Childhood cancer survivors: Evidence and care

Sieswerda, E.

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Chapter 2

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


1 Joint first authorship with E. Sieswerda

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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 published studies 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 ≥5-years 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 ≥5 years since diagnosis. In January 2009, 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 late effects of childhood cancer treatment and will continuously contribute in reducing evidence gaps concerning risks and risk groups within this vulnerable population.
Introduction

More effective treatment strategies dramatically improved survival of childhood cancer. In the 1960s only 30% of childhood cancer patients survived at least five years, while nowadays five-year survival reaches 80%. 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. 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 quality of life of current and future childhood cancer survivors in different ways. First, it may lead to 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 strengths and limitations of our study design it is essential to provide a complete overview of the methodology and baseline characteristics of a study.

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 characteristics 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 five 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, also information on medical follow-up of the patients who survived at least five years since primary cancer diagnosis are prospectively collected and registered. 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 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 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 decease 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 (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 one, two, or five 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 five 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
### 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)\(^a\)

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Who</th>
<th>Medical history</th>
<th>Physical examination</th>
<th>Laboratory diagnostics</th>
<th>Other diagnostic testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>General</td>
<td>All survivors</td>
<td>General medical history, complaints, medication, smoking, substance abuse</td>
<td>General physical examination</td>
<td>ESR, complete blood count, white blood cell differential, hepatic function panel, serum creatinine, estimated GFR</td>
<td>-</td>
</tr>
<tr>
<td>Psychosocial</td>
<td>All survivors</td>
<td>Psychosocial history, including education, work, household and insurance issues</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Neuroendocrine</td>
<td>Cranial surgery, cranial radiotherapy, survivors of a brain tumour</td>
<td>Neurropsychiatric symptoms, endocrine related symptoms, vision, hearing, oral health, dysphagia</td>
<td>-</td>
<td>TSH, FT4, thyroglobulin, IGF-1, prolactin</td>
<td>X-wrist(^b) Audiogram(^c)</td>
</tr>
<tr>
<td></td>
<td>Cisplatin, carboplatin, cranial radiotherapy &gt;50 Gy</td>
<td>Ear pain, tinnitus, hearing</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Corticosteroids, cranial radiotherapy</td>
<td>Vision</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Radiotherapy neck/cervical vertebrae or thoracic radiotherapy</td>
<td>Endocrine related symptoms, voice, stridor</td>
<td>Thyroid palpation</td>
<td>TSH, FT4, thyroglobulin, calcium, albumin</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Spinal radiotherapy</td>
<td>Paresthesia, sensory and motor function</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Reproductive</td>
<td>Males treated with cranial radiotherapy, abdominal/pelvic radiotherapy, pelvic surgery, genital surgery or any chemotherapy</td>
<td>Reproductive health</td>
<td>Pubic hair, testes size, Tanner stage</td>
<td>FSH, LH, testosterone</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Females treated with cranial radiotherapy, abdominal/pelvic radiotherapy, pelvic surgery, genital surgery or any chemotherapy</td>
<td>Reproductive health, menstrual cycle</td>
<td>Pubic hair, Tanner stage</td>
<td>if not on OCP: FSH, LH, progesterone, estradiol</td>
<td>-</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Thoracic surgery, thoracic radiotherapy, anthracyclines, mitoxantrone, high-dose cyclophosphamide</td>
<td>Angina pectoris, palpitations, pedal edema, nycturia, dyspnea</td>
<td>Blood pressure, cardiac examination</td>
<td>-</td>
<td>Echocardiogram(^d), electrocardiogram(^e)</td>
</tr>
</tbody>
</table>

\(^{a}\) Organ system is defined in the context of the clinical scenario.
### 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 (continued)

<table>
<thead>
<tr>
<th>Organ system</th>
<th>Who</th>
<th>Medical history</th>
<th>Physical examination</th>
<th>Laboratory diagnostics</th>
<th>Other diagnostic testing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lungs</td>
<td>Thoracic surgery, thoracic radiotherapy, bleomycin, mitomycin, nitrosoureas</td>
<td>Cough, dyspnoea, chest pain, upper respiratory tract infections</td>
<td>Lung examination</td>
<td>-</td>
<td>Spirometry: vital capacity, FEV1, diffusion capacity</td>
</tr>
<tr>
<td>Kidneys / bladder</td>
<td>Abdominal/pelvic surgery, abdominal/ pelvic radiotherapy, cisplatin, carboplatin, ifosfamide, high-dose cyclophosphamide, high-dose methotrexate</td>
<td>Urinary tract infections, kidney stones, polyuria, polydipsia</td>
<td>Blood pressure</td>
<td>Urinalysis, calcium, phosphate, albumin, sodium, potassium, magnesium, bicarbonate, uric acid, osmolality</td>
<td>Renal ultrasound³</td>
</tr>
<tr>
<td>Gastrointestinal tract</td>
<td>Abdominal surgery, abdominal radiotherapy</td>
<td>Dysphagia, gastric complaints, abdominal pain, bowel movement frequency and stool consistency, food intolerance</td>
<td>Abdominal examination</td>
<td>Screening hepatitis B and C⁴</td>
<td>Abdominal ultrasound⁵</td>
</tr>
<tr>
<td></td>
<td>Rectal surgery, rectal radiotherapy</td>
<td>Sphincter control, pain, stool abnormalities</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Corticosteroids</td>
<td>Bone pain, fractures</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Spinal radiotherapy</td>
<td>Pain</td>
<td>Scoliosis, kyphosis</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Thoracic surgery, thoracic radiotherapy</td>
<td>-</td>
<td>Sitting height</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Secondary malignancies</td>
<td>Females who received thoracic radiotherapy</td>
<td>Changes of the breast</td>
<td>Breast exam</td>
<td>-</td>
<td>Mammography⁶</td>
</tr>
</tbody>
</table>

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.

¹ In 2010 nationwide, evidence- and consensus-based long-term follow-up guidelines have been implemented. ² Two-yearly, until end of growth. ³ Performed every 5 years. ⁴ Performed every 2-5 year, depending on cardiotoxic treatment, previous abnormalities and pregnancies. ⁵ Performed once at first visit. ⁶ Performed every 5 years, only after abdominal/pelvic radiotherapy or abdominal/pelvic surgery. ⁷ Two-yearly, starting at age 25.

Abbreviations: EKZ/AMC, Emma Children’s Hospital / Academic Medical Center; ESR: erythrocyte sedimentation rate; 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.
once by a psychologist or late-effects nurse. Since 2010, nationwide long-term follow-up guidelines have been implemented. These guidelines include evidence- 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.

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: www.skion.nl). These distributions have not changed substantially over the last decades.

We also summarized 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.
Chapter 2

**Results**

**The current EKZ/AMC 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 five years since diagnosis (Figure 1).

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

- 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 focussing on clinical end points (i.e. mortality, second malignancies)

**Abbreviations:** $N$: number; EKZ/AMC: Emma Children’s Hospital/Academic Medical Center
Table 2 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 date 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 3 shows detailed treatment information for primary cancer, recurrences and second cancers within the first five year 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 (Figure 1).

Table 2 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.
Table 2  Clinical characteristics of the EKZ/AMC childhood cancer survivor cohort at 1 January 2009

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total N=1822</th>
<th>Medical follow-up late effects outpatient clinic N=1452</th>
<th>Other medical follow-up EKZ/AMC N=125</th>
<th>No medical follow-up EKZ/AMC N=245</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1004 (55.1)</td>
<td>794 (54.7)</td>
<td>64 (51.2)</td>
<td>146 (59.6)</td>
</tr>
<tr>
<td>Female</td>
<td>818 (44.9)</td>
<td>658 (45.3)</td>
<td>61 (48.8)</td>
<td>99 (40.4)</td>
</tr>
<tr>
<td>Primary childhood cancer diagnosis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leukemia</td>
<td>481 (26.4)</td>
<td>380 (26.2)</td>
<td>37 (29.6)</td>
<td>64 (26.1)</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>347 (19.0)</td>
<td>303 (20.9)</td>
<td>10 (8.0)</td>
<td>34 (13.9)</td>
</tr>
<tr>
<td>Brain/CNS tumor</td>
<td>129 (7.1)</td>
<td>86 (5.9)</td>
<td>17 (13.6)</td>
<td>26 (10.6)</td>
</tr>
<tr>
<td>Bone tumor</td>
<td>149 (8.2)</td>
<td>109 (7.5)</td>
<td>15 (12.0)</td>
<td>25 (10.2)</td>
</tr>
<tr>
<td>Soft tissue sarcoma</td>
<td>195 (10.7)</td>
<td>157 (10.8)</td>
<td>14 (11.2)</td>
<td>24 (9.8)</td>
</tr>
<tr>
<td>Renal tumor</td>
<td>239 (13.1)</td>
<td>209 (14.4)</td>
<td>7 (5.6)</td>
<td>23 (9.4)</td>
</tr>
<tr>
<td>Hepatic tumor</td>
<td>25 (1.4)</td>
<td>20 (1.4)</td>
<td>1 (0.8)</td>
<td>4 (1.6)</td>
</tr>
<tr>
<td>Germ cell tumor</td>
<td>70 (3.8)</td>
<td>53 (3.7)</td>
<td>5 (4.0)</td>
<td>12 (4.9)</td>
</tr>
<tr>
<td>Neuroblastoma</td>
<td>128 (7.0)</td>
<td>97 (6.7)</td>
<td>13 (10.4)</td>
<td>18 (7.3)</td>
</tr>
<tr>
<td>Retinoblastoma</td>
<td>14 (0.8)</td>
<td>8 (0.6)</td>
<td>2 (1.6)</td>
<td>4 (1.6)</td>
</tr>
<tr>
<td>Other tumors</td>
<td>45 (2.5)</td>
<td>30 (2.0)</td>
<td>4 (3.2)</td>
<td>11 (4.5)</td>
</tr>
<tr>
<td>Age at diagnosis, median (range) yr</td>
<td>6.0 (0.0-17.8)</td>
<td>5.9 (0.0-17.8)</td>
<td>5.5 (0.0-17.6)</td>
<td>6.9 (0.0-17.8)</td>
</tr>
<tr>
<td>0-4 yr</td>
<td>799 (43.9)</td>
<td>639 (44.0)</td>
<td>57 (45.6)</td>
<td>103 (42.0)</td>
</tr>
<tr>
<td>5-9 yr</td>
<td>492 (27.0)</td>
<td>398 (27.4)</td>
<td>31 (24.8)</td>
<td>63 (25.7)</td>
</tr>
<tr>
<td>10-14 yr</td>
<td>413 (22.7)</td>
<td>330 (22.7)</td>
<td>21 (16.8)</td>
<td>62 (25.3)</td>
</tr>
<tr>
<td>15-18 yr</td>
<td>118 (6.5)</td>
<td>85 (5.9)</td>
<td>16 (12.8)</td>
<td>17 (6.9)</td>
</tr>
<tr>
<td>Attained age, median (range) yr</td>
<td>24.8 (5.2-52.3)</td>
<td>26.6 (6.6-52.3)</td>
<td>16.9 (5.9-42.9)</td>
<td>19.8 (5.2-50.9)</td>
</tr>
<tr>
<td>5-9 yr</td>
<td>71 (3.9)</td>
<td>28 (1.9)</td>
<td>18 (14.4)</td>
<td>25 (10.2)</td>
</tr>
<tr>
<td>10-14 yr</td>
<td>212 (11.6)</td>
<td>138 (9.5)</td>
<td>29 (23.2)</td>
<td>45 (18.4)</td>
</tr>
<tr>
<td>15-19 yr</td>
<td>299 (16.4)</td>
<td>214 (14.7)</td>
<td>44 (35.2)</td>
<td>41 (16.7)</td>
</tr>
<tr>
<td>20-24 yr</td>
<td>331 (18.2)</td>
<td>269 (18.5)</td>
<td>24 (19.2)</td>
<td>38 (15.5)</td>
</tr>
<tr>
<td>25-29 yr</td>
<td>304 (16.7)</td>
<td>282 (19.4)</td>
<td>4 (3.2)</td>
<td>18 (7.3)</td>
</tr>
<tr>
<td>30-34 yr</td>
<td>250 (13.7)</td>
<td>226 (15.6)</td>
<td>3 (2.4)</td>
<td>21 (8.6)</td>
</tr>
<tr>
<td>35-39 yr</td>
<td>188 (10.3)</td>
<td>169 (11.6)</td>
<td>2 (1.6)</td>
<td>17 (6.9)</td>
</tr>
<tr>
<td>≥40 yr</td>
<td>137 (7.5)</td>
<td>126 (8.7)</td>
<td>1 (0.8)</td>
<td>10 (4.1)</td>
</tr>
<tr>
<td>Unknown</td>
<td>30 (1.6)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>30 (12.2)</td>
</tr>
<tr>
<td>Follow-up duration, median (range) yr</td>
<td>17.7 (5.0-42.5)</td>
<td>19.2 (5.0-42.5)</td>
<td>7.7 (5.0-28.8)</td>
<td>10.9 (5.0-38.3)</td>
</tr>
<tr>
<td>5-9 yr</td>
<td>386 (21.2)</td>
<td>200 (13.8)</td>
<td>84 (67.2)</td>
<td>102 (41.6)</td>
</tr>
<tr>
<td>10-14 yr</td>
<td>345 (18.9)</td>
<td>291 (20.0)</td>
<td>16 (12.8)</td>
<td>38 (15.5)</td>
</tr>
</tbody>
</table>
Table 2  Clinical characteristics of the EKZ/AMC childhood cancer survivor cohort (continued)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Total N=1822</th>
<th>Medical follow-up late effects outpatient clinic N=1452</th>
<th>Other medical follow-up EKZ/AMC N=125</th>
<th>No medical follow-up EKZ/AMC N=245</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
</tr>
<tr>
<td>15-19 yr</td>
<td>321 (17.6)</td>
<td>288 (19.8)</td>
<td>17 (13.6)</td>
<td>16 (6.5)</td>
</tr>
<tr>
<td>20-24 yr</td>
<td>287 (15.8)</td>
<td>257 (17.7)</td>
<td>6 (4.8)</td>
<td>24 (9.8)</td>
</tr>
<tr>
<td>25-29 yr</td>
<td>248 (13.6)</td>
<td>225 (15.5)</td>
<td>2 (1.6)</td>
<td>21 (8.6)</td>
</tr>
<tr>
<td>30-34 yr</td>
<td>142 (7.8)</td>
<td>135 (9.3)</td>
<td>0 (0.0)</td>
<td>7 (2.9)</td>
</tr>
<tr>
<td>35-39 yr</td>
<td>53 (2.9)</td>
<td>46 (3.2)</td>
<td>0 (0.0)</td>
<td>7 (2.9)</td>
</tr>
<tr>
<td>≥40 yr</td>
<td>10 (0.5)</td>
<td>10 (0.7)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
</tr>
<tr>
<td>Lost-to-follow-up before 5-yr survival</td>
<td>30 (1.6)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>30 (12.1)</td>
</tr>
</tbody>
</table>

Treatment period

<table>
<thead>
<tr>
<th>Year</th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1965-1969</td>
<td>40 (2.2)</td>
<td>27 (1.9)</td>
<td>0 (0.0)</td>
<td>13 (5.3)</td>
</tr>
<tr>
<td>1970-1974</td>
<td>126 (6.9)</td>
<td>84 (5.8)</td>
<td>0 (0.0)</td>
<td>42 (17.1)</td>
</tr>
<tr>
<td>1975-1979</td>
<td>229 (12.6)</td>
<td>181 (12.5)</td>
<td>3 (2.4)</td>
<td>45 (18.4)</td>
</tr>
<tr>
<td>1980-1984</td>
<td>322 (17.7)</td>
<td>268 (18.5)</td>
<td>9 (7.2)</td>
<td>45 (18.4)</td>
</tr>
<tr>
<td>1985-1989</td>
<td>301 (16.5)</td>
<td>261 (18.0)</td>
<td>9 (7.2)</td>
<td>31 (12.7)</td>
</tr>
<tr>
<td>1990-1994</td>
<td>310 (17.0)</td>
<td>247 (17.0)</td>
<td>36 (28.8)</td>
<td>27 (11.0)</td>
</tr>
<tr>
<td>1995-1999</td>
<td>320 (17.6)</td>
<td>262 (18.0)</td>
<td>31 (24.8)</td>
<td>27 (11.0)</td>
</tr>
<tr>
<td>2000-2002</td>
<td>174 (9.5)</td>
<td>122 (8.4)</td>
<td>37 (29.6)</td>
<td>15 (6.1)</td>
</tr>
</tbody>
</table>

Overall treatment modality

<table>
<thead>
<tr>
<th>Modality</th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy only</td>
<td>467 (25.6)</td>
<td>380 (26.2)</td>
<td>41 (32.8)</td>
<td>46 (18.8)</td>
</tr>
<tr>
<td>Radiotherapy only</td>
<td>18 (1.0)</td>
<td>15 (1.0)</td>
<td>0 (0.0)</td>
<td>3 (1.2)</td>
</tr>
<tr>
<td>Surgery only</td>
<td>182 (10.0)</td>
<td>124 (8.5)</td>
<td>26 (20.8)</td>
<td>32 (13.1)</td>
</tr>
<tr>
<td>Chemotherapy with radiotherapy</td>
<td>215 (11.8)</td>
<td>176 (12.1)</td>
<td>7 (5.6)</td>
<td>32 (13.1)</td>
</tr>
<tr>
<td>Chemotherapy with surgery</td>
<td>587 (31.7)</td>
<td>490 (33.7)</td>
<td>30 (24.0)</td>
<td>58 (23.7)</td>
</tr>
<tr>
<td>Radiotherapy with surgery</td>
<td>89 (4.9)</td>
<td>61 (4.2)</td>
<td>3 (2.4)</td>
<td>25 (10.2)</td>
</tr>
<tr>
<td>Chemotherapy with radiotherapy and surgery</td>
<td>257 (14.1)</td>
<td>203 (14.0)</td>
<td>15 (12.0)</td>
<td>39 (15.9)</td>
</tr>
<tr>
<td>None</td>
<td>8 (0.4)</td>
<td>3 (0.2)</td>
<td>3 (2.4)</td>
<td>2 (0.8)</td>
</tr>
<tr>
<td>Unknown</td>
<td>8 (0.4)</td>
<td>0 (0.0)</td>
<td>0 (0.0)</td>
<td>8 (3.3)</td>
</tr>
</tbody>
</table>

Recurrence of primary tumor

<table>
<thead>
<tr>
<th>Recurrence</th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>339 (18.6)</td>
<td>204 (14.0)</td>
<td>43 (34.4)</td>
<td>92 (37.6)</td>
</tr>
<tr>
<td>No</td>
<td>1483 (81.4)</td>
<td>1248 (86.0)</td>
<td>82 (65.6)</td>
<td>153 (62.4)</td>
</tr>
</tbody>
</table>

Vital status at end of follow-up

<table>
<thead>
<tr>
<th>Status</th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive</td>
<td>1653 (90.7)</td>
<td>1424 (98.1)</td>
<td>86 (68.8)</td>
<td>143 (58.4)</td>
</tr>
<tr>
<td>Deceased</td>
<td>169 (9.3)</td>
<td>28 (1.9)</td>
<td>39 (31.2)</td>
<td>102 (41.6)</td>
</tr>
</tbody>
</table>

a For 33 survivors treatment characteristics for 1 or 2 modalities were missing.

Abbreviations: CNS: central nervous system; EKZ/AMC: Emma Children’s Hospital / Academic Medical Center; N: number; yr: year.
Table 3 Treatment characteristics of the EKZ/AMC childhood cancer survivor cohort for primary cancer, recurrences and second cancers within the first five years since primary cancer diagnosis

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Primary cancer</th>
<th>Recurrences of primary cancer</th>
<th>Second cancers</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td></td>
</tr>
<tr>
<td>No. of childhood cancer survivors</td>
<td>1822 (100)</td>
<td>339 (18.6)</td>
<td>206 (11.3)</td>
</tr>
</tbody>
</table>

**Type of chemotherapy**

**Any**

| 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) |

**Cytotoxic antibiotics**

| Actinomycines | 492 (27.0) | 62 (18.3) | 15 (7.3) |
| Anthracyclines a | 698 (38.3) | 121 (35.7) | 19 (9.2) |
| Other cytotoxic antibiotics | 199 (10.9) | 22 (6.5) | 2 (1.0) |

**Alkylating agents**

| 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) |

**Anti-metabolites**

| 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) |

**Vinca-alkaloids and other natural products**

| 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) |

**Other antineoplastic agents**

| 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) |

**Radiotherapy**

**Any**

| Yes b | 579 (31.8) | 172 (50.7) | 40 (19.4) |
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 4 and 5). 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 less than five 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,\(^{11, 12, 14, 16}\) to subclinical (asymptomatic) late effects in 11 studies,\(^{13, 17-26}\) and psychosocial late effects in 11 studies.\(^{27-37}\) Four studies assessed the total burden, including clinical and subclinical late effects.\(^{3, 15, 38, 39}\) Important clinical events studied within our cohort included cause-specific mortality,\(^{11}\) second malignancies,\(^{12}\) and clinical heart failure.\(^{14, 16}\) Subclinical events included endocrine outcomes,\(^{18, 22, 23, 25}\) asymptomatic cardiac disease and cardiovascular risk factors,\(^{13, 17, 19, 24}\) pulmonary,\(^{21}\) renal,\(^{20}\) and hepatic toxicity.\(^{26}\)

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 4 studies investigating clinical events, i.e. cause-specific mortality, clinical heart failure, second malignancies,\(^{11, 12, 14, 16}\) and in 3 studies investigating total burden of adverse events.\(^{3, 15, 39}\) For the other studies the representativeness varied from 50.0% in a study investigating cardiovascular risk factors in leukemia and Wilms’ tumor survivors,\(^{17}\) to 88.7% in a study investigating pulmonary function impairment.\(^{21}\) 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\(^{27}\) up to 100% in 11 studies evaluating endocrine, cardiovascular and psychosocial late adverse effects.\(^{14, 16-19, 28-31, 34, 37}\)
Table 4: Overview of studies conducted within the EKZ/AMC childhood cancer survivor cohort

<table>
<thead>
<tr>
<th>Study topic and publication</th>
<th>Neuro-endocrine sequelae in medullo-blastoma survivors</th>
<th>Cardiovascular risk factors in brain tumor survivors</th>
<th>Experience of fatigue</th>
<th>Adult height and age at menarche</th>
<th>Alexithymia</th>
<th>Excess fatigue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period of childhood cancer diagnosis</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Aged ≥18 yr at investigation</td>
<td>Aged ≥16 yr at investigation</td>
</tr>
<tr>
<td>Additional inclusion criteria</td>
<td>Diagnosed with medulloblastoma; aged ≥18 yr at investigation; no seizures; no symptomatic ischemic heart disease; not pregnant</td>
<td>Diagnosed with brain cancer; aged ≥18 yr at investigation; no seizures; not pregnant; no growth hormone substitution</td>
<td>Aged ≥18 yr at investigation</td>
<td>Aged ≥18 yr at investigation</td>
<td>Aged ≥16 yr at investigation</td>
<td>Aged ≥16 yr at investigation</td>
</tr>
<tr>
<td>Survival</td>
<td>≥5 yr after end treatment</td>
<td>≥5 yr after end treatment</td>
<td>≥5 yr after end treatment</td>
<td>≥5 yr after end treatment</td>
<td>≥5 yr after end treatment</td>
<td>≥5 yr after end treatment</td>
</tr>
<tr>
<td>End date follow-up outcome assessment</td>
<td>Not reported</td>
<td>Not reported</td>
<td>1-1-1999</td>
<td>1-1-1997</td>
<td>Not reported</td>
<td>1-7-1999</td>
</tr>
<tr>
<td>N original cohort b</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>N study group (%) c</td>
<td>20</td>
<td>26</td>
<td>83</td>
<td>285</td>
<td>72</td>
<td>416 (90.6% of invited)</td>
</tr>
<tr>
<td>N follow-up group (%) d/ Completeness of follow-up</td>
<td>20 (100%)</td>
<td>26 (100%)</td>
<td>35 (42.2%)</td>
<td>244 (85.6%)</td>
<td>72 (100%)</td>
<td>416 (100%)</td>
</tr>
<tr>
<td>Follow-up duration</td>
<td>Median 16 (8-25) yr after end treatment</td>
<td>Mean 15.7 (9-25) yr after end treatment</td>
<td>Median 17 (8-25) yr after end treatment</td>
<td>Mean 14.6 (5-31) yr after end treatment</td>
<td>Not reported</td>
<td>15 (5-33) yr after end treatment</td>
</tr>
<tr>
<td>Control group</td>
<td>None</td>
<td>29 healthy siblings or college students</td>
<td>None</td>
<td>Dutch population</td>
<td>222 matched controls</td>
<td>1026 patients from 179 general practitioners without cancer history</td>
</tr>
</tbody>
</table>
Table 4 Overview of studies conducted within the EKZ/AMC childhood cancer survivor cohort (continued)

<table>
<thead>
<tr>
<th>Primary outcome</th>
<th>Medical assessment:</th>
<th>Medical assessment: Risk factors cardiovascular disease (CVD)</th>
<th>Semi-structured interviews: Fatigue from survivor's perspective</th>
<th>Medical assessment: Adult height, stratified for males and females, and age at menarche; effects treatment and age at diagnosis</th>
<th>Questionnaires: Incidence and medical determinants associated with alexithymia, stratified for males and females</th>
<th>Questionnaires: Level of fatigue; fatigue severity compared with controls</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical assessment: Endocrine function, i.e. growth hormone (GH), hypothalamus-pituitary-gonadal (HPG) axis, hypothalamus-pituitary-thyroid (HPT) axis, hypothalamus-pituitary-adrenocortical axis</td>
<td>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</td>
<td>Risk of CVD increased due to dyslipidemia, central obesity and elevated systolic blood pressure, particularly for those with growth hormone deficiency</td>
<td>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</td>
<td>Cranial with or without spinal radiotherapy leads to a significant reduction in adult height in both males and females, especially when given at age ≤8 yr; cranial radiotherapy resulted in earlier menarche</td>
<td>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</td>
<td>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</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Study topic and publication</th>
<th>Education, employment and living situation</th>
<th>Thyroid dysfunction</th>
<th>Cause-specific mortality</th>
<th>Posttraumatic stress symptoms</th>
<th>Quality of life, self-esteem and worries</th>
<th>Course of life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Period of childhood cancer diagnosis</td>
<td>Not reported</td>
<td>Not reported</td>
<td>1-1-1966 to 1-1-1996</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>-------------------------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>---------------------</td>
<td>-------------</td>
<td>-------------</td>
<td>-------------</td>
</tr>
<tr>
<td>Additional inclusion criteria</td>
<td>Aged ≥16 yr at investigation</td>
<td>Treated with cranial, craniospinal, cervical, mediastinal, thoracic or total body radiotherapy (RT)</td>
<td>None</td>
<td>Aged ≥16 yr at investigation</td>
<td>Aged ≥16 yr at investigation</td>
<td>Aged 18-30 yr at investigation; ability to understand Dutch questionnaires</td>
</tr>
<tr>
<td>Survival</td>
<td>≥5 yr after end treatment</td>
<td>≥5 yr after end treatment</td>
<td>≥5 yr after diagnosis</td>
<td>≥5 yr after end treatment</td>
<td>≥5 yr after end treatment</td>
<td>≥5 yr after end treatment</td>
</tr>
<tr>
<td>End date follow-up outcome assessment</td>
<td>1-7-1999</td>
<td>Not reported</td>
<td>1-1-1998</td>
<td>1-7-1999</td>
<td>1-1-1999</td>
<td>2002</td>
</tr>
<tr>
<td>N original cohort</td>
<td>Not reported (543 invited)</td>
<td>Not reported</td>
<td>1378</td>
<td>Not reported (543 invited)</td>
<td>Not reported (443 invited)</td>
<td>Not reported (449 invited)</td>
</tr>
<tr>
<td>N study group (%)</td>
<td>500 (92.1% of invited)</td>
<td>207</td>
<td>1378 (100%)</td>
<td>500 (92.1% of invited)</td>
<td>400 (90.3% of invited)</td>
<td>355 (71.1% of invited)</td>
</tr>
<tr>
<td>N follow-up group (%)</td>
<td>500 (100%)</td>
<td>205 (99.0%)</td>
<td>1365 (99.1%)</td>
<td>500 (100%)</td>
<td>400 (100%)</td>
<td>353 (99.4%)</td>
</tr>
<tr>
<td>Follow-up duration</td>
<td>Median 15 (5-33) yr after end treatment</td>
<td>Mean 19.1 yr after end treatment</td>
<td>Median 16.1 (5-30) yr after diagnosis</td>
<td>Median 15 (5-33) yr after end treatment</td>
<td>Median 15 (5-33) yr after end treatment</td>
<td>Mean 15.5 (4.9-30.3) yr after end treatment</td>
</tr>
<tr>
<td>Control group</td>
<td>1026 patients from 179 general practitioners without cancer history</td>
<td>None</td>
<td>General population</td>
<td>None</td>
<td>560 patients from 179 general practitioners without cancer history</td>
<td>508 patients from 82 general practitioners without cancer history</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Questionnaires: Level and determinants educational achievement, employment, living situation, marital status and off-spring</td>
<td>Medical assessment: Effect radiotherapy and chemotherapy on thyroid axis</td>
<td>Assessment of vital status: Standardized mortality ratio (SMR) and absolute excess risk (AER)</td>
<td>Questionnaires: Posttraumatic stress symptoms (PSS) and predictors</td>
<td>Questionnaires: Quality of life, self-esteem and worries; impact of demographic, medical and treatment factors, and self-esteem on quality of life and worries</td>
<td>Questionnaires: Course of life and socio-demographic outcomes</td>
</tr>
</tbody>
</table>
**Table 4** Overview of studies conducted within the EKZ/AMC childhood cancer survivor cohort (continued)

<table>
<thead>
<tr>
<th>Study topic and publication</th>
<th>Clinical heart failure and pregnancy</th>
<th>Health-related quality of life and current coping</th>
<th>Second malignancies</th>
<th>Total burden of adverse events</th>
<th>Course of life and health-related quality of life</th>
<th>Health-related quality of life prediction model</th>
</tr>
</thead>
<tbody>
<tr>
<td>van Dalen et al. Eur J Cancer 2006</td>
<td>Not reported</td>
<td>Aged 18-30 yr at investigation; ability to understand Dutch questionnaires</td>
<td>None</td>
<td>None</td>
<td>Aged 18-30 yr at investigation; ability to understand Dutch questionnaires</td>
<td>Aged 18-30 yr at investigation; ability to understand Dutch questionnaires</td>
</tr>
<tr>
<td>Stam et al. Psychooncology 2006</td>
<td>Not reported</td>
<td>Aged 18-30 yr at investigation; ability to understand Dutch questionnaires</td>
<td>None</td>
<td>None</td>
<td>Aged 18-30 yr at investigation; ability to understand Dutch questionnaires</td>
<td>Aged 18-30 yr at investigation; ability to understand Dutch questionnaires</td>
</tr>
<tr>
<td>Cardous-Ubbink et al. Eur J Cancer 2007</td>
<td>1-1-1966 to 1-1-1996</td>
<td>Aged 18-30 yr at investigation; ability to understand Dutch questionnaires</td>
<td>None</td>
<td>None</td>
<td>Aged 18-30 yr at investigation; ability to understand Dutch questionnaires</td>
<td>Aged 18-30 yr at investigation; ability to understand Dutch questionnaires</td>
</tr>
<tr>
<td>Geenen et al. JAMA 2007</td>
<td>1-1-1966 to 1-1-1996</td>
<td>Aged 18-30 yr at investigation; ability to understand Dutch questionnaires</td>
<td>None</td>
<td>None</td>
<td>Aged 18-30 yr at investigation; ability to understand Dutch questionnaires</td>
<td>Aged 18-30 yr at investigation; ability to understand Dutch questionnaires</td>
</tr>
<tr>
<td>Maurice-Stam et al. J Psychosoc Oncol 2007</td>
<td>Not reported</td>
<td>Aged 18-30 yr at investigation; ability to understand Dutch questionnaires</td>
<td>None</td>
<td>None</td>
<td>Aged 18-30 yr at investigation; ability to understand Dutch questionnaires</td>
<td>Aged 18-30 yr at investigation; ability to understand Dutch questionnaires</td>
</tr>
<tr>
<td>Maurice-Stam et al. Eur J Cancer Care 2009</td>
<td>Not reported</td>
<td>Aged 18-30 yr at investigation; ability to understand Dutch questionnaires</td>
<td>None</td>
<td>None</td>
<td>Aged 18-30 yr at investigation; ability to understand Dutch questionnaires</td>
<td>Aged 18-30 yr at investigation; ability to understand Dutch questionnaires</td>
</tr>
</tbody>
</table>

**Main results**
- Survivors less likely to complete high-school, more often unemployed, and lower rates of marriage and parenthood compared to controls; cranial irradiation dose ≤25 Gray prognostic factor for lower educational achievement
- 27% thyroid dysfunction; 18% thyroid 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
- 12% 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 psychosexual development, or achieved milestones at older age; survivors' education level was as high as that of controls
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>N original cohort b</td>
<td>206 female survivors; 53 delivered ≥1 children</td>
<td>Not reported (499 invited)</td>
<td>1368</td>
<td>1362</td>
<td>Not reported (449 invited)</td>
<td>Not reported (449 invited)</td>
</tr>
<tr>
<td>N study group (%) c</td>
<td>206 (100%); 53 (100%)</td>
<td>355 (71.1% of invited)</td>
<td>1368 (100%)</td>
<td>1362 (100%)</td>
<td>355 (71.1% of invited)</td>
<td>355 (71.1% of invited)</td>
</tr>
<tr>
<td>N follow-up group (%) d/ Completeness of follow-up</td>
<td>206 (100%)</td>
<td>353 (99.4%)</td>
<td>1358 (99.3%)</td>
<td>1284 (94.3%)</td>
<td>353 (99.4%)</td>
<td>353 (99.4%)</td>
</tr>
<tr>
<td>Follow-up duration</td>
<td>Mean 16.7 (0.30-29.8) yr after 1st anthracycline dose; mean 20.3 (5.8-28) yr for women who delivered ≥1 children</td>
<td>Mean 15.5 (4.9-30.3) yr after end treatment</td>
<td>Median 16.8 (5-30) yr after diagnosis</td>
<td>Median 17.0 (5-25) yr after diagnosis</td>
<td>Mean 15.5 (4.9-30.3) yr after end treatment</td>
<td>Mean 15.5 (4.9-30.3) yr after end treatment</td>
</tr>
<tr>
<td>Control group</td>
<td>None</td>
<td>507 patients from 82 general practitioners without cancer history</td>
<td>General population</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Medical assessment: Cumulative incidence peripartum clinical anthracycline-induced heart failure</td>
<td>Questionnaires: Medical assessment: Health-related quality of life (HRQoL); cognitive coping in relation to HRQoL</td>
<td>Medical assessment: Standardized incidence ratio (SIR) and absolute excess risk (AER) second malignancies</td>
<td>Medical assessment: Prevalence and severity treatment-specific adverse events (AEs)</td>
<td>Questionnaires: Impact medical determinants on course of life; impact course of life on quality of life</td>
<td>Questionnaires: Prediction of factors affecting health-related quality of life (HRQoL) using a theoretical model</td>
</tr>
<tr>
<td>Study topic and publication</td>
<td>Hypertension</td>
<td>Adverse events in Wilms’ tumor survivors</td>
<td>Cardiovascular risk factors in ALL and Wilms’ tumor survivors</td>
<td>Cardiac dysfunction</td>
<td>Adverse outcomes after bilateral Wilms’ tumor</td>
<td>Application for disability benefits</td>
</tr>
<tr>
<td>----------------------------</td>
<td>--------------</td>
<td>------------------------------------------</td>
<td>---------------------------------------------------------------</td>
<td>-------------------</td>
<td>-----------------------------------------------</td>
<td>-----------------------------------</td>
</tr>
<tr>
<td>Additional inclusion criteria</td>
<td>None</td>
<td>Diagnosed with Wilms’ tumor</td>
<td>Diagnosed with acute lymphoblastic leukemia (ALL) or Wilms’ tumor; aged ≥18 yr at investigation</td>
<td>Treated with potentially cardiotoxic therapy; aged ≥18 yr at investigation</td>
<td>Diagnosed with bilateral Wilms’ tumor</td>
<td>Aged 18-30 yr at investigation; ability to understand Dutch questionnaires</td>
</tr>
<tr>
<td>Survival</td>
<td>≥5 yr after diagnosis</td>
<td>≥5 yr after diagnosis</td>
<td>≥5 yr after diagnosis</td>
<td>≥5 yr after diagnosis</td>
<td>≥5 yr after diagnosis</td>
<td>≥5 yr after diagnosis</td>
</tr>
<tr>
<td>End date follow-up outcome assessment</td>
<td>Not reported</td>
<td>1-1-2004</td>
<td>1-10-2002</td>
<td>1-4-2004</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>$N$ original cohort $^b$</td>
<td>1362</td>
<td>185</td>
<td>282</td>
<td>735</td>
<td>32</td>
<td>Not reported</td>
</tr>
<tr>
<td>$N$ study group (%) $^c$</td>
<td>1145 (84.1%)</td>
<td>185 (100%)</td>
<td>141 (50%)</td>
<td>601 (81.8%)</td>
<td>28 (87.5%)</td>
<td>366</td>
</tr>
</tbody>
</table>
Table 4 Overview of studies conducted within the EKZ/AMC childhood cancer survivor cohort (continued)

<table>
<thead>
<tr>
<th>N follow-up group (%)</th>
<th>%/ Completeness of follow-up</th>
<th>Follow-up duration</th>
<th>Control group</th>
<th>Primary outcome</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1080 (94.3%); 44</td>
<td>97.8%</td>
<td>Median 20.4 (5-30)</td>
<td>123 matched controls from EKZ/AMC cohort</td>
<td>Medical assessment: Risk factors hypertension</td>
<td>Body mass index only risk factor associated with hypertension; cisplatin, cyclophosphamide, and abdominal radiotherapy associated with non-significant increased risk</td>
</tr>
<tr>
<td></td>
<td></td>
<td>yr after diagnosis</td>
<td></td>
<td>Medical assessment: Prevalence and severity adverse events (AEs) and treatment-related risk factors</td>
<td>68% ≥1 AE; 21% ≥5 AEs; 24% severe or life-threatening AEs; 85% of all AEs mild to moderate; radiotherapy to flank/abdomen increased risk of any AE, orthopedic events, second tumors and cardiovascular events</td>
</tr>
<tr>
<td>181 (97.8%)</td>
<td>100%</td>
<td>Mean 20.8 yr after</td>
<td>69 siblings of included survivors</td>
<td>Medical assessment: Prevalence cardiovascular risk factors (CRFs) (hypertension, diabetes mellitus, hypercholesterolemia, obesity, renal insufficiency)</td>
<td>≥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 ≥1 CRF</td>
</tr>
<tr>
<td>525 (87.4%)</td>
<td>100%</td>
<td>Median 15.4 (5-25)</td>
<td>None</td>
<td>Medical assessment: Prevalence and determinants left ventricular dysfunction</td>
<td>27% subclinical cardiac dysfunction (left ventricular shortening fraction (LVSF) &lt;30%); higher anthracycline dose, radiation to thorax, and younger age at diagnosis associated with reduced LVSF</td>
</tr>
<tr>
<td>25 (89.3%)</td>
<td>100%</td>
<td>Median 10.5 (5-34)</td>
<td>None</td>
<td>Medical assessment: Survival, renal at effects, secondary tumors</td>
<td>78% 10-yr overall survival; 52% significant morbidity; 32% renal failure including 20% renal transplantation; 20% secondary tumors</td>
</tr>
<tr>
<td>366 (100%)</td>
<td></td>
<td>Not reported</td>
<td>508 patients from 82 general practitioners without cancer history</td>
<td>Questionnaires: Relation between unfavorable psychosocial developmental trajectory while growing up and likelihood of labor participation in adult life</td>
<td>Survivors with disability benefits vs. without disability benefits vs. controls lower social and psychological scale scores; survivors with unfavorable developmental trajectory while growing up more likely to apply for disability benefits</td>
</tr>
</tbody>
</table>

The EKZ/AMC childhood cancer survivor cohort study
<table>
<thead>
<tr>
<th>Study topic and publication</th>
<th>Pulmonary function impairment</th>
<th>Reproductive status</th>
<th>Adverse events after cranial radiotherapy</th>
<th>Renal dysfunction and hypertension</th>
<th>Hepatic late adverse effects</th>
<th>Symptomatic cardiac events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Additional inclusion criteria</td>
<td>Treated with bleomycin/ pulmonary radiotherapy (RT) / pulmonary surgery, aged ≥18 yr at investigation</td>
<td>Male survivors aged ≥18 yr at investigation</td>
<td>None</td>
<td>None</td>
<td>No history of veno-occlusive disease; free of hepatitis virus infection</td>
<td>None</td>
</tr>
<tr>
<td>Survival</td>
<td>≥5 yr after diagnosis</td>
<td>≥5 yr after diagnosis</td>
<td>≥5 yr after diagnosis</td>
<td>≥5 yr after diagnosis</td>
<td>≥5 yr after diagnosis</td>
<td>≥5 yr after diagnosis</td>
</tr>
<tr>
<td>End date follow-up outcome assessment</td>
<td>1-1-2009</td>
<td>1-1-2008</td>
<td>1-1-2004</td>
<td>Not reported</td>
<td>1-1-2010</td>
<td>1-1-2006</td>
</tr>
<tr>
<td>N original cohort</td>
<td>248</td>
<td>879</td>
<td>1362</td>
<td>1845</td>
<td>1795</td>
<td>1362</td>
</tr>
<tr>
<td>N study group (%)</td>
<td>220 (88.7%)</td>
<td>565 (64.3%)</td>
<td>1362 (100%)</td>
<td>1442 (78.2%)</td>
<td>1404 (78.2%)</td>
<td>1362 (100%)</td>
</tr>
<tr>
<td>N follow-up group (%)</td>
<td>193 (87.7%)</td>
<td>488 (86.4%)</td>
<td>1284 (94.3%)</td>
<td>1378 (95.6%)</td>
<td>1362 (97.0%)</td>
<td>1362 (100%)</td>
</tr>
<tr>
<td>Follow-up duration</td>
<td>Median 17.9 (5.6-36.8) yr after diagnosis</td>
<td>Median 15.0 (5.0-39.0) yr after diagnosis</td>
<td>Median 17.0 (5-25) yr after diagnosis</td>
<td>Median 12.1 (5.0-36.1) yr after diagnosis</td>
<td>Median 12.4 (5.0-36.1) yr after diagnosis</td>
<td>Median 22.2 (5-44.5) yr after diagnosis</td>
</tr>
<tr>
<td>Control group</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Primary outcome</td>
<td>Medical assessment: Prevalence and risk factors obstructive and restrictive pulmonary function impairment, and diffusion capacity impairment</td>
<td>Medical assessment: Prevalence and risk factors obstructive and restrictive pulmonary function impairment, and diffusion capacity impairment</td>
<td>Medical assessment: Dose-effect relationships for the prevalence and severity of adverse events (AEs) after cranial radiotherapy (CRT)</td>
<td>Medical assessment: Prevalence and risk factors renal dysfunction and hypertension</td>
<td>Medical assessment: Prevalence and risk factors hepaticocellular dysfunction (elevated alanine aminotransferase (ALT)) and biliary tract dysfunction (elevated gamma-glutamyltransferase (γGT))</td>
<td>Medical assessment: Incidence and risk factors symptomatic cardiac events (CEs)</td>
</tr>
</tbody>
</table>
Table 4 Overview of studies conducted within the EKZ/AMC childhood cancer survivor cohort (continued)

| Main results | 44% pulmonary function impairment; RT, RT and bleomycin, and RT and surgery associated with highest risk pulmonary function impairment | >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 nephrototoxic 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 elevated ALT and γGT levels | 8.7% elevated liver enzymes; radiotherapy, higher BMI, higher alcohol intake, and longer follow-up time associated with elevated ALT and γGT levels |
| | 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 | | | 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 |

a 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.

b The patients in the original cohort represent the whole original group of childhood cancer survivors eligible for inclusion.

c The patients in the study group are the childhood cancer survivors included in the study.

d The patients in the follow-up group are the childhood cancer survivors with relevant outcome measures.

Abbreviations: yr: year; N: number; CI: confidence interval; EKZ/AMC: Emma Children’s Hospital/Academic Medical Center. Other abbreviation explained in text of specific study column.
**Table 5  Late effects studies including patients from the EKZ/AMC childhood cancer survivor cohort**

<table>
<thead>
<tr>
<th>Author(s)</th>
<th>Reference</th>
</tr>
</thead>
</table>
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 6).

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 6).

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. The Childhood Cancer Survivor Study (CCSS) from North America encompasses survivors from multiple hospitals, while the British Childhood Cancer Survivor Study (BCSS), the Childhood Adolescent and Young Adult Cancer Survivors (CAYACS) Research Program, and the Swiss Childhood Cancer Survivor Study (SCCSS) cover a complete nation- or state-wide 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, our cohort, as well as the SJLIFE and SCCSS cohorts, spans the complete history of contemporary cancer treatment in children, including recent treatment eras.

Table 5 Late effects studies including patients from the EKZ/AMC childhood cancer survivor cohort (continued)


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 6).

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### Table 6 Summary of published childhood cancer survivor cohort studies

<table>
<thead>
<tr>
<th>Study</th>
<th>EKZ/AMC Childhood Cancer Survivor Cohort</th>
<th>Childhood Cancer Survivor Study (CCSS)</th>
<th>British Childhood Cancer Survivor Study (BCCSS)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Year established</td>
<td>1996</td>
<td>1994</td>
<td>2006</td>
</tr>
<tr>
<td>Study design</td>
<td>Single center retrospective cohort study with prospective medical screening and evaluation</td>
<td>Multicenter retrospective cohort study</td>
<td>Population-based retrospective cohort study</td>
</tr>
<tr>
<td>Age at childhood cancer diagnosis</td>
<td>&lt;18 years</td>
<td>&lt;21 years</td>
<td>&lt;15 years</td>
</tr>
<tr>
<td>Survival since primary cancer diagnosis</td>
<td>≥5 years</td>
<td>≥5 years</td>
<td>≥5 years</td>
</tr>
<tr>
<td>Additional inclusion criteria</td>
<td>Diagnosed and treated for a primary malignancy; Diagnosed in the Netherlands; Treated primarily in the EKZ/AMC</td>
<td>Diagnosed and treated for specific primary malignancies; 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</td>
<td>Diagnosed and treated for a malignancy; Current age ≥16 years; Resident of Britain</td>
</tr>
<tr>
<td>Original childhood cancer survivor cohort (N)</td>
<td>1822</td>
<td>20720</td>
<td>17866</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>4.5%</td>
<td>14.6%</td>
<td>0.1%</td>
</tr>
<tr>
<td>End date current cohort description</td>
<td>31 Dec 2008</td>
<td>Nov 2000</td>
<td>17 Sep 2006</td>
</tr>
<tr>
<td>Availability of treatment characteristics</td>
<td>Chemotherapy agents, radiotherapy fields, surgery, other treatments, and treatment for recurrences available for 1781 survivors (97.7%); Cumulative doses available for some treatments</td>
<td>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%)</td>
<td>Chemotherapy available for 12450 survivors (69.7%), radiotherapy available for 12850 survivors (71.9%), and surgery available for 13215 survivors (73.9%)</td>
</tr>
<tr>
<td>Availability of biological samples</td>
<td>Collection of samples possible, but not systematically obtained</td>
<td>Buccal cells, saliva, peripheral blood, tumor tissue of subsequent neoplasms</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Comparison group</td>
<td>Not available</td>
<td>Sibling cohort</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Outcome assessment</td>
<td>Medical evaluation using cancer treatment follow-up protocols; Psychological assessment; Since 2010, medical evaluation using risk-based strategies recommended in the DCOG guideline</td>
<td>Comprehensive health questionnaires</td>
<td>Comprehensive health questionnaires</td>
</tr>
<tr>
<td>Study</td>
<td>Childhood Adolescent and Young Adult Cancer Survivors (CAYACS) Research Program</td>
<td>St. Jude Lifetime Cohort Study (SJLIFE)</td>
<td>Swiss Childhood Cancer Survivor Study (SCCSS)</td>
</tr>
<tr>
<td>----------------------------------------------------------------------</td>
<td>--------------------------------------------------------------------------------</td>
<td>----------------------------------------</td>
<td>-------------------------------------------</td>
</tr>
<tr>
<td>Year established</td>
<td>Not mentioned</td>
<td>2010</td>
<td>2007</td>
</tr>
<tr>
<td>Study design</td>
<td>Population-based retrospective cohort study</td>
<td>Single center retrospective cohort study with prospective medical screening and evaluation</td>
<td>Population-based retrospective cohort study</td>
</tr>
<tr>
<td>Age at childhood cancer diagnosis</td>
<td>&lt;25 years</td>
<td>Not mentioned (childhood malignancy)</td>
<td>&lt;15 years</td>
</tr>
<tr>
<td>Survival since primary cancer diagnosis</td>
<td>≥5 years</td>
<td>≥10 years</td>
<td>≥5 years</td>
</tr>
<tr>
<td>Additional inclusion criteria</td>
<td>Diagnosed and treated for a primary malignancy; Resident of British Columbia at time of diagnosis; Identified in Cancer Registry</td>
<td>Diagnosed and treated for a childhood malignancy at SJCRH; Current age ≥18 years</td>
<td>Diagnosed for specific primary malignancies; Resident of Switzerland at time of diagnosis; Identified in Swiss Childhood Cancer Registry</td>
</tr>
<tr>
<td>Original childhood cancer survivor cohort (N)</td>
<td>3841</td>
<td>3900</td>
<td>3115</td>
</tr>
<tr>
<td>Lost to follow-up</td>
<td>4.4%</td>
<td>&lt;10%</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>End date current cohort description</td>
<td>31 Dec 2000</td>
<td>1 Jan 2010</td>
<td>31 Dec 2010</td>
</tr>
<tr>
<td>Availability of treatment characteristics</td>
<td>Chemotherapy, radiotherapy and surgery available for 2975 survivors (77.4%)</td>
<td>Chemotherapy agents and cumulative doses, and radiotherapy fields available for 3612 survivors (92.6%)</td>
<td>Surgery, chemotherapy (agents will be studied in detail), radiotherapy (dose will be studied in detail), bone marrow transplantation</td>
</tr>
<tr>
<td>Availability of biological samples</td>
<td>Not available</td>
<td>Blood, urine</td>
<td>Not mentioned</td>
</tr>
<tr>
<td>Comparison group</td>
<td>British Columbia population (complete or reference sample)</td>
<td>Not mentioned</td>
<td>Sibling cohort; General population</td>
</tr>
<tr>
<td>Outcome assessment</td>
<td>Extraction of data from Cancer Registry; Linkage to (health) administrative databases</td>
<td>Medical evaluation using risk-based strategies recommended in the COG guideline; Comprehensive health questionnaires</td>
<td>Comprehensive health questionnaires; Medical evaluation in a small subgroup between 1994 and 1996; Extraction of data from and linkage with different registries</td>
</tr>
</tbody>
</table>

a 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.
b Treatment characteristics as described in Robison et al. Med Pediatr Oncol 2002;38:229-239.
c Diagnosis of leukemias, lymphomas, central nervous system tumors, malignant solid tumors, or Langerhans cell histiocytosis.

Abbreviations: 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.
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. 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 has 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/or population registries, 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. 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. In addition, for specific
outcomes appropriate population-based reference values are available, such as values of pulmonary, renal, hepatic and cardiac function.

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 under- or overestimation of the risk.\textsuperscript{47, 48} This is a similar issue that studies using questionnaires face,\textsuperscript{41-43, 45} while medical record linkage studies are less at risk of this type of bias.\textsuperscript{44} 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 LATER (LATe Effect Registry) project, which includes >6000 survivors whom are offered regular medical follow-up according to national evidence-based guidelines.\textsuperscript{10}

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.⁴⁹ 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.⁵⁰

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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The EKZ/AMC childhood cancer survivor cohort study


