Late effects of childhood cancer: Epidemiology and patient education
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Chapter 1

General introduction and outline of the thesis
This thesis addresses long-term survivorship after childhood cancer. More specifically, we investigated two topics in relation to childhood cancer survivors: epidemiology of two specific late effects of childhood cancer and patient education. The first topic, epidemiology of late effects, was investigated in the context of the cohort of childhood cancer survivors of the Emma's Children Hospital/Academic Medical Center Amsterdam (EKZ/AMC), whereas patient education was investigated in the context of the Dutch Childhood Oncology Group (DCOG) Late Effects of Childhood Cancer (DCOG LATER) project. In this chapter we will introduce both research topics and provide relevant background information about the EKZ/AMC cohort as well as the DCOG LATER project. The chapter concludes with the research questions of this thesis and an outline of the remaining chapters.

**Childhood cancer: incidence and survival**

In Western countries, the age-standardized incidence rate of childhood cancer ranges between 121 and 160 cases per million person-years.\(^1\) In 2010, 598 invasive tumours were diagnosed in Dutch children aged 0-17 years.\(^2\) Tumours of the central nervous system (26%), leukaemia (23%, predominantly acute lymphoblastic leukaemia) and lymphoma (12%) were the diagnoses with the highest incidence.\(^2\)

The survival rates of children with a paediatric malignancy have increased dramatically over the last 50 years.\(^3\) In the 1960s only 30% of childhood cancer patients survived more than five years, whereas nowadays five-year survival reaches 80%.\(^4\) The use of combination- and adjuvant chemotherapy in multimodal treatment strategies and improvements in diagnostic procedures, surgery, radiotherapy and supportive care all contributed to the rise in survival rates.\(^5\) The increase in survival rates resulted in the emergence of a new group of individuals/patients: childhood cancer survivors. It is estimated that approximately 1 in every 600 individuals aged between 20 and 39 is currently a survivor of a paediatric tumour and it sure that this number will continue to rise, as is illustrated in Figure 1.\(^6\)
Mortality and morbidity in childhood cancer survivors

As the number of childhood cancer survivors steadily grew, it became apparent that five-year survival was by no means the end-point for the majority of survivors. These long-term survivors are still at risk of life-threatening late effects of their malignancy or its treatment, including second malignancies, late recurrence of the primary tumour and toxicity to major organ systems. In the EKZ/AMC cohort described below, Cardous-Ubbink et al showed that the standardized mortality rate (SMR) was 17-fold increased for survivors in comparison to the general population. Slightly lower SMR’s of 10.7 and 8.4 were reported by respectively the British Childhood Cancer Survivor Study Group (BCCSSG) and the Childhood Cancer Survivor Study (CCSS, United States of America). Recurrence of the primary tumour is the main cause of death in survivors, with cumulative mortality due to recurrence increasing rapidly with time from diagnosis up to 8.9% 15 years after diagnosis, but then levelling off to 12.4% 50 years after diagnosis (Figure 2). As the cumulative mortality due to recurrence levels off in this 35 year period, the cumulative mortality due to second malignancies, cardiac and...
Figure 2. Cumulative mortality of causes of death among survivors of childhood cancer - Reulen et al. JAMA. 2010;304(2):172-179.

Figure 3. Cumulative mortality due to recurrence of cancer, second malignancy, cardiac disease, pulmonary disease, external causes, and all other causes - Mertens et al. J Natl Cancer Inst 2008;100:1368-1379.
pulmonary disease (Figure 3) and other causes increases continuously.\textsuperscript{8,9}

Besides increased mortality, the improved prognosis for children with cancer has also been accompanied by a rising incidence of treatment-related morbidity, often referred to as late effects. These clinical and sub-clinical late effects of cancer treatment can severely impair quality of life, cause chronic disease and ultimately reduce the life expectancy of childhood cancer survivors. The prevalence of late morbidity is very high: in the EKZ/AMC cohort approximately 75\% of all 5-year survivors has had at least one adverse event and 25\% had 5 or more adverse events.\textsuperscript{10} Furthermore 40\% suffered from at least one severe or life-threatening adverse event as defined by the Common Terminology Criteria for Adverse Events version 3.0 (CTCAEv3). As with the mortality statistics, the American CCSS study reported slightly lower numbers: 62\% of the CCSS population had at least 1 chronic condition and 28\% had a severe or life-threatening condition.\textsuperscript{11}

**Late effects affecting the kidney**

One of the potential adverse effects of a range of anti-cancer treatments is nephrotoxicity. Nephrotoxicity is the development of kidney damage after exposure to specific types of chemotherapy, radiation or kidney surgery. Acute nephrotoxicity can be a dose-limiting factor for several types of anti-cancer treatment and can even contraindicate potentially curative treatment, reducing the ability to deliver optimal care and the chance on survival.\textsuperscript{12} Chronic or late nephrotoxicity may result in a variety of functional consequences, including impairment of glomerular function, tubular function, blood pressure control and renal endocrine function.\textsuperscript{13} Most of the available evidence on long-term renal dysfunction after childhood cancer was gathered in cohorts of patients treated with specific nephrotoxic treatments, often with short or incomplete follow-up.\textsuperscript{13,14} The prevalence of and risk factors for long-term nephrotoxicity remain unclear for childhood cancer survivors. In **Chapters 2 to 4** we present a Cochrane systematic review on late nephrotoxicity after childhood cancer and two studies on nephrotoxicity in the EKZ/AMC cohort of childhood cancer survivors.
Impact of childhood cancer treatment on final height

Another potential late effect of childhood cancer treatment is growth impairment, resulting in a reduced final height in adulthood. Growth impairment can negatively impact quality of life, for example by hampering the social development of these survivors, who often already feel different from their peers due to other late effects. Although it is already known that skeletal growth can be influenced directly by radiotherapy or indirectly by damage to the hypothalamic-pituitary axis, evidence on the influence of chemotherapy and constitutional factors like height at diagnosis remains unclear. In Chapter 5 we assessed the prevalence for short stature in the EKZ/AMC cohort of childhood cancer survivors and analysed risk factors including type of chemotherapy, radiotherapy and height at diagnosis.

Patient education in relation to late effects

As became clear in the previous paragraphs, survivors have a significantly increased risk for chronic health conditions and late adverse effects. However, many (adult) childhood cancer survivors are unaware of the details of their previous disease, the treatment they received and especially the increased risk of late complications due to the therapy. This is a logical consequence of several factors intrinsic to the disease. Due to the young age at diagnosis, it is often the parents who give consent for treatment and hence receive all relevant information needed for decision making. During the aging process of both child and parents this information may be forgotten or may not be passed on from parent to child either consciously or unconsciously. Unlike survivors of a malignancy in adulthood, childhood cancer survivors often have limited or no access to their old medical records regarding their malignancy and treatment. Also, as families move, medical records can get lost, replaced or mislabeled and may not be easily retrievable when needed. In addition, several other factors can contribute to survivors’ lack of knowledge of their previous disease, treatment and the risk for late effects.
These knowledge deficits in survivors may hamper their ability to seek appropriate care and to participate in designated follow-up programs such as the EKZ/AMC outpatient clinic. An additional health risk for CCS is that, due to low incidences of childhood cancer, health care providers are usually not familiar with cancer-related health risks and late effects. Hereby the first symptoms of cancer treatment-related late effects can easily be missed.

To fill the knowledge gap that can arise in CCS, an online information source seems an appropriate medium in the 21st century. Chapters 6 to 8 present the information needs assessment, development and evaluation of a patient information website aimed at childhood cancer survivors and their family.

Introducing the research contexts

The research projects described in this thesis regarding the prevalence and risk factors of late effects of childhood cancer were performed in the context of the EKZ/AMC cohort of childhood cancer survivors. The DCOG LATER project constituted the research projects related to patient information needs and patient education. Both overarching research projects are described briefly below.

The EKZ/AMC cohort of childhood cancer survivors

In 1996 the EKZ/AMC childhood cancer survivor study was started to investigate late effects of cancer treatment in long-term survivors of childhood cancer and to define associated risk factors. Rationale for the study was that the acquired knowledge could be used to ameliorate the quality of life of survivors, for example by the development of less toxic treatment protocols, by raising awareness about late effects amongst health care professionals and survivors and by providing a basis for intervention research for secondary prevention and/or treatment of late effects.

The EKZ/AMC childhood cancer survivor cohort is an on-going single-centre cohort study of patients who survived at least 5 years since their primary cancer diagnosis. New survivors enter the study continuously and are identified through
the hospital based childhood cancer registry which was established in 1966. All childhood cancer patients who have been treated in the EKZ/AMC since then were prospectively included, with detailed information regarding diagnosis, treatment, recurrences and vital status. Since 1996 also data on medical follow-up are prospectively collected and registered of all patients who survived at least five years since their primary cancer diagnosis.

To be eligible for inclusion in the EKZ/AMC childhood cancer survivor cohort, patients have to meet the following criteria: (1) diagnosed and treated for a primary malignancy; (2) diagnosed from January 1, 1966 onwards; (3) aged <18 years at diagnosis; (4) diagnosed in the Netherlands; (5) treated primarily in the EKZ/AMC; and (6) survived ≥5 years after diagnosis, regardless of disease or treatment status. It is important to realize that the EKZ/AMC cohort is a dynamic cohort: due to continuous data updates (e.g. regarding mortality, [revised] diagnoses, and treatment characteristics) and inclusion of new survivors, the total number of survivors included in studies within the cohort varies, depending on the study date.

Synchronous with the start of inclusion of patients in the EKZ/AMC cohort, a late effects outpatient clinic was started in 1996 [Polikliniek Late Effecten Kindertumoren (PLEK/LATER)]. The outpatient clinic offers medical follow-up for the assessment of late adverse effects of childhood cancer treatment in 5-year survivors and follow-up care. Great efforts are put into the tracing of 5-year survivors, which are invited to the outpatient clinic on a regular basis. Adult survivors are seen by an adult physician, whereas children [<18 years] are seen by their paediatric oncologist. A full medical assessment is performed according to standardized follow-up protocols based on the previous treatment modalities. This includes a medical history, a physical examination, additional risk-based diagnostic tests and counselling. Survivors are seen at regular intervals, based on their previous cancer diagnosis and [expected risk for] late effects. For survivors who are eligible and alive, but who do not visit the late-effects outpatient clinic, regular attempts are made to obtain medical follow-up data from other physicians who do see these patients.
The Dutch Childhood Oncology Group LATER project (DCOG LATER)

In the early 2000’s Dutch paediatric oncologists, gathered in the DCOG, created a national, multidisciplinary task force [LAnge TERmijneffecten na kinderkanker (LATER)] in cooperation with radiation oncologists, internists, general practitioners, psychologists, other involved specialisms, the Dutch Childhood Cancer Parents Organisation (DCCPO) and insurances companies. The goal of DCOG LATER is to improve care for survivors of childhood cancer by national and multidisciplinary cooperation regarding [organisation of] patient care, systematic and structured data registry, scientific research and patient education. To improve the quality of screening and to ensure that survivors are screened in a uniform and systematic manner, national evidence-based guidelines were developed, published and implemented in 2010. In March 2013 a large research project [DCOG LATER Q2008] will start wherein the complete cohort of Dutch childhood cancer survivors (N=6384) will be invited for a full assessment of (a)symptomatic health problems.

Aims and outline of the thesis

Based on the existing knowledge as presented in this introduction (Chapter 1), we identified gaps in knowledge and formulated research questions to address them. The answers to these research questions are presented in this thesis. The general aim of this thesis is two-fold: 1) to assess prevalence and risk factors of two specific late effects of childhood cancer: renal toxicity and short stature in adulthood, and 2) to investigate the methodology for the development and evaluation of patient information websites, in this case aimed on long-term survivors of childhood cancer.

Part 1: epidemiology of late effects of childhood cancer

In Chapter 2, we present the results of a Cochrane systematic review on the prevalence and risk factors for renal toxicity in childhood cancer survivors treated with cisplatin, carboplatin, ifosfamide, nephrectomy or irradiation on the kidney
region.

**Chapter 3** continues with renal function, presenting a cross-sectional cohort study on glomerular and tubular function as well elevated blood pressure in the EKZ/AMC cohort of childhood cancer survivors.

In **Chapter 4**, we investigated trends of glomerular function over time and assessed risk factors associated with glomerular function over time.

**Chapter 5** reports on the prevalence of short stature in adult survivors of childhood cancer and its associated risk factors.

**Part 2: methods for the development and evaluation of a patient information website for childhood cancer survivors**

In **Chapter 6**, we present an assessment of the health information needs of childhood cancer survivors and their family based on a questionnaire evaluation.

In **Chapter 7**, a concise and practical framework is described for the development and evaluation of specific patient information websites, aiming at high usability and low costs. The implementation of the framework is described in a case study on the development and evaluation of a website for childhood cancer survivors.

In **Chapter 8**, we evaluate the usability and content of the website for childhood cancer survivors that we developed during the studies presented in Chapters 6 and 7.

Finally, **Chapter 9** covers the general discussion, where the conclusions, recommendations for clinical practice and recommendations for future research are discussed. This thesis concludes with a summary in both English and Dutch.

**References**

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