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

<table>
<thead>
<tr>
<th>Country</th>
<th>Recruitment period</th>
<th>Population recruited</th>
<th>Follow-up period</th>
<th>Study population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Cancer survivors⁹</td>
<td>Population comparisons</td>
<td>Survivors⁹</td>
</tr>
<tr>
<td>Finland</td>
<td>1953–2008</td>
<td>9 147</td>
<td>45 665</td>
<td>1983–2009</td>
</tr>
<tr>
<td>Norway</td>
<td>1953–2008</td>
<td>9 127</td>
<td>45 443</td>
<td>2008–2010</td>
</tr>
<tr>
<td>All countries</td>
<td>NA</td>
<td>43 909</td>
<td>219 131</td>
<td>NA</td>
</tr>
</tbody>
</table>

⁹ Survivors of childhood cancer diagnosed in recruitment period and alive at the start of national population registration

³ Period for which outcome data were available from the hospital registries

⁸ One-year survivors alive at start of follow-up period

⁸ 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. 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


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).

<table>
<thead>
<tr>
<th>Sex</th>
<th>Attained age (years)</th>
<th>Time since cancer diagnosis (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Both</td>
<td>20–29</td>
<td>5–9</td>
</tr>
<tr>
<td>Men</td>
<td>30–39</td>
<td>10–19</td>
</tr>
<tr>
<td>Women</td>
<td>40–49</td>
<td>20–29</td>
</tr>
<tr>
<td></td>
<td>50–59</td>
<td>30–39</td>
</tr>
<tr>
<td></td>
<td>60–69</td>
<td>40–49</td>
</tr>
<tr>
<td></td>
<td>70–79</td>
<td>50–59</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>No. of 5-year cancer survivors</th>
<th>No of hospitalizations&lt;sup&gt;a&lt;/sup&gt;</th>
<th>RR (95% CI)</th>
<th>AER&lt;sup&gt;c&lt;/sup&gt; (95% CI)</th>
<th>Observed no of bed days</th>
<th>SBDR&lt;sup&gt;d&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Observed</td>
<td>Expected</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

<sup>a</sup> Hospitalizations for selected diseases; see Material and methods for details.

<sup>b</sup> Per 100,000 person-years

<sup>c</sup> Absolute excess risk per 100,000 person-years

<sup>d</sup> 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.

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>Obs, RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cancer survivors</td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td></td>
</tr>
<tr>
<td>Lymphoma</td>
<td></td>
</tr>
<tr>
<td>CNS</td>
<td></td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td></td>
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<tr>
<td>Retinoblastoma</td>
<td></td>
</tr>
<tr>
<td>Renal tumors</td>
<td></td>
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<tr>
<td>Hepatic tumors</td>
<td></td>
</tr>
<tr>
<td>Bone tumors</td>
<td></td>
</tr>
<tr>
<td>Soft tissue sarcomas</td>
<td></td>
</tr>
<tr>
<td>Germ cell neoplasms</td>
<td></td>
</tr>
<tr>
<td>Carcinomas</td>
<td></td>
</tr>
<tr>
<td>Other and unspec.</td>
<td></td>
</tr>
</tbody>
</table>

1.0  1.5  2.0  2.5  3.0  RR (95% CI)
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.

<table>
<thead>
<tr>
<th>Main Diagnostic Group</th>
<th>Obs. AR (95% CI)</th>
<th>Survivors at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lymphoid and blood forming organs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemia and myelodysplasia</td>
<td></td>
<td></td>
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<tr>
<td>Malignant lymphomas</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney cancer, extrarenal renal and other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease of respiratory system</td>
<td></td>
<td></td>
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<tr>
<td>Digestive system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease of nervous system and sense organs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease of skin and subcutaneous tissue</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease of genital organs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease of ear and mastoid process</td>
<td></td>
<td></td>
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<tr>
<td>Disease of female reproductive organs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease of male reproductive organs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease of bone and cartilage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injuries and violence*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*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

<table>
<thead>
<tr>
<th>Main diagnostic group</th>
<th>Disease category</th>
<th>No. of hospitalizations</th>
<th>RR (95% CI)</th>
<th>AER (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Observed</td>
<td>Expected</td>
<td></td>
</tr>
<tr>
<td>Total no. of hospitalizations</td>
<td>xx,xxx</td>
<td>xx,xxx</td>
<td>x.x (x.x to x.x)</td>
<td>x,xxx (x,xxx to x,xxx)</td>
</tr>
</tbody>
</table>

**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
- Syphilis and other venereal 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 parts 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 hypofunction
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
Cataract
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 abdominal 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).