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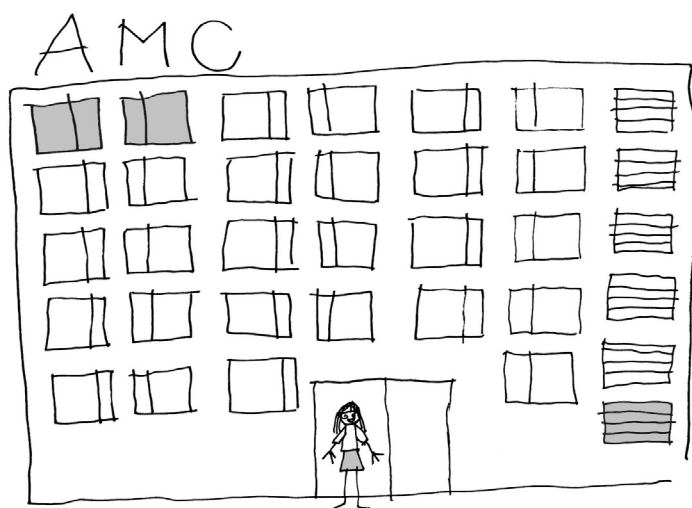
Chapter 2

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 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.¹ In the 1960s only 30% of childhood cancer patients survived at least five years, while nowadays five-year survival reaches 80%.² 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 mortality³⁻⁷ 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.⁸

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.⁹ 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 ≥ 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 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 (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

Organ system	Who	Medical history	Physical examination	Laboratory diagnostics	Other diagnostic testing
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, prolactine	X-wrist ^b
	Cisplatin, carboplatin, cranial radiotherapy >50 Gy	Ear pain, tinnitus, hearing	-	-	Audiogram ^c
	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, ^d electrocardiogram ^e

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*)

Organ system	Who	Medical history	Physical examination	Laboratory diagnostics	Other diagnostic testing
Lungs	Thoracic surgery, thoracic radiotherapy, bleomycine, mitomycine, nitrosureas	Cough, dyspnoea, chest pain, upper respiratory tract infections	Lung examination	-	Spirometry: ^c 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 ^f
Gastro-intestinal 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 ^e	Abdominal ultrasound ^f
	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 ^g

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.

^a In 2010 nationwide, evidence- and consensus-based long-term follow-up guidelines have been implemented. ^b Two-yearly, until end of growth. ^c Performed every 5 years. ^d Performed every 2-5 year, depending on cardiotoxic treatment, previous abnormalities and pregnancies. ^e Performed once at first visit. ^f Performed every 5 years, only after abdominal/pelvic radiotherapy or abdominal/pelvic surgery. ^g 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.¹⁰ 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.^{3, 11-15}

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.

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).

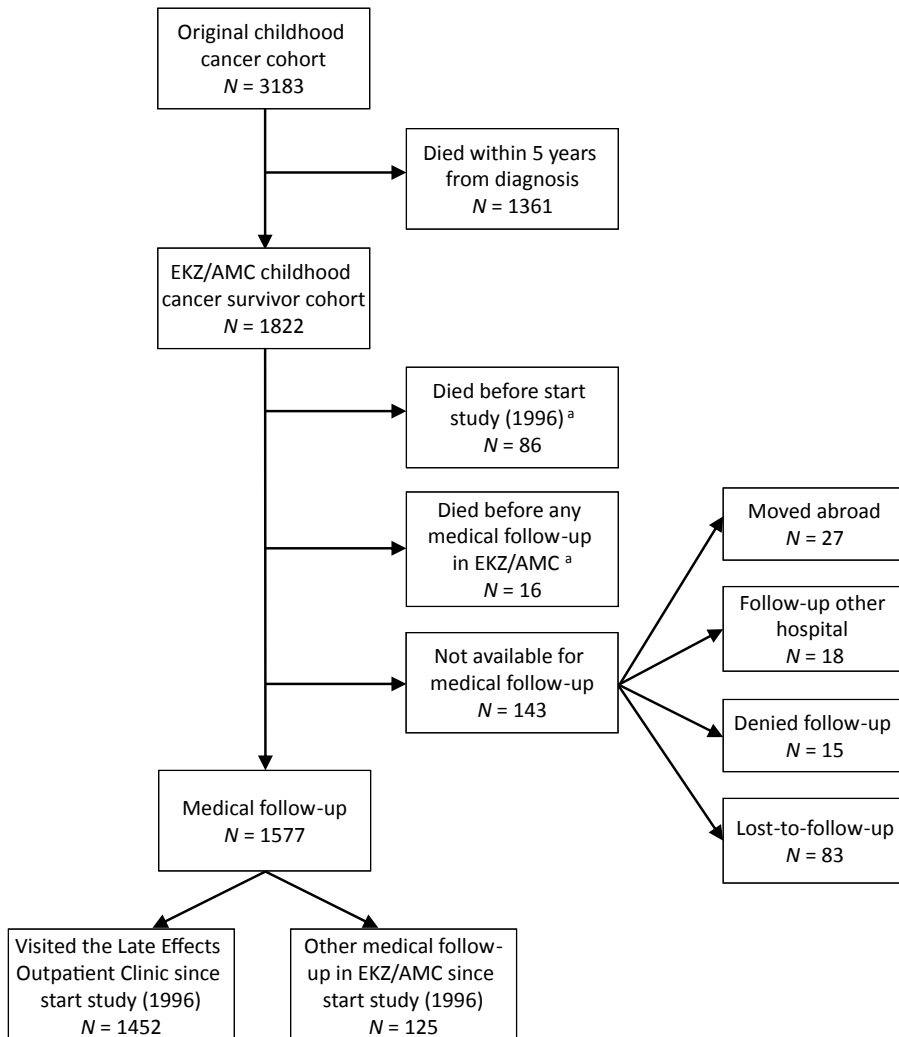


Figure 1 Flowchart of patients included in the EKZ/AMC cohort of childhood cancer survivors at 1 January 2009

^a 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

Characteristic	Total N=1822	Medical follow- up late effects outpatient clinic N=1452	Other medical follow-up EKZ/ AMC N=125	No medical follow-up EKZ/AMC N=245
	N (%)	N (%)	N (%)	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)
<i>Primary childhood cancer diagnosis</i>				
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)
<i>Age at diagnosis, median (range) yr</i>	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)
<i>Attained age, median (range) yr</i>	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)
<i>Follow-up duration, median (range) yr</i>	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)

Table 2 Clinical characteristics of the EKZ/AMC childhood cancer survivor cohort (*continued*)

Characteristic	Total N=1822	Medical follow- up late effects outpatient clinic N=1452	Other medical follow-up EKZ/ AMC N=125	No medical follow-up EKZ/AMC N=245
	N (%)	N (%)	N (%)	N (%)
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)
<i>Treatment period</i>				
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)
<i>Overall treatment modality^a</i>				
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)
<i>Recurrence of primary tumor</i>				
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)
<i>Vital status at end of follow-up</i>				
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)

^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 year since primary cancer diagnosis

Treatment	Primary cancer	Recurrences of primary cancer	Second cancers
	N (%)	N (%)	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 ^a	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 musterd 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>Anti-metabolites</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)
<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)
Radiotherapy			
<i>Any</i>			
Yes ^b	579 (31.8)	172 (50.7)	40 (19.4)

Table 3 Treatment characteristics of the EKZ/AMC childhood cancer survivor cohort for primary cancer, recurrences and second cancers within the first five year since primary cancer diagnosis (continued)

Treatment	Primary cancer	Recurrences of primary cancer	Second cancers
	N (%)	N (%)	N (%)
No	1228 (67.4)	156 (46.0)	131 (63.6)
Unknown	15 (0.8)	11 (3.2)	35 (17.0)
<i>Field^{b, c}</i>			
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)

^a 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.

^b 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.

^c Multiple fields possible.

Abbreviations: CNS: central nervous system; EKZ/AMC: Emma Children's Hospital / Academic Medical Center; N: number; TBI: total body irradiation.

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 fatigue²⁷ 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 ^a

Study topic and publication	Neuro-endocrine 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	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
Additional inclusion criteria	Diagnosed with medulloblastoma; aged ≥18 yr at investigation; no seizures; no symptomatic ischemic heart disease; not pregnant	Diagnosed with brain cancer; aged ≥18 yr at investigation; no seizures; not pregnant; no growth hormone substitution	Aged ≥18 yr at investigation; extremely fatigued survivors	Aged ≥18 yr at investigation	Aged ≥16 yr at investigation	Aged ≥16 yr at investigation
Survival	≥5 yr after end treatment	≥5 yr after end treatment	≥5 yr after end treatment	≥5 yr after end treatment	≥5 yr after end treatment	≥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 ^b	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported (459 invited)
N study group (%) ^c	20	26	83	285	72	416 (90.6% of invited)
N follow-up group (%) ^d /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 4 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)	Semi-structured 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 ≤ 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, effects associated with fatigue; results suggest that level of fatigue is more or less equal in survivors and controls
Study topic and publication	<i>Langeveld et al. Psychooncology 2003</i> ²⁹	<i>van Santen et al. J Clin Endocrinol Metab 2003</i> ²⁵	<i>Carous-Ubbink et al. Pediatr Blood Cancer 2004</i> ¹¹	<i>Langeveld et al. Pediatr Blood Cancer 2004</i> ³⁰	<i>Langeveld et al. Psychooncology 2004</i> ³¹	<i>Stam et al. Psychooncology 2005</i> ³⁵

Table 4 Overview of studies conducted within the EKZ/AMC childhood cancer survivor cohort (*continued*)

Period of childhood cancer diagnosis	Not reported	1-1-1966 to 1-1-1996	Not reported	Not reported	Not reported
Additional inclusion criteria	Not reported	1-1-1966 to 1-1-1996	Not reported	Not reported	Not reported
Survival	Aged ≥16 yr at investigation	Treated with cranial, craniospinal, cervical, mediastinal, thoracic or total body radiotherapy (RT)	None	Aged ≥16 yr at investigation	Aged 18-30 yr at investigation; ability to understand Dutch questionnaires
End date follow-up outcome assessment	≥5 yr after end treatment	≥5 yr after end treatment	≥5 yr after diagnosis	≥5 yr after end treatment	≥5 yr after end treatment
N original cohort ^b	1-7-1999	Not reported	1-1-1998	1-7-1999	2002
N study group (%) ^c	Not reported (543 invited)	Not reported	1378	Not reported (543 invited)	Not reported (449 invited)
N follow-up group (%) ^c	500 (92.1% of invited)	207	1378 (100%)	500 (92.1% of invited)	355 (71.1% of invited)
^d /Completeness of follow-up	500 (100%)	205 (99.0%)	1365 (99.1%)	500 (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	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	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: Course of life and socio-demographic outcomes

Table 4 Overview of studies conducted within the EKZ/AMC childhood cancer survivor cohort (*continued*)

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% 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	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 psychosocial development, sexual development, or achieved milestones at older age; survivors' education level was as high as that of controls
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Study topic and publication	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
van Dalen <i>et al.</i> <i>Eur J Cancer</i> 2006 ¹⁶	Between 1966 and 1998	<i>Stam et al.</i> <i>Psychooncology</i> 2006 ³⁶	<i>Cardous-Ubbink et al.</i> <i>Eur J Cancer</i> 2007 ¹²	<i>Geenen et al.</i> <i>JAMA</i> 2007 ³	<i>Maurice-Stam et al.</i> <i>J Psychosoc Oncol</i> 2007 ³²	<i>Maurice-Stam et al.</i> <i>Eur J Cancer Care</i> 2009 ³³
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 ≥ 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	≥ 5 yr after diagnosis	≥ 5 yr after end treatment	≥ 5 yr after diagnosis	≥ 5 yr after diagnosis	≥ 5 yr after end treatment	≥ 5 yr after end treatment

Table 4 Overview of studies conducted within the EKZ/AMC childhood cancer survivor cohort (continued)

End date follow-up outcome assessment	1-1-2003	2002	1-1-2001	1-1-2004	2002	2002
<i>N</i> original cohort ^b	206 female survivors; 53 delivered ≥1 children	Not reported (499 invited)	1368	1362	Not reported (449 invited)	Not reported (449 invited)
<i>N</i> study group (%) ^c	206 (100%); 53 (100%)	355 (71.1% of invited)	1368 (100%)	1362 (100%)	355 (71.1% of invited)	355 (71.1% of invited)
<i>N</i> follow-up group (%) ^d	206 (100%)	353 (99.4%)	1358 (99.3%)	1284 (94.3%)	353 (99.4%)	353 (99.4%)
^d / Completeness of follow-up						
Follow-up duration	Mean 16.7 (0.30-29.8) yr after 1 st anthracycline dose; mean 20.3 (5.8-28) yr for women who delivered ≥1 children	Mean 15.5 (4.9-30.3) yr after end treatment	Median 16.8 (5-≥30) yr after diagnosis	Median 17.0 (5-≥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

Table 4 Overview of studies conducted within the EKZ/AMC childhood cancer survivor cohort (continued)

	N follow-up group (%)	1080 (94.3%); 44 hypertension	181 (97.8%)	141 (100%)	525 (87.4%)	25 (89.3%)	366 (100%)
^{d/} Completeness of follow-up							
Follow-up duration	Median 20.4 (5-≥30) yr after diagnosis	Median 18.9 (5-36.7) yr after diagnosis	Median 20.8 yr after end of treatment	Median 15.4 (5-≥25) yr after diagnosis	Median 10.5 (5.5-34) yr after diagnosis	None	Not reported
Control group	123 matched controls from EKZ/AMC cohort	None	69 siblings of included survivors	None	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 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
Main results	Body mass index only risk factor associated with hypertension; cisplatin, cyclophosphamide, and abdominal radiotherapy associated with non-significant increased risk	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	≥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	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 transplantation; 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	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

Table 4 Overview of studies conducted within the EKZ/AMC childhood cancer survivor cohort (continued)

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

Table 4 Overview of studies conducted within the EKZ/AMC childhood cancer survivor cohort (*continued*)

Main results	44% pulmonary function impairment; 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 $\geq 50\%$ ≥ 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 γ GT 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
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^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

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

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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).

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.⁴⁰ The Childhood Cancer Survivor Study (CCSS) from North America encompasses survivors from multiple hospitals,^{41, 42} while the British Childhood Cancer Survivor Study (BCSS),⁴³ the Childhood Adolescent and Young Adult Cancer Survivors (CAYACS) Research Program,⁴⁴ and the Swiss Childhood Cancer Survivor Study (SCCSS)⁴⁵ 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,⁴¹⁻⁴⁴ our cohort, as well as the SJLIFE and SCCSS cohorts,^{40, 45} spans the complete history of contemporary cancer treatment in children, including recent treatment eras.

Table 6 Summary of published childhood cancer survivor cohort studies

Study	EKZ/AMC Childhood Cancer Survivor Cohort	Childhood Cancer Survivor Study (CCSS) ^{41,42}	British Childhood Cancer Survivor Study (BCCSS) ⁴³
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; ^a 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%) ^b	Chemotherapy available for 12450 survivors (69.7%), radiotherapy available for 12850 survivors (71.9%), and surgery available for 13215 survivors (73.9%)
Availability of biological samples	Collection of samples possible, but not systematically obtained	Buccal cells, saliva, peripheral blood, tumor tissue of subsequent neoplasms	Not mentioned
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

Study	Childhood Adolescent and Young Adult Cancer Survivors (CAYACS) Research Program ⁴⁴	St. Jude Lifetime Cohort Study (SJLIFE) ⁴⁰	Swiss Childhood Cancer Survivor Study (SCCSS) ⁴⁵
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; ^c 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
Availability of biological samples	Not available	Blood, urine	Not mentioned
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

^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.⁴⁶ 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,⁴¹⁻⁴⁴ 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.^{41, 42, 44, 45} 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.⁸ 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.^{47, 48} This is a similar issue that studies using questionnaires face,^{41-43, 45} while medical record linkage studies are less at risk of this type of bias.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.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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