Respiratory tract (160–164)	44	2.1	1.5 to 2.8	23 (3)
Female genital organs (171–176)	47	1.4	1.0 to 1.9	13 (2)
Male genital organs (177–179)	33	1.3	0.9 to 1.8	7 (1)
Unspecified sites (198–199)	19	3.3	2.0 to 5.1	13 (2)

* SIR = standardized incidence ratio; CI = confidence interval; ICD-7 = *International Classification of Diseases*, seventh revision.

Of a total of 824 second cancers in excess among Nordic survivors, 229 or 28% were located in the brain. This large proportion is not only a result of a substantial eightfold increased relative risk for second brain tumors during teenage years and young adulthood (virtually identical to that reported in the SEER-based study on second cancer from the United States) (24) but also of the fact, as shown in this study, that the highly increased relative risk stretches

into the older age range when the rates of brain tumors in the general population increase exponentially. We cannot exclude the possibility that some of the excess of second brain tumors is due to inclusion of asymptomatic cases of meningiomas discovered in brain imaging studies of childhood cancer survivors. Brain imaging applied selectively to childhood cancer survivors would constitute surveillance bias and could lead to falsely increased risk estimates.

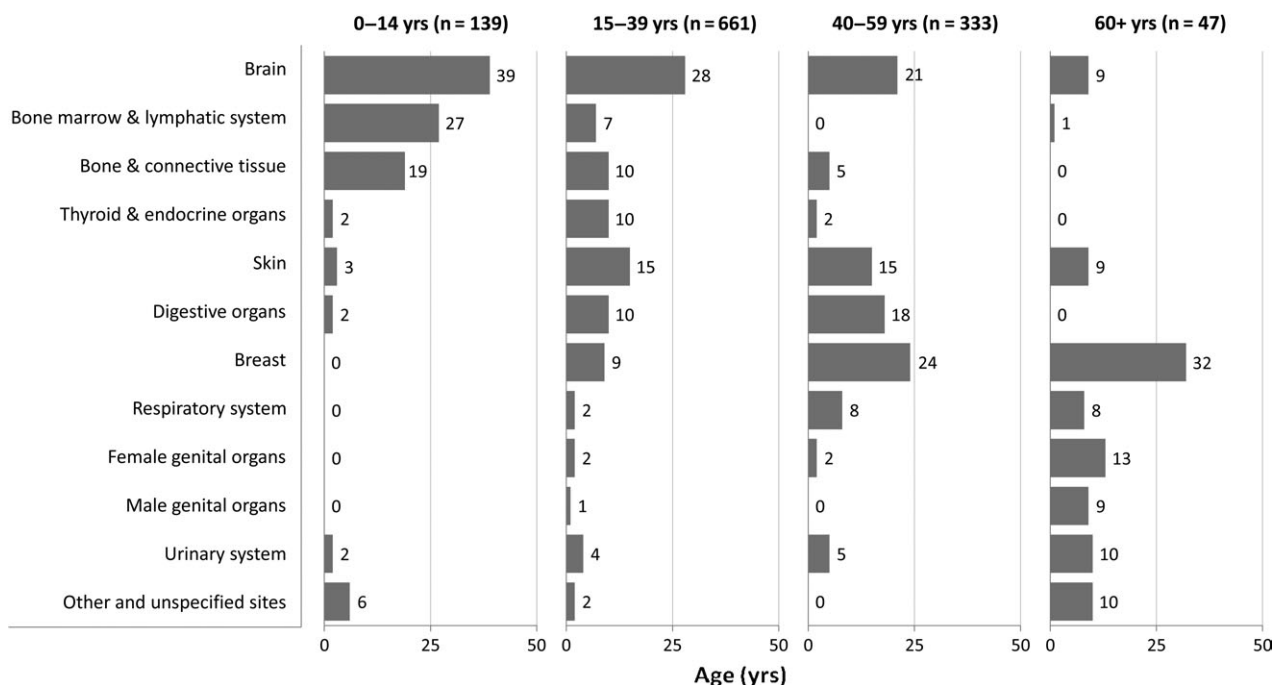


Figure 3. Percent distribution of excess numbers of second primary cancers by site within each of the age intervals 0–14, 15–39, 40–59 and ≥60 years.

Table 4. Numbers and types of second cancers and associated standardized incidence ratio among Nordic childhood cancer survivors diagnosed in age range 40–79 years by main diagnostic group of childhood cancer (category included only if five or more outcomes were observed)*

First cancer (International Classification Scheme for Childhood Cancer group†) Second cancer (ICD-7)	No. of second cancers (n = 380)	SIR	95% CI
Leukemias (I)			
All sites combined (140–205)	7	2.4	1.0 to 5.0
Malignant lymphomas (II)			
All sites combined (140–205)	83	3.4	2.7 to 4.2
Digestive organs (150–159)	14	3.7	2.0 to 6.1
Lung (162)	8	3.9	1.7 to 7.6
Breast (170)	28	5.9	3.9 to 8.5
Skin (190–191)	9	2.6	1.2 to 5.0
Brain (193)	6	4.8	1.7 to 10
CNS neoplasms (III)			
All sites combined (140–205)	78	1.6	1.3 to 2.0
Digestive organs (150–159)	8	1.1	0.5 to 2.2
Breast (170)	13	1.2	0.6 to 2.0
Skin (190–191)	11	1.5	0.8 to 2.7
Brain (193)	24	10.4	6.7 to 16
SNS neoplasms (IV)			
All sites combined (140–205)	6	3.5	1.3 to 7.6
Retinoblastoma (V)			
All sites combined (140–205)	15	3.5	2.0 to 5.8
Renal tumors (VI)			
All sites combined (140–205)	10	3.6	1.7 to 6.6
Malignant bone tumors (VIII)			
All sites combined (140–205)	23	1.6	1.0 to 2.4
Soft tissue sarcomas (IX)			
All sites combined (140–205)	37	1.6	1.2 to 2.3
Digestive organs (150–159)	6	1.7	0.6 to 3.7
Breast (170)	7	1.5	0.6 to 3.0
Skin (190–191)	6	1.8	0.7 to 4.0
Gonadal neoplasms (X)			
All sites combined (140–205)	41	2.2	1.6 to 3.0
Digestive organs (150–159)	12	5.0	2.6 to 8.7
Corpus uteri (172)	5	7.0	2.2 to 16
Skin (190–191)	7	3.3	1.3 to 6.7
Malignant epithelial tumors (XI)			
All sites combined (140–205)	76	1.4	1.1 to 1.7
Lung (162)	7	1.6	0.6 to 3.3
Breast (170)	24	1.5	1.0 to 2.3
Skin (190–191)	10	1.4	0.7 to 12

* SIR = standardized incidence ratio; CI = confidence interval; ICD-7 = *International Classification of Diseases*, seventh revision; CNS = central nervous system; SNS = sympathetic nervous system.

† International Classification Scheme for Childhood Cancer; groups VII (hepatic tumors) and XII (other and unspecified malignant neoplasms) were excluded from the table due to zero and four observed second cancers, respectively.

However, in the Nordic countries, it has not been common to do routine brain imaging studies in survivors or to conduct other screening activities among asymptomatic adult childhood cancer survivors, indicating that this type of bias is of limited importance.

The age-specific relative risk estimates for a second cancer changed somewhat with the calendar period of initial treatment, the highest risks being observed for children treated during the most recent treatment period, 1975–2005, with widespread use of intensive multiple-agent chemotherapy, as compared with those treated during the intermediate period 1960–1974, characterized

by first-generation single-agent chemotherapy, and the period before 1960, with no chemotherapy at all. This increase in relative risk occurred despite the clear advances in radiation treatment during the 1970s and 1980s, including replacement of orthovoltage by megavoltage radiation, which markedly reduced the radiation doses during treatment. In agreement with the findings of our nested case-control study and similar studies (25,26), these trends suggest that chemotherapeutic agents play a role in the etiology of second primary cancers in survivors, either as independent risk factors for second malignancies or by enhancing the carcinogenic effect of radiation.

The usefulness of the Nordic cancer registry files in the research of late effects in childhood cancer survivors is limited by information on treatment variables that is insufficient or completely lacking in the individual patient record. The existing information is too crude to allow for meaningful analyses linking type and dose of chemotherapy and radiation with site-specific second cancers. Another limitation of this study is a lack of well-defined rules for coding of second primary cancer during the first two or three decades of cancer registration. However, less than 9% of the observed cases of second cancer were diagnosed before 1980, due to the age composition of the survivor cohort.

In our Nordic study, we observed an excess of 824 second primary cancers attributable to the status of cohort members as former childhood cancer patients. Although detailed information on treatment was not available in this study, a previous case-control study nested in the Nordic survivor cohort (26) and similar studies of other cohorts have shown that radiotherapy and chemotherapy directed against a first cancer in childhood play a major role in the occurrence of second cancers later in life. It is conceivable that inherited predisposition to cancer plays a role; however, our previous studies of cancer in first-degree relatives, that is, parents (27), siblings (28), and offspring (29), of childhood cancer patients indicate that shared genetic susceptibility is limited to rare families with well-known dominant familial cancer syndromes. More than one-fourth of the excess tumors detected over a lifespan in all age groups during follow-up in this study were located in the brain. Other types of cancer, such as in the hematopoietic tissues, which accounted for 8% of the excess, appeared to be a problem only during the age range 0–39 years, whereas breast cancer, accounting for 10% of cases, increased in relative importance throughout life. Awareness of this changing pattern of second cancers is recommended in the long-term care and screening of childhood cancer patients.

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