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### Radiation-associated adverse events after childhood cancer

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# Chapter 2

The EKZ/AMC childhood cancer survivor cohort:  
methodology, clinical characteristics and data availability

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## Abstract

### Purpose

Childhood cancer survivors are at high risk of late adverse effects of cancer treatment, but there are still many gaps in evidence about these late effects. We described the methodology, clinical characteristics, data availability and outcomes of our cohort study of childhood cancer survivors.

### Methods

The Emma Children's Hospital/Academic Medical Center (EKZ/AMC) childhood cancer survivor cohort is an ongoing single-center cohort study of  $\geq 5$ -year childhood cancer survivors, which started in 1996 simultaneously with regular structured medical outcome assessments at our outpatient clinic.

### Results

From 1966 to 2003, 3183 eligible children received primary cancer treatment in the EKZ/AMC of which 1822 (57.2%) survived  $\geq 5$  years since diagnosis. Follow-up time ranged from 5.0-42.5 years (median, 17.7). Baseline primary cancer treatment characteristics were complete for 1781 (97.7%) survivors and 1452 (79.7%) survivors visited our outpatient clinic. Baseline characteristics of survivors who visited the clinic did not differ from those without follow-up. Within our cohort, 54 studies have been conducted studying a wide range of late treatment-related effects.

### Conclusions

The EKZ/AMC childhood cancer survivor cohort provides a strong structure for ongoing research on the late effects of childhood cancer treatment and will continuously contribute in reducing evidence gaps concerning risks and risk groups within this vulnerable population.

### Implications for Cancer Survivors

Our large cohort study of childhood cancer survivors with complete baseline characteristics and unique, long-term medical follow-up decreases gaps in evidence about specific risks of late effects and high-risk groups, with the ultimate goal of improving the quality of care for childhood cancer survivors.

## Introduction

More effective treatment strategies dramatically improved survival of childhood cancer.<sup>1</sup> In the 1960s only 30% of childhood cancer patients survived at least 5 years, while nowadays, 5-year survival reaches 80%.<sup>2</sup> However, it has now been widely acknowledged that childhood cancer survivors are at significant risk of treatment-related late adverse effects, causing mild to severe morbidity and increased mortality.<sup>3-7</sup> Although the evidence on the risks of late effects is expanding, there are still many gaps in evidence concerning the specific risks and associated risk factors, especially regarding the effects of aging of survivors, risks of more recent cancer treatments, and optimal follow-up that survivors should receive.

In 1996, our ongoing hospital-based cohort study in the Emma Children's Hospital/Academic Medical Center (EKZ/AMC) was started to investigate late effects of cancer treatment in long-term childhood cancer survivors and to define associated risk factors. Acquired knowledge may contribute to improvements in the quality of life of current and future childhood cancer survivors in different ways. First, it may lead to the development of less toxic treatment protocols for childhood cancer patients or possible preventive interventions in childhood cancer treatment trials. Second, it allows physicians involved in the care for childhood cancer survivors to be aware of specific health problems, to counsel survivors, to consult other physicians, and if possible, to start timely and appropriate treatment. Finally, it provides a basis for intervention research in childhood cancer survivors for secondary prevention and/or treatment of late effects.

Thus far, only a short summary of the methodology and baseline characteristics of our cohort study was published in the methods sections of several papers published by our research group. However, in order to give readers the opportunity to assess the strengths and limitations of our study design, it is essential to provide a complete overview of the methodology and baseline characteristics of a study.<sup>8</sup>

The objective of this paper was to describe the methodology, clinical characteristics, and data availability of our ongoing cohort study of childhood cancer survivors. In addition, we describe its unique features and potential biases. Finally, we provide an overview of results of the studies performed within our cohort.

## Methods

### Study methodology of the EKZ/AMC childhood cancer survivor cohort

#### *Patients and data collection*

The EKZ/AMC childhood cancer survivor cohort is an ongoing single-center cohort study of patients who survived at least 5 years since primary cancer diagnosis. New survivors enter the cohort continuously and are identified using our hospital-based EKZ/AMC Childhood Cancer Registry, established in 1966. All childhood cancer patients who have been treated in the

EKZ/AMC since then were prospectively included in the registry, with detailed information regarding diagnosis, treatment, recurrences, and vital status. Since 1996, information on medical follow-up of the patients who survived at least 5 years since primary cancer diagnosis are also prospectively collected and registered.<sup>9</sup> Experienced data managers, supervised by a pediatric oncologist, are responsible for the enrollment of eligible patients, data collection and updates, using structured protocols.

To be eligible for enrollment in the EKZ/AMC childhood cancer survivor cohort, patients should 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  $\geq 5$  years after diagnosis, regardless of disease or treatment status.

The EKZ/AMC childhood cancer survivor cohort is a dynamic cohort that changes due to continuous data updates (e.g., regarding mortality, (revised) diagnoses, and treatment characteristics) and enrollment of new survivors. As a result, the cohort characteristics, including the total number of survivors, demographics, diagnoses, and treatment, varied in the studies performed within our cohort and will vary in our future studies. For the current paper, we froze the EKZ/AMC childhood cancer survivor cohort at January 1, 2009. The cohort described here includes survivors diagnosed between January 1, 1966 and January 1, 2003. Once survivors die during the course of follow-up, they are not excluded from the cohort, but censored at the date of death.

Since 1996, special attempts are made regularly to invite 5-year survivors to our outpatient clinic. We offer medical follow-up at our late-effects outpatient clinic (Polikliniek Late Effecten Kindertumoren (PLEK/LATER)) for the assessment of late adverse effects of childhood cancer treatment in 5-year survivors and follow-up care. Survivors are seen by an adult physician or a pediatric oncologist (if <18 years) who performs a full medical assessment according to standardized follow-up protocols. These protocols are based on previous treatment modalities and include follow-up care recommendations for organ-specific and general late effects of treatment (Supplementary Table 1). They are consensus-based and were developed at the start of our outpatient clinic in 1996. The medical assessment includes a medical history, a physical examination, and additional risk-based diagnostic tests and counseling. Survivors are generally seen at the outpatient clinic at regular intervals (every 1, 2, or 5 years), depending on previous cancer treatment and (expected risk for) late effects. For example, very-low-risk childhood cancer survivors (e.g., survivors treated with surgery only) are invited every 5 years, while high-risk survivors (e.g., survivors treated with radiotherapy) are invited every year. Although the protocols set the standard clinical follow-up that needs to be provided, the physician can deviate from the protocol based on his or her clinical impression. In addition, most survivors have been seen at least once by a psychologist or late-effects nurse. Since 2010, nationwide long-term follow-up guidelines have been implemented.<sup>10</sup> These guidelines include evidence-based and consensus-based recommendations developed by multidisciplinary groups involved in the care for childhood cancer survivors.

For survivors who are eligible and alive, but who do not visit the late-effects outpatient clinic, we regularly try to obtain medical follow-up data from other physicians who see these patients. In general, these are either patients who were recently treated for their primary cancer or recurrence or low-risk patients who get specific surveillance from another medical specialty, such as neurosurgery, dermatology or orthopedics. Information on follow-up and (sub)clinical disorders that were detected during medical follow-up has been registered in the EKZ/AMC Registry. It should be noted that we registered all disorders that occurred, irrespective of their (assumed) relationship with previous cancer treatment.

Baseline patient, cancer, and treatment characteristics and medical follow-up data are retrieved from the EKZ/AMC Registry. We extract additional information from medical records and from other sources when necessary, depending on the research question. We have linked our cohort to the laboratory system of the EKZ/AMC and to several national registries in order to obtain more outcomes, like kidney and liver function tests, and rates of mortality, secondary malignancy, and hospitalization. Several outcomes have been validated for individual studies, depending on the outcome of interest.<sup>3,11-15</sup>

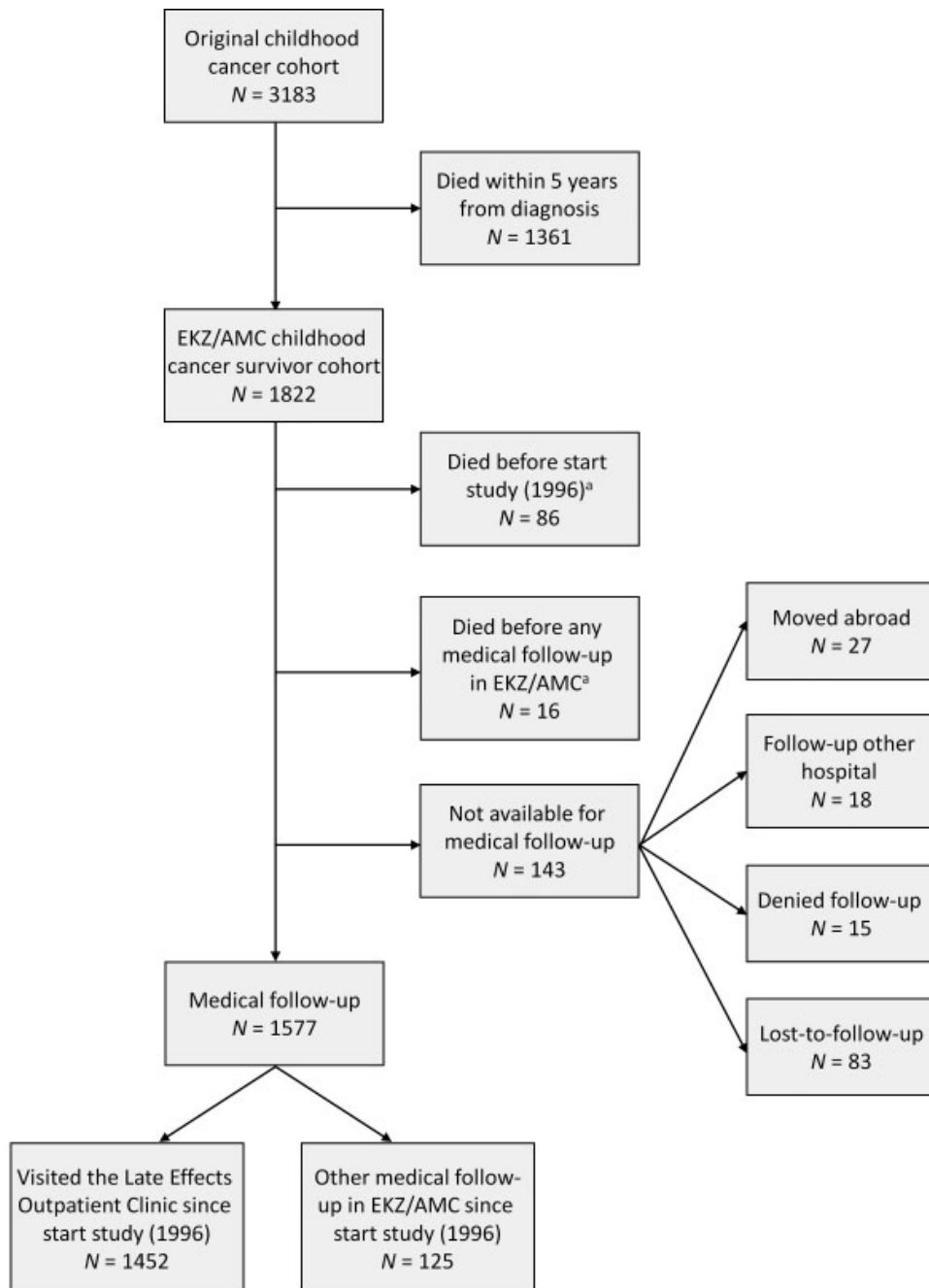
#### *Informed consent*

The EKZ/AMC institutional review board reviewed and approved the data collection. Written informed consent was obtained from all childhood cancer patients treated in the EKZ/AMC and from survivors attending the late-effects outpatient clinic.

### **Overview of the current cohort and previous studies**

For the current overview of the EKZ/AMC childhood cancer survivor cohort, we described and compared baseline characteristics of the complete study cohort, the cohort that visited our late-effects outpatient clinic and the survivors who did not. We described the number of outpatient clinic visits as well as the number of echocardiograms performed in survivors treated with anthracyclines (who should undergo echocardiograms according to the follow-up protocol). To assess the difference of distributions of primary childhood cancer diagnosis between the EKZ/AMC and the complete Dutch population, we used national childhood cancer incidence data from the Dutch Childhood Oncology registration over 2005 to 2009 (available at: <http://www.skion.nl>). These distributions have not changed substantially over the last decades.

We also summarized the characteristics of all studies performed within the EKZ/AMC childhood cancer survivor cohort, investigating late adverse effects in at least 20 survivors. We provided references of all other studies that included survivors from our cohort.



**Figure 1.** Flowchart of patients included in the EKZ/AMC cohort of childhood cancer survivors at January 1, 2009.

<sup>a</sup> Childhood cancer survivors who died before the start of the study and before they had any medical follow-up in the EKZ/AMC are eligible for inclusion in studies focusing on clinical end points (i.e., mortality, second malignancies).

N number, EKZ/AMC Emma Children’s Hospital/Academic Medical Center

## Results

### The EKZ/AMC childhood cancer survivor cohort

#### *Patients included in the current childhood cancer survivor cohort*

From January 1, 1966 until January 1, 2003, 3183 eligible children received primary cancer treatment in the EKZ/AMC; 1822 (57.2%) survived at least 5 years since diagnosis (Fig. 1).

Table 1 shows the clinical characteristics of the complete EKZ/AMC childhood cancer survivor cohort. As of January 1, 2009, baseline patient and cancer characteristics (i.e., date of birth, gender, cancer incidence date, and cancer diagnosis) are complete for all survivors. There are slightly more males (55.1%) than females (44.9%). The large majority (93.5%) is diagnosed before age 15 years. Leukemia (26.4%, predominantly acute lymphoblastic leukemia) is the most common cancer, followed by lymphoma (19.0%) and renal tumors (13.1%). At most recent follow-up, the median attained age is 24.8 years, with 1467 (80.6%) survivors younger than 35 years. The median follow-up duration from diagnosis is 17.7 years (range, 5.0-42.5). As of January 1, 2009, 169 (9.3%) survivors had died, the majority during primary cancer treatment or recurrence >5 years after childhood cancer diagnosis.

Baseline primary cancer treatment characteristics (i.e., start and end dates of treatment and if treatment included any surgery, radiotherapy, chemotherapy, and/or other therapy) are complete for 1781 (97.7%) survivors. For the remaining 41 survivors, baseline primary cancer treatment characteristics are partly complete in 33 and completely missing in 8 survivors. The majority has been treated with a combination of chemotherapy and surgery (31.7%), followed by chemotherapy only (25.6%) and a combination of chemotherapy, radiotherapy, and surgery (14.1%).

Table 2 shows the detailed treatment information for primary cancer, recurrences and second cancers within the first 5 years since primary cancer diagnosis. Over time, therapy data have become more detailed and complete. Most cumulative chemotherapy doses are available for >90% of patients. Also, information on radiation doses and radiation fields is complete for most survivors. More detailed, cumulative radiation doses have been calculated for several organ systems including the heart, the head and neck and the abdomen. These calculations will be extended to more organ systems in the future.

Up to January 2009, 1452 (79.7%) of the 1822 eligible survivors visited the late-effects outpatient clinic for a total of 6979 times (median number of visits, 4; range, 1 to 15). The median accrual rate of new survivors per year was 80 (range, 53 to 246). One hundred twenty-five (6.9%) survivors received any other form of medical follow-up at the EKZ/AMC related to their previous cancer and treatment. Eighty-six (4.7%) survivors died before the start of our study and 16 (0.9%) survivors died before they received medical follow-up in the EKZ/AMC. For 143 (7.8%) survivors no medical follow-up is available due to various reasons (Fig. 1).

**Table 1.** Clinical characteristics of the EKZ/AMC childhood cancer survivor cohort at January 1, 2009

Characteristic	Total	Medical follow-up late effects outpatient clinic	Other medical follow-up EKZ/ AMC	No medical follow-up EKZ/ AMC
	N=1822 N (%)	N=1452 N (%)	N=125 N (%)	N=245 N (%)
Sex				
Male	1004 (55.1)	794 (54.7)	64 (51.2)	146 (59.6)
Female	818 (44.9)	658 (45.3)	61 (48.8)	99 (40.4)
Primary childhood cancer diagnosis				
Leukemia	481 (26.4)	380 (26.2)	37 (29.6)	64 (26.1)
Lymphoma	347 (19.0)	303 (20.9)	10 (8.0)	34 (13.9)
Brain/CNS tumor	129 (7.1)	86 (5.9)	17 (13.6)	26 (10.6)
Bone tumor	149 (8.2)	109 (7.5)	15 (12.0)	25 (10.2)
Soft tissue sarcoma	195 (10.7)	157 (10.8)	14 (11.2)	24 (9.8)
Renal tumor	239 (13.1)	209 (14.4)	7 (5.6)	23 (9.4)
Hepatic tumor	25 (1.4)	20 (1.4)	1 (0.8)	4 (1.6)
Germ cell tumor	70 (3.8)	53 (3.7)	5 (4.0)	12 (4.9)
Neuroblastoma	128 (7.0)	97 (6.7)	13 (10.4)	18 (7.3)
Retinoblastoma	14 (0.8)	8 (0.6)	2 (1.6)	4 (1.6)
Other tumors	45 (2.5)	30 (2.0)	4 (3.2)	11 (4.5)
Age at diagnosis, median (range), years	6.0 (0.0-17.8)	5.9 (0.0-17.8)	5.5 (0.0-17.6)	6.9 (0.0-17.8)
0-4 yr	799 (43.9)	639 (44.0)	57 (45.6)	103 (42.0)
5-9 yr	492 (27.0)	398 (27.4)	31 (24.8)	63 (25.7)
10-14 yr	413 (22.7)	330 (22.7)	21 (16.8)	62 (25.3)
15-18 yr	118 (6.5)	85 (5.9)	16 (12.8)	17 (6.9)
Attained age, median (range), years	24.8 (5.2-52.3)	26.6 (6.6-52.3)	16.9 (5.9-42.9)	19.8 (5.2-50.9)
5-9 yr	71 (3.9)	28 (1.9)	18 (14.4)	25 (10.2)
10-14 yr	212 (11.6)	138 (9.5)	29 (23.2)	45 (18.4)
15-19 yr	299 (16.4)	214 (14.7)	44 (35.2)	41 (16.7)
20-24 yr	331 (18.2)	269 (18.5)	24 (19.2)	38 (15.5)
25-29 yr	304 (16.7)	282 (19.4)	4 (3.2)	18 (7.3)
30-34 yr	250 (13.7)	226 (15.6)	3 (2.4)	21 (8.6)
35-39 yr	188 (10.3)	169 (11.6)	2 (1.6)	17 (6.9)
≥40 yr	137 (7.5)	126 (8.7)	1 (0.8)	10 (4.1)
Unknown	30 (1.6)	0 (0.0)	0 (0.0)	30 (12.2)
Follow-up duration, median (range), years	17.7 (5.0-42.5)	19.2 (5.0-42.5)	7.7 (5.0-28.8)	10.9 (5.0-38.3)
5-9 yr	386 (21.2)	200 (13.8)	84 (67.2)	102 (41.6)
10-14 yr	345 (18.9)	291 (20.0)	16 (12.8)	38 (15.5)
15-19 yr	321 (17.6)	288 (19.8)	17 (13.6)	16 (6.5)
20-24 yr	287 (15.8)	257 (17.7)	6 (4.8)	24 (9.8)
25-29 yr	248 (13.6)	225 (15.5)	2 (1.6)	21 (8.6)
30-34 yr	142 (7.8)	135 (9.3)	0 (0.0)	7 (2.9)
35-39 yr	53 (2.9)	46 (3.2)	0 (0.0)	7 (2.9)
≥40 yr	10 (0.5)	10 (0.7)	0 (0.0)	0 (0.0)
Lost-to-follow-up before 5-yr survival	30 (1.6)	0 (0.0)	0 (0.0)	30 (12.1)
Treatment period				
1965-1969	40 (2.2)	27 (1.9)	0 (0.0)	13 (5.3)
1970-1974	126 (6.9)	84 (5.8)	0 (0.0)	42 (17.1)
1975-1979	229 (12.6)	181 (12.5)	3 (2.4)	45 (18.4)
1980-1984	322 (17.7)	268 (18.5)	9 (7.2)	45 (18.4)
1985-1989	301 (16.5)	261 (18.0)	9 (7.2)	31 (12.7)
1990-1994	310 (17.0)	247 (17.0)	36 (28.8)	27 (11.0)
1995-1999	320 (17.6)	262 (18.0)	31 (24.8)	27 (11.0)
2000-2002	174 (9.5)	122 (8.4)	37 (29.6)	15 (6.1)

**Table 1.** Clinical characteristics of the EKZ/AMC childhood cancer survivor cohort at January 1, 2009 (continued)

Overall treatment modality <sup>a</sup>				
Chemotherapy only	467 (25.6)	380 (26.2)	41 (32.8)	46 (18.8)
Radiotherapy only	18 (1.0)	15 (1.0)	0 (0.0)	3 (1.2)
Surgery only	182 (10.0)	124 (8.5)	26 (20.8)	32 (13.1)
Chemotherapy with radiotherapy	215 (11.8)	176 (12.1)	7 (5.6)	32 (13.1)
Chemotherapy with surgery	587 (31.7)	490 (33.7)	30 (24.0)	58 (23.7)
Radiotherapy with surgery	89 (4.9)	61 (4.2)	3 (2.4)	25 (10.2)
Chemotherapy with radiotherapy and surgery	257 (14.1)	203 (14.0)	15 (12.0)	39 (15.9)
None	8 (0.4)	3 (0.2)	3 (2.4)	2 (0.8)
Unknown	8 (0.4)	0 (0.0)	0 (0.0)	8 (3.3)
Recurrence of primary tumor				
Yes	339 (18.6)	204 (14.0)	43 (34.4)	92 (37.6)
No	1483 (81.4)	1248 (86.0)	82 (65.6)	153 (62.4)
Vital status at end of follow-up				
Alive	1653 (90.7)	1424 (98.1)	86 (68.8)	143 (58.4)
Deceased	169 (9.3)	28 (1.9)	39 (31.2)	102 (41.6)

CNS central nervous system, EKZ/AMC Emma Children's Hospital/Academic Medical Center, N number

<sup>a</sup>For 33 survivors treatment characteristics for 1 or 2 modalities were missing

**Table 2.** Treatment characteristics of the EKZ/AMC childhood cancer survivor cohort for primary cancer, recurrences, and second cancers within the first 5 years since primary cancer diagnosis

Treatment	Primary cancer N (%)	Recurrences of primary cancer N (%)	Second cancers N (%)
No. of childhood cancer survivors	1822 (100)	339 (18.6)	206 (11.3)
Type of chemotherapy			
<i>Any</i>			
Yes	1517 (83.3)	282 (83.2)	49 (23.8)
No	294 (16.1)	48 (14.2)	122 (59.2)
Unknown	11 (0.6)	9 (2.7)	35 (17.0)
<i>Cytotoxic antibiotics</i>			
Actinomycines	492 (27.0)	62 (18.3)	15 (7.3)
Anthracyclines <sup>a</sup>	698 (38.3)	121 (35.7)	19 (9.2)
Other cytotoxic antibiotics	199 (10.9)	22 (6.5)	2 (1.0)
<i>Alkylating agents</i>			
Alkyl sulfonates	11 (0.6)	6 (1.8)	1 (0.5)
Epoxides	0 (0.0)	1 (0.3)	0 (0)
Ethylene imines	0 (0.0)	1 (0.3)	0 (0)
Nitrogen mustard analogues	789 (43.3)	175 (51.6)	25 (12.1)
Nitrosoureas	15 (0.8)	10 (2.9)	3 (1.5)
Other alkylating agents	59 (3.2)	10 (2.9)	1 (0.5)
<i>Antimetabolites</i>			
Folic acid analogues	579 (31.8)	127 (37.5)	9 (4.4)
Purine analogues	466 (25.6)	101 (29.8)	4 (1.9)
Pyrimidine analogues	476 (26.1)	118 (34.8)	10 (4.9)
<i>Vinca alkaloids and other natural products</i>			
Podophyllotoxin derivatives	269 (14.8)	150 (44.2)	12 (5.8)
Taxanes	0 (0.0)	0 (0)	1 (0.5)
Vinca alkaloids	1299 (71.3)	228 (67.3)	26 (12.6)

**Table 2.** Treatment characteristics of the EKZ/AMC childhood cancer survivor cohort for primary cancer, recurrences, and second cancers within the first 5 years since primary cancer diagnosis (*continued*)

<i>Other antineoplastic agents</i>			
Platinum compounds	217 (11.9)	67 (19.8)	12 (5.8)
Glucocorticoids	786 (43.1)	162 (47.8)	10 (4.9)
Methylhydrazines	171 (9.4)	23 (6.8)	2 (1.0)
Monoclonal antibodies	0 (0.0)	2 (0.6)	0 (0)
Protein kinase inhibitors	1 (0.1)	1 (0.3)	3 (1.5)
Other antineoplastic agents	407 (22.3)	98 (28.9)	10 (4.9)
<b>Radiotherapy</b>			
Any			
Yes <sup>b</sup>	579 (31.8)	172 (50.7)	40 (19.4)
No	1228 (67.4)	156 (46.0)	131 (63.6)
Unknown	15 (0.8)	11 (3.2)	35 (17.0)
Field <sup>b,c</sup>			
Abdomen	107 (5.9)	8 (2.4)	1 (0.5)
Part of abdomen	9 (0.5)	6 (1.8)	0 (0)
CNS	57 (3.1)	11 (3.2)	9 (4.4)
Part of CNS	15 (0.8)	5 (1.5)	3 (1.5)
Extremities	50 (2.7)	15 (4.4)	0 (0)
Facial	21 (1.2)	11 (3.2)	4 (1.9)
Genitals	0 (0.0)	5 (1.5)	0 (0)
Head	199 (10.9)	35 (10.3)	5 (2.4)
Inverse Y	2 (0.1)	3 (0.9)	0 (0)
Neck	44 (2.4)	19 (5.6)	1 (0.5)
Mantle	9 (0.5)	1 (0.3)	0 (0)
Mediastinum	12 (0.7)	7 (2.1)	0 (0)
Pelvis	13 (0.7)	10 (2.9)	1 (0.5)
Spine/myelum	76 (4.2)	30 (8.8)	2 (1.0)
TBI	15 (0.8)	20 (5.9)	4 (1.9)
Thorax	41 (2.3)	36 (10.6)	2 (1.0)
Part of thorax	9 (0.5)	7 (2.1)	7 (3.4)
Other	2 (0.1)	3 (0.9)	0 (0)

CNS central nervous system, EKZ/AMC Emma Children's Hospital/Academic Medical Center, *N* number, TBI total body irradiation

<sup>a</sup> Total cumulative anthracycline dose registered in 674 (97%) of 698 anthracycline-treated survivors with a primary cancer diagnosis, in 110 (88%) of 125 anthracycline-treated survivors with a recurrence, and in 14 (74%) of 19 anthracycline-treated survivors with second cancers

<sup>b</sup> Maximum radiation dose registered in 664 (98%) of 681 radiation fields for primary cancer, in 221 (95%) of 232 radiation fields for recurrences, and in 35 (90%) of 39 radiation fields for second cancers

<sup>c</sup> Multiple fields possible

Table 1 shows differences in characteristics between all survivors, survivors with medical follow-up at the late-effects outpatient clinic, survivors seen by other specialists in the EKZ/AMC, and survivors without any medical follow-up in the EKZ/AMC. There were no substantial differences in the most important prognostic factors (gender, age at diagnosis and treatment) between the cohort that visited the late-effects outpatient clinic and the complete cohort. Survivors without medical follow-up at the late-effects outpatient clinic generally had shorter follow-up time and a lower attained age at the end of follow-up. A larger proportion of these survivors also had suffered a recurrence, and had died at the end of follow-up.

Overall, the adherence to the medical follow-up protocols was good. For example, of 698 survivors treated with anthracyclines, 589 (84%) visited our outpatient clinic. Of these

589 survivors, 507 (86%) survivors underwent 1972 echocardiograms (median 3; range, 0–28).

The EKZ/AMC treats around one fifth of all children primarily diagnosed with cancer in the Netherlands. The distribution of primary childhood cancer diagnoses within EKZ/AMC differed somewhat from the distribution of diagnoses in the complete Dutch population. Compared to the complete population, the EKZ/AMC treats on average more children with solid tumors (47 versus 32%), less children with leukemia and lymphoma (34 versus 46%) and slightly less children with central nervous system tumors (18 versus 22%).

#### *Studies conducted within the EKZ/AMC childhood cancer survivor cohort*

Since the start of the EKZ/AMC childhood cancer survivor cohort in 1996, 54 studies have been conducted within our cohort (Table 3 and Supplementary Table 2 in the Online Resource). Thirty (56.6%) studies included solely patients meeting all EKZ/AMC childhood cancer survivor cohort eligibility criteria (Table 3). The other 23 studies also included patients who survived their childhood cancer for <5 years since diagnosis or included patients diagnosed and treated in other pediatric oncology centers in the Netherlands.

The study outcomes varied from clinical (symptomatic) late effects in 4 studies<sup>11,12,14,16</sup> to subclinical (asymptomatic) late effects in 11 studies,<sup>13,17-26</sup> and psychosocial late effects in 11 studies.<sup>27-37</sup> Four studies assessed the total burden, including clinical and subclinical late effects.<sup>3,15,38,39</sup> Important clinical events studied within our cohort included cause-specific mortality,<sup>11</sup> second malignancies<sup>12</sup> and clinical heart failure.<sup>14,16</sup> Subclinical events included endocrine outcomes,<sup>18,22,23,25</sup> asymptomatic cardiac disease and cardiovascular risk factors,<sup>13,17,19,24</sup> pulmonary,<sup>21</sup> renal<sup>20</sup> and hepatic toxicity.<sup>26</sup>

To assess the potential presence of selection bias within a study, it is important to evaluate the representativeness of the study group, i.e., what percentage of the original cohort was studied. The representativeness of the study groups was 100% in all four studies investigating clinical events, i.e., cause-specific mortality, clinical heart failure, second malignancies,<sup>11,12,14,16</sup> and in three studies investigating total burden of adverse events.<sup>3,15,39</sup> For the other studies the representativeness varied from 50.0% in a study investigating cardiovascular risk factors in leukemia and Wilms' tumor survivors<sup>17</sup> to 88.7% in a study investigating pulmonary function impairment.<sup>21</sup> Fifteen studies did not report the patients included in the original cohort, so the representativeness of these studies could not be calculated.

The potential presence of attrition bias within a study can be assessed by evaluating the completeness of follow-up within the study group. The completeness of follow-up varied from 42.2% in a small study evaluating the experiences of fatigue<sup>27</sup> up to 100% in 11 studies evaluating endocrine, cardiovascular, and psychosocial late adverse effects.<sup>14,16-19,28-31,34,37</sup>

**Table 3.** Overview of studies conducted within the EKZ/AMC childhood cancer survivor cohort

Study topic	Neuroendocrine sequelae in medulloblastoma survivors	Cardiovascular risk factors in brain tumor survivors	Experience of fatigue	Adult height and age at menarche	Alexithymia	Excess fatigue
Period of childhood cancer diagnosis	Heikens <i>et al.</i> , <i>Eur J Cancer</i> 1998 <sup>18</sup>	Heikens <i>et al.</i> , <i>Cancer</i> 2000 <sup>19</sup>	Langeveld <i>et al.</i> , <i>Eur J Oncol Nurs</i> 2000 <sup>27</sup>	Noorda <i>et al.</i> , <i>Eur J Cancer</i> 2001 <sup>22</sup>	van Dijk <i>Met al.</i> , <i>Pediatr Rehabil</i> 2002 <sup>27</sup>	Langeveld <i>et al.</i> , <i>Eur J Cancer</i> 2003 <sup>28</sup>
Additional inclusion criteria	Diagnosed with medulloblastoma; aged $\geq 18$ yr at investigation; no seizures; no symptoms; no symptomatic ischemic heart disease; not pregnant	Diagnosed with brain cancer; aged $\geq 18$ yr at investigation; no seizures; not pregnant; no growth hormone substitution	Aged $\geq 18$ yr at investigation; extremely fatigued survivors	Aged $\geq 18$ yr at investigation	Aged $\geq 16$ yr at investigation	Aged $\geq 16$ yr at investigation
Survival	$\geq 5$ yr after end treatment	$\geq 5$ yr after end treatment	$\geq 5$ yr after end treatment	$\geq 5$ yr after end treatment	$\geq 5$ yr after end treatment	$\geq 5$ yr after end treatment
End date follow-up outcome assessment	Not reported	Not reported	1-1-1999	1-1-1997	Not reported	1-7-1999
N original cohort <sup>a</sup>	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported (459 invited)
N study group (%) <sup>b</sup>	20	26	83	285	72	416 (90.6% of invited)
N follow-up group (%) <sup>c</sup> / completeness of follow-up	20 (100%)	26 (100%)	35 (42.2%)	244 (85.6%)	72 (100%)	416 (100%)
Follow-up duration	Median 16 (8-25) yr after end treatment	Mean 15.7 (9-25) yr after end treatment	Median 17 (8-25) yr after end treatment	Mean 14.6 (5-31) yr after end treatment	Not reported	15 (5-33) yr after end treatment
Control group	None	29 healthy siblings or college students	None	Dutch population	222 matched controls	1026 patients from 179 general practitioners without cancer history

**Table 3.** Overview of studies conducted within the EKZ/AMC childhood cancer survivor cohort (continued)

Primary outcome	Medical assessment: Endocrine function, i.e. growth hormone (GH), hypothalamus-pituitary-gonadal (HPG) axis, hypothalamus-pituitary-thyroid (HPT) axis, hypothalamus-pituitary-adrenocortical axis	Medical assessment: Risk factors cardiovascular disease (CVD)	Semistructured interviews: Fatigue from survivor's perspective	Medical assessment: Adult height, stratified for males and females, and age at menarche; effects treatment and age at diagnosis	Questionnaires: Incidence and medical determinants associated with alexithymia, stratified for males and females	Questionnaires: Level of fatigue; fatigue severity compared with controls
Main results	25% normal hormonal profiles; 35% GH deficiency, 29% with hypogonadism and hypothyroidism, 14% with hypogonadism, 14% with hypothyroidism; 35% subnormal GH responses without HPG/HPT axis impairment; 14.3% marginal hypothyroidism without other impairment	Risk of CVD increased due to dyslipidemia, central obesity and elevated systolic blood pressure, particularly for those with growth hormone deficiency	Survivors report fatigue as having a negative impact on their daily lives; fatigue is a serious problem for some young adult survivors and affects many aspects of quality of life	Cranial with or without spinal radiotherapy leads to a significant reduction in adult height in both males and females, especially when given at age $\leq 8$ yr; cranial radiotherapy resulted in earlier menarche	Male survivors scored lower on alexithymia compared to healthy males; stress due to childhood cancer does not affect alexithymia scores of females; no medical determinant was associated with alexithymia	Female sex, being unemployed, depression, diagnosis, and severe late effects associated with fatigue; results suggest that level of fatigue is more or less equal in survivors and controls

**Table 3.** Overview of studies conducted within the EKZ/AMC childhood cancer survivor cohort (continued)

Study topic	Education, employment and living situation	Thyroid dysfunction	Cause-specific mortality	Posttraumatic stress symptoms	Quality of life, self-esteem and worries	Course of life
	<i>Langeveld et al. Psychooncology 2003</i> <sup>29</sup>	<i>van Santen et al. J Clin Endocrinol Metab 2003</i> <sup>25</sup>	<i>Cardous-Ubbink et al. Pediatr Blood Cancer 2004</i> <sup>17</sup>	<i>Langeveld et al. Pediatr Blood Cancer 2004</i> <sup>30</sup>	<i>Langeveld et al. Psychooncology 2004</i> <sup>31</sup>	<i>Stam et al. Psychooncology 2005</i> <sup>35</sup>
Period of childhood cancer diagnosis	Not reported	Not reported	1-1-1966 to 1-1-1996	Not reported	Not reported	Not reported
Additional inclusion criteria	Aged ≥16 yr at investigation	Treated with cranial, craniospinal, cervical, mediastinal, thoracic or total body radiotherapy (RT)	None	Aged ≥16 yr at investigation	Aged ≥16 yr at investigation	Aged 18-30 yr at investigation; ability to understand Dutch questionnaires
Survival	≥5 yr after end treatment	≥5 yr after end treatment	≥5 yr after diagnosis	≥5 yr after end treatment	≥5 yr after end treatment	≥5 yr after end treatment
End date follow-up outcome assessment	1-7-1999	Not reported	1-1-1998	1-7-1999	1-1-1999	2002
N original cohort <sup>a</sup>	Not reported (543 invited)	Not reported	1378	Not reported (543 invited)	Not reported (443 invited)	Not reported (449 invited)
N study group (%) <sup>b</sup>	500 (92.1% of invited)	207	1378 (100%)	500 (92.1% of invited)	400 (90.3% of invited)	355 (71.1% of invited)
N follow-up group (%) <sup>c</sup> completeness of follow-up	500 (100%)	205 (99.0%)	1365 (99.1%)	500 (100%)	400 (100%)	353 (99.4%)
Follow-up duration	Median 15 (5-33) yr after end treatment	Mean 19.1 yr after end treatment	Median 16.1 (5-≥30) yr after diagnosis	Median 15 (5-33) yr after end treatment	Median 15 (5-33) yr after end treatment	Mean 15.5 (4.9-30.3) yr after end treatment
Control group	1026 patients from 179 general practitioners without cancer history	None	General population	None	560 patients from 179 general practitioners without cancer history	508 patients from 82 general practitioners without cancer history
Primary outcome	Questionnaires: Level and determinants educational achievement, employment, living situation, marital status and off-spring	Medical assessment: Effect radiotherapy and chemotherapy on thyroid axis	Assessment of vital status: Standardized mortality ratio (SMR) and absolute excess risk (AER)	Questionnaires: Posttraumatic stress symptoms (PSS) and predictors	Questionnaires: Quality of life, self-esteem and worries; impact demographic, medical and treatment factors, and self-esteem on quality of life and worries	Questionnaires: Course of life and socio-demographic outcomes

**Table 3.** Overview of studies conducted within the EKZ/AMC childhood cancer survivor cohort. (continued)

<b>Main results</b>	Survivors less likely to complete high-school, more often unemployed, and lower rates of marriage and parenthood compared to controls; cranial irradiation dose $\leq 25$ Gray prognostic factor for lower educational achievement	27% thyroid dysfunction; 18% thyroidal disease; brain tumor patients at increased risk thyroid dysfunction; high risk RT field, higher RT dose, and diagnosis of non-Hodgkin lymphoma / Hodgkin's disease associated with thyroid disease; chemotherapy does not contribute to damage of thyroid axis inflicted by RT	SMR: 17.2 (95% CI 14.3-20.6); AER: 7 per 1000 person-years; combined treatment modality and recurrence associated with highest risk	1.2% severe PSS; 20% females vs. 6% males; female sex, being unemployed, lower education level, type of diagnosis, and severe late effects associated with PSS	Quality of life and level of self-esteem survivors not different from controls; survivors no more worries about health issues than controls; female sex, unemployment, severe late effects, low self-esteem predictors of worse quality of life; age at follow-up, unemployment, years since end treatment, and low self-esteem predictors of higher degree of worries	Course of life hampered in survivors as compared with controls; survivors achieved fewer milestones with respect to autonomy, social and psycho-sexual development, or achieved milestones at older age; survivors' education level was as high as that of controls
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**Table 3.** Overview of studies conducted within the EKZ/AMC childhood cancer survivor cohort. (continued)

Study topic	Clinical heart failure and pregnancy	Health-related quality of life and current coping	Second malignancies	Total burden of adverse events	Course of life and health-related quality of life	Health-related quality of life prediction model
	<i>van Dalen et al. Eur J Cancer 2006</i> <sup>16</sup>	<i>Stam et al. Psychooncology 2006</i> <sup>36</sup>	<i>Cardous-Ubbink et al. Eur J Cancer 2007</i> <sup>72</sup>	<i>Geenen et al. JAMA 2007</i> <sup>73</sup>	<i>Maurice-Stam et al. J Psychosoc Oncol 2007</i> <sup>22</sup>	<i>Maurice-Stam et al. Eur J Cancer Care 2009</i> <sup>23</sup>
Period of childhood cancer diagnosis	Between 1966 and 1998	Not reported	1-1-1966 to 1-1-1996	1-1-1966 to 1-1-1996	Not reported	Not reported
Additional inclusion criteria	Female survivors $\geq 17$ yr on 1-1-2003 (or date of death) treated with anthracyclines	Aged 18-30 yr at investigation; ability to understand Dutch questionnaires	None	None	Aged 18-30 yr at investigation; ability to understand Dutch questionnaires	Aged 18-30 yr at investigation; ability to understand Dutch questionnaires
Survival	$\geq 5$ yr after diagnosis	$\geq 5$ yr after end treatment	$\geq 5$ yr after diagnosis	$\geq 5$ yr after diagnosis	$\geq 5$ yr after end treatment	$\geq 5$ yr after end treatment
End date follow-up outcome assessment	1-1-2003	2002	1-1-2001	1-1-2004	2002	2002

**Table 3.** Overview of studies conducted within the EKZ/AMC childhood cancer survivor cohort (continued)

N original cohort <sup>a</sup>	206 female survivors; 53 delivered $\geq 1$ children	Not reported (499 invited)	1368	1362	Not reported (449 invited)	Not reported (449 invited)
N study group (%) <sup>b</sup>	206 (100%); 53 (100%)	355 (71.1% of invited)	1368 (100%)	1362 (100%)	355 (71.1% of invited)	355 (71.1% of invited)
N follow-up group (%) <sup>c</sup> / completeness of follow-up	206 (100%)	353 (99.4%)	1358 (99.3%)	1284 (94.3%)	353 (99.4%)	353 (99.4%)
Follow-up duration	Mean 16.7 (0.30-29.8) yr after 1 <sup>st</sup> anthracycline dose; mean 20.3 (5.8-28) yr for women who delivered $\geq 1$ children	Mean 15.5 (4.9-30.3) yr after end treatment	Median 16.8 (5- $\geq 30$ ) yr after diagnosis	Median 17.0 (5- $\geq 25$ ) yr after diagnosis	Mean 15.5 (4.9-30.3) yr after end treatment	Mean 15.5 (4.9-30.3) yr after end treatment
Control group	None	507 patients from 82 general practitioners without cancer history	General population	None	None	None
Primary outcome	Medical assessment: Cumulative incidence peripartum clinical anthracycline-induced heart failure	Questionnaires: Health-related quality of life (HRQoL); cognitive coping in relation to HRQoL	Medical assessment: Standardized incidence ratio (SIR) and absolute excess risk (AER) second malignancies	Medical assessment: Prevalence and severity treatment-specific adverse events (AEs)	Questionnaires: Impact medical determinants on course of life; impact course of life on quality of life	Questionnaires: Prediction of factors affecting health-related quality of life (HRQoL) using a theoretical model
Main results	Cumulative incidence: 0% (95% CI 0-5.7%); risk factors could not be evaluated	HRQoL of survivors lower compared with controls; health status and coping associated with HRQoL	SIR: 11.2 (95% CI 8.5-14.4); AER: 3.2 per 1000 person-years; radiotherapy associated with highest risk	75% $\geq 1$ AEs; 25% $\geq 5$ AEs; 40% $\geq 1$ severe or life-threatening AEs; radiotherapy associated with highest risk	Brain tumor survivors; and survivors treated with radiotherapy reported achievement of fewer milestones in psycho-sexual and social domain; survivors who achieved fewer milestones in social domain scored worse on quality of life	Model fitted data closely; effect medical and demographic characteristics on HRQoL mediated by coping; survivors treated with both chemotherapy and radiotherapy at highest risk for lower HRQoL

**Table 3.** Overview of studies conducted within the EKZ/AMC childhood cancer survivor cohort. (continued)

Study topic	Hypertension	Adverse events in Wilms' tumor survivors	Cardiovascular risk factors in ALL and Wilms' tumor survivors	Cardiac dysfunction	Adverse outcomes after bilateral Wilms' tumor	Application for disability benefits
Period of childhood cancer diagnosis	<i>Cardous-Ubbink et al. Eur J Cancer 2010</i> <sup>3</sup> 1-1-1966 to 1-1-1996	<i>van Dijk I et al. Int J Radiat Oncol Biol Phys 2010</i> <sup>15</sup> 1-1-1966 to 1-1-1996	<i>Geenen et al. Pediatr Blood Cancer 2010</i> <sup>7</sup> 1-1-1966 to 1-1-1991	<i>van der Pal et al. Arch Intern Med 2010</i> <sup>24</sup> 1-1-1966 to 1-8-1997	<i>Aronson et al. Pediatr Blood Cancer 2011</i> <sup>38</sup> 1-1-1967 to 1-1-2007	<i>Maurice-Stam et al. Psychooncology 2011</i> <sup>34</sup> Not reported
Additional inclusion criteria	None	Diagnosed with Wilms' tumor	Diagnosed with acute lymphoblastic leukemia (ALL) or Wilms' tumor; aged ≥ 18 yr at investigation	Treated with potentially cardiotoxic therapy; aged ≥ 18 yr at investigation	Diagnosed with bilateral Wilms' tumor	Aged 18-30 yr at investigation; ability to understand Dutch questionnaires
Survival	≥5 yr after diagnosis	≥5 yr after diagnosis	≥5 yr after diagnosis	≥5 yr after diagnosis	≥5 yr after diagnosis	≥5 yr after diagnosis
End date follow-up outcome assessment	Not reported	1-1-2004	1-10-2002	1-4-2004	Not reported	Not reported
N original cohort <sup>a</sup>	1362	185	282	735	32	Not reported
N follow-up group (%) <sup>b</sup>	1145 (84.1%)	185 (100%)	141 (50%)	601 (81.8%)	28 (87.5%)	366
% completeness of follow-up	1080 (94.3%); 44 hypertension	181 (97.8%)	141 (100%)	525 (87.4%)	25 (89.3%)	366 (100%)
Follow-up duration	Median 20.4 (5-≥30) yr after diagnosis	Median 18.9 (5-36.7) yr after diagnosis	Mean 20.8 yr after end of treatment	Median 15.4 (5-≥25) yr after diagnosis	Median 10.5 (5.5-34) yr after diagnosis	Not reported
Control group	123 matched controls from EKZ/AMC cohort	None	69 siblings of included survivors	None	None	508 patients from 82 general practitioners without cancer history
Primary outcome	Medical assessment: Risk factors hypertension	Medical assessment: Prevalence and severity adverse events (AEs) and treatment-related risk factors	Medical assessment: Prevalence cardiovascular risk factors (CRFs) (hypertension, diabetes mellitus, hypercholesterolemia, obesity, renal insufficiency)	Medical assessment: Prevalence and determinants left ventricular dysfunction	Medical assessment: Survival, renal late effects, secondary tumors	Questionnaires: Relation between unfavorable psychosocial developmental trajectory while growing up and likelihood of labor participation in adult life

**Table 3.** Overview of studies conducted within the EKZ/AMC childhood cancer survivor cohort. (continued)

Main results	Body mass index only risk factor associated with hypertension; cisplatin, cyclophosphamide, and abdominal radiotherapy associated with non-significant increased risk	68% $\geq 1$ AE; 21% $\geq 5$ life-threatening AEs; 24% severe or moderate; radiotherapy to flank/abdomen increased risk of any AE, orthopedic events, second tumors and cardiovascular events	$\geq 1$ CRF in 23% of ALL, and 32% of Wilms' tumor survivors treated with radiotherapy and chemotherapy; survivors treated with chemotherapy alone no higher prevalence of CRFs than controls; abdominal radiation, positive family history, and age at screening associated with having $\geq 1$ CRF	27% subclinical cardiac dysfunction (left ventricular shortening fraction (LVSF) $< 30\%$ ); higher anthracycline dose, radiation to thorax, and younger age at diagnosis associated with reduced LVSF	78% 10-yr overall survival; 52% significant morbidity; 32% renal failure including 20% renal transplantations; 20% secondary tumors	Survivors with disability benefits vs. without disability benefits vs. controls lower social and psychosocial development scale scores; survivors with unfavorable developmental trajectory while growing up more likely to apply for disability benefits
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**Table 3.** Overview of studies conducted within the EKZ/AMC childhood cancer survivor cohort. (continued)

Study topic	Pulmonary function impairment	Reproductive status	Adverse events after cranial radiotherapy	Renal dysfunction and hypertension	Hepatic late adverse effects	Symptomatic cardiac events
Period of childhood cancer diagnosis	Mulder et al. <i>Thorax</i> 2011 <sup>21</sup>	Tromp et al. <i>Hum Reprod</i> 2011 <sup>23</sup>	van Dijk et al. <i>Int J Radiat Oncol Biol Phys</i> 2012 <sup>39</sup>	Krijnenburg et al. <i>Clin J Am Soc Nephrol</i> 2012 <sup>20</sup>	Mulder et al. <i>Eur J Cancer</i> 2012 <sup>26</sup>	van der Pal et al. <i>J Clin Oncol</i> 2012 <sup>14</sup>
Additional inclusion criteria	1-1-1966 to 1-1-1996	1-1-1966 to 1-1-2003	1-1-1966 to 1-1-1996	1-1-1966 to 1-1-2003	1-1-1996 to 1-1-2003	1-1-1966 to 1-1-1996
	Treated with bleomycin/pulmonary radiotherapy (RT)/pulmonary surgery; aged $\geq 18$ yr at investigation	Male survivors aged $\geq 18$ yr at investigation	None	None	No history of veno-occlusive disease; free of hepatitis virus infection	None
Survival	$\geq 5$ yr after diagnosis	$\geq 5$ yr after diagnosis	$\geq 5$ yr after diagnosis	$\geq 5$ yr after diagnosis	$\geq 5$ yr after diagnosis	$\geq 5$ yr after diagnosis
End date follow-up outcome assessment	1-1-2009	1-1-2008	1-1-2004	Not reported	1-1-2010	1-1-2006
N original cohort <sup>a</sup>	248	879	1362	1845	1795	1362
N study group (%) <sup>b</sup>	220 (88.7%)	565 (64.3%)	1362 (100%)	1442 (78.2%)	1404 (78.2%)	1362 (100%)
N follow-up group (%) <sup>c</sup> / completeness of follow-up	193 (87.7%)	488 (86.4%)	1284 (94.3%)	1378 (95.6%)	1362 (97.0%)	1362 (100%)

**Table 3.** Overview of studies conducted within the EKZ/AMC childhood cancer survivor cohort. (continued)

Follow-up duration	Median 17.9 (5.6-36.8) yr after diagnosis	Median 15.0 (5.0-39.0) yr after diagnosis	Median 17.0 (5-≥25) yr after diagnosis	Median 12.1 (5.0-36.1) yr after diagnosis	Median 12.4 (5.0-36.1) yr after diagnosis	Median 22.2 (5-44.5) yr after diagnosis
Control group	None	None	None	None	None	None
Primary outcome	Medical assessment: Prevalence and risk factors obstructive and restrictive pulmonary function impairment, and diffusion capacity impairment	Medical assessment: Prevalence and risk factors of abnormal reproductive endocrinology	Medical assessment: Dose-effect relationships for the prevalence and severity of adverse events (AEs) after cranial radiotherapy (CRT)	Medical assessment: Prevalence and risk factors renal dysfunction and hypertension	Medical assessment: Prevalence and risk factors hepatocellular dysfunction (elevated alanine aminotransferase(ALT)) and biliary tract dysfunction (elevated gamma-glutamyltransferase (γGT))	Medical assessment: Incidence and risk factors symptomatic cardiac events (CEs)
Main results	44% pulmonary function impairment; RT, RT and bleomycin, and RT and surgery associated with highest risk pulmonary function impairment	33% elevated FSH; 12% decreased testosterone; 73 men (56 naturally conception) reported 120 conceptions resulting in 103 live births; procarbazine, cyclophosphamide, vinca-alkaloids, other alkylating agents, pelvic/abdominal irradiation, total body irradiation, and testicular surgery associated with elevated FSH; FSH is a sensitive marker for the need of assisted reproductive techniques	>80% CRT group >1 AE and ≈50% ≥5 AEs; AEs in CRT group more often severe, life-threatening or disabling compared to AEs in non-CRT group; significant CRT dose-effect relationships for prevalence and severity of AEs, and a number of selected outcomes, stratified for brain tumor survivors and survivors of other cancer types	28% ≥1 renal adverse effect or hypertension; 14.8% hypertension; 14.5% albuminuria; 4.5% diminished glomerular filtration rate; especially after nephrotoxic chemotherapy, radiation and surgery; nephrectomy associated with highest risk of renal adverse effects; radiotherapy and nephrectomy, male sex, higher body mass index, and longer time since treatment associated with hypertension	8.7% elevated liver enzymes; radiotherapy, higher BMI, higher alcohol intake, and longer follow-up time associated with elevated ALT and γGT levels	42 survivors developed 50 CEs, including 27 congestive heart failures; anthracycline (dose), cardiac irradiation (dose), combination of these treatments, and congenital heart disease associated with CE; exponential relationship between cumulative anthracycline dose, cardiac irradiation dose and risk of CE

To be eligible for inclusion in the EKZ/AMC childhood cancer survivor cohort patients had to meet the following criteria: diagnosed and treated for a primary malignancy; diagnosed from January 1, 1966 onwards; aged <18 years at diagnosis; diagnosed in the Netherlands; treated primarily in the EKZ/AMC; survived ≥5 year after diagnosis  
<sup>a</sup> N number, CI confidence interval, EKZ/AMC Emma Children's Hospital/Academic Medical Center (Ooher abbreviations are explained in text of the specific study column)  
<sup>b</sup> The patients in the original cohort represent the whole original group of childhood cancer survivors eligible for inclusion  
<sup>c</sup> The patients in the study group are the childhood cancer survivors included in the study  
<sup>d</sup> The patients in the follow-up group are the childhood cancer survivors with relevant outcome measures

## Discussion

The EKZ/AMC childhood cancer survivor cohort study is a large cohort of childhood cancer survivors, with near-complete patient, cancer, and treatment characteristics and unique, long-term medical follow-up. We described the methodology, clinical characteristics, and data availability of our ongoing cohort study of childhood cancer survivors from the EKZ/AMC that provides insights in the specific risks and the associated risk factors of childhood cancer survivors. In this discussion, we will further elaborate on strengths and weaknesses of our cohort and place them into perspective of other large childhood cancer survivor cohort studies (Table 4).

The EKZ/AMC cohort of childhood cancer survivors includes a population of survivors primarily treated in one hospital in the Netherlands across a long period of time. In design and size, our cohort is comparable to the St. Jude Lifetime Cohort (SJLIFE) of 10-year childhood cancer survivors that was recently initiated.<sup>40</sup> The Childhood Cancer Survivor Study (CCSS) from North America encompasses survivors from multiple hospitals,<sup>41,42</sup> while the British Childhood Cancer Survivor Study (BCCSS),<sup>43</sup> the Childhood Adolescent and Young Adult Cancer Survivors (CAYACS) Research Program<sup>44</sup> and the Swiss Childhood Cancer Survivor Study (SCCSS)<sup>45</sup> cover a complete nationwide or statewide population of survivors. An important strength of our cohort is that we were able to identify all childhood cancer patients diagnosed in the EKZ/AMC in a specific calendar period who subsequently survived 5 years or more. Hereby, we selected a cohort independent of the outcome of interest and prevented selection bias based on outpatient clinic visit or diagnosis of late adverse effects. Also, while other cohorts study childhood cancer survivors diagnosed during limited calendar periods,<sup>41-44</sup> our cohort, as well as the SJLIFE and SCCSS cohorts<sup>40,45</sup>, spans the complete history of contemporary cancer treatment in children, including recent treatment eras.

Another strength of our cohort study is the comprehensive and detailed treatment information for each survivor. In addition, exposure information in our cohort is not only complete for primary cancer treatment, but also for recurrences and subsequent cancers. Our study can thus make more precise estimations of treatment exposure than some of the other childhood cancer survivor studies, thereby reducing the risk of misclassification of exposure.<sup>46</sup> Furthermore, all detailed information about baseline patient, cancer, and treatment characteristics has been derived from patient files by experienced data managers, supervised by a pediatric oncologist. The majority of the data have been derived prospectively at the moment of childhood cancer treatment, so that we acquired high-quality data independent of the outcome of interest.

A unique methodological strength of our cohort is the long and almost complete medical follow-up, especially of clinical events. Our follow-up duration ranged from 5 to 42.5 years and the completeness of medical follow-up in our studies ranged from 84% to 100%. Complete follow-up and, thus, a low risk of attrition bias is crucial to obtain valid risk estimates.

Finally, while many other survivor cohorts obtain outcomes from questionnaires and/

**Table 4.** Summary of published childhood cancer survivor cohort studies

Study	EKZ/AMC Childhood Cancer Survivor Cohort	Childhood Cancer Survivor Study (CCSS) <sup>41,42</sup>	British Childhood Cancer Survivor Study (BCCSS) <sup>43</sup>
Year established	1996	1994	2006
Study design	Single center retrospective cohort study with prospective medical screening and evaluation	Multicenter retrospective cohort study	Population-based retrospective cohort study
Period of childhood cancer diagnosis	1966 – 2002	1970 – 1986	1940 – 1991
Age at childhood cancer diagnosis	<18 years	<21 years	<15 years
Survival since primary cancer diagnosis	≥5 years	≥5 years	≥5 years
Additional inclusion criteria	Diagnosed and treated for a primary malignancy; Diagnosed in the Netherlands; Treated primarily in the EKZ/AMC	Diagnosed and treated for specific primary malignancies; <sup>a</sup> Diagnosed in one of 26 participating centers in the United States and Canada; English or Spanish speaking; Resident of the United States or Canada at time of initial follow-up	Diagnosed and treated for a malignancy; Current age ≥16 years; Resident of Britain
Original childhood cancer survivor cohort (N)	1822	20720	17866
Lost to follow-up	4.5%	14.6%	0.1%
End date current cohort description	31 Dec 2008	Nov 2000	17 Sep 2006
Availability of treatment characteristics	Chemotherapy agents, radiotherapy fields, surgery, other treatments, and treatment for recurrences available for 1781 survivors (97.7%); Cumulative doses available for some treatments	Chemotherapy agents, radiotherapy and surgery available in 14908 of 20276 survivors (73.5%); For some chemotherapy agents cumulative doses available for 12455 of 20276 survivors (61.4%) <sup>b</sup>	Chemotherapy available for 12450 survivors (69.7%), radiotherapy available for 12850 survivors (71.9%), and surgery available for 13215 survivors (73.9%)
Comparison group	Not available	Sibling cohort	Not mentioned
Outcome assessment	Medical evaluation using cancer treatment follow-up protocols; Psychological assessment; Since 2010, medical evaluation using risk-based strategies recommended in the DCOG guideline	Comprehensive health questionnaires	Comprehensive health questionnaires

**Table 4.** Summary of published childhood cancer survivor cohort studies (*continued*)

Study	Childhood Adolescent and Young Adult Cancer Survivors (CAYACS) Research Program <sup>44</sup>	St. Jude Lifetime Cohort Study (SJLIFE) <sup>40</sup>	Swiss Childhood Cancer Survivor Study (SCCSS) <sup>45</sup>
Year established	Not mentioned	2010	2007
Study design	Population-based retrospective cohort study	Single center retrospective cohort study with prospective medical screening and evaluation	Population-based retrospective cohort study
Period of childhood cancer diagnosis	1970 – 1995	Not mentioned	1976 – 2003
Age at childhood cancer diagnosis	<25 years	Not mentioned (childhood malignancy)	<15 years
Survival since primary cancer diagnosis	≥5 years	≥10 years	≥5 years
Additional inclusion criteria	Diagnosed and treated for a primary malignancy; Resident of British Columbia at time of diagnosis; Identified in Cancer Registry	Diagnosed and treated for a childhood malignancy at SJCRH; Current age ≥18 years	Diagnosed for specific primary malignancies; <sup>c</sup> Resident of Switzerland at time of diagnosis; Identified in Swiss Childhood Cancer Registry
Original childhood cancer survivor cohort (N)	3841	3900	3115
Lost to follow-up	4.4%	<10%	Not mentioned
End date current cohort description	31 Dec 2000	1 Jan 2010	31 Dec 2010
Availability of treatment characteristics	Chemotherapy, radiotherapy and surgery available for 2975 survivors (77.4%)	Chemotherapy agents and cumulative doses, and radiotherapy fields available for 3612 survivors (92.6%)	Surgery, chemotherapy (agents will be studied in detail), radiotherapy (dose will be studied in detail), bone marrow transplantation
Comparison group	British Columbia population (complete or reference sample)	Not mentioned	Sibling cohort; General population
Outcome assessment	Extraction of data from Cancer Registry; Linkage to (health) administrative databases	Medical evaluation using risk-based strategies recommended in the COG guideline; Comprehensive health questionnaires	Comprehensive health questionnaires; Medical evaluation in a small subgroup between 1994 and 1996; Extraction of data from and linkage with different registries

COG Children's Oncology Group, DCOG Dutch Childhood Oncology Group, EKZ/AMC Emma Children's Hospital/Academic Medical Center, SJCRH, St. Jude Children's Research Hospital

<sup>a</sup> Diagnosis and treatment of leukemia, central nervous system malignancy (excluding meningioma and craniopharyngioma), Hodgkin disease, non-Hodgkin lymphoma, neuroblastoma, soft tissue sarcoma, kidney cancer, or bone cancer

<sup>b</sup> Treatment characteristics as described in Robison et al.<sup>41</sup>

<sup>c</sup> Diagnosis of leukemias, lymphomas, central nervous system tumors, malignant solid tumors, or Langerhans cell histiocytosis

or population registries,<sup>41-44</sup> outcomes in our cohort are based on medical follow-up with an attempt for complete collection of late health outcomes. Medical follow-up also enabled us to collect additional and reliable information on risk factors associated with lifestyle, such as smoking, alcohol consumption, and obesity. The overall completeness of baseline and follow-up data within our cohort allows us to adjust for different types of important confounders in our analyses.

Our study also has limitations. A criticism to our design could be that the cohort is hospital-based and not population-based. It is possible that, historically, patients with more complicated childhood cancer diagnoses have been treated in the EKZ/AMC and, as a consequence, treatment was more intensive in our cohort than in a population-based study. Compared to the complete Dutch population of childhood cancer patients, the EKZ/AMC treats a relatively high proportion of children with solid tumors, and a relatively low number of children with leukemia, lymphoma or central nervous system tumors. It is, however, difficult to speculate how these differences may affect the risk of late effects. If our cohort was indeed treated more extensively, it will only affect the external validity of studies (the generalizability of results to other patients or populations) and not the internal validity, because treatment-specific risk estimates are not affected by a lower generalizability.

An important limitation of the EKZ/AMC childhood cancer survivor study is that we do not have a readily available control population, in contrast to some other cohorts.<sup>41,42,44,45</sup> Due to the clinic-based follow-up, it is not possible to periodically assess controls in a similar way as survivors. An acceptable solution is comparing risks between treatment groups. A subgroup that did not receive a certain exposure is preferred. When this is impossible, a low risk exposure, like surgery only can serve as a reference group.<sup>8</sup> In addition, for specific outcomes appropriate population-based reference values are available, such as values of pulmonary, renal, hepatic and cardiac functions.

Regarding the outcomes studied, it should be noted that, due to the medical nature of our follow-up, it is not possible to blind the physician in the outpatient clinic to prognostic factors. However, by using standardized protocols, we reduced the risk of detection bias. The change from local to nationwide follow-up guidelines in 2010 may influence the detection of late adverse effects in future studies with longer follow-up. This will be a focus for future research. Furthermore, due to the clinical nature of our follow-up, survivors do not always attend from the same follow-up year onwards, for example, because of cancer recurrence treatment. Therefore, we always adjust our analyses for the follow-up duration of that individual patient.

Although we have a high rate of completeness of medical follow-up, attrition bias might be present in our study. This risk is due to the fact that survivors with late effects could be either less or more likely to visit the outpatient clinic than survivors without medical problems, leading to an underestimation or overestimation of the risk.<sup>47,48</sup> This is a similar issue that studies using questionnaires face,<sup>41-43,45</sup> while medical record linkage studies are less at risk of this type of bias.<sup>44</sup> A final limitation of our cohort study is that the sample sizes of

patients in some of the treatment groups are relatively small. Consequently, it is not always feasible to examine late adverse effects in relation to these detailed chemotherapy and radiotherapy groups.

To overcome some of these limitations, in 2004 a nationwide population-based study has been initiated in the Netherlands. All centers of the Dutch Childhood Oncology Group collaborate on the LATE Effect Registry (LATER) project, which includes >6000 survivors who are offered regular medical follow-up according to national evidence-based guidelines.<sup>10</sup>

The study design of the EKZ/AMC childhood cancer survivor cohort cannot be used to answer all relevant questions in survivors. To assess, for example, the effect of different screening options, other study designs should be used, focusing on diagnostic accuracy and process evaluation, weighing the benefits of surveillance and potential harms. Other studies, preferably randomized trials, should evaluate interventions to prevent further deterioration of late adverse effects. In addition, as we discussed in this paper, all large CCS cohort studies have specific strengths, limitations and opportunities to study. These studies together will, therefore, increase our knowledge of late effects of childhood cancer treatment and their clinical impact.

New fields of research in childhood cancer survivors include the role of genetic susceptibility in the development of late adverse effects in childhood cancer survivors. Genetic predisposition and its interaction with therapeutic exposure may increase the toxic effects of childhood cancer treatment. Genetic studies may give more insights into the individual variability in the occurrence of treatment-related health outcomes in childhood cancer survivors. Although we do not have access to biological samples of all survivors in our cohort, we are able to contribute to genetic studies in survivors with a specific outcome such as anthracycline-induced cardiotoxicity.<sup>49</sup> We recommend new childhood cancer survivor studies to systematically collect DNA to enable the assessment of gene-treatment interactions in the pathogenesis of late adverse effects.<sup>50</sup>

In conclusion, childhood cancer survivors are a growing group of individuals with a high risk of tumor and treatment-related morbidity and mortality. Ongoing high-quality research will result in more understanding of the specific risks and risk factors of late adverse effects. Our EKZ/AMC childhood cancer survivor cohort – and in the near future the Dutch nationwide LATER childhood cancer survivor cohort – provides ongoing research opportunities to focus on gaps in the current evidence. As a result, we can hopefully improve the quality of care and thereby the quality of life of these vulnerable patients.

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**Supplementary Table 1.** Consensus-based follow-up care recommendations for organ-specific and general late effects of treatment in childhood cancer survivors at the EKZ/AMC outpatient clinic (1996 – 2010)<sup>a</sup>

Organ system	Who	Medical history	Physical examination	Laboratory diagnostics	Other diagnostics
General	All survivors	General medical history, complaints, medication, smoking, substance abuse	General physical examination	ESR, complete blood count, white blood cell differential, hepatic function panel, serum creatinine, estimated GFR	-
Psychosocial	All survivors	Psychosocial history, including education, work, household and insurance issues	-	-	-
Neuroendocrine	Cranial surgery, cranial radiotherapy, survivors of a brain tumour	Neuropsychiatric symptoms, endocrine related symptoms, vision, hearing, oral health, dysphagia	-	TSH, ft4, thyroglobulin, IGF-1, prolactin	X-wrist <sup>b</sup>
	Cisplatin, carboplatin, cranial radiotherapy >50 Gy	Ear pain, tinnitus, hearing	-	-	Audiogram <sup>c</sup>
	Corticosteroids, cranial radiotherapy	Vision	-	-	-
	Radiotherapy neck/cervical vertebrae or thoracic radiotherapy	Endocrine related symptoms, voice, stridor	Thyroid palpation	TSH, ft4, thyroglobulin, calcium, albumin	-
	Spinal radiotherapy	Paresthesia, sensory and motor function	-	-	-
Reproductive	Males treated with cranial radiotherapy, abdominal/pelvic radiotherapy, pelvic surgery, genital surgery or any chemotherapy	Reproductive health	Pubic hair, testes size, Tanner stage	FSH, LH, testosterone	-
	Females treated with cranial radiotherapy, abdominal/pelvic radiotherapy, pelvic surgery, genital surgery or any chemotherapy	Reproductive health, menstrual cycle	Pubic hair, Tanner stage	if not on OCP: FSH, LH, progesterone, estradiol	-
Cardiovascular	Thoracic surgery, thoracic radiotherapy, anthracyclines, mitoxantrone, high-dose cyclophosphamide	Angina pectoris, palpitations, pedal edema, nycturia, dyspnea	Blood pressure, cardiac examination	-	Echocardiogram <sup>d</sup> , electrocardiogram <sup>e</sup>

**Supplementary Table 1.** Consensus-based follow-up care recommendations for organ-specific and general late effects of treatment in childhood cancer survivors at the EKZ/AMC outpatient clinic (1996 – 2010)<sup>a</sup> (*continued*)

Organ system	Who	Medical history	Physical examination	Laboratory diagnostics	Other diagnostics
Lungs	Thoracic surgery, thoracic radiotherapy, bleomycine, mitomycine, nitrosureas	Cough, dyspnoea, chest pain, upper respiratory tract infections	Lung examination	-	Spirometry <sup>c</sup> : vital capacity, FEV1, diffusion capacity
Kidneys / bladder	Abdominal/pelvic surgery, abdominal/pelvic radiotherapy, cisplatin, carboplatin, ifosfamide, high-dose cyclophosphamide, high-dose methotrexate	Urinary tract infections, kidney stones, polyuria, polydipsia	Blood pressure	Urinanalysis, calcium, phosphate, albumin, sodium, potassium, magnesium, bicarbonate, uric acid, osmolality	Renal ultrasound <sup>f</sup>
Gastrointestinal tract	Abdominal surgery, abdominal radiotherapy	Dysphagia, gastric complaints, abdominal pain, bowel movement frequency and stool consistency, food intolerance	Abdominal examination	Screening hepatitis B and C*	Abdominal ultrasound <sup>c</sup>
	Rectal surgery, rectal radiotherapy	Sphincter control, pain, stool abnormalities	-	-	-
Musculoskeletal	Corticosteroids	Bone pain, fractures	-	-	-
	Spinal radiotherapy	Pain	Scoliosis, kyphosis	-	-
	Thoracic surgery, thoracic radiotherapy	-	Sitting height	-	-
Secondary malignancies	Females who received thoracic radiotherapy	Changes of the breast	Breast exam	-	Mammography <sup>g</sup>

EKZ/AMC Emma Children's Hospital / Academic Medical Center, FEV1 Forced expiratory volume in 1 second, GFR Glomerular filtration rate, Gy gray, OCP oral contraceptive pill, FSH follicle-stimulating hormone, LH luteinizing hormone, TSH thyroid-stimulating hormone, fT4 free thyroxine, CCS childhood cancer survivor. Recommendations are followed at every visit unless specified otherwise. CCS treated with surgery only were invited for five-yearly follow-up, CCS treated with minimally toxic chemotherapy (i.e. not mentioned in this table) were invited for two-yearly follow-up. All other CCS were invited for yearly follow-up visits. In case of symptoms or other abnormalities additional physical examination, diagnostic testing or consulting of other physicians was performed.

<sup>a</sup> In 2010 nationwide, evidence- and consensus-based long-term follow-up guidelines have been implemented. <sup>b</sup> Two-yearly, until end of growth. <sup>c</sup> Performed every 5 years. <sup>d</sup> Performed every 2-5 year, depending on cardiotoxic treatment, previous abnormalities and pregnancies. <sup>e</sup> Performed once at first visit. <sup>f</sup> Performed every 5 years, only after abdominal/pelvic radiotherapy or abdominal/pelvic surgery. <sup>g</sup> Two-yearly, starting at age 25.

**Supplementary Table 2.** Late effects studies including patients from the EKZ/AMC childhood cancer survivor cohort

Heikens J, Behrendt H, Adriaanse R, et al. Irreversible gonadal damage in male survivors of pediatric Hodgkin's disease. <i>Cancer</i> 1996;78(9):2020-4.
Kremer LC, van Dalen EC, Offringa M, et al. Anthracycline-induced clinical heart failure in a cohort of 607 children: long-term follow-up study. <i>J Clin Oncol</i> 2001;19(1):191-6.*
van Santen HM, de Kraker J, van Eck BL, et al. High incidence of thyroid dysfunction despite prophylaxis with potassium iodide during (131)I-meta-iodobenzylguanidine treatment in children with neuroblastoma. <i>Cancer</i> 2002;94(7):1395-401.
van den Berg H, Furstner F, van den Bos C, et al. Decreasing the number of MOPP courses reduces gonadal damage in survivors of childhood Hodgkin disease. <i>Pediatr Blood Cancer</i> 2004;42(3):210-215.
van Santen HM, Aronson DC, Vulsma T, et al. Frequent adverse events after treatment for childhood-onset differentiated thyroid carcinoma: a single institute experience. <i>Eur J Cancer</i> 2004;40(11):1743-51.
van Santen HM, de Kraker J, Vulsma T. Endocrine late effects from multi-modality treatment of neuroblastoma. <i>Eur J Cancer</i> 2005;41(12):1767-74.
Hartman A, van den Bos C, Stijnen T, et al. Decrease in motor performance in children with cancer is independent of cumulative dose of vincristine. <i>Cancer</i> 2006;106(6):1395-401.
Stam H, Hartman EE, Deurloo JA, et al. Young adult patients with a history of pediatric disease: impact on course of life and transition into adulthood. <i>J Adolesc Health</i> 2006;39(1):4-13.
van Dalen EC, van der Pal HJ, Kok WE, et al. Clinical heart failure in a cohort of children treated with anthracyclines: a long-term follow-up study. <i>Eur J Cancer</i> 2006;42(18):3191-8. <sup>a</sup>
van Beek RD, Smit M, van den Heuvel-Eibrink MM, et al. Inhibin B is superior to FSH as a serum marker for spermatogenesis in men treated for Hodgkin's lymphoma with chemotherapy during childhood. <i>Hum Reprod</i> 2007;22(12):3215-22.
van Beek RD, van den Heuvel-Eibrink MM, Laven JS, et al. Anti-Mullerian hormone is a sensitive serum marker for gonadal function in women treated for Hodgkin's lymphoma during childhood. <i>J Clin Endocrinol Metab</i> 2007;92(10):3869-74.
Hartman A, van den Bos C, Stijnen T, et al. Decrease in peripheral muscle strength and ankle dorsiflexion as long-term side effects of treatment for childhood cancer. <i>Pediatr Blood Cancer</i> 2008;50(4):833-7.
Huisman J, Aukema EJ, Deijnen JB, et al. The usefulness of growth hormone treatment for psychological status in young adult survivors of childhood leukaemia: an open-label study. <i>BMC Pediatr</i> 2008;20:8-25.
Aukema EJ, Caan MW, Oudhuis N, et al. White matter fractional anisotropy correlates with speed of processing and motor speed in young childhood cancer survivors. <i>Int J Radiat Oncol Biol Phys</i> 2009;74(3):837-43.
De Bruin ML, Burgers JA, Baas P, et al. Malignant mesothelioma after radiation treatment for Hodgkin lymphoma. <i>Blood</i> 2009;113(16):3679-81.
De Bruin ML, Dorresteijn LD, van't Veer MB, et al. Increased risk of stroke and transient ischemic attack in 5-year survivors of Hodgkin lymphoma. <i>J Natl Cancer Inst</i> 2009;101(13):928-37
De Bruin ML, Sparidans J, van't Veer MB, et al. Breast cancer risk in female survivors of Hodgkin's lymphoma: lower risk after smaller radiation volumes. <i>J Clin Oncol</i> . 2009;27(26):4239-46.
Jagt CT, Zuckermann M, Ten Kate F, et al. Venous occlusive disease as a complication of preoperative chemotherapy for Wilms tumor: A clinico-pathological analysis. <i>Pediatr Blood Cancer</i> 2009;53(7):1211-5.
Maurice-Stam H, Silberbusch LM, Last BF, et al. Evaluation of a psycho-educational group intervention for children treated for cancer: a descriptive pilot study. <i>Psychooncology</i> 2009;18(7):762-6.
van Beek RD, van den Heuvel-Eibrink MM, Hakvoort-Cammel FG, et al. Bone mineral density, growth, and thyroid function in long-term survivors of pediatric Hodgkin's lymphoma treated with chemotherapy only. <i>J Clin Endocrinol Metab</i> 2009;94(6):1904-9.
van den Berg MH, Overbeek A, van der Pal HJ, et al. Using web-based and paper-based questionnaires for collecting data on fertility issues among female childhood cancer survivors: differences in response characteristics. <i>J Med Internet Res</i> 2011; 13(3):e76.
van den Heijkant S, Hoorweg-Nijman G, Huisman J, et al. Effects of growth hormone therapy on bone mass, metabolic balance, and well-being in young adult survivors of childhood acute lymphoblastic leukemia. <i>J Pediatr Hematol Oncol</i> 2011;33:e231-8.
Daams M, Schuitema I, van Dijk BW, et al. Long-term effects of cranial irradiation and intrathecal chemotherapy in treatment of childhood leukemia: a MEG study of power spectrum and correlated cognitive dysfunction. <i>BMC Neurol</i> . 2012;12(1):84.
Visscher H, Ross CJ, Rassekh SR et al; Canadian Pharmacogenomics Network for Drug Safety Consortium. Pharmacogenomic prediction of anthracycline-induced cardiotoxicity in children. <i>J Clin Oncol</i> . 2012;30(13):1422-8.

## References

1. Curry HL, Parkes SE, Powell JE, *et al.* Caring for survivors of childhood cancers: the size of the problem. *Eur J Cancer* 2006; 42(4):501-508.
2. Gatta G, Zigon G, Capocaccia R, *et al.* Survival of European children and young adults with cancer diagnosed 1995-2002. *Eur J Cancer* 2009; 45(6):992-1005.
3. Geenen MM, Cardous-Ubbink MC, Kremer LC, *et al.* Medical assessment of adverse health outcomes in long-term survivors of childhood cancer. *JAMA* 2007; 297(24):2705-2715.
4. Mertens AC, Liu Q, Neglia JP, *et al.* Cause-specific late mortality among 5-year survivors of childhood cancer: the Childhood Cancer Survivor Study. *J Natl Cancer Inst* 2008; 100(19):1368-1379.
5. Oeffinger KC, Mertens AC, Sklar CA, *et al.* Chronic health conditions in adult survivors of childhood cancer. *N Engl J Med* 2006; 355(15):1572-1582.
6. Reulen RC, Winter DL, Frobisher C, *et al.* Long-term cause-specific mortality among survivors of childhood cancer. *JAMA* 2010; 304(2):172-179.
7. Reulen RC, Frobisher C, Winter DL, *et al.* Long-term risks of subsequent primary neoplasms among survivors of childhood cancer. *JAMA* 2011; 305(22):2311-2319.
8. Oeffinger KC, van Leeuwen FE, Hodgson DC. Methods to assess adverse health-related outcomes in cancer survivors. *Cancer Epidemiol Biomarkers Prev* 2011; 20(10):2022-2034.
9. Jaspers MW, Caron H, Behrendt H, *et al.* The development of a new information model for a pediatric cancer registry on late treatment sequelae in The Netherlands. *Stud Health Technol Inform* 2000; 77:895-899.
10. Dutch Childhood Oncology Group. Richtlijn follow-up na kinderanker meer dan 5 jaar na diagnose. SKION, Den Haag/Amsterdam. 2010.
11. Cardous-Ubbink MC, Heinen RC, Langeveld NE, *et al.* Long-term cause-specific mortality among five-year survivors of childhood cancer. *Pediatr Blood Cancer* 2004; 42(7):563-573.
12. Cardous-Ubbink MC, Heinen RC, Bakker PJ, *et al.* Risk of second malignancies in long-term survivors of childhood cancer. *Eur J Cancer* 2007; 43(2):351-362.
13. Cardous-Ubbink MC, Geenen MM, Schade KJ, *et al.* Hypertension in long-term survivors of childhood cancer: a nested case-control study. *Eur J Cancer* 2010; 46(4):782-790.
14. van der Pal HJ, van Dalen EC, van DE, *et al.* High risk of symptomatic cardiac events in childhood cancer survivors. *J Clin Oncol* 2012; 30(13):1429-1437.
15. van Dijk IW, Oldenburger F, Cardous-Ubbink MC, *et al.* Evaluation of late adverse events in long-term wilms' tumor survivors. *Int J Radiat Oncol Biol Phys* 2010; 78(2):370-378.
16. van Dalen EC, van der Pal HJ, van den Bos C, *et al.* Clinical heart failure during pregnancy and delivery in a cohort of female childhood cancer survivors treated with anthracyclines. *Eur J Cancer* 2006; 42(15):2549-2553.
17. Geenen MM, Bakker PJ, Kremer LC, *et al.* Increased prevalence of risk factors for cardiovascular disease in long-term survivors of acute lymphoblastic leukemia and Wilms tumor treated with radiotherapy. *Pediatr Blood Cancer* 2010; 55(4):690-697.
18. Heikens J, Michiels EM, Behrendt H, *et al.* Long-term neuro-endocrine sequelae after treatment for childhood medulloblastoma. *Eur J Cancer* 1998; 34(10):1592-1597.
19. Heikens J, Ubbink MC, van der Pal HP, *et al.* Long term survivors of childhood brain cancer have an increased risk for cardiovascular disease. *Cancer* 2000; 88(9):2116-2121.
20. Knijnenburg SL, Jaspers MW, van der Pal HJ, *et al.* Renal Dysfunction and Elevated Blood Pressure in Long-Term Childhood Cancer Survivors. *Clin J Am Soc Nephrol* 2012.
21. Mulder RL, Thonissen NM, van der Pal HJ, *et al.* Pulmonary function impairment measured by pulmonary function tests in long-term survivors of childhood cancer. *Thorax* 2011; 66(12):1065-1071.
22. Noorda EM, Somers R, van Leeuwen FE, *et al.* Adult height and age at menarche in childhood cancer survivors. *Eur J Cancer* 2001; 37(5):605-612.
23. Tromp K, Claessens JJ, Knijnenburg SL, *et al.* Reproductive status in adult male long-term survivors of childhood cancer. *Hum Reprod* 2011; 26(7):1775-1783.
24. van der Pal HJ, van Dalen EC, Hauptmann M, *et al.* Cardiac function in 5-year survivors of childhood cancer: a long-term follow-up study. *Arch Intern Med* 2010; 170(14):1247-1255.
25. van Santen HM, Vulpsma T, Dijkgraaf MG, *et al.* No damaging effect of chemotherapy in addition to radiotherapy on the thyroid axis in young adult survivors of childhood cancer. *J Clin Endocrinol Metab* 2003; 88(8):3657-3663.

26. Mulder RL, Kremer LC, Koot BG, *et al.* Surveillance of hepatic late adverse effects in a large cohort of long-term survivors of childhood cancer: Prevalence and risk factors. *Eur J Cancer* 2012.
27. Langeveld N, Ubbink M, Smets E. 'I don't have any energy': The experience of fatigue in young adult survivors of childhood cancer. *Eur J Oncol Nurs* 2000; 4(1):20-28.
28. Langeveld NE, Grootenhuis MA, Voute PA, *et al.* No excess fatigue in young adult survivors of childhood cancer. *Eur J Cancer* 2003; 39(2):204-214.
29. Langeveld NE, Ubbink MC, Last BF, *et al.* Educational achievement, employment and living situation in long-term young adult survivors of childhood cancer in the Netherlands. *Psychooncology* 2003; 12(3):213-225.
30. Langeveld NE, Grootenhuis MA, Voute PA, *et al.* Posttraumatic stress symptoms in adult survivors of childhood cancer. *Pediatr Blood Cancer* 2004; 42(7):604-610.
31. Langeveld NE, Grootenhuis MA, Voute PA, *et al.* Quality of life, self-esteem and worries in young adult survivors of childhood cancer. *Psychooncology* 2004; 13(12):867-881.
32. Maurice-Stam H, Grootenhuis MA, Caron HN, *et al.* Course of life of survivors of childhood cancer is related to quality of life in young adulthood. *J Psychosoc Oncol* 2007; 25(3):43-58.
33. Maurice-Stam H, Oort FJ, Last BF, *et al.* A predictive model of health-related quality of life in young adult survivors of childhood cancer. *Eur J Cancer Care (Engl)* 2009; 18(4):339-349.
34. Maurice-Stam H, Verhoof EJ, Caron HN, *et al.* Are survivors of childhood cancer with an unfavourable psychosocial developmental trajectory more likely to apply for disability benefits? *Psychooncology* 2011.
35. Stam H, Grootenhuis MA, Last BF. The course of life of survivors of childhood cancer. *Psychooncology* 2005; 14(3):227-238.
36. Stam H, Grootenhuis MA, Caron HN, *et al.* Quality of life and current coping in young adult survivors of childhood cancer: positive expectations about the further course of the disease were correlated with better quality of life. *Psychooncology* 2006; 15(1):31-43.
37. van Dijk M, Grootenhuis MA, de BM, *et al.* Alexithymia in long-term survivors of childhood cancer. *Pediatr Rehabil* 2002; 5(4):203-207.
38. Aronson DC, Slaar A, Heinen RC, *et al.* Long-term outcome of bilateral Wilms tumors (BWT). *Pediatr Blood Cancer* 2011; 56(7):1110-1113.
39. van Dijk IW, Cardous-Ubbink MC, van der Pal HJ, *et al.* Dose-Effect Relationships for Adverse Events After Cranial Radiation Therapy in Long-term Childhood Cancer Survivors. *Int J Radiat Oncol Biol Phys* 2013; 85(3):768-775.
40. Hudson MM, Ness KK, Nolan VG, *et al.* Prospective medical assessment of adults surviving childhood cancer: study design, cohort characteristics, and feasibility of the St. Jude Lifetime Cohort study. *Pediatr Blood Cancer* 2011; 56(5):825-836.
41. Robison LL, Mertens AC, Boice JD, *et al.* Study design and cohort characteristics of the Childhood Cancer Survivor Study: a multi-institutional collaborative project. *Med Pediatr Oncol* 2002; 38(4):229-239.
42. Robison LL, Armstrong GT, Boice JD, *et al.* The Childhood Cancer Survivor Study: a National Cancer Institute-supported resource for outcome and intervention research. *J Clin Oncol* 2009; 27(14):2308-2318.
43. Hawkins MM, Lancashire ER, Winter DL, *et al.* The British Childhood Cancer Survivor Study: Objectives, methods, population structure, response rates and initial descriptive information. *Pediatr Blood Cancer* 2008; 50(5):1018-1025.
44. McBride ML, Rogers PC, Sheps SB, *et al.* Childhood, adolescent, and young adult cancer survivors research program of British Columbia: objectives, study design, and cohort characteristics. *Pediatr Blood Cancer* 2010; 55(2):324-330.
45. Kuehni CE, Rueegg CS, Michel G, *et al.* Cohort profile: the Swiss childhood cancer survivor study. *Int J Epidemiol* 2012; 41(6):1553-1564.
46. Stricker BH, Stijnen T. Analysis of individual drug use as a time-varying determinant of exposure in prospective population-based cohort studies. *Eur J Epidemiol* 2010; 25(4):245-251.
47. Grimes DA, Schulz KF. Cohort studies: marching towards outcomes. *Lancet* 2002; 359(9303):341-345.
48. Laupacis A, Wells G, Richardson WS, *et al.* Users' guides to the medical literature. V. How to use an article about prognosis. Evidence-Based Medicine Working Group. *JAMA* 1994; 272(3):234-237.
49. Visscher H, Ross CJ, Rassekh SR, *et al.* Pharmacogenomic prediction of anthracycline-induced cardiotoxicity in children. *J Clin Oncol* 2012; 30(13):1422-1428.
50. Bhatia S. Role of genetic susceptibility in development of treatment-related adverse outcomes in cancer survivors. *Cancer Epidemiol Biomarkers Prev* 2011; 20(10):2048-2067.