Copenhagen, May 2015

Protocol

Disease burden in Adult Life after Childhood Cancer in Scandinavia

Background

The group of childhood cancer survivors is increasing steadily due to an amazing increase in survival rates during the last four decades. In the Nordic countries four in every five childhood cancer patients can expect to be long-term survivors.[1] However, these major improvements in survival come at a price. Because of intensive exposure to radiation and highly toxic compounds during treatment, many survivors of childhood cancer now face significant sequelae, most of which become clinically apparent many years after the child has been cured from its cancer. Around two-thirds of survivors experience at least one chronic late effect of treatment and around one third experiences severe or life-threatening late effects.[2] Previous studies of hospital admissions among 5-year survivors of childhood cancer have shown that survivors were at increased risk of being hospitalised and had longer stays and bed days at hospital.[3 4]

In a population-based Nordic cohort study with virtually no loss to follow-up and by the exclusive use of medically verified diagnostic information from individual in-patient records, we will study the full range of somatic morbidities requiring hospitalization in 33,160 one-year childhood cancer survivors diagnosed in the period 1943-2008.
This study will give us a comprehensive picture of the disease burden in childhood cancer survivors, because all somatic discharge diagnoses are included and for all childhood cancers, which has not previously been possible in a large cohort study with a randomly selected control group.

Material and methods

This study is part of the Nordic cohort study 'Adult Life after Childhood Cancer in Scandinavia' (ALiCCS), investigating late complications after treatment for childhood cancer (www.aliccs.org).

Patient and comparison cohorts

The basic ALiCCS childhood cancer cohort comprised 43,909 people who had been reported to the cancer registries of the Nordic countries with a cancer diagnosed before the age of 20 years between the start of the registries in the 1940s and 1950s, and 31 December 2008. To be included in the cohort, patients had to be alive on or after the date on which centralised registration of residents of each country was operational with all required variables (Iceland, 1955; Norway, 1960; Denmark and Sweden, 1968; and Finland, 1971) (Table 1). All Nordic cancer registries are nationwide, and a cancer diagnosis is reported from multiple sources, ensuring virtually 100% coverage.[5-7] From the registries, we have obtained information on type of cancer and date of diagnosis, and patients were assigned to the 12 main diagnostic groups of the International Classification Scheme for Childhood Cancer.[8] Since the start of centralised civil registration in the Nordic countries, all residents have been assigned a unique personal identification number, which allows accurate linkage of information between registries.

To measure rates of morbidity in the background population, we will use a randomly selected population comparison cohort of 219,131 individuals from the population registries of the five countries. For each patient of childhood cancer, five comparisons are chosen, who were alive on the date of cancer diagnosis of the corresponding patient, of the same sex, age, country (Denmark and Iceland) or the same county or municipality of residence (Finland, Norway and Sweden), and without a cancer diagnosis in the age-range 0–19 years. Information on vital status and migration during follow-up was collected from the population registers for both patients and population comparisons.

Before starting analyses for this study and linking study subjects to the hospital registers, we have excluded those in whom more than one primary cancer was diagnosed in childhood as they cannot be classified unambiguously; those who died or emigrated before the start of the national hospital register; and those who died or emigrated during the first year after the date of cancer diagnosis or an equivalent time lag for the population comparisons. This resulted in a cohort of 33,160 one-year survivors of childhood cancer and a cohort of 212,892 population comparisons, ready to be included in this study of disease burden (table 1).

Table 1. Study population and period of follow-up by country

Country	Recruitment period	Population recruited		Follow-up period[b]	Study population	
		Cancer survivors[a]	Population comparisons		Survivors[c]	Comparisons
Denmark	1943–2008	9 859	49 160	1977–2010	7 580	47 895
Finland	1953–2008	9 147	45 665	1983–2009	7 190	45 537
Iceland	1955–2008	699	3 495	1999–2008	411	3 350
Norway	1953–2008	9 127	45 443	2008–2010	5 274	41 001
Sweden	1958–2008	15 077	75 368	1968–2009[e]	12 705	75 109
All countries	**NA**	**43 909**	**219 131**	**NA**	**33 160**	**219 131**

[a] Survivors of childhood cancer diagnosed in recruitment period and alive at the start of national population registration
[b] Period for which outcome data were available from the hospital registries
[c] One-year survivors alive at start of follow-up period
[e] From 1968–1987, dependent on county.

Hospital admissions for somatic disease

The nationwide hospital registers contain information on all non-psychiatric hospital admissions in the five countries.[9 10] Registration is mandatory and submitted electronically by the treating physician. Each hospital admission initiates a record, which includes the personal identification number of the patient, dates of admission and discharge, a primary discharge diagnosis, and a varying number of supplementary diagnoses coded according to the International Classification of Diseases, 7th to 10th revisions (ICD-7 to ICD-10).

Cancer survivors and comparisons will be linked to the files of the five national hospital registries to extract a complete hospital history with associated discharge diagnoses for each study subject with previous contact to a hospital. On the basis of information from the hospital registries we plan to further exclude study subjects registered with congenital malformations, congenital diseases, and chromosomal abnormalities as these disorders could potentially confound causal associations between cancer treatment and chronic disorders.

In this study we will identify all hospital admissions with a primary discharge diagnosis. We will define our outcomes by the main diseases in the ICD-8. The diagnostic categories of ICD-7, ICD-9 and ICD-10 will be adapted to those of the ICD-8 as far as possible. Follow-up for malignant neoplasms will only include new primary cancers. We will rely on the cancer registries for this information as the hospital registries do not distinguish completely between relapse and new primary cancer. We do not plan to include mental disorders in this study as these are kept in a separate registry and are not available in all five countries.

Statistical analysis

Follow-up for somatic disease in the hospital registers is starting one year after the date of diagnosis of childhood cancer (and the corresponding date for the equivalent comparisons) or at the start of the hospital registers, whichever occurred latest. Follow-up will end on the date of death, the date of emigration, or the closing date of the study, whichever occurred first. If study subjects have more than one hospital contact for the same disease entity, only the first record will be retained. The observed number of first hospital admissions for a given disease among childhood cancer survivors will be compared with expected numbers derived from the appropriate country-, sex-, age- and calendar period specific morbidity rates of the population comparison cohort. The standardised hospitalisation rate ratio (RR, the observed-to-expected number of hospital contacts for each defined disease entity) with corresponding 95% confidence intervals (CIs) will be estimated assuming a Poisson distribution. The absolute excess risk (AER) were calculated as the difference between the observed and expected number of hospital admissions divided by the number of person-years at risk, with corresponding 95% CIs. The AER reflects the additional burden of hospitalization beyond background levels.

We also plan to investigate the distribution of cancer survivors and comparisons with hospitalisations in 1, 2 or ≥3 different disease categories and calculate the cumulated number of days admitted to hospital. The number of days in hospital will be calculated as a bed days ratio (BDR) to take into account the higher survival rate in the comparison cohort and therefore the longer follow-up period. BDR will be indirectly standardised by sex, age and country.

Please see Appendix with suggested tables and figures.

Discussion

One of the major strengths of our study is that we are able to retrieve information from medical registers on all incident cases of childhood cancer and all somatic hospital admissions, because registration is mandatory and nationwide in all five Nordic countries. By using register-based data we also eliminate the risk of recall bias which is a severe potential bias in studies based on self-report such as the Childhood Cancer Survivor Study (CCSS).[11]

The CCSS cohort has a mean age of 26 years at follow-up. Therefore late effects in survivors exceeding the age of 40 years is practically unknown. In this study, we will have a long follow-up period for hospital admissions, which allows precise risk estimates, also in the age group above 40 years. This is possible because the registration of cancer in the Nordic countries goes back to the 1940s and 1950s. Finally, this study will contribute knowledge about the consequences of treatment given in Denmark and the other Nordic countries over time. Treatment has developed remarkably over the study period and this study can evaluate whether newer treatments with improved survival lead to a higher prevalence of late effects leading to hospital admissions in long-term survivors.

References

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Appendix. Suggested Tables and Figures for presentation of results

Table 1. Observed and expected number of hospitalizations among xx,xxx 5-year survivors of childhood cancer with associated standardized hospitalization rate ratios (RRs) and absolute excess risks (AERs) with corresponding 95% confidence intervals (CIs).

	No. of 5-year cancer survivors	No of hospitalizations[a]		RR (95% CI)	AER[c] (95% CI)	Observed no of bed days	SBDR[d]
		Observed	Expected				
Sex							
Both							
Men							
Women							
Attained age (years)							
20–29							
30–39							
40–49							
50–59							
60–69							
70–79							
Time since cancer diagnosis (years)							
5–9							
10–19							
20–29							
30–39							
40–49							
50–59							

[a] Hospitalizations for selected diseases; see Material and methods for details.

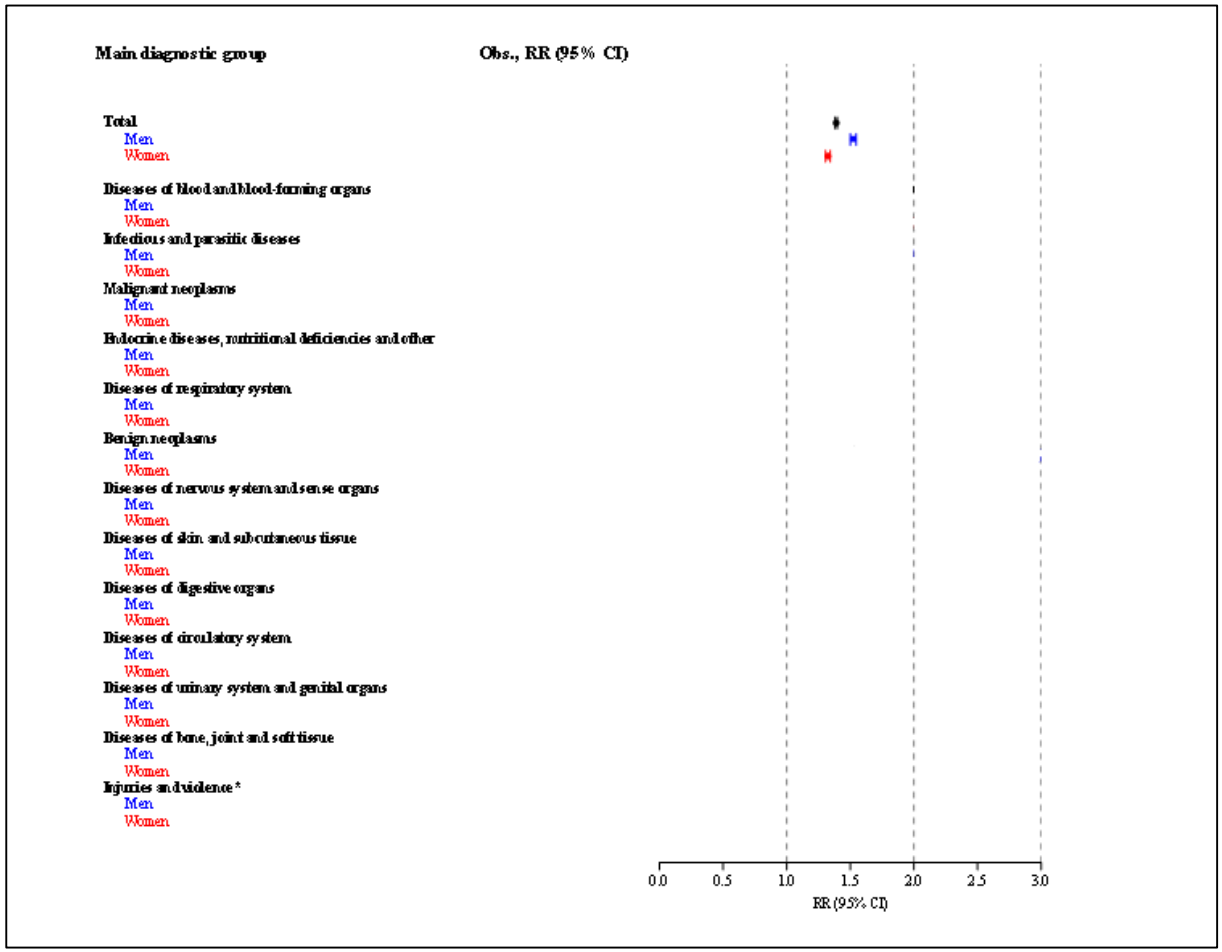
[b] Per 100,000 person-years

[c] Absolute excess risk per 100,000 person-years

[d] Standardized bed days ratio

RR: standardized hospitalization rate ratio; CI: confidence interval

Figure 1. Forest plot showing risk estimates for the 12 main diagnostic groups; for men and women combined (black circles) and for men (blue squares) and women (red circles) separately.



*The risk estimate for injuries and violence was not included in the total risk estimate.

Figure 2. Forest plot of risk for hospitalization of survivors by type of childhood cancer.

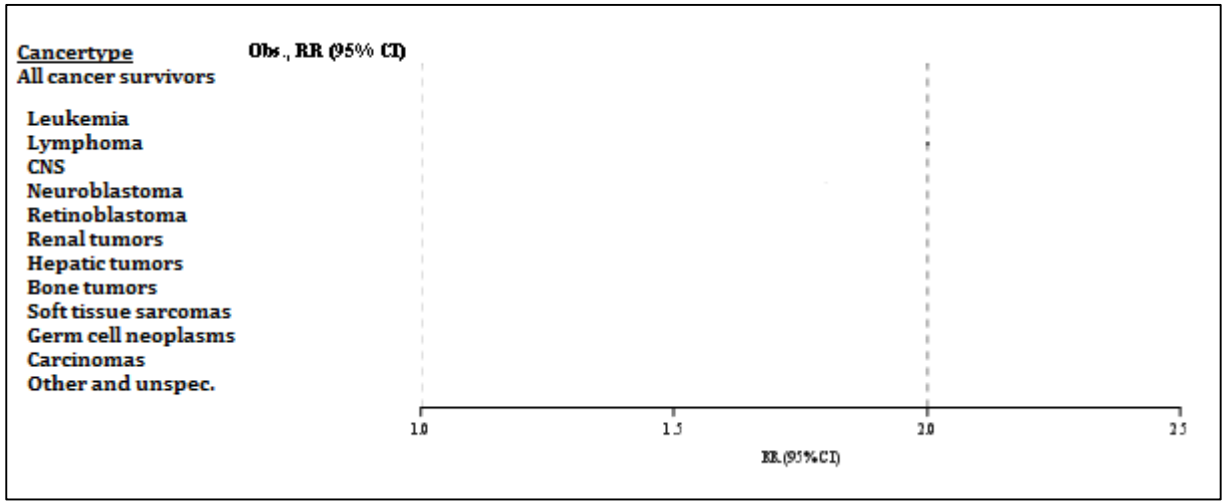
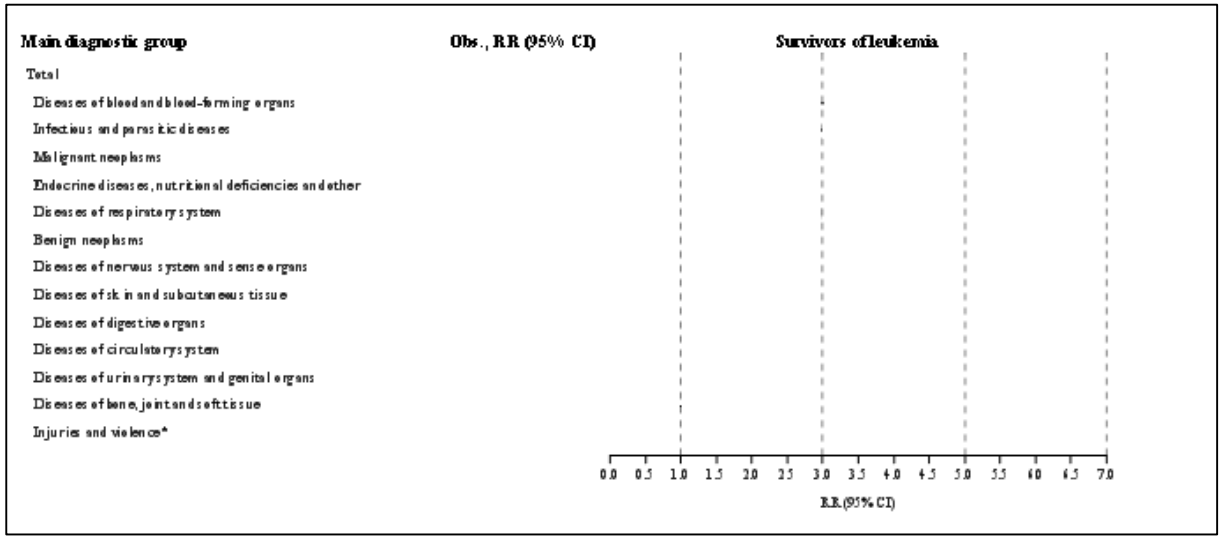


Figure 3. Appendix or web figure.
13 Forest plots showing the risks for hospitalization of the cohort of xx,xxx 5-year survivors of childhood cancer. Risks are shown for each of the 13 childhood cancers (lymphoma divided into Hodgkin and Non-Hodgkin) by main diagnostic group.



*The risk estimate for injuries and violence was not included in the total risk estimate.

This is just an example of the forest plots. A total of 13 forest plots will be made, one for each cancer type.

Table 2. Appendix or web table.
Standardized hospitalization rate ratios (RRs) and absolute excess risks (AERs) with corresponding 95% confidence intervals (CIs) for all main diagnostic groups and disease categories for the cohort of xx,xxx 5-year survivors of childhood cancer

Main diagnostic group / Disease category	No. of hospitalizations		RR (95% CI)	AER (95% CI)
	Observed	Expected		
Total no. of hospitalizations	**xx,xxx**	**xx,xxx**	**x.x (x.x to x.x)**	**x,xxx (x,xxx to x,xxx)**
Infectious and parasitic diseases				
Intestinal infectious diseases				
Tuberculosis				
Other bacterial diseases				
Enterovirus diseases of CNS				
Herpes zooster				
Other viral diseases with exanthem				
Infectious hepatitis, HIV (only in ICD-9 and 10) and other viral diseases				
Syfilis and other veneral diseases				
Mycoses				
Other infectious and parasitic diseases				
Other infectious and parasitic diseases				
Malignant neoplasms				
(new primary cancer)				
Cancer of buccal cavity and pharynx				
Cancer of digestive organs				
Cancer of respiratory system and intrathoracic organs				
Cancer of bones, joints and articular cartilage				
Malignant melanoma of skin				
Non-melanoma skin cancer				
Mesothelium and connective tissue				
Cancer of breast				
Cancer of female genital organs incl. skin				
Cancer of male genital organs incl. skin				
Cancer of urinary tract				
Cancer of eye, brain and other perts of central nervous system				
Cancer of endocrine organs				
Malignant lymphomas				
Multiple myeloma				
Leukemia				
Ill-defined and unspecified cancer				
Benign neoplasms				
Endocrine diseases, nutritional deficiencies and other metabolic diseases				

- Diseases of the thyroid gland
- Diabetes mellitus
- Pituitary hHypofunction
- Ovarian dysfunction
- Testicular dysfunction
- Nutritional deficiencies
- Other endocrine and metabolic diseases
- Male sterility
- Disorders of menstruation and female sterility

Diseases of blood and blood-forming organs

- Anaemias
- Coagulation defects, purpura and other haemorrhagic conditions
- Agranulocytosis
- Other diseases of blood and blood-forming organs

Diseases of nervous system and sense organs

- Meningitis
- Other inflammatory diseases of CNS
- Multiple sclerosis and other demyelinating diseases of CNS
- Parkinson disease and other movement disorders
- Epilepsy
- Migraine and other diseases of brain and spinal cord
- Senile and presenile dementia
- Diseases of nerves and peripheral ganglia
- Inflammatory and other diseases of the eye
- Cateract
- Inflammatory diseases of ear
- Ménière's disease and othosclerosis
- Other diseases of ear and deafness

Diseases of circulatory system

- Acute rheumatic fever
- Chronic rheumatic heart disease
- Hypertensive disease
- Ischemic heart disease
- Pulmonary heart disease
- Pericardial-, myocardial- and endocardial disease
- Valvular disease (non-rheumatic)
- Heart failure
- Conduction disorders
- Cerebrovascular disease

- Diseases of arteries, arterioles and capillaries
- Venous and lymphatic disease
- Other complications of the circulatory system

Diseases of respiratory system

- Acute respiratory infections
- Influenza
- Pneumonia
- Bronchitis and emphysema
- Asthma
- Other diseases of respiratory system

Diseases of digestive organs

- Diseases of the teeth and supporting structures
- Other diseases of the oral cavity and salivary glands
- Diseases of esophagus
- Diseases of stomach and duodenum
- Appendicitis
- Hernia of abdomal cavity
- Other diseases of intestine and peritoneum
- Diseases of liver
- Diseases of gallbladder and biliary ducts
- Diseases of pancreas

Diseases of urinary system and genital organs

- Glomerular diseases
- Acute renal failure
- Chronic kidney disease
- Urolithiasis
- Obstructive uropathy
- Infections of the urinary system
- Other an unspecified disorders of the urinary system
- Diseases of prostate
- Other diseases of male genital organs
- Chronic cystic disease and other diseases of breast
- Other diseases of female genital organs

Diseases of skin and subcutaneous tissue

- Infections of skin and subcutaneous tissue
- Other inflammatory conditions of skin and subcutaneous tissue
- Radiodermatitis

Disorders of skin appendages (hair, nails, sweat glands)

Other disorders of the skin and subcutaneous tissue

Diseases of bone, joints and soft tissue

Arthritis and rheumatism

Osteomyelitis and other diseases of bone and joint

Other diseases of musculoskeletal system

Injuries and violence

Injuries

Adverse effects of pharmaceuticals

Toxic effects of other substances

Complications of surgical procedures and medical care

Note: The following chapters in ICD-8 were not included in the analyses: Chap. 5 (Psychiatric diseases), Chap. 11 (Diseases in pregnancy, during birth and perinatal diseases), Chap. 14 (Congenital malformations), Chap. 15 (Certain causes of diseases in the perinatal period and death due to this), Chap. 16 (Symptoms and ill-defined conditions), Chap. 18 (External cause of accident). Also, diseases with the following ICD-10 kodes were not included in the analyses: C97: Cancer arisen independently at several locations, D37-D48: Neoplasms of unknown character, E65-E68: Obesity (ICD-8: 277 and ICD-9: 278).