Long-term excess mortality and morbidity following treatment of childhood cancer

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General Introduction

GENERAL INTRODUCTION

The studies described in this thesis deal with the long-term adverse effects of childhood cancer survivors. As a general introduction, this chapter begins with a short review of relevant background information. First some epidemiological aspects of paediatric oncology and the risks of long-term adverse effects are discussed. Next, some information will be given about the long-term follow-clinic in the Emma Children's Hospital/ Academic Medical Centre (EKZ/AMC), where childhood cancer survivors are regularly screened. Furthermore, some methodological considerations are described. Finally, the outline of this thesis is given.

EPIDEMIOLOGICAL ASPECTS OF CHILDHOOD CANCER

Incidence of childhood cancer

Paediatric and adolescent cancers account for only a small proportion of the world-wide cancer burden (1). Approximately 480 children (age 0-14 years) with cancer are registered annually by the Netherlands Cancer Registry, leading to an age-standardised annual incidence rate (ASR) of 140.3 per million (95% CI 134.9-145.6) (2;3).
The characteristics of malignant tumours in childhood differ greatly from those in adults, not only with regard to the affected sites but also with regard to histology. Table 1.1 shows the distribution by morphological type of cancer among children aged 0-14 years.

Table 1.1: Distribution of the different childhood cancer diagnoses in children aged 0-14 years (Source: the Netherlands Cancer Registry 2006; www.ikcnet.nl)

Diagnosis	Total N	Boys N	Girls N
Leukaemia	136	73	63
Brain/ CNS tumour	89	49	40
Lymphoma	58	35	23
Soft tissue tumour	39	18	21
Nephroblastoma	31	16	15
Bone tumour	26	14	12
Neuroblastoma	25	13	12
Carcinomas	18	12	6
Other (like retinoblastoma, germ cell tumours, hepatic tumours)	40	27	13
Total	462	257	205

Leukaemia (predominantly acute lymphoblastic leukaemia), brain and central nervous system tumours and lymphoma are the most common cancers in children. Diagnoses of childhood cancer are not equally common in both sexes, for example leukaemias and lymphomas occur more often in boys. Figure 1.1 shows the European age-specific cancer

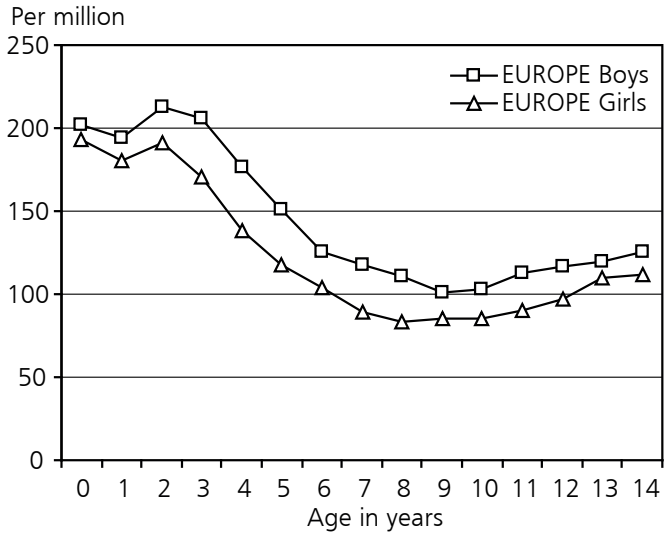

Figure 1.1: Age-specific cancer incidence among children in Europe as a whole by single year of age, separately for boys and girls, 1988–1997. Source: ACCIS (Automated Childhood Cancer Information System (3)).

incidence among children separately for boys and girls (3). The data used are form the Automated Childhood Cancer Information System (ACCIS); a collaborative project of the European cancer registries, aiming at collection, analysis, interpretation, and dissemination of data on cancer incidence and survival of children and adolescents in Europe. The ACCIS database contains data from some 80 population-based cancer registries, which cover about 50% of the European population aged 0-14 years, living in the 35 participating countries, including the Netherlands (4). It is well known that there are only small differences in childhood cancer incidence between the different European countries.

The age-specific incidence curves varies between diagnostic groups (5). There is a peak in incidence in the age groups younger than 5 years of age for many of the childhood cancers (i.e. leukaemias, tumours of the central nervous system, neuroblastoma, retinoblastoma, Wilms` tumour and hepatoblastoma) and an increasing incidence with age in others (i.e. Hodgkin´s lymphoma, bone tumours, thyroid cancer and melanoma) (6).

Survival of childhood cancer

The overall survival of childhood cancer survivors improved dramatically over the last decades. Where in the late sixties only 30% of childhood cancer patients survived five or more years; the survival is nowadays around 75% for patients aged 0-14 years (2;7-10). The improved survival rates are reflected in decreasing mortality rates of childhood cancer. Figure 1.2 shows improved survival rates for different diagnosis in Europe, based on ACCIS data (11). Unfortunately, there are no more recent European data available.

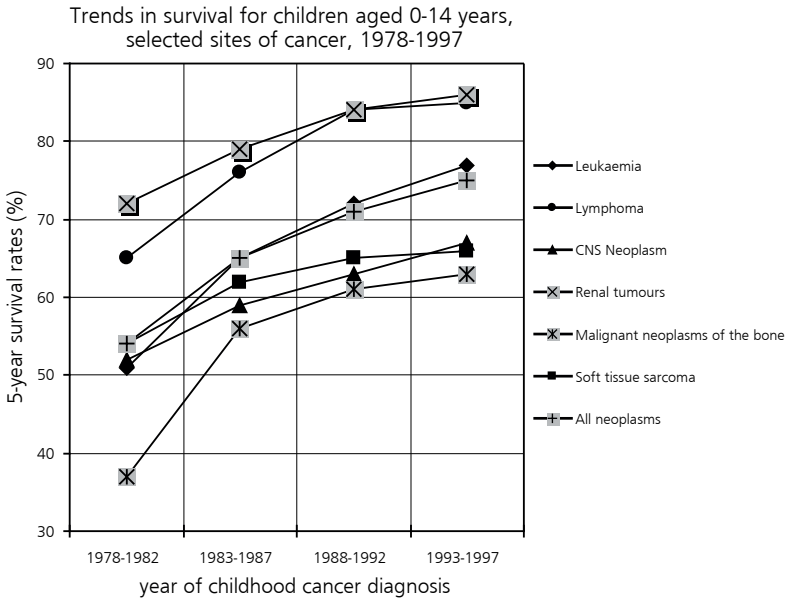

Figure 1.2: Trends in 5-year survival for children under age of 15. Source: ACCIS (Automated Childhood Cancer Information System) (11)

Figure 1.3 shows the relative survival of childhood cancer in the IKA-region in the Netherlands, which is the area covering the provinces of Noord-Holland and Flevoland, according to year of diagnosis. In the most recent time period the survival is still improving. Not all regional cancer registries collect follow-up data and therefore national data are not available. However, the IKA-region is a large region in the Netherlands with reliable data.

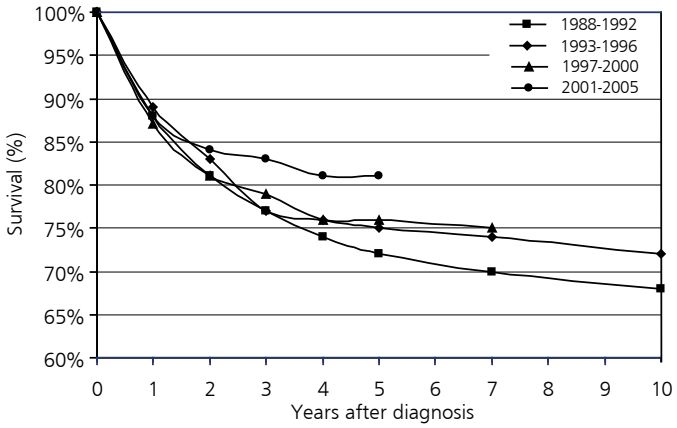

Figure 1.3: Relative survival of childhood cancer (in children 0-14 years) in the IKA region in the Netherlands (Province of Noord-Holland and Flevoland), according to year of diagnosis (Source: www.ikcnet.nl)

As shown in the figures above, the introduction of more effective treatment modalities for childhood cancer from the 1970s onwards, has dramatically improved survival rates, implying that childhood cancer survivors are a rapidly growing group of young adults (3;12;13). Due to the excellent survival rates this yields an estimated prevalence (at June 1st 2008) of more than 6000 childhood cancer survivors aged 0-17 years at time of diagnosis (diagnosed between 1960 and 2003) in the Netherlands.

Long-term adverse effects

Unfortunately, improved prognosis has been accompanied by a rising incidence of treatment-related complications. These long-term adverse effects are often referred to as early or late. Early adverse effects occur within days to weeks of treatment, of which some will become chronic. Adverse effects that occur one or more years later are usually called long-term adverse effects. Adverse effects can occur after any type of treatment, including surgery, chemotherapy and radiotherapy. The severity of the treatment complications depends on the type of cancer treated, the location of the disease, the age of the child at time of treatment, and the treatment modality and intensity of the treatment. Long-term adverse effects may manifest themselves in different ways, like (1) clinically obvious effects, (2) clinically subtle effects noticeable to the trained observer and (3) subclinical effects detectable only by laboratory screening or medical imaging techniques.

Already in 1975 Meadows et al published an article of long-term adverse effects of cancer treatment in children (14). Since then numerous articles have been published of all kinds of long-term adverse effects (15-19). These effects include second neoplasms (20-22), organ dysfunction (23-26), endocrine and metabolic disorders (27-29), orthopaedic problems (30), and psychosocial and cognitive problems (31-33). These late effects may adversely affect the quality of life of survivors and predispose them to early morbidity and mortality (15;34).

Recently, Oeffinger and colleagues (15) described an overview of the incidence and severity of long-term chronic health conditions in the Childhood Cancer Survivor Study in the United States (US), a multi-institutional, retrospectively ascertained cohort of adults who have survived for at least 5 years after treatment of childhood cancer. Survivors were diagnosed in one of the 26 collaborating institutions, between 1970 and 1986, and had an age less than 21 years at diagnosis. The occurrence of adverse events in this study was compared with siblings. Frequencies of chronic health problems were calculated for 10397 adult survivors and 3034 siblings. After a median follow-up of 26.6 years 62.3% had at least one chronic health condition and 27.5% had a severe or life-threatening condition. Survivors were 3.3 times as likely as their siblings to have a chronic health condition (95% Confidence Interval (CI): 3.0-3.5); for a severe or life-threatening condition, the risk was 8.2 (95% CI: 6.9-9.7). Among survivors, the cumulative incidence of a chronic health condition reached 73.4% 30 years after the primary cancer diagnosis.

Limitations of this study include the incomplete follow-up for 30 % of the survivors and the fact that the information of adverse events was based on self-reported health outcomes in questionnaires.
In 2008, Mertens et al (34) reported on cause-specific late mortality among 5-year survivors of childhood cancer in the same Childhood Cancer Survivor Study cohort as described in the study by Oeffinger and collaborators. In the cohort of 20483 childhood cancer survivors, 2821 (13.8%) 5-year survivors had died by the end of the follow-up period (December 31, 2002). The cause of death was obtained for 2534 individuals, with 57.5% of deaths attributed to recurrent disease. The overall Standardised Mortality Ratio (SMR) was 8.4 (95%CI: 8.0-8.7) compared to the US population. The absolute excess risk of death from any cause was 7.4 deaths per 1000 person-years. Increases in cause-specific mortality were mainly seen for deaths due to subsequent malignancy (SMR = 15.2; 95% CI: 13.9-16.6), cardiac causes (SMR = 7.0; 95% CI: 5.9-8.2), and pulmonary causes (SMR = 8.8; 95% CI: 6.8-11.2). Twenty-five years after first cancer diagnosis, the death rate due to a subsequent malignancy exceeded that due to all other causes. This study with extended follow-up indicates that excess mortality persists long after diagnosis.
All anti-cancer treatment regimens can cause long-term adverse effects (35). Radiotherapy can, for example, cause second malignant neoplasms in previously irradiated fields, reduced growth of bones and muscles in the irradiated area (especially in the youngest children), vascular damage in the arteries or veins, and hearing loss. Some chemotherapeutic agents can, for example, lead to pulmonary dysfunction, reduced kidney function and infertility, and especially anthracyclines can cause cardiac dysfunction. Mobility problems are direct consequences of amputation, but infertility, pulmonary dysfunction and hypertension can also be caused by surgery.

Long-term follow-up clinic

Due to insight into the large number of potential long-term effects occurring in childhood cancer survivors, follow-up care is becoming more important and uniformly recognized. Early detection of (sub)clinical adverse events makes it possible to take preventive measures or to treat adverse effects. In the last decades in the United States, United Kingdom and the Nordic Countries nationwide initiatives also started to identify five-year survivors of childhood cancer (36-41). In these countries research was initiated into the magnitude of the burden from late effects in long-term survivors and identification of treatment-related risk factors. Since the 1980s more and more paediatric oncology centres have developed programs designed specifically for childhood cancer survivors (42). But only few paediatric institutions have provisions for follow-up into the adult years (43).
In the Netherlands the EKZ/AMC identified their childhood cancer survivor population using the Childhood Cancer Registry of the EKZ/AMC started in 1966. Therefore, in 1996, the Emma Children's Hospital Academic Medical Center in Amsterdam established

an outpatient clinic (PLEK EKZ/AMC) for the assessment of long-term adverse effects of childhood cancer treatment. Already 1080 childhood cancer survivors visited PLEK EKZ/AMC.

AIM OF THE THESIS

It is increasingly important to evaluate to which extent the occurrence of long-term complications affects (the quality of) the long-term survival of childhood cancer patients (44;45). Most studies in the past focused only on one type of adverse event and the majority of the studies examined late effects after one specific childhood cancer diagnosis. Our cohort is, as far as we know, one of the first cohorts worldwide determining the total burden of adverse health outcomes in a complete cohort including all childhood cancer diagnoses.
Therefore, the aim of the studies described in this thesis "Long-term excess mortality and morbidity following treatment of childhood cancer" is to explore the frequency of and risk factors for long-term adverse effects after treatment for childhood cancer. The study population consists of survivors who had a follow-up of at least five years after diagnosis of the initial childhood cancer.

Description of relevant methodology

Study designs

Several epidemiologic study designs are appropriate to evaluate the risk of long-term adverse effects among childhood cancer survivors. Two commonly used observational designs, cohort studies and case-control studies, have both been used in the studies described in this thesis. Three out of 4 studies were cohort studies; the fourth study was a nested case-control study within the cohort.
A cohort is a group of individuals with a common characteristic, such as childhood cancer in our cohort, within a defined period. The occurrence of disease in the cohort (incidence, mortality) can be compared with a reference population, such as the general population. However, an internal comparison of disease occurrence between different subgroups within the cohort can also be made.
Defining our cohort could be done efficiently and validly, because there is a hospital-based childhood cancer registry in the EKZ/AMC. The registry could be used to retrospectively define the cohort of all 5-year survivors who had been treated for childhood cancer in the past. The registry already exists from 1966 onwards and contains detailed information regarding patient characteristics, the primary diagnosis including all primary treatments, and second malignancies. The inclusion criteria of our cohort were accurately defined:

- Age of childhood cancer below 18 years;
- Calendar period of diagnosis between 1966 and 1996;

- Diagnosed and treated in the EKZ/AMC in Amsterdam, the Netherlands;
- Survived at least 5 year after diagnosis.

Subsequently, data were extracted regarding patient, tumour and treatment characteristics, like dates of birth and diagnosis, treatment details and other risk factors for long-term adverse effects. Missing data regarding patient and treatment characteristics as well as missing follow-up data were completed by tracing the medical records or approaching patients' general practitioners or other treating physicians, or by checking the most recent address at the municipal registries if patient was still alive.

Finally, the cohort consisted of 1362 childhood cancer survivors, of whom 1080 visited PLEK EKZ/AMC. The median follow-up of the cohort was 17 years with a median attained age of 24 years at end of follow-up. The medical follow-up was complete for more than 94%.

The advantages of our cohort are the very long-term follow-up and the high level of completeness of follow-up, and the fact that survivors underwent a medical assessment by our own physicians using standardized follow-up protocols based on previous treatments.

Case-control studies are used to identify risk factors for a medical condition by comparing subjects who have the disease of interest ('cases') with patients who do not have this disease ('controls') (46). Ideally, cases and controls should be selected from the same source population to prevent selection bias, i.e. to be certain that when an increased risk is observed, this can be attributed to the treatment. A nested case-control study is a study design where cases and controls are derived from the same cohort ("nested"). Compared with a case-control study, a nested case-control study strongly reduces selection bias, and compared with a cohort study, a nested case-control study can reduce cost and save time. The data collection for case-control studies is less labour-intensive compared to cohort studies, because for fewer records data need to be collected. For the selected records, however, more detailed data need to be collected, which is much more efficient than detailed data collection for the full cohort.

Our fourth study was a nested case-control study within the cohort of childhood cancer survivors. In our case-control study, survivors who developed hypertension are the so-called cases, whereas survivors who did not develop hypertension are selected as controls. In our nested case-control study, cases and controls are derived from the same childhood cancer cohort. Controls are matched to the cases with regard to sex, age and year of diagnosis, and Wilms' - non Wilms'; in addition it was required that controls had not developed the event of interest after a follow-up duration at least as long as the interval between childhood cancer diagnosis and hypertension in the corresponding case. The matching procedure ensures a similar distribution among cases and controls of important characteristics which could distort the association between the exposure and the event of interest (confounding factors).

Measures of disease occurrence

In our studies several outcome measures are used, like incidence, prevalence and mortality. Incidence refers to new cases of disease occurring among previously unaffected individuals (47). The incidence rate is defined as the incidence per total number of person-years of observation among those who have not yet developed the disease. Unlike incidence measures, which focus on new events in a well- defined time span, prevalence focuses on the disease status, and may be defined as the proportion of a population that has the disease of interest at a cross-sectional point in time (48). Mortality is a specific type of incidence.

OUTLINE OF THE THESIS

After this general introduction (Chapter 1), chapter 2 report the results of the overall assessment of long-term adverse effects in our cohort of long-term childhood cancer survivors. In this study we assessed the total burden of adverse events in our cohort, and determined treatment-related risk factors for the development of various long-term adverse events. Childhood cancer survivors are known to be at increased risk for second malignancies. Only a few studies examined treatment-specific risk over extended follow-up periods. In chapter 3 we report on long-term second cancer risk in our 5-year survivors of childhood cancer and the treatment-related risk factors. Chapter 4 describes the very long-term overall and cause-specific mortality in our study cohort. In chapter 5 we report on our case-control study of hypertension. In this study we identified treatment-related risk factors for hypertension. Finally, in the general discussion (Chapter 6) main conclusions, methodological and theoretical reflections, implications for clinical practice and recommendations for future research are described. A summary in both English and Dutch concludes this thesis.

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