ORIGINAL ARTICLE

Psychiatric Hospitalizations among Survivors of Cancer in Childhood or Adolescence

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ABSTRACT

BACKGROUND

We investigated whether children and adolescents who survive cancer are at increased risk for psychiatric hospitalization.

METHODS

In a nationwide, population-based, retrospective cohort study, 3710 persons who survived at least three years after a diagnosis of cancer in childhood or adolescence in the period from 1943 to 1990, and who were alive on January 1, 1970, or were born after that date, were identified in the Danish Cancer Registry. This population was followed up for psychiatric hospitalization from January 1, 1970, through 1993 by linkage with the Danish national Psychiatric Central Register. The number of expected cases was based on the national rates of hospitalization for psychiatric disease.

RESULTS

Among the 3710 survivors of cancer in childhood or adolescence, there was a total of 88 psychiatric hospitalizations. The risk of hospitalization for any psychiatric disease was higher among the survivors than in the general population, but the excess risk was restricted to survivors of brain tumor (the standardized hospitalization ratio [SHR], corresponding to the ratio of observed to expected cases of hospitalization for psychiatric disease, was 1.8; 95 percent confidence interval, 1.5 to 2.2). An increased risk of psychoses of somatic, cerebral causes (SHR, 7.7; 95 percent confidence interval, 4.1 to 13.2), psychiatric disorders in somatic disease (SHR, 5.1; 95 percent confidence interval, 2.5 to 9.1), and schizophrenia and related disorders (SHR, 2.4; 95 percent confidence interval, 1.2 to 4.4) was observed among survivors of brain tumor. There was no evidence of a significantly increased risk of major depression.

CONCLUSIONS

The risk of hospitalization for a psychiatric disorder is not increased among survivors of cancer in childhood or adolescence, except among survivors of brain tumor.

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THE DIAGNOSIS AND TREATMENT OF cancer in children can cause substantial stress in the survivors, beginning at an early age, and psychosocial sequelae may also develop later in life.[1] This problem is important, because in Denmark, for example, 1 in 600 persons under 50 years of age will be a survivor of childhood cancer by 2020.[2]

The rates of psychosocial maladjustment and impaired sexual function are higher among survivors of childhood cancer than in a healthy control population.[3,4] Impaired intellectual function has been reported in small studies of survivors of brain tumor[5,6] and among survivors of acute lymphatic leukemia who were treated with cranial irradiation.[6,7] Only two studies[8,9] have investigated the risk of major psychiatric illness after cancer in childhood or adolescence. No link was found, but these studies, which were based on only 450 survivors of cancer in childhood and 27 survivors of cancer in adolescence, had low statistical power to detect any association.

We investigated the rates of hospitalization for psychiatric disorders in a large, population-based cohort of 3710 survivors of childhood or adolescent cancer in Denmark with up to 24 years of follow-up (January 1, 1970, through December 31, 1993) and compared those rates with the appropriate rates in the general population. We calculated risk estimates that took into account the treatment and the type and site of the cancer.

METHODS

Using the files of the Danish Cancer Registry,[10] we identified 3710 persons who had survived at least three years after receiving a diagnosis of cancer; in whom a cancer was diagnosed before they were 20 years of age during the period from January 1, 1943, to December 31, 1990; and who were still alive on January 1, 1970 (or were born thereafter). We obtained information with the use of the personal identification number (which encodes sex and date of birth and which is assigned to all live-born infants and all new residents in Denmark) on the date of diagnosis, the type of cancer (morphologic type as well as site), and whether or not radiation treatment was administered. Since January 1, 1978, cases reported to the Cancer Registry have been coded according to the *International Classification of Diseases for Oncology* (ICD-O).[11] For childhood cancers registered before 1978, the full diagnosis given on the notification forms was reviewed and an ICD-O code was assigned, so that the classification scheme for childhood cancers proposed by the International Agency for Research on Cancer[12] could be applied to the data for the entire study period. With the exception of arteriovenous malformations and benign hemangiomas and lymphangiomas of the brain, all benign brain tumors diagnosed during the study period were included (and are also included under the term "cancer" in this report), according to the standard procedure of the Danish Cancer Registry.[13] The 3710 subjects included 24 in whom two or more tumors were diagnosed.

We used the personal identification numbers to link data on the 3710 survivors obtained from the Cancer Registry with data in the files of the nationwide Danish Psychiatric Central Register.[14] The Psychiatric Central Register contains information on all admissions to psychiatric hospitals and to psychiatric departments in general hospitals since April 1, 1969. The admission record includes the hospital department, the date of admission, the date of discharge, one primary psychiatric diagnosis, and up to three auxiliary diagnoses. The psychiatric diagnoses were classified according to the *International Classification of Diseases, 8th Revision* (ICD-8) during the study period[15] and grouped as follows: psychoses of somatic, cerebral causes, such as dementia and psychoses due to epilepsy, trauma, or infection (ICD-8 codes 292.09 through 294.99); psychiatric disorders in somatic diseases, such as nonpsychotic disease due to epilepsy, trauma, medication, or infection (codes 309.09 through 309.99); schizophrenia and related disorders (codes 295.09 through 295.99, 297.09 through 297.99, 298.39, 301.29, and 301.83); bipolar affective disorders (codes 296.19, 296.39, and 298.19); nonreactive unipolar affective disorders (296.09, 296.29, 296.89, and 296.99); reactive unipolar affective disorders (code 298.09); neuroses and personality disorders in the affective spectrum (codes 300.49 and 301.19); other reactive psychoses (codes 298.29 and 298.89); other neuroses and personality disorders (codes 300.09 through 300.39, 300.59 through 300.99, 301.09, 301.39 through 301.82, and 301.84 through 301.99); dementia (codes 290.09 through 290.19); substance or alcohol abuse (codes 291.09 through 291.99 and 303.09 through 304.99); psychiatric disorders in children, such as nonpsychotic disease due to epilepsy, trauma, infection, or impaired circulation of the blood (codes 308.00 through 308.09); transient maladaptation (code 307.99); and others (codes

298.99, 299.00 through 299.09, 302.19 through 302.99, 305.09 through 306.99, and 309.09 through 309.99). Multiple outcomes for the same person were recorded, but only the first admission in each diagnostic group was counted.

Follow-up for psychiatric admissions began three years after the diagnosis of cancer or on January 1, 1970, whichever came later, and was continued until the date of death (in the case of 596 subjects), emigration (48 subjects), or December 31, 1993 (3066 subjects), whichever came first, whether or not the subject was free of cancer during the follow-up period. However, we excluded the first three years of follow-up after the diagnosis of cancer to avoid bias due to the inclusion of psychiatric conditions associated with the symptoms of cancer or to short-term side effects of treatment of the disease. For patients with more than one tumor, follow-up began three years after the diagnosis of the last tumor, which was also the tumor used for stratification in the tumor-specific analyses.

The rate of psychiatric diagnosis and hospitalization during follow-up was compared with the rates of hospitalization for psychiatric disease expected for the age and sex distribution of the general population of Denmark and the calendar period. The annual rates of a first hospitalization for particular psychiatric disorders were computed by dividing the number of patients with a first admission to a psychiatric hospital or psychiatric department in a general hospital for each group of diagnoses (primary and auxiliary diagnoses) by the corresponding mean number of person-years for men and women in the population in five-year age groups and for five-year intervals. Thus, multiple outcomes for the same person were accepted, but only the first admission in each diagnostic group was counted, in accordance with the approach used for counting psychiatric outcomes among the study population. The expected number of psychiatric diagnoses was obtained by multiplying the age-, sex-, and period-specific number of person-years of follow-up by the national rates of hospitalization for specific causes. A standardized hospitalization ratio (SHR), corresponding to the ratio of observed to expected cases of psychiatric disease, was calculated as a measure of the incidence of psychiatric disease in the study cohort, relative to the national average; 95 percent confidence intervals were calculated on the assumption of a Poisson distribution of the observed number of psychiatric admissions. Byar's approximation was used.[16]

RESULTS

The average period of follow-up from the date of diagnosis of cancer among the 3710 members of the study cohort (Table 1) was 14.9 years. The ratio of male to female subjects was 1.23. A total of 44,136 person-years during which survivors were at risk for a psychiatric hospitalization were accrued between 3 and 27 years after the diagnosis of cancer. Of the 3710 persons, 2607 (70 percent) were at risk for a psychiatric hospitalization for 5 years or more, since they were followed for 8 years or more after receiving the diagnosis of cancer, and 1918 (52 percent) were at risk for 10 years or more (hospitalizations during the first 3 years of follow-up were excluded from the analysis). The average age at entry into a psychiatric hospital or psychiatric department in a general hospital was 15.4 years (range, 3 to 46). The cancers most frequently diagnosed in the 3710 members of the study cohort were tumors of the central nervous system (in 973 subjects), leukemia (in 586), malignant lymphoma (in 497), and carcinomas and other malignant epithelial neoplasms (in 425) (Table 1).

Among the 3710 survivors, there were 217 first admissions for psychiatric disease in all the diagnostic groups combined, resulting in a significantly increased risk of hospitalization for a psychiatric diagnosis (SHR, 1.3; 95 percent confidence interval, 1.1 to 1.4) (Table 2). Each member of the study cohort could be admitted for a first hospitalization and receive a diagnosis in more than one of the psychiatric-diagnosis groups; the 217 first admissions were accounted for by 126 survivors of childhood or adolescent cancer. Fifty-three survivors (42 percent of those admitted) received two or more different psychiatric diagnoses, as compared with 45 percent of psychiatric patients in the general population (data not shown). The highest risks were observed for the following groups of diagnoses: psychoses of somatic, cerebral cause (SHR, 3.0; 95 percent confidence interval, 1.8 to 4.7), psychiatric disorders in somatic diseases (SHR, 2.5; 95 percent confidence interval, 1.5 to 3.9), and psychiatric disorders in children (SHR, 2.2; 95 percent confidence interval, 0.9 to 4.6), although the increase in risk did not reach statistical significance. A significant increase in risk was also observed for schizophrenia and related disorders (SHR, 1.6; 95 percent confidence interval, 1.1 to 2.3) (Table 2). The survivors of cancer in childhood or adolescence did not have significantly altered risks for any other psychiatric

diagnoses, including affective (for example, depressive) disorders.

The higher rates of hospitalization were due almost entirely to the 88 admissions among survivors of brain tumor (as compared with 48.3 expected admissions; SHR, 1.8; 95 percent confidence interval, 1.5 to 2.2). Of the 973 survivors of brain tumor, 51 had one or more psychiatric hospitalizations, with significant increases in the risk of admission for schizophrenia and related disorders (SHR, 2.4; 95 percent confidence interval, 1.2 to 4.4), psychoses of somatic, cerebral causes (SHR, 7.7; 95 percent confidence interval, 4.1 to 13.2), psychiatric disorders in children (SHR, 5.2; 95 percent confidence interval, 1.4 to 13.2), and psychiatric disorders in somatic diseases (SHR, 5.1; 95 percent confidence interval, 2.5 to 9.1). We observed no excess risk of hospitalization for affective disorders (SHR, 1.0; 95 percent confidence interval, 0.4 to 2.1).

As Figure 1 shows, the use of radiotherapy to the brain in the treatment of childhood brain tumors did not significantly increase the risk of schizophrenia and related psychiatric disorders. The SHR for schizophrenia and related disorders among the 385 survivors of brain tumor who received radiotherapy was 3.8 (95 percent confidence interval, 1.4 to 8.2), and among the 588 survivors who did not receive radiotherapy, it was 1.7 (95 percent confidence interval, 0.6 to 4.0) (P=0.15). The SHR for psychoses of somatic, cerebral causes and psychiatric disorders in somatic diseases was 6.8 among patients who received radiotherapy to the brain (95 percent confidence interval, 3.1 to 12.8) and 6.0 (95 percent confidence interval, 3.3 to 9.8) among those who did not receive radiotherapy (P=0.46). The SHR for other psychiatric diseases among patients treated with radiotherapy was 1.6 (95 percent confidence interval, 1.0 to 2.4), and it was 1.2 (95 percent confidence interval, 0.8 to 1.7) for patients who had not been treated with radiotherapy (P=0.18). Among survivors of brain tumor, there was no clear trend in the risk of hospitalization for any of the groups of psychiatric diagnoses according to length of time since receiving the diagnosis of cancer or to age at treatment of cancer (data not shown).

We were able to retrieve the medical records of 7 of the 11 survivors of brain tumors in whom schizophrenia later developed. One patient was apparently misclassified in the Cancer Registry as not having received radiotherapy, although according to the medical record she had received this treatment. The survivors who had been treated with radiotherapy had received total doses of 42 to 71 Gy to the brain. Three of the seven subjects who had schizophrenia were reported in the medical records as having a familial predisposition to psychosis.

Because prophylactic cranial irradiation is some-

Table 1. Characteristics of 3710 Subjects in Whom Cancer Was Diagnosed in Childhood or Adolescence, during the Period from 1943 to 1990, Who Were Alive on January 1, 1970, or Born after That Date.*

Characteristic	No. (%)
Sex	
Male	2049 (55)
Female	1661 (45)
Type of cancer	
Leukemia	586 (16)
Lymphoma and other neoplasms of the reticuloendothelial system	497 (13)
Tumor of the central nervous system and miscellaneous intracranial and intraspinal neoplasms	973 (26)
Tumor of the sympathetic nervous system	111 (3)
Retinoblastoma	166 (4)
Renal tumor	177 (5)
Hepatic tumor	8 (<1)
Malignant bone tumor	161 (4)
Soft-tissue sarcoma	274 (7)
Germ-cell, trophoblastic, and other gonadal tumor	286 (8)
Carcinoma and other malignant epithelial neoplasms	425 (11)
Other neoplasm, including unspecified malignant neoplasm	46 (1)
Age at diagnosis (yr)	
0–4	1087 (29)
5–9	656 (18)
10–14	734 (20)
15–19	1233 (33)
Year of diagnosis	
1943–1953	300 (8)
1954–1963	430 (12)
1964–1973	758 (20)
1974–1983	1160 (31)
1984–1990	1062 (29)

* Cancers are grouped according to the classification system of Birch and Marsden.[12] For the 24 subjects in whom more than one cancer was diagnosed before the age of 20 years, only the last cancer diagnosed was counted.

Table 2. Standardized Hospitalization Ratios during Follow-up among 3710 Survivors of Cancer in Childhood or Adolescence in Denmark, 1970–1993.*

Psychiatric Diagnosis	All Cancers (N=3710)		Brain Tumor (N=973)		Other Cancers (N=2737)	
	Observed No.	SHR (95% CI)	Observed No.	SHR (95% CI)	Observed No.	SHR (95% CI)
All diagnoses	217	1.3 (1.1–1.4)	88	1.8 (1.5–2.2)	129	1.0 (0.9–1.2)
Psychoses of somatic, cerebral causes	18	3.0 (1.8–4.7)	13	7.7 (4.1–13.2)	5	1.1 (0.4–2.7)
Psychiatric disorders in somatic diseases	19	2.5 (1.5–3.9)	11	5.1 (2.5–9.1)	8	1.5 (0.6–2.9)
All other diagnoses	180	1.1 (1.0–1.3)	64	1.4 (1.1–1.8)	116	1.0 (0.8–1.2)
Schizophrenia and related disorders	26	1.6 (1.1–2.3)	11	2.4 (1.2–4.4)	15	1.3 (0.7–2.1)
All affective disorders	18	0.8 (0.5–1.3)	6	1.0 (0.4–2.1)	12	0.8 (0.4–1.4)
Bipolar psychoses	3	0.7 (0.1–2.0)	3	2.4 (0.5–7.1)	0	—
Nonreactive unipolar psychoses	9	1.0 (0.5–2.0)	4	1.6 (0.4–4.2)	5	0.8 (0.3–1.9)
Reactive unipolar psychoses	8	1.2 (0.5–2.4)	3	1.6 (0.3–4.8)	5	1.1 (0.4–2.5)
Neuroses and personality disorders	4	0.6 (0.2–1.5)	1	0.5 (0.0–2.9)	3	0.6 (0.1–1.8)
Other reactive psychoses	6	1.6 (0.6–3.5)	2	1.9 (0.2–6.8)	4	1.5 (0.4–3.8)
Other neuroses and personality disorders	43	1.0 (0.7–1.4)	15	1.2 (0.7–2.1)	28	0.9 (0.6–1.3)
Dementia	1	1.1 (0.0–5.9)	0	—	1	1.4 (0.0–8.0)
Substance abuse or alcohol abuse	35	1.0 (0.7–1.4)	9	0.9 (0.4–1.8)	26	1.0 (0.7–1.5)
Psychiatric disorders in children	7	2.2 (0.9–4.6)	4	5.2 (1.4–13.2)	3	1.3 (0.3–3.7)
Transient maladaptation	25	1.3 (0.8–1.9)	7	1.3 (0.5–2.6)	18	1.3 (0.8–2.0)
Others	13	1.2 (0.6–2.0)	5	1.6 (0.5–3.8)	8	1.0 (0.4–2.0)

* The standardized hospitalization ratio (SHR) is the ratio of the number of observed cases of first hospitalization for a disorder in a given group of psychiatric diagnoses during follow-up to the number expected on the basis of rates in the general population. CI denotes confidence interval. Hospitalizations for psychiatric disease during the first three years after receiving a diagnosis of cancer were excluded from this analysis. More than one hospitalization per patient may be listed, but only the first admission in each group of diagnoses was counted.

times included in the treatment of acute lymphatic leukemia, we conducted a similar analysis for schizophrenia and related disorders among survivors treated for acute lymphatic leukemia after stratification according to information on radiotherapy in the Danish Cancer Registry. Only 2 of the 586 survivors of leukemia were later hospitalized for schizophrenia, and neither subject was among the 153 survivors who had undergone prophylactic irradiation.

DISCUSSION

Among long-term survivors of cancer in childhood or adolescence, we observed a significant increase in the overall risk of admission to a psychiatric hospital or psychiatric department in a general hospital, as compared with the risk in the general Danish population. The excess risk, however, was confined to subjects in whom brain tumors had been diagnosed, indicating a biologic rather than a psychosocial vulnerability. This finding was reflected in the rates of psychiatric hospitalization for disorders that occurred more often in the subjects than in the general population — specifically, psychiatric disorders of somatic, cerebral causes in patients with somatic disease. Furthermore, a significantly increased risk of schizophrenia was clearly seen among survivors who had been treated with radio-

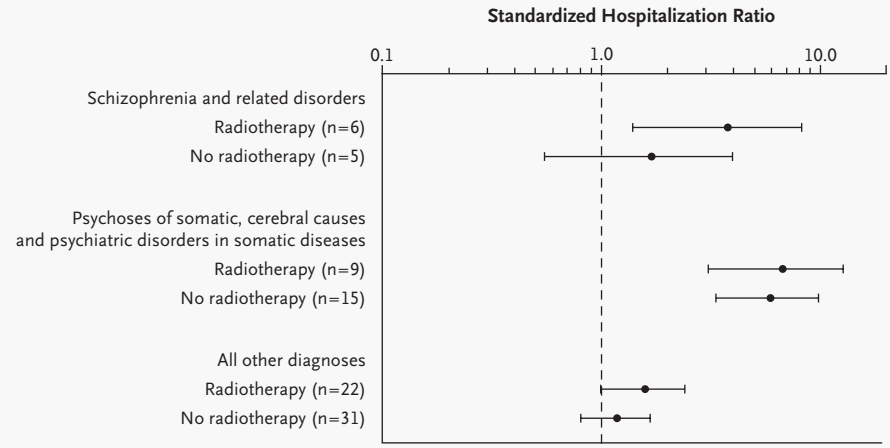

Figure 1. Standardized Hospitalization Ratios among 973 Survivors of Cancer of the Central Nervous System Diagnosed in Childhood or Adolescence, According to Whether They Received Radiotherapy to the Brain, 1970 through 1993.

The standardized hospitalization ratio is the ratio of the number of observed cases of first hospitalization for a disorder in a given group of psychiatric diagnoses during follow-up to the number expected on the basis of rates in the general population. Values are shown on a logarithmic scale. Psychiatric hospitalizations during the first three years after a diagnosis of cancer were excluded from this analysis. More than one hospitalization per patient may be listed, but only the first admission in a general group of diagnoses was counted.

therapy. The survivors of cancer in childhood or adolescence did not have a significantly altered risk of any other psychiatric diagnoses, including affective disorders. This finding is consistent with the findings of a number of studies that showed no excess prevalence of anxiety,[17] depression,[17,18] or overall mood disorder[19] among survivors of childhood or adolescent cancer as compared with controls without cancer. In a retrospective cohort study, the lifetime frequency of a major depression among 450 survivors of cancer in childhood or adolescence was not significantly different from that among their 587 siblings or in the general population of the United States.[8] In a cross-sectional study, the prevalence of major psychiatric disorders did not differ significantly between 27 survivors of childhood cancer and 202 healthy persons.[9]

The advantages of our study of psychiatric outcomes after childhood or adolescent cancer are the large sample and the long follow-up period. The data on survivors of cancer in childhood or adolescence were drawn from a nationwide cancer registry, which is regarded as virtually complete,[10] ensuring identification of all cases since 1943. The information on treatment obtained from the Danish Cancer Registry may, however, be inaccurate, because it is not routinely validated. We retrieved the medical records of only 7 of 11 survivors of brain tumor who were later hospitalized for schizophrenia, and these records showed that 1 patient had been misclassified. Another study[20] of the full medical records of 189 of the children and adolescents in the population from which members of the present study cohort were drawn found that 97 of 110 patients treated with radiotherapy (88 percent) and 78 of 79 patients not treated with radiotherapy (99 percent) were correctly coded in the Cancer Registry.[20] If the treatment variable was misclassified, the estimate of the risk for psychiatric hospitalizations after radiotherapy we obtained may have been conservative.

The validity of the data from the Psychiatric Central Register is good,[21,22] and the classification system used for the register was the one used throughout the period to categorize all psychiatric admissions in Denmark. The data are collected on a routine basis for administrative purposes, thereby reducing the possibility of selective inclusion. Since only patients with major psychiatric disease are admitted to psychiatric hospitals or psychiatric departments in general hospitals, the risk of minor psychosocial difficulties could not be investigated in this study. In Denmark, the number of available beds in psychiatric hospitals decreased by about 55 per-

cent from 1971 to 1993, when approximately 8 beds were available per 10,000 total population.[23,24] Thus, the treatment of psychiatric disease has changed over the years. Since we compared the rate of psychiatric hospitalization of survivors of cancer with that in the general population within five-year intervals, bias would have been introduced only if the criteria for hospitalization for psychiatric disease among survivors of cancer had not undergone the same changes as those for hospitalization among members of the general population. Advances in the treatment of cancer and improved survival rates in our study population after 1943 and the delayed start of follow-up (beginning in 1970) might have led to selection bias if persons in whom cancer was diagnosed before 1970 who survived until the beginning of follow-up had more favorable psychiatric outcomes than persons with cancer who died in 1970 or later. However, taking the year of the diagnosis of cancer into account did not reveal any general trend in the SHRs for psychiatric disorders after diagnosis of a brain tumor.

Caution should be exercised in interpreting the hospitalization ratios for single psychiatric diagnoses, because psychoses of somatic, cerebral causes or psychiatric disorders in somatic diseases, among others, can be misclassified as schizophrenia, and vice versa. Such misclassification could "wash out" the effect of radiotherapy on the risk of schizophrenia.

Recently, it was suggested that schizophrenia may develop as a result of the elimination of synaptic connectivity in the central nervous system during the perinatal period or adolescence,[25] and several studies have shown schizophrenia to be associated with brain dysmorphology,[26] which may accelerate with age.[26-29] The intriguing hypothesis that ionizing radiation may contribute to the development of schizophrenia in a person with a predisposition to the disorder was proposed on the basis of an increased incidence of schizophrenia among survivors of the nuclear accident at Chernobyl.[30] Although we found no statistically significant difference in the risk of schizophrenia among survivors of brain tumor treated with radiotherapy and those who were not so treated, our results cannot completely rule out the possibility that cranial irradiation may increase the risk of schizophrenia among survivors of brain tumor.

In conclusion, we found no evidence of a significant increase in the risk of major depressive illness among survivors of cancer in childhood or adolescence. The significantly increased risk of any psychiatric hospitalization after a diagnosis of cancer during childhood or adolescence in our study was confined to the subgroup of survivors who had had brain tumors. The particularly high hospitalization rates for psychoses with a somatic component point to a biologic rather than a psychological vulnerability among survivors of cancer.

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