Introduction

Five-year survival rates for childhood cancer survivors (CCS) have considerably improved in the last 25 years [1]. In Europe and the United States, overall 5 year survival after cancer is above 80% in children, adolescents, and young adults [2, 3]. This growing population of survivors is at an increased risk of chronic health conditions, with 75% of survivors experiencing at least one health problem after a median follow-up of 17 years since cancer diagnosis [4, 5]. By age 45 years, 80.5% of survivors will experience a serious/disabling or life threatening chronic disease.
Risk of Hospitalization in CCS

been shown to be feasible and valid within the Dutch
and approved the data collection for our study cohort.
[22]. The Institutional Review Board of the EKZ/AMC reviewed
the date of 5-year survival, recurrences, and subsequent cancers
characteristics, cancer diagnosis, all cancer treatment before
and were still alive at 1st January 1995 (N = 1564).
18 years, who survived at least 5 years after diagnosis
January 1999, with a primary diagnosis before the age of
Medical Center (Dutch acronym: EKZ/AMC) primarily
treated at EKZ/AMC between 1st January 1966 and 1st
January 1999, with a primary diagnosis before the age of
18 years, who survived at least 5 years after diagnosis
and were still alive at 1st January 1995 (N = 1564).

As in our previous study we were not able to study in
detail these four specific hospital diagnoses, in this study
our aim was to determine the hospitalization rates and
trends of hospitalization over time for neoplasms, diseases
of the circulatory system, endocrine/nutritional/metabolic
diseases and diseases of the eye. These four
disease groups together accounted for a quarter of the
total number of hospitalizations in CCS [21].

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detail these four specific hospital diagnoses, in this study
our aim was to determine the hospitalization rates and
trends of hospitalization over time for neoplasms, diseases
of the circulatory system, endocrine/nutritional/metabolic
diseases and diseases of the eye in comparison with a
random sample of the general population, and to examine
the associated risk factors within the survivors group.

**Methods**

**Study population and linkage procedure**

Our eligible population included all CCS within our sur-
vivors cohort at the Emma Children’s Hospital/Academic
Medical Center (Dutch acronym: EKZ/AMC) primarily
treated at EKZ/AMC between 1st January 1966 and 1st
January 1999, with a primary diagnosis before the age of
18 years, who survived at least 5 years after diagnosis
and were still alive at 1st January 1995 (N = 1564).

We were able to retrieve detailed information on patient
characteristics, cancer diagnosis, all cancer treatment before
the date of 5-year survival, recurrences, and subsequent cancers
[22]. The Institutional Review Board of the EKZ/AMC reviewed
and approved the data collection for our study cohort.

We used a two-step medical record linkage that has
been shown to be feasible and valid within the Dutch
CCS context [23, 24]. A detailed description of the meth-
odology can be found elsewhere [24]. In short, we linked
our dataset of 1564 eligible CCS to the Municipal Personal
Records Database (GBA) and subsequently, we identified
the hospital admissions of the individuals retrieved from
GBA (N = 1477) by linking them to the Hospital Discharge
Register (Dutch acronym: LMR) [25]. Details on the
included study patients within the EKZ/AMC cohort and the
sampled reference population from GBA can be found
in our previous publication [21]. The LMR contains elec-
tronic information on all hospitalizations (day case admis-
sions and clinical hospitalizations) of almost every hospital
in The Netherlands from 1995 onwards (coverage > 99%
until 2004 and 96.7% in 2005), but coverage decreased
after 2005 due to administrative changes in the Dutch
health care system [26]. The LMR does not contain infor-
mation on admissions for uncomplicated deliveries [27].
From LMR we retrieved hospitalization from 1995 to 2005.

We obtained a random sample of reference persons from
the Dutch general population in GBA. We sampled 20
reference persons at maximum with corresponding year of
birth and gender per CCS retrieved in GBA. To these refer-
ence persons, we assigned the starting date of follow-up
of the corresponding cancer CCS, namely 5 years after the
date of primary cancer diagnosis of the corresponding CCS.

In order to avoid overestimation of hospitalizations due
to the likelihood of increased treatment-related hospitali-
izations at recurrence, we censored late primary cancer
recurrences. Full censoring applied to 90 CCS and partial
censoring applied to 35 CCS [24].

**Outcome definition**

We obtained hospitalization-related health problems by
retrieving the primary diagnosis code at hospital discharge
according to the International Classification of Diseases
version 9-clinical modification (ICD9-CM) [28]. We
defined hospitalization-related health problems as health
problems that led to day or hospitalization admission with
a diagnosis code within one of the four categories neo-
plasms, diseases of the circulatory system, endocrine/
nutritional/metabolic diseases and diseases of the eye.

**Statistical analysis**

In our previous study we used multivariable Poisson regres-
sion models to quantify all hospitalization rates in CCS
compared to a random sample of the general population,
and to determine the risk factors for hospitalization within
our study cohort of CCS [24]. In this study, we used the
same Poisson regression model. In the first stage of the
analysis we estimated the average hospitalization rates in
CCS for the hospitalization-related health problems for
### Table 1. Characteristics of CCS and reference persons contributing to unique follow-up time.

|                         | Total | Total (censoring) | CCS | Reference persons |
|-------------------------|-------|-------------------|-----|-------------------|
|                         | CCS   | Reference persons | CCS | Reference persons |
|                         | n = 1382 | n = 26,583 | n = 1292 | n = 23,567 |
| **n (%)**               | n (%) | n (%) | n (%) | n (%) |
| **Gender**              |       |       |       |       |
| Male                    | 738 (53.4) | 14,347 (54.0) | 688 (53.3) | 12,508 (53.1) |
| Female                  | 644 (46.6) | 12,236 (46.0) | 604 (46.7) | 11,059 (46.9) |
| **Year of birth**       |       |       |       |       |
| 1954–1969               | 205 (14.8) | 4066 (15.3) | 194 (15.0) | 3647 (15.5) |
| 1970–1985               | 819 (59.3) | 15,462 (58.2) | 760 (58.8) | 14,060 (59.7) |
| 1986–1999               | 358 (25.9) | 7055 (26.5) | 338 (26.2) | 5860 (24.9) |
| **Age at primary cancer diagnosis** |       |       |       |       |
| Median (years)          | 6.0   | 6.0   | 6.0   | 6.1   |
| Interquartile range     | 2.9–11.2 | 2.9–11.1 | 2.9–11.1 | 3.0–11.2 |
| 0–4 years               | 606 (43.8) | 11,518 (43.3) | 568 (44.0) | 10,123 (43.0) |
| 5–9 years               | 365 (26.4) | 7197 (27.1) | 344 (26.6) | 6335 (26.9) |
| 10–14 years             | 319 (23.1) | 6118 (23.0) | 296 (22.9) | 5526 (23.4) |
| 15–18 years             | 92 (6.7) | 1750 (6.6) | 84 (6.5) | 1583 (6.7) |
| **Calendar year of primary cancer diagnosis** |       |       |       |       |
| 1966–1974               | 117 (8.5) | 2309 (8.7) | 109 (8.4) | 2066 (8.8) |
| 1975–1984               | 464 (33.6) | 8932 (33.6) | 433 (33.5) | 8101 (34.4) |
| 1985–1994               | 529 (38.3) | 10,037 (37.8) | 493 (38.2) | 9019 (38.3) |
| 1995–1999               | 272 (19.7) | 5305 (20) | 257 (19.9) | 4381 (18.6) |
| **Primary childhood cancer diagnosis** |       |       |       |       |
| Leukemia/lymphoma       | 624 (45.2) | NA | 576 (44.6) | NA |
| CNS tumor               | 98 (7.1) | NA | 86 (6.7) | NA |
| Sarcoma                 | 269 (19.5) | NA | 251 (19.4) | NA |
| Other solid tumors      | 356 (25.8) | NA | 349 (27.0) | NA |
| Other tumors            | 35 (2.5) | NA | 30 (2.3) | NA |
| **Cancer treatment groups before 5 year survival** |       |       |       |       |
| No chemotherapy/radiotherapy (+/− surgery) | 112 (8.1) | NA | 107 (8.3) | NA |
| Chemotherapy (+/− surgery) | 726 (52.5) | NA | 694 (53.7) | NA |
| Radiotherapy (+/− surgery) | 83 (6.0) | NA | 78 (6.0) | NA |
| Chemotherapy + Radiotherapy (+/−OK) | 460 (33.3) | NA | 412 (31.9) | NA |
| **Specific cancer treatment before 5 year survival** |       |       |       |       |
| Anthracyclines          | 586 (42.4) | NA | 543 (42.0) | NA |
| Alkylating agents       | 700 (50.7) | NA | 657 (50.9) | NA |
| Other chemotherapy      | 364 (26.3) | NA | 342 (26.5) | NA |
| Radiotherapy to head and/or neck | 374 (27.1) | NA | 330 (25.5) | NA |
| Radiotherapy to thoracic and/or abdominal region | 302 (21.9) | NA | 278 (21.5) | NA |
| Radiotherapy to extremities | 92 (6.7) | NA | 80 (6.2) | NA |
| **Vital status at the end of follow-up** |       |       |       |       |
| Alive                   | 1334 (96.5) | 26,491 (99.7) | 1272 (98.5) | 23,485 (99.7) |
| Deceased                | 48 (3.5) | 92 (0.3) | 20 (1.5) | 82 (0.3) |
| **Attained age at the end of follow-up** |       |       |       |       |
| Median                  | 25.3   | 25.3   | 25.3   | 25.5   |
| Interquartile range     | 19.5–32.1 | 19.4–32.1 | 19.5–32.0 | 19.7–32.3 |
| **Follow-up time since (corresponding) date of cancer diagnosis** |       |       |       |       |
| Median                  | 18.0   | 18.1   | 18.0   | 18.4   |
| Interquartile range     | 11.8–24.5 | 12.0–24.4 | 12.0–24.4 | 12.4–24.5 |
| **Observed period at risk for hospitalization (1995–2005)** |       |       |       |       |
| Sum                     | 10,622.25 | 194,094.51 | 10,030.93 | 173,961.22 |
| Median                  | 8.8     | 8.1     | 8.8     | 8.2     |
| Interquartile range     | 4.9–11.0 | 4.2–11.0 | 5.0–11.0 | 4.3–11.0 |
We followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines for reporting of cohort studies (Table S1). We performed analyses using statistical software R version 2.15.0. Two-sided $P$-values $<0.05$ were considered statistically significant. As per Statistics Netherlands (CBS) confidentiality regulations, we do not present frequency tables with $<10$ units.

**Results**

After record linkage to LMR, the study population that contributed to unique follow-up time consisted of 1382 CCS and of 26,583 reference persons (both 94% of the persons retrieved from GBA). We censored late primary cancer recurrences and this resulted in 1292 CCS and 23,567 reference persons (88% and 84% respectively of the persons retrieved from GBA). In particular, after censoring 5-year CCS (and corresponding reference persons) at the incidence date of first primary cancer recurrence after the date of 5-year survival or at the date of 5-year survival if there was on-going primary cancer recurrence treatment for a primary cancer recurrence at that moment. Characteristics of the total group of hospitalized CCS and reference persons were comparable (Table 1).

**Average relative hospitalization rates per hospitalization-related health problems within the selected disease groups**

The overall RHR and AER for all the four disease groups in CCS compared to the general population were 7.2 (95% confidence interval [CI]: 5.5–9.4) and $38$ per 1000 person-years at risk, respectively. Total average RHRs and AERs were increased in CCS compared to the general population for all four disease groups (Table 2).

All hospitalizations examined for specific neoplasms diagnosis presented an increased RHR. The highest average RHR concerned malignant neoplasm of respiratory and intrathoracic organs (RHR: 44.4 [95% CI: 7.5–261.6]; AER: 1.8 per 1000 person year), followed by hospitalizations for malignant neoplasm of bone, connective tissue,
Table 2. Average hospitalization rates, relative hospitalization rates and absolute excess rates for ICD9CM hospitalization diagnosis in CCS and matched reference persons hospitalized for neoplasms, diseases of the circulatory system, endocrine/nutritional/metabolic diseases and diseases of the eye.

|                                | CCS                     | Matched reference persons | RHR (95% CI) | AER per 1000 PY at risk |
|--------------------------------|-------------------------|---------------------------|--------------|-------------------------|
|                                | Hospitalizations        | Hospitalizations          | Hospitalization rate per 1000 PY at risk |           |
| Neoplasms (total)              | 269                     | 433                       | 2.5          | 10.7 (7.1–16.3)         | 24.3 |
| Malignant neoplasm of lip, oral | 0.3                     | <10                       | –            | NA                      | 0.3  |
| Neoplasms of digestive organs  | 0.3                     | 13                        | 0.1          | NA                      | 0.2  |
| and pharynx                    |                          |                           |              |                         |
| Malignant neoplasm of respiratory and intrathoracic organs | 18 | <10 | – | 44.4 (7.5–261.6) | 1.8 |
| Malignant neoplasm of bone, connective tissue, skin, and breast | 61 | 36 | 0.2 | 29.2 (11.5–74.1) | 5.9 |
| Malignant neoplasm of genitourinary organs | <10 | 22 | 0.1 | 6.3 (1.0–39.7) | 0.7 |
| Malignant neoplasm of lymphatic and hematopoietic tissue | 27 | 61 | 0.4 | 7.6 (1.9–30.2) | 2.3 |
| Benign neoplasms               | 67                      | 187                       | 1.1          | 6.2 (4.0–9.6)           | 5.6  |
| Other neoplasms                | 82                      | 105                       | 0.6          | 13.5 (5.6–32.2)         | 7.6  |
| Diseases of the circulatory system (total) | 61 | 300 | 1.7 | 3.5 (2.4–5.1) | 4.4 |
| Heart disease                  | 24                      | 103                       | 0.6          | 4.0 (2.0–8.1)           | 1.8  |
| Ischemic heart diseases        | 10                      | <10                       | –            | NA                      | 1.0  |
| Other form of heart diseases   | 21                      | 74                        | 0.4          | 4.9 (2.2–10.6)          | 1.7  |
| Heart failure                  | 10                      | <10                       | –            | NA                      | 0.5  |
| Myocarditis                    | 10                      | <10                       | –            | NA                      | 0.5  |
| Pericarditis                   | 10                      | <10                       | –            | NA                      | 0.5  |
| Valve                          | 10                      | <10                       | –            | NA                      | 0.5  |
| Arhythmia                      | 10                      | 55                        | 0.3          | NA                      | 0.5  |
| Other form of heart disease, unspecified | 10 | <10 | – | NA | – |
| Hypertension                   | <10                     | <10                       | –            | NA                      | 0.2  |
| Diseases of pulmonary circulation | <10 | <10 | <10 | <10 | <10 |
| Cerebrovascular diseases       | <10                     | <10                       | –            | 2.6 (0.7–9.0)           | 0.2  |
| Other                          | 23                      | 156                       | 0.9          | 2.5 (1.4–4.5)           | 1.4  |
| Endocrine/nutritional/metabolic diseases (total) | 74 | 174 | 1.0 | 7.3 (4.6–11.7) | 6.4 |
| Disorders of thyroid gland     | <10                     | 15                        | 0.1          | 10.4 (4.4–24.6)         | 0.8  |
| Diseases of other endocrine glands | 48 | 84 | 0.5 | 9.9 (5.8–16.9) | 4.3 |
| Diabetes mellitus              | <10                     | 59                        | 0.3          | 2.0 (0.4–9.5)           | 0.4  |
| Pituitary gland                | 30                      | 13                        | 0.1          | NA                      | 0.2  |
| Other                          | 11                      | 12                        | 0.1          | NA                      | 0.2  |
| Other metabolic disorders and immunity disorders | 17 | 75 | 0.4 | 3.9 (1.5–10.1) | 1.3 |
| Diseases of the eye (total)    | 38                      | 149                       | 0.9          | 4.4 (2.7–7.3)           | 2.9  |
| Disorders of eyelid, lacrimal system and orbit and conjunctiva | 16 | 45 | 0.3 | 6.1 (2.7–13.9) | 1.3 |
| Disorders of sclera, cornea, iris and ciliary body, lens and choroid and retina | 11 | 38 | 0.2 | 5.0 (2.0–12.7) | 0.9 |
| Glaucoma and disorders of vitreous body and globe | <10 | – | <10 | – | NA |
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Within diseases of the circulatory system, the following disease groups had an increased RHR: “other form of heart diseases” (composed of cerebrovascular diseases (RHR: 11.9 [95% CI: 4.5–31.6]; AER: 0.8 per 1000 person year); heart failure, myocarditis, pericarditis, valve, arrhythmia and other form of heart disease (RHR: 4.9 [95% CI: 2.2–10.6]; AER: 1.7 per 1000 person year); and the combined group “diseases of arteries, arterioles, and capillaries” together with “diseases of veins, lymphatic vessels, and lymph nodes not elsewhere specified” (RHR: 2.5 [95% CI: 1.4–4.5]; AER: 1.4 per 1000 person year).

Within hospitalizations for endocrine/nutritional/metabolic diseases, the highest average RHR concerned diseases of the thyroid gland (RHR: 10.4 [95% CI: 4.4–24.6]; AER: 0.8 per 1000 person year), followed by the group comprising diabetes mellitus and pituitary gland disorders (RHR: 9.9 [95% CI: 5.8–16.9]; AER: 4.3 per 1000 person year). Hospitalizations under “other metabolic disorders and immunity disorders” also presented an increased hospitalization rate in CCS compared to the general population (RHR: 3.9 [95% CI: 1.5–10.1]; AER: 1.3 per 1000 person year).

The highest average RHR within hospitalizations for diseases of the eye concerned “disorders of eyelid, lacrimal system and orbit” together with “disorders of conjunctiva” (RHR: 6.1 [95% CI: 2.7–13.9]; AER: 1.3 per 1000 person year). This was followed by “disorders of sclera, cornea, iris and ciliary body, lens, choroid and retina” (RHR: 5.0 [95% CI: 2.0–12.7]; AER: 0.9 per 1000 person year).

When we examined trends in hospitalization rates over time since childhood cancer diagnosis in each disease group, we found that hospitalization rates in CCS for neoplasms were highest right after the 5-year survival and (to a much lesser extent) between 20 years and 30 years after primary cancer diagnosis (Fig. 1A), for diseases of the circulatory system there was a weakly linear upward trend (Fig. 1B), for endocrine/nutritional/metabolic diseases there was a strong linear upward trend (Fig. 1C) and for diseases of the eye highest rates were found right after the 5-year survival (Fig. 1D). We observed that the trends in hospitalization rates over time for neoplasms remained very similar after excluding benign neoplasms. The main difference was a slightly lower increase in hospitalization rates between 20 years and 30 years after primary cancer diagnosis (Fig. S1). In the subgroups of neoplasms, hospitalization rates for malignant neoplasms of lymphatic and hematopoietic tissue hospitalization rates were increased 5–10 years after primary cancer diagnosis and decreasing to almost zero after 15 years (Fig. S2), hospitalization rates for solid tumors...
were increased right after the 5 year survival (Fig. S3) and for benign only neoplasms hospitalization rates were the highest 20–30 years after primary cancer diagnosis (Fig. S4).

Risk factor analysis

The four multivariate models of risk factors for hospitalizations of neoplasms, diseases of the circulatory system, endocrine/nutritional/metabolic diseases and diseases of the eye are presented in Table 3. In the model of hospitalization rates for neoplasms we observed that these were higher after radiotherapy ($P < 0.001$). For diseases of the circulatory system, hospitalization rates were higher after anthracyclines (RHR: 2.5; 95% CI: 1.1–5.5) and radiotherapy to thorax and/or abdomen (RHR: 9.3; 95% CI: 2.4–36.6). Hospitalizations for endocrine/nutritional/metabolic diseases were increased after radiotherapy to head and/or neck (RHR: 6.7; 95% CI: 3.5–12.7). For diseases of the eye, radiotherapy to head and/or neck (RHR: 3.6; 95% CI: 1.5–8.9) increased, while higher age at primary cancer diagnosis (RHR: 0.2; 95% CI: 0.06–0.6) decreased the risk of hospitalization.

Discussion

In this study we were able to show a detailed report on the type of diseases and related risk factors for longitudinal hospitalization rates in CCS. We found that 5-year CCS had significantly increased average hospitalization rates for almost all diagnosis subgroups of neoplasms, diseases of the circulatory system, endocrine/nutritional/
metabolic diseases and diseases of the eye in comparison with the general population. Hospitalization rates for endocrine/nutritional/metabolic diseases seem to increase with longer time since primary cancer diagnosis up to 30 years after primary cancer diagnosis. CCS originally treated with radiotherapy had increased hospitalization rates for neoplasms, CCS originally treated with anthracyclines and radiotherapy to thorax and/or abdomen had increased hospitalization rates for diseases of the circulatory system and CCS originally treated with radiotherapy to head and/or neck had increased hospitalization rates for endocrine/nutritional/metabolic diseases and diseases of the eye.

This study adds important information to the current knowledge of chronic health conditions in CCS. The strengths of our study are that we compared hospitalization rates to an appropriate reference group and the data presented no risk of selection bias and low risk of differential misclassification. We took into account the repeated hospitalizations within one individual as a way to comprehensively quantify the burden of chronic health conditions in CCS.

Several studies have assessed hospitalization-related health problems in CCS and they also found an increase in hospitalizations for neoplasms, diseases of the circulatory system, endocrine/nutritional/metabolic diseases and diseases of the eye [12–15, 18, 29–31]. Of these studies, some provided overall information on hospital diagnosis [10, 12, 13, 18], while others reported specific diagnosis subgroups for hospitalizations in CCS such as endocrine disorders, diabetes mellitus, and cardiovascular diseases [14, 15, 29–31]. One study presented hospitalization rates per cancer diagnosis and took into account all hospitalizations within one individual, but authors made use of self-reported data at risk of selection and reporting bias [10]. Other studies used the first hospitalization event in their analyses [12–15, 18, 29–31]. Repeated measures of hospitalizations are likely to present more reliable results than the use of the first hospital admission only [7,8]. In addition, multivariate detailed treatment-related risk factor analyses to be able to define specific high-risk groups of CCS are lacking in most studies [12–15, 18, 29, 31]. Secondary primary malignancies are recognized in the literature as long-term health problems experienced by...
CCS [32–35]. Our findings confirm this by showing higher hospitalization rates for neoplasms in CCS compared to the general population, especially for malignant neoplasm of respiratory and intrathoracic organs. In a subanalysis not reported here, we observed that hospitalizations for leukemia’s occurred earlier (8.9 years, range = 5.0–31.1 years) than hospitalizations for other solid tumors, such as small intestine and colorectal cancers (23.1 years, range = 7.0–29.4 years). This is consistent with previous literature [32], showing therefore that well-known increased risks of adverse health outcomes translate into clinically relevant outcomes such as hospitalizations.

In line with our findings, reports that studied hospital admissions specifically for diseases of the circulatory system in CCS also presented increased hospitalization rates [29, 31]. A study focused on hospitalizations for cardiovascular diseases that presented a risk factor analysis with anthracyclines and chest radiotherapy [30]. It is well known that anthracyclines [36–39] and radiotherapy to thorax and/or abdomen [40] are associated with cardiac events among CCS. An important finding in this study is that we could confirm that these treatment modalities increase the risk for also health problems that are severe enough to require hospitalizations for diseases in the circulatory system. We observed that the highest average RHR was for hospitalizations of cerebrovascular diseases. This is likely to be related to having received cranial radiotherapy and supradiaphragmatic radiotherapy during treatment [41].

We showed increased average hospitalization rates for endocrine/nutritional/metabolic diseases, in concordance with previous studies [13, 18, 42]. Comparisons with previous reports focusing specifically on endocrine hospitalizations for CCS are difficult as these differ from the current study by having an inclusion/exclusion criteria in relation to tumor groups, using 1-year survivors, a median follow-up time of 10 years and different time of treatment (recruitment started in the 1940s and 1950s) [14, 15].

In this study our risk factor analysis was able to identify that radiotherapy to head and/or neck for childhood cancer increased the hospitalizations rate for endocrine/nutritional/metabolic diseases and diseases of the eye in CCS. This suggests that the known association between endocrinopathies and radiotherapy affects this patient group with disorders that require hospitalization [43–45]. An important finding in our study is the suggestion of the increased hospitalizations for endocrine/nutritional/metabolic diseases compared to the general population with longer time since childhood cancer diagnosis. This is likely to represent complications of already existing endocrine/nutritional/metabolic diseases in CCS [46] and thus, implies that these are clinically relevant later in life.

To the best of our knowledge, hospitalizations for diseases of the eye in CCS are not presented separately in other studies [10, 12, 13, 18]. As these have been mainly described in the literature for specific disease groups [47–49]. When we examined risk factors for hospitalizations of the eye among survivors, we found that those CCS treated with radiotherapy to the head and/or neck had an increased risk of hospitalization for diseases of the eye, in concordance with previous reports focusing on eye disease only (and not studies studying hospitalizations for eye diseases) [46]. Furthermore, we observed that CCS diagnosed at an earlier age was more at risk to be hospitalized for diseases of the eye. The trends of hospitalization for diseases of the eye over time we observed in CCS are mostly caused by acute cataracts (data not shown). After 20 years of primary cancer diagnosis, the number of hospitalizations for diseases of the eye in CCS is very small.

As a limitation, our study did not have information on outpatient visits or general practitioner visits. This might have resulted in an underestimation of the healthcare consumption among CCS. However, we were able to study the long-term morbidity that is severe enough to require hospitalization. Furthermore, the unavailability of reliable hospitalization data after 2005 means that we analyzed data with an outcome period of 11 years (1995–2005) [21].

In summary, this medical record linkage study shows that 5-year CCS have higher average hospitalization rates for almost all diagnosis subgroups of neoplasms, diseases of the circulatory system, endocrine/nutritional/metabolic diseases and diseases of the eye in comparison with the general population. Over time, hospitalization rates seem to increase with longer time since primary cancer diagnosis for endocrine/nutritional/metabolic diseases, even up to 30 years after primary cancer diagnosis. Survivors originally treated with radiotherapy had increased hospitalization rates for neoplasms, those originally treated with anthracyclines and radiotherapy to thorax and/or abdomen had increased hospitalization rates for diseases of the circulatory system and those originally treated with radiotherapy to head and/or neck had increased hospitalization rates for endocrine/nutritional/metabolic diseases and diseases of the eye.

Our study emphasizes that long-term health problems resulting in hospitalizations are still clinically relevant later in life of CCS. In addition, our findings support the prioritization of further research and follow-up care for the risk groups we identified, namely those originally treated with anthracyclines and radiotherapy to thorax and/or abdomen and head and/or neck.

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Conflict of Interest
None.

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Supporting Information

Additional supporting information may be found in the online version of this article:

Figure S1. Hospitalization rate for neoplasms (excluding benign neoplasms) in CCS and matched reference persons over time, from 5 years after primary childhood cancer diagnosis.

Figure S2. Hospitalization rate for malignant neoplasms of lymphatic and hematopoietic tissue in CCS and matched reference persons over follow-up time since date of primary childhood cancer diagnosis.

Figure S3. Hospitalization rate for solid tumors (excluding benign neoplasms) in CCS and matched reference persons over follow-up time since date of primary childhood cancer diagnosis.

Figure S4. Hospitalization rate for benign neoplasms in CCS and matched reference persons over follow-up time since date of primary childhood cancer diagnosis.

Table S1. STROBE statement—checklist of items that should be included in reports of cohort studies.