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Long-Term Non-Cancer Mortality in Pediatric and Young Adult Cancer Survivors in Finland

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Abstract

BACKGROUND—Excess late mortality has been reported among pediatric cancer survivors, but there is a need to further establish risk profiles for non-cancer death and to examine cause-specific mortality among survivors of young adult cancers.

PROCEDURES—In a nationwide record linkage study in Finland, we identified 9,245 five-year cancer survivors diagnosed before age 35 and treated between 1966 -1999, and followed them for mortality endpoints from 1971 through 2008. Standardized mortality ratios (SMRs) and 95% confidence intervals (95% CIs) were calculated to compare the observed number of deaths with those expected in the general Finnish population. Primary endpoints included death from cardiovascular and respiratory diseases; death from malignant diseases was excluded.

RESULTS—Non-malignant disease mortality in the cohort was 90% higher [SMR=1.9, 95%CI 1.7-2.2] than expected, with SMRs for circulatory and respiratory disease similarly elevated [SMR=1.9, 95%CI 1.5-2.3 and SMR=2.3, 95% CI 1.3-3.8, respectively]. Important differences were noted amongst patient subgroups, with risk greatest for survivors of central nervous system (CNS) cancer, Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL). The SMR's for circulatory disease were 6.6 (95% CI 4.8-8.9) for HL and 4.8 (95% CI 2.6-8.1) for NHL for the entire population; but these risks remained elevated for survivors diagnosed between 15-34 years of age.

CONCLUSIONS—Previous studies have shown that there is an elevated risk of non cancer mortality in childhood cancer survivors; this is one of the first studies that show an increase in cardiovascular and respiratory mortality in long term survivors of adolescent and young adult cancers.

Keywords

cancer; mortality; pediatrics; adolescent; survival; cardiovascular diseases

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Conflict of interests statement

The authors of this paper do not have any financial interest in the subject matter discussed. This includes ownership of stock, membership on a standing advisory council or committee, a seat on the board of directors, or being publicly associated with a company or its products.

INTRODUCTION

With advances in risk-adapted multimodality treatment, it is estimated that close to 80% of childhood cancer patients are initially cured of their malignancy. (1) While a number of studies (2-12) have evaluated late mortality among survivors of childhood cancer, there have been few studies that included survivors of cancer diagnosed between the ages of 20-34 years. Young adults tend to develop some cancers that are similar to their younger counterparts such as acute lymphoblastic leukemia (ALL) and Hodgkin lymphoma (HL), as well as a broader spectrum of other diagnoses such as thyroid and germ cell tumors. It is only recently that adolescents and young adults (AYA) with cancer have received special emphasis in clinical care and follow-up for adverse long-term outcomes following successful treatment of their malignancies. (13, 14)

With a growing proportion of surviving childhood and AYA cancer patients, there has been an increased interest in long term consequences of therapy. It has become apparent that there are long term adverse physical and psychological effects that accompany survivorship such as cardiac and pulmonary toxicity, infertility, fatigue and neurocognitive effects. (15-23) Pediatric cancer survivors are known to be at increased risk for late effects that may result in death, and two recent large-scale studies have examined such mortality risks. (24, 25) Death is largely due to recurrence of the primary malignancy, though there have also been studies that demonstrated risk of increased mortality from diseases of the circulatory and respiratory systems. (2, 19, 25, 26) However, there are few studies that have examined causes of mortality in survivors of adolescent and young adult cancers diagnosed between the ages of 19 years and 35 years.

The goal of the present study was to evaluate non-malignant mortality patterns (specifically circulatory and respiratory disease deaths) among five-year survivors of AYA cancers in a large, Finnish population-based cohort, and to compare these rates to those in the general population.

METHODS

Cohort identification

Cancer patients were identified from the files of the Finnish Cancer Registry, which started systematic registration in 1953. The registry is population-based and nationwide, and the coverage is very high (100% for solid tumors and over 90% for hematological malignancies). (27) Each record in the Cancer Registry contains, among other data, the patient's personal identity code (a unique identifier assigned to Finnish residents linkable across the national registries), cancer diagnosis (with date), and the patient's age and sex. We identified all individuals who were diagnosed before age 35 with invasive cancer from 1966-1999, and who survived at least five years past their index cancer diagnosis. The upper limit of 35 years was an *ad hoc* output cutpoint intended to distinguish an age when the cancer site pattern changes notably to cancers of older age, such as lung, breast and colorectal cancer. A total of 9,245 individuals (4,218 male, 5,027 female) meeting these criteria formed the final cohort. National reference rates for mortality in Finland (needed for the standardized mortality ratio (SMR) analysis) were systematically available starting in 1971, and our total period of follow-up observation was 1971-2008.

Mortality Follow-up

The National Population Register in Finland was used to ascertain all deaths in the cohort from January 1, 1971 through December 31, 2008. Information on emigration was also

obtained from this register to censor cohort members' person-time upon emigration from Finland so no patients were lost to follow-up. Causes of death were available from data maintained by Statistics Finland. This information was extracted and coded from the original death certificates, where assignment of the cause was largely based on medical evidence, or from forensic determination when the death was not the clear result of an illness, was accidental or violent, or was caused by a treatment procedure or an occupational disease. (28)

Statistical analysis

Individual person-time was calculated from the five-year anniversary of the index diagnosis until death, emigration or December 31, 2008, whichever came first. The number of expected deaths was calculated by multiplying age-, sex- and calendar year-specific mortality rates (expected rates) from the general population by the person-time accrued in the cohort. For the expected rates we used five-year age categories and the calendar year periods 1971-78, 1979-86, 1987-94, 1995-2002, and 2003-8. The number of observed deaths was divided by the number of expected deaths, producing a standardized mortality ratio (SMR) with exact 95% confidence intervals calculated assuming that the observed events followed a Poisson probability distribution. (29) SMRs were calculated for causes of death corresponding to the fixed categories for which Statistics Finland produces routine mortality rates. The ICD-10 equivalents for the categories relevant to the present analysis were broken down into 4 categories which included malignant disease (codes C00-C97), all non-malignant disease causes (codes A00-R99 minus codes C00-C97), disease of the circulatory system (codes I00-I99) and diseases of the respiratory system (codes J00-J99). The non-malignant disease grouping included deaths from all non-cancer diseases and disorders affecting any organ system including circulatory, respiratory, digestive, musculoskeletal, genitourinary, endocrine, nervous system, and infectious diseases. This grouping did not include external causes of death such as injury, poisoning, or accidents. Further sub-categories of circulatory and respiratory disease were utilized. Circulatory diseases were broken down into 4 categories which included: ischemic heart disease (codes I20-I25), other heart diseases (codes I30-I52), cerebrovascular diseases and other diseases of the circulatory system. Ischemic heart disease included myocardial infarction, atherosclerotic CVD or heart disease, and coronary artery aneurysm. Other heart disease included pericarditis, endocarditis, myocarditis, non-rheumatic valve disorders, cardiomyopathy, arrhythmias and conduction disorders, cardiac arrest, and heart failure Cerebrovascular diseases were defined as intracranial hemorrhage, ischemic and other stroke; whereas other diseases of the circulatory system included rheumatic heart disease, pulmonary embolism, disease of pulmonary vessels, atherosclerosis, peripheral vascular disease, arterial and venous embolism or thrombosis, diseases of arteries, capillaries, veins, or lymphatic vessels, and hypotension. In a similar manner, respiratory diseases were broken down into death due to pneumonia (codes J12-J18), asthma (codes J45-J46), influenza (codes J10-J11), and other diseases of the respiratory system (codes J00-J09, J19-J39, J48-J99). Other diseases of the respiratory system was comprised of acute upper respiratory infections, acute bronchitis, lung disease due to external agents, pulmonary edema, abscess of lung, pyothorax, pleural effusion, and pneumothorax.

SMRs are presented for selected causes of death for the cohort overall, and were also evaluated for subgroups defined by age at diagnosis, calendar year at diagnosis, index cancer type, and follow-up time. Age at diagnosis was categorized into groups roughly characterized as children (age 0-14 years), adolescents (age 15-19 years) and young adults (age 20-34 years). All p-values presented are two-sided.

RESULTS

The cohort members, consisting of 9,245 five-year cancer survivors, were followed for a total of 147,446 person-years, or an average of 15.9 years (range 0 – 38 years) past their five-year survival mark, during which 14.8% (N=1,366) died. Table I shows the distribution of initial cancer diagnoses for the three groups of survivors classified by their age at diagnosis. For cohort members aged 0-14 at the time of initial diagnosis, the most common diagnoses were leukemias (28.9%) and central nervous system (CNS) tumors (25.5%). As the age at diagnosis increased, the proportion of patients with leukemia decreased and there was a shift towards HL and solid tumors. Survivors of young adult onset cancer (aged 20-34 at diagnosis) were more likely to have thyroid cancers (13.8%), HL (13.5%), melanoma (10.1%), and germ cell tumors (9.5%).

The cohort members had an overall mortality rate from disease (including ultimate cancer death) seven times as high as the general Finnish population [SMR=7.3, 95%CI 6.9-7.7] (Supplemental Index), and the SMR for malignancy-related deaths was 18.2 [95%CI 17.1-19.3, including deaths from the original or any subsequent cancer]. The total mortality excess was strongest for patients diagnosed at age 0-14 [SMR=9.3, 95% CI 8.3-10.4] and attenuated with increasing age at diagnosis [SMR=5.9, 95% CI 5.1-6.8 for age 15-19; SMR=4.6, 95% CI 4.3-4.9 for age 20-34] Supplemental Material).

Table II shows SMRs for malignant and non-malignant disease death and the subsets of circulatory and respiratory disease death, within strata of age at diagnosis, sex, follow-up time, and calendar year of diagnosis. Non-malignant disease mortality in the cohort was 90% higher [SMR=1.9] than in the general Finnish population, and the SMRs for circulatory and respiratory disease were similarly elevated at 1.9 and 2.3, respectively. Risk of death due to circulatory disease was significantly elevated for the childhood, adolescent, and young adult patients, with a trend towards the younger patients having the higher excess risks. The SMRs for circulatory disease death were similar for males and females and the SMRs for respiratory disease deaths were slightly higher for males than females. Due to the small number of deaths from respiratory disease we were unable to examine the significance of the discrepancy between genders. We did not observe consistent trends regarding mortality patterns in relation to follow-up time or calendar year of diagnosis for either circulatory or respiratory disease.

For circulatory disease, we observed 93 deaths compared to 50.3 expected, noting that the significant mortality excess extended beyond 25 years of follow-up (or 30 years past diagnosis) [SMR for follow-up of 25+ years =1.5, 95%CI 1.0-2.3]. Deaths from respiratory disease (15 total observed) were less common than circulatory disease, leaving a small number of events with which to evaluate risk across strata of follow-up time or age at diagnosis. Of the 15 deaths due to respiratory disease, 11 were due to pneumonia, 2 to asthma, 1 to influenza, and 1 to other diseases of the respiratory system. For the only age group where observed numbers permitted reliable SMR estimates (age 20-34 at diagnosis), the risk of death from respiratory disease was significantly elevated by 140% [SMR=2.4, 95%CI 1.3-4.1].

Evaluating mortality according to index cancer type (Table III), five-year survivors of CNS cancer, non-Hodgkin lymphoma (NHL), and HL all showed significantly elevated SMRs for non-malignant disease mortality (SMRs ranging from 2.6 to 8.8). This was in contrast to survivors of melanoma, retinoblastoma, and bone, breast, germ cell, salivary gland and thyroid cancer, for whom there was little suggestion of elevated non-cancer mortality. Survivors of other cancer types (soft tissue sarcoma, leukemia, kidney cancer, and neuroblastoma) had some SMRs in excess of 1.5 based on small numbers of events that did

not reach statistical significance. The mortality excess from circulatory disease was largely confined to lymphoma survivors, with the number of deaths almost five times (for NHL survivors) and almost seven times (for HL survivors) higher than expected (Table III). Further evaluation of mortality from circulatory disease showed an increase in mortality in each of the 4 subgroups, ischemic heart disease, other heart diseases, cerebrovascular disease and other diseases of the circulatory system (Table IV) in both NHL and HL survivors, though the results were based on small numbers. Furthermore, the risk of circulatory disease death was elevated for HL and NHL survivors diagnosed at all ages (Table IV) not just children diagnosed before the age of 15 years. For cerebrovascular disease death, only survivors of CNS cancer had an elevated risk that reached statistical significance, with 8 observed cases vs. 0.98 expected [SMR=8.2, 95% CI 3.5-16.1]. Survivors of HL and CNS cancer were the only groups that exhibited significantly increased mortality from respiratory disease [SMR=8.8, 95% CI 3.6-18.2 for HL; SMR=7.6, 95% CI 2.1-19.6 for CNS]. Six of the seven respiratory disease deaths among the HL survivors were due to pneumonia (the remaining from “other diseases of the respiratory system”, see Methods), as were three of the four deaths among CNS cancer survivors (the remaining from influenza).

DISCUSSION

In this population-based study we evaluated long term mortality risks from major non-malignant diseases in five-year survivors of childhood and AYA cancer. Our main focus on non-cancer death indicated a substantial (90%) excess risk from non-cancer causes overall, and specifically from circulatory disease (90% excess risk) and respiratory disease (130% excess risk) that was strongly manifested in the childhood patients, where expected rates of death from these causes are lowest. However, the relative risk of death was also substantially elevated for the young adult patients, particularly lymphoma survivors. Cancer type was an important factor, as many subgroups of the Finnish cancer survivors displayed no elevated risk of non-cancer death, including those initially diagnosed with melanoma, retinoblastoma, and bone, breast, germ cell, salivary gland and thyroid cancer, and the higher total non-malignant mortality experienced by the youngest cancer patients partly reflects the spectrum of cancers (and associated treatments) experienced by this group. Our finding that patients with bone cancers did not have an elevated risk of death from cardiovascular disease does appear to differ from some previous findings (30), although the number of deaths observed in our study for this group was small. Patients with bone cancer, including the subset of Ewing sarcoma, are treated with chemotherapeutic agents with known cardiac toxicity. (31)

Cardiovascular late effects are a recognized cause of increased mortality among survivors of childhood and AYA cancer, and are primarily related to mediastinal radiotherapy and chemotherapy with anthracyclines. In a previous study following over 7,000 HL survivors for 30 years, the risk of myocardial infarction was increased by two-fold compared to the general population. (32) This risk of death from myocardial infarction after treatment remained high for at least 25 years. Historically, HL is treated with a combination of chemotherapy, including anthracyclines and radiotherapy. The Childhood Cancer Survivor Study (CCSS) has reported an 8-fold increase in risk for cardiac deaths associated with chest irradiation (26) which is consistent with longstanding observations that mediastinal and chest radiation can have sequelae including constrictive pericarditis, cardiomyopathy, valvular heart disease and coronary artery disease, (22, 33-37); they have also reported adverse cardiac outcomes associated with anthracycline exposure in a recent study. (38)

Cardiotoxicity has been seen in studies where patients are treated with high doses of anthracyclines, (38-41) and late onset ventricular dysfunction and arrhythmias can develop

decades after their administration. (42) We observed significantly elevated mortality from circulatory disease throughout our entire follow-up period. Cancers such as HL, NHL, and neuroblastoma involve therapy with a large amount of anthracyclines, and when index diagnoses were examined in our study, HL and NHL survivors had among the highest excess cardiac mortality, with a 4.8 to 6.6-fold risk. The small number of survivors of neuroblastoma precluded a stable estimate of their cardiac mortality risk.

The CCSS cohort has also demonstrated adverse respiratory late effects among childhood cancer survivors, noting that even more than 25 years from original diagnosis there was an eleven-fold risk of death from pulmonary causes (pneumonia, pulmonary fibrosis, and other conditions) amongst the cohort. (9) The magnitude of the association with respiratory disease death was lower in our Finnish cohort, although statistically significant and representing potential concern for cancer survivors. The concern should be placed in context of the rarity of the outcome, because for the two high-risk groups including HL and CNS cancer survivors, 0.6% and 0.3%, respectively, died from respiratory disease during the follow-up period. Pulmonary toxicity can occur secondary to both chemotherapy and radiotherapy. Lung function is affected by exposure to drugs such as bleomycin, cyclophosphamide, busulfan, lomustine and carmustine. (43-45) The lungs are one of the most radiosensitive organs in the body, and along with acute effects, exposure can result in long-term effects that include pulmonary fibrosis with manifestations of cough, pleurisy or pneumonia. (46) The respiratory mortality excesses we found for survivors of CNS cancer and HL were not as high as those recently reported by the CCSS (SMRs ranging from 6.6 to 20.7 for CNS tumors, and 10.8 for HL). (9) A contributor to these differences may be differing study periods, as in the 1960's (covered by this Finnish study but not the CCSS), CNS tumors were generally treated with primary surgical resection alone and not, chemotherapy agents with pulmonary toxicity. When long term mortality for CNS tumor patients was recently examined in a study from the St. Jude Children's Research Hospital, the investigators noted that 58% of survivors died of progressive disease from their primary tumor and 18% died from a secondary medical condition which included metabolic collapse, cardiopulmonary complications or sepsis. (11)

The strengths of our study include its nationwide coverage with systematic follow-up and coding for deaths. The large population of nearly 10,000 survivors also allowed for stratification of findings by a number of patient characteristics. This is also one of the few and largest studies to include survivors of cancers diagnosed in childhood, adolescence, and young adulthood, with the latter group, aged 20-34, constituting more than half of the total cohort with 4,968 survivors and over 80,000 person-years of follow-up, which allowed us to document that the strong association between lymphoma and circulatory disease mortality is also quite relevant for the older patient groups. Previously the CCSS and a large Nordic based study examined mortality in patients diagnosed younger than 21, (25, 30) however the AYA group of patients diagnosed between the ages of 20-34 years of age had not been examined. Our study also allowed us to examine various cancers which include breast cancer, melanoma and germ cell cancer that are not frequently seen in the children less than 20 years of age, but are commonly seen in patients 20-34 years of age. Our study also includes the more modern treatment era of 1990-1999 that has not been previously studied by the CCSS.

Despite the study size, however, the infrequency of death from respiratory disease did not allow for definitive characterization of risk subgroups. Also, the limited level of treatment details present in the Cancer Registry files precluded us from evaluating specific treatments in relation to these outcomes. However, given the fairly standard treatment regimens in use for various cancers, we believe we can reasonably interpret our findings on the basis of treatment effects, particularly for survivors of HL, NHL and CNS cancer.

Recurrent cancer is still the primary cause of late mortality in pediatric cancer survivors. However, there has been relatively little published on the mortality experience of AYA cancer patients and non-malignant causes of late mortality. This study demonstrates that there is an increased risk of mortality due to non-malignant disease in the AYA group. As therapy for both childhood and AYA cancer improves, it is imperative for physicians to screen for long term sequelae and adverse effects that may shorten lives. Since late effects from cancer therapy is an evolving entity, it is important to promote the concept of risk-based health care for survivors. An ideal approach to cancer survivorship care should be longitudinal, proactive, and anticipatory and should include a systematic plan of prevention and surveillance based on risks associated with the previous cancer, cancer therapy, genetic predispositions, lifestyle behaviors, and co-morbid health conditions. (22).

Our findings support the importance of continued follow-up in survivors of childhood and AYA cancer with an emphasis on surveillance for not only secondary malignancies but also cardiac and pulmonary sequelae. It is imperative that pediatric and adult physicians taking care of the AYA population screen for late effects. AYA's are also susceptible to long term effects of their treatment and the knowledge of these complications is crucial to plan interventions aimed at decreasing late mortality.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table I

Distribution of initial cancer diagnosis

Index cancer diagnosis	All patients			Age 0-14 at diagnosis			Age 15-19 at diagnosis			Age 20-34 at diagnosis		
	N	%	person-years	N	%	person-years	N	%	person-years	N	%	person-years
CNS tumor	1346	14.6	19880	752	25.5	12034	188	14.1	3092	406	8.2	4753
Hodgkin lymphoma	1084	11.7	15590	136	4.6	2086	275	20.7	3688	673	13.5	9817
Leukemia	1064	11.5	14322	852	28.9	11924	90	6.8	1102	122	2.5	1296
Thyroid	867	9.4	15687	41	1.4	649	139	10.5	2635	687	13.8	12403
Melanoma	598	6.5	9530	21	0.7	410	73	5.5	1206	504	10.1	7915
Germ cell tumor	625	6.8	9402	66	2.2	1088	86	6.5	1204	473	9.5	7110
NHL	557	6.0	8395	200	6.8	3086	79	5.9	1077	278	5.6	4232
Bone tumor	317	3.4	6143	101	3.4	1820	77	5.8	1491	139	2.8	2831
Soft tissue sarcoma	292	3.2	5049	125	4.2	2122	39	2.9	783	128	2.6	2144
Kidney	277	3.0	4953	232	7.9	4153	6	0.5	80	39	0.8	720
Breast	236	2.6	3451	1	0.03	22	6	0.5	115	229	4.6	3314
Neuroblastoma	161	1.7	2579	151	5.1	2467	2	0.2	5	8	0.2	108
Retinoblastoma	115	1.2	2297	115	3.9	2297	-	0	-	-	0	-
Salivary gland	65	0.7	1180	9	0.3	230	10	0.8	135	46	0.9	815
All other cancers combined (including unknown type)	1641	17.8	28990	146	5.0	9928	259	19.5	4392	1236	24.9	22556
Total	9,245	100%	147,446	2,948	100%	46,412	13,29	100%	21,004	4,968	100%	80,031

Abbreviations: CNS, central nervous system; NHL, non-Hodgkin lymphoma.

Table II

SMR for selected causes of death in 5 year cancer survivors

	Number of		Death due to malignant disease ¹				Death due to any non-malignant disease ²				Death due to circulatory disease				Death due to respiratory disease			
	Patients	Person-years	Obs/Exp ³	SMR	95% CI	Obs/Exp ³	SMR	95% CI	Obs/Exp ³	SMR	95% CI	Obs/Exp ³	SMR	95% CI	Obs/Exp ³	SMR	95% CI	
All patients	9245	147446	1035/56.8	18.2	17.1-19.3	227/116.5	1.9	1.7-2.2	93/50.3	1.9	1.5-2.3	15/6.5	2.3	1.3-3.8				
Age at diagnosis (yrs)																		
0-14	2948	46412	242/3.6	67.6	59.4-76.4	36/9.6	3.7	2.6-5.2	7/2.6	2.7	1.1-5.5	2/0.5	4.2	0.5-15.0				
15-19	1329	21004	128/5.2	24.5	20.5-29.0	33/12.3	2.7	1.8-3.8	16/4.5	3.5	2.0-5.7	0/0.6	0	0.0-6.0				
20-34	4968	80031	665/48.0	13.9	12.8-14.9	158/94.6	1.7	1.4-2.0	70/43.1	1.6	1.3-2.1	13/5.4	2.4	1.3-4.1				
Sex																		
Male	4218	65497.1	493/22.9	21.5	19.7-23.5	145/77.2	1.9	1.6-2.2	66/35.2	1.9	1.5-2.4	10/3.9	2.6	1.2-4.7				
Female	5027	81949.2	542/33.9	16.0	14.7-17.4	82/39.3	2.1	1.7-2.6	27/15.1	1.8	1.2-2.6	5/2.6	1.9	0.6-4.5				
Follow-up time ⁴ (yrs)																		
0-4	9245 ⁵	44150	554/4.4	124.8	114.7-135.0	27/11.7	2.3	1.5-3.4	3/3.6	0.8	0.2-2.4	4/0.6	6.3	1.7-16.1				
5-9	8239 ⁵	36045	203/5.9	34.2	29.7-39.1	45/15.4	2.9	2.1-3.9	14-5.5	2.6	1.4-4.3	1/0.8	1.3	0.0-7.3				
10-14	6212 ⁵	26672	82/8.0	10.3	8.2-12.7	41/18.9	2.2	1.6-2.9	15/7.4	2.0	1.1-3.3	2/0.9	2.2	0.3-7.8				
15-19	4480 ⁵	18637	77/10.0	7.7	6.1-9.6	39/21.0	1.9	1.3-2.5	17/8.9	1.9	1.1-3.1	3/1.1	2.9	0.6-8.3				
20-24	2996 ⁵	11845	57/10.8	5.3	4.0-6.9	34/20.0	1.7	1.2-2.4	20/9.3	2.2	1.3-3.3	4/1.1	3.6	1.0-9.1				
25+	1806 ⁵	10096	62/17.7	3.5	2.7-4.5	41/29.6	1.4	1.0-1.9	24/15.6	1.5	1.0-2.3	1/2.0	0.5	0.0-2.8				
Calendar year at diagnosis																		
1966-1979	2685	66285.8	543/41.5	13.1	12.0-14.2	148/79.1	1.9	1.6-2.2	73/37.9	1.9	1.5-2.4	8/4.8	1.7	0.7-3.3				
1980-1989	2946	50251.6	302/12.1	24.9	22.2-27.8	63/28.8	2.2	1.7-2.8	15/9.9	1.5	0.9-2.5	6/1.4	4.4	1.6-9.6				
1990-1999	3614	30908.9	190/3.2	59.7	51.5-68.4	16/8.7	1.8	1.1-3.0	5/2.5	2.0	0.7-4.7	1/0.3	3.0	0.1-16.8				

Abbreviations: SMR, standardized mortality ratio; 95% CI, 95% confidence interval; Obs, observed; Exp, expected; yrs, years

¹Death due to malignant disease = death from primary and secondary malignancies²Death due to any non-malignant disease = death from all diseases – death due to malignant causes

³ Obs/Exp = number of observed deaths divided by the number of expected deaths based on age-, sex-, and calendar year-specific mortality rates in the general Finnish population

⁴ Follow-up time starts five years after the initial diagnosis

⁵ Represents the number of patients alive at the beginning of each follow-up period (and thus contributing person-time to each period).

Table III

SMR for selected causes of death in 5 year cancer survivors stratified by diagnosis

Index cancer diagnosis	Death due to malignant disease ¹			Death due to any non-malignant disease ²			Death due to circulatory disease			Death due to respiratory disease		
	Obs/Exp ³	SMR	95% CI	Obs/Exp ³	SMR	95% CI	Obs/Exp ³	SMR	95% CI	Obs/Exp ³	SMR	95% CI
CNS tumor	264/4.1	63.7	56.3-71.6	44/10.0	4.4	3.2-5.9	10/3.8	2.6	1.3-4.8	4/0.5	7.6	2.1-19.6
Hodgkin lymphoma	207/6.1	34.2	29.7-39.0	72/15.1	4.8	3.7-6.0	44/6.6	6.6	4.8-8.9	7/0.8	8.8	3.6-18.2
Leukemia	124/1.1	113.1	94.0-133	5/3.1	1.6	0.5-3.8	1/0.9	1.1	0.03-6.3	0/0.2	0	0-25.2
Thyroid	17/8.5	2.0	1.2-3.2	6/13.4	0.4	0.2-1.0	1/5.7	0.2	0-1.0	1/0.8	1.3	0.03-7.0
Melanoma	59/4.7	12.7	9.7-16.4	48/8	0.5	0.1-1.2	1/3.8	0.3	0.01-1.5	0/0.5	0	0-7.4
Germ cell tumor	25/4.1	6.1	4.0-9.0	15/12.6	1.2	0.7-2.0	5/5.7	0.9	0.3-2.0	0/0.6	0	0-5.8
NHL	42/2.6	16.2	11.7-21.9	21/6.9	3.0	1.9-4.6	14/2.9	4.8	2.6-8.1	1/0.4	2.8	0.1-15.8
Bone tumor	29/3.0	9.8	6.6-14.1	5/7.1	0.7	0.2-1.6	4/3.4	1.2	0.3-3.0	0/0.4	0	0-9.2
Soft tissue sarcoma	43/1.9	23.0	16.7-31.0	5/3.7	1.3	0.4-3.1	0/1.6	0	0-2.3	1/0.2	4.8	0.1-26.6
Kidney	12/0.8	15.8	8.1-27.5	4/1.7	2.3	0.6-6.0	0/0.7	0	0-5.4	0/0.1	0	0-38.2
Breast	70/2.3	30.0	23.4-38.0	1/2.6	0.4	0.01-2.2	0/1.1	0	0-3.5	0/0.2	0	0-20.8
Neuroblastoma	10/0.2	62.0	29.7-114.0	1/0.3	3.3	0.1-18.6	1/0.08	12.1	0.3-67.4	0/0.02	0	0-193
Retinoblastoma	4/0.1	29.5	8.0-75.5	0/0.4	0	0-10.5	0/0.08	0	0-46.1	0/0.02	0	0-193
Salivary gland	6/0.7	9.1	3.4-19.8	1/1.3	0.8	0.02-4.3	0/0.6	0	0-6.1	0/0.08	0	0-49.2

Abbreviations: SMR, standardized mortality ratio; 95% CI, 95% confidence interval; Obs, observed; Exp, expected; CNS, central nervous system; NHL, non-Hodgkin lymphoma

¹Death due to malignant disease = death from primary and secondary malignancies

²Death due to any non-malignant disease = death from all diseases – death due to malignant causes

³Obs/Exp = number of observed deaths divided by the number of expected deaths based on age-, sex-, and calendar year- specific mortality rates in the general Finnish population.

Table IV

SMR for circulatory disease for five-year cancer survivors of HL, NHL and CNS tumors

Cancer Diagnosis	Death due to Circulatory Disease			Death due to Ischemia			Death due to other heart diseases			Death due to cerebrovascular diseases			Death due to other circulatory diseases		
	Obs/Exp	SMR	95% CI	Obs/Exp	SMR	95% CI	Obs/Exp	SMR	95% CI	Obs/Exp	SMR	95% CI	Obs/Exp	SMR	95% CI
HL															
Age at diagnosis (yrs)															
0-14	1/0.2	5.2	0.1-28.8	1/0.1	15.9	0.4-88.4	-	-	-	-	-	-	-	-	-
15-19	6/0.7	8.4	3.1-18.2	5/0.3	16.3	5.3-38.1	1/0.1	6.9	0.2-38.4	-	-	-	-	-	-
20-34	37/5.7	6.5	4.6-8.9	30/3.1	9.5	6.4-13.6	5/0.8	6.1	2.0-14.1	1/1.3	0.8	0.02-4.3	1/0.4	2.2	0.1-12.2
NHL															
Age at diagnosis (yrs)															
0-14	14/2.9	4.8	2.6-8.1	6/1.5	4.0	1.5-8.6	3/0.5	6.2	1.3-18	3/0.7	4.5	0.9-13.3	2/0.3	8.1	1.0-29.3
15-19	5/0.2	21.8	7.1-50.8	2/0.1	19.5	2.4-70.4	1/0.05	20.2	0.5-112	1/0.1	17.8	0.4-99.1	1/0.02	46.8	1.2-260
20-34	8/2.4	3.3	1.4-6.5	3/1.3	2.3	0.5-6.6	2/0.4	5.4	0.7-19.6	2/0.5	3.7	0.4-13.4	1/0.2	5.0	0.1-28.1
CNS tumor															
Age at diagnosis (yrs)															
0-14	10/3.8	2.6	1.3-4.8	1/1.8	0.6	0.01-3.1	-	-	-	8/0.98	8.2	3.5-16.1	1/0.4	2.8	0.1-15.3
15-19	2/0.8	2.5	0.3-9.2	-	-	-	-	-	-	2/0.2	8.9	1.1-32.3	-	-	-
20-34	1/0.9	1.2	0.03-6.6	1/0.4	2.5	0.1-13.8	-	-	-	-	-	-	-	-	-
	7/2.2	3.2	1.3-6.5	-	-	-	-	-	-	6/0.5	10.9	4.0-23.8	1/0.2	5.2	0.1-29.0

Abbreviations: SMR, standardized mortality ratio; 95% CI, 95% confidence interval; Obs, observed; Exp, expected; yrs, years

Obs/Exp = number of observed deaths divided by the number of expected deaths based on age-, sex-, and calendar year- specific mortality rates in the general Finnish population