CHAPTER 1

Introduction and outline of the thesis
CHILDHOOD CANCER

In the Netherlands (17 million population), approximately 550 children under the age of 19 years are diagnosed with cancer annually. Childhood cancer represents only a very small proportion (0.5%) of the total annual cancer incidence. Leukemias (30%) are the most frequently occurring type of childhood cancer, followed by tumors of the central nervous system (21%), and lymphomas (15%) (Figure 1).

FIGURE 1. Number of childhood cancer diagnoses in 2015 in the Netherlands, by tumor subtype

The introduction of multi-agent chemotherapy treatment and improvements in radiotherapy techniques have led to major improvements in survival of childhood cancer over the last decades. Overall five-year survival rates of childhood cancer are around 80% in developed countries nowadays (Figure 2), but survival rates differ between childhood cancer types. For example, childhood leukemia carried a very poor prognosis in the beginning of the 1970s (five-year survival around 30%), but five-year survival has improved to about 90% for those diagnosed in 2006-2010 (Figure 3). Although survival of childhood cancer has improved substantially, it is still the leading cause of disease-related mortality among children in developed countries. In the Netherlands, we estimated that there were about 10,000 survivors of childhood cancer (initially diagnosed at age 0-14 years) on January 1, 2018, which is 0.09% of the population aged 0-50 years.

---

*a The prevalence was estimated by as follows: ([published estimated prevalence of childhood cancer survivors on January 2000 for those who were diagnosed in the period 1970-1999: 4,068] * ([estimated survival of this group in period 2000-2017: 0.90] + ([incidence of childhood cancer survivors who were diagnosed in the period 2000-2017: 7,526] * [estimated average survival probability in period 2000-2017: 0.80] = 9,682. The percentage of childhood cancer survivors from the total population 0-50 years was calculated by dividing the estimated number of survivors (N=9,682) by the population size in the age category 0-50 years (N=10,380,283).
FIGURE 2. Survival of childhood cancer patients (0-14 years) diagnosed 1971-2010 in Great Britain

FIGURE 3. Survival of childhood leukemia patients (0-14 years) diagnosed 1971-2010 in Great Britain
LONG-TERM ADVERSE HEALTH OUTCOMES

Patients who survive childhood cancer are at a substantial risk for long-term adverse health outcomes later in life. It has been estimated that at 45 years of age, 95.5% of survivors will have developed at least one chronic health condition and 80.5% will have developed a serious/disabling or life-threatening condition. Compared to their siblings, childhood cancer survivors face more chronic health conditions, have multiple chronic health conditions more often, and their health problems occur at an earlier age. Long-term adverse health outcomes can include both somatic disorders, such as subsequent malignant neoplasms, cardiovascular events, endocrine disorders, or organ dysfunctions, as well as psychological or cognitive disorders. The intensive treatments for childhood cancer, with radiotherapy, chemotherapy, surgery, and/or other therapy, are important contributors to this increased risk of long-term adverse health outcomes.

SUBSEQUENT NEOPLASMS

Subsequent malignant neoplasms (SMNs)
Subsequent malignant neoplasms are among the most serious adverse health events and are, after recurrence or progression of the childhood cancer, the largest contributor to late excess mortality. Previous studies have estimated that childhood cancer survivors are at a 3-6 fold increased risk of developing a subsequent malignant neoplasm compared to what is expected based on general population rates. The largest relative risks compared to the general population have been observed for sarcomas, CNS tumors, head and neck cancer, and thyroid cancer, while the largest absolute excess risks have been observed for cancers of the breast, CNS, and digestive organs. Leukemia risk is mainly increased in the first ten years after childhood cancer diagnosis. In contrast, absolute risk of solid cancer is minimally increased in the first ten years after diagnosis and remains to be elevated even decades after childhood cancer diagnosis.

Treatment-related risk factors SMN
Radiotherapy is a well-recognized and strong risk factor for subsequent malignant neoplasms. Among childhood cancer survivors, radiation dose-effect relationships have been established for various cancers, such as breast cancer, thyroid cancer, colorectal cancer, sarcoma, central nervous system tumors, and skin cancer. In survivors of adult cancers, dose-response relationships have also been shown for stomach cancer, esophageal cancer, pancreatic cancer, and lung cancer. Certain classes of chemotherapeutics are known risk factors for developing subsequent
leukemia, in particular, acute myeloid leukemia (AML). Alkylating agent-associated AML is characterized by an average latency of 5-7 years after treatment and usually presents first as a myelodysplastic syndrome. AML after topoisomerase II inhibitors (e.g. epipodophyllotoxins and anthracyclines) usually arises within 3 years after treatment and presents without a preleukemic phase. Before we initiated the research described in this thesis, not much was known about the role of specific chemotherapy agents in the etiology of subsequent solid cancers. Alkylating agents as a group had been associated with increased risks of sarcoma in childhood cancer survivors, lung cancer in Hodgkin lymphoma survivors, and stomach cancers in Hodgkin lymphoma and testicular cancer survivors. Anthracyclines had been suggested to increase sarcoma risk among childhood cancer survivors in one study. Only few studies had identified specific chemotherapeutic agents associated with solid cancer risk. Procarbazine was found to increase risk of stomach cancer in Hodgkin lymphoma and testicular cancer survivors and cyclophosphamide to increase bladder cancer risk in (young) adult cancer survivors.

Gastrointestinal cancer
In a French/UK cohort of 4,230 survivors of pediatric solid tumors, subsequent cancer of the gastrointestinal tract was found to be the leading cause of SMN-related mortality, accounting for almost 25% of all SMN-related deaths. In the general population and in high-risk populations with genetic predisposition syndromes, evidence-based screening and surveillance guidelines have been developed for colorectal cancer. More knowledge about risk factors for gastrointestinal cancer among childhood cancer survivors can help in identifying subgroups at high risk that might benefit from similar surveillance efforts.

Skin cancer
Skin cancers are the most common subsequent SMN among childhood cancer survivors. Basal cell carcinoma (BCC) is by far the most frequently occurring skin cancer among survivors. Although BCCs are highly curable, the cosmetic outcome can be disfiguring. Ascertainment of BCC and squamous cell carcinoma (SCC) in large cohorts has been difficult, because most cancer registries do not routinely register those skin cancers. Radiotherapy has been shown to be an important risk factor for BCC and a linear dose-response relationship has been established. Little is known about effects of chemotherapy agents on skin cancer risk.

Benign neoplasms
Although subsequent benign tumors are usually not life-threatening, their occurrence can have serious clinical consequences. For example, survivors who received cranial radiotherapy have an increased risk of developing subsequent meningiomas, which
can cause significant neurologic morbidity.\textsuperscript{57} Also, some benign tumors are precursors for subsequent malignant neoplasms. For example, in the general population, it is well known that most colorectal cancers develop through an adenoma-to-carcinoma sequence.\textsuperscript{59,60} Early detection and timely removal of premalignant lesions might prevent their progression to an invasive disease stage. So far, research on the risk of benign tumors in large cohorts of childhood cancer survivors has been difficult. Cancer registries usually do not collect information on benign tumors, with few exceptions, and thus linkage-based information on benign tumors can then not be retrieved.

**Survival of SMN**

Survival from SMNs might be different to survival from their equivalent first malignant (de novo) neoplasms (FMNs) for several reasons. Survival from SMNs may be better because of earlier detection due to general medical and/or cancer surveillance among survivors. However, it may be worse because of limited treatment options due to previous childhood cancer treatment or due to a higher frequency of other potentially lethal long-term chronic health conditions. Finally, differences in tumor characteristics of SMNs and FMNs, for example, due to a different pathogenesis between SMNs and FMNs, may lead either to a better or worse survival of SMNs compared to FMNs. Several studies have evaluated prognostic and clinical characteristics of solid SMNs among cancer survivors versus comparable FMNs in the general population.\textsuperscript{61-70} Only few studies have addressed whether a decreased survival was caused by a higher disease-specific mortality or due to higher mortality rates from other causes, such as late recurrences of childhood cancer or other long-term morbidities.\textsuperscript{65,67} Furthermore, only few focused on young cancer survivors initially treated in childhood or adolescence.\textsuperscript{63,65,68}

**DCOG-LATER COHORT**

In this thesis, we used data from the Dutch Childhood Cancer Oncology Group–Long-Term Effects After Childhood Cancer (DCOG-LATER) cohort. The DCOG-LATER study is a nationwide collaboration of the Dutch Childhood Oncology Group (DCOG) and all seven pediatric oncology and stem cell transplantation centers (Emma Children’s Hospital/Academic medical Center, VU University Medical Center, Willem-Alexander Children’s Hospital/Leiden University Medical Center, Sophia Children’s Hospital/Erasmus Medical Center, Beatrix Children’s Hospital/University Medical Center Groningen, Radboud University Medical Center Nijmegen, and Wilhelmina Children’s Hospital/University Medical Center Utrecht). The DCOG-LATER cohort includes childhood cancer patients who were diagnosed and/or treated in one of these seven centers between 1963 and 2002, before
the age of 18 years, and who survived at least 5 years post diagnosis. Eligible survivors were identified from prospective registries and from listings of pediatric patients with newly diagnosed cancer. For the period between 1963 and 1990 the cohort is clinic-based. However, most of the patients who were diagnosed with childhood cancer before the age of 16 years in this period in the Netherlands received treatment in one of the included clinics. For the period from 1990 onwards, the study population represents a nationwide complete cohort, except for lymphomas among 16-17 years olds treated in hematology departments, certain types of brain tumors treated by neurosurgeons, and thyroid cancer, treated by endocrinologists. The starting period varied by clinic (1963 to 1977) based on the completeness of the source. In total, 6,165 5-year childhood cancer survivors were included in the DCOG-LATER cohort. From these survivors, details on prior cancer diagnosis and treatment of primary tumor and all recurrences have been collected by trained data managers. For chemotherapy, this included details on start and end date, drug name, and cumulative dose. Radiotherapy details included prescribed dose, field, and boost/surdosage information. Data on other drugs and on hematopoietic cell transplantation (HCT) were also recorded.

**OBJECTIVE AND OUTLINE OF THIS THESIS**

The general objective of this thesis is to increase the knowledge on the risk of, risk factors for, and survival of subsequent neoplasms among long-term survivors of childhood cancer. More insight into the role of treatments is crucially important to identify those survivors who are at highest risks of developing subsequent neoplasms. This information can be used in developing more evidence-based surveillance recommendation for childhood cancer survivors. Chapter 2 describes the overall risk of subsequent malignant neoplasms in the nationwide DCOG-LATER cohort, thereby focusing on the role of specific chemotherapeutic agents on risk of solid subsequent malignant neoplasms. In chapter 3, we present results of a systematic review on the risk of subsequent gastrointestinal cancer in childhood cancer survivors. In chapter 4 we report on the risk of histologically confirmed colorectal adenomas and cancer in the DCOG-LATER cohort and in a sibling comparison group and evaluated the effects of specific childhood cancer treatments on adenoma risk. In chapter 5, we address the long-term risks of skin cancer in the DCOG-LATER cohort, with specific assessments of the effect of radiotherapy volume and dose and other treatment factors. Chapter 6 presents an overview of all benign subsequent neoplasms in the DCOG-LATER cohort and treatment-related risk factors for any benign subsequent neoplasm, fibroadenoma of the breast, and uterine myoma. In Chapter 7, we describe the independent and joint roles of cranial radiotherapy, age at treatment, and
exposed cranial volume on the risk of histologically confirmed meningioma in the DCOG-LATER cohort. **Chapter 8** describes the overall and cause-specific survival of selected subsequent malignant neoplasms in the DCOG-LATER cohort versus comparable samples of first malignant neoplasms in the general population. Finally, in **Chapter 9**, our main findings in this thesis are summarized, strengths and weaknesses are described, and implications for clinical practice and future research are discussed.
REFERENCES

1. Dutch Childhood Oncology Group (DCOG). Annual report 2016 [Jaarverslag 2016]. https://www.skion.nl/work-
   csr/1975_2015/, based on November 2017 SEER data submission, posted to the SEER web site, April 2018.
   Cancer Intelligence Network (NCIN) 2012.
   uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/bulletsins/childhoodinfantandperinatalmor-
   talityinenglandandwales/2016/pdf.
9. Signaleringssmissie Kanker, KWF Kankerbestrijding: Kanker in Nederland tot 2020: Trends en Prognoses. Ois-
   terwijk, the Netherlands, VDB Almedeon bv, 2011.
    &D1=0&D2=0&D3=0,101-110&D4=1&HDR=G3,T&STB=G1,G2&W=T.
13. Hudson MM, Ness KK, Gurney JG et al. Clinical ascertainment of health outcomes among adults treated for child-
16. Fidler MM, Reulen RC, Winter DL et al. Long term cause specific mortality among 34 489 five year survivors of
17. Garwicz S, Anderson H, Olsen JH et al. Late and very late mortality in 5-year survivors of childhood cancer: chang-
    ing pattern over four decades--experience from the Nordic countries. Int J Cancer 2012; 131: 1659-1666.
    childhood cancer. JAMA 2011; 305: 2311-2319.
20. Turcotte LM, Liu Q, Yasui Y et al. Temporal trends in treatment and subsequent neoplasm risk among 5-year sur-


39. Kleinerman RA, Smith SA, Holowaty E et al. Radiation dose and subsequent risk for stomach cancer in long-term survi...


58. Patterson BC, Chen Y, Sklar CA et al. Growth hormone exposure as a risk factor for the development of subse-


