

## Risk and Temporal Changes of Heart Failure Among 5-Year Childhood Cancer Survivors: a DCOG-LATER Study

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**Background**—Heart failure is one of the most important late effects after treatment for cancer in childhood. The goals of this study were to evaluate the risk of heart failure, temporal changes by treatment periods, and the risk factors for heart failure in childhood cancer survivors (CCS).

**Methods and Results**—The DCOG-LATER (Dutch Childhood Oncology Group–Long-Term Effects After Childhood Cancer) cohort includes 6,165 5-year CCS diagnosed between 1963 and 2002. Details on prior cancer diagnosis and treatment were collected for this nationwide cohort. Cause-specific cumulative incidences and risk factors of heart failure were obtained. Cardiac follow-up was complete for 5,845 CCS (94.8%). After a median follow-up of 19.8 years and at a median attained age of 27.3 years, 116 survivors developed symptomatic heart failure. The cumulative incidence of developing heart failure 40 years after childhood cancer diagnosis was 4.4% (3.4%–5.5%) among all CCS. The cumulative incidence of heart failure grade  $\geq 3$  among survivors treated in the more recent treatment periods was higher compared with survivors treated earlier (Gray test,  $P=0.05$ ). Mortality due to heart failure decreased in the more recent treatment periods (Gray test,  $P=0.02$ ). In multivariable analysis, survivors treated with a higher dose of mitoxantrone or cyclophosphamide had a higher risk of heart failure than survivors who were exposed to lower doses.

**Conclusions**—CCS treated with mitoxantrone, cyclophosphamide, anthracyclines, or radiotherapy involving the heart are at a high risk for severe, life-threatening or fatal heart failure at a young age. Although mortality decreased, the incidence of severe or life-threatening heart failure increased with more recent treatment periods. (*J Am Heart Assoc.* 2019;8:e009122. DOI: 10.1161/JAHA.118.009122)

**Key Words:** childhood cancer survivors • heart failure

Childhood cancer 5-year survival rates have improved considerably, from 20% in the 1940s<sup>1</sup> to 70% to 80% at present.<sup>2</sup> It is well established that (childhood) cancer

treatments can induce chronic health conditions in childhood cancer survivors (CCS).<sup>3–5</sup> As a result of better survival over the years, the survivor population continues to grow in size. It

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Accompanying Data S1, S2, Tables S1, S2, and Figures S1 through S4 are available at <https://www.ahajournals.org/doi/suppl/10.1161/JAHA.118.009122>

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## Clinical Perspective

### What Is New?

- In a nationwide cohort of 6165 5-year childhood cancer survivors, we observed an increase in cumulative incidence of severe or life-threatening heart failure in recent treatment periods (compared with earlier periods); a dose-response relation of mitoxantrone and an association of cyclophosphamide with symptomatic heart failure were observed. These results should be replicated in a larger cohort.

### What Are the Clinical Implications?

- As the current cohort study demonstrates, childhood cancer survivors treated with cardiotoxic treatment have a high risk of developing heart failure at a relatively young age.
- Therefore, it may be worthwhile to be vigilant of symptoms that suggest cardiac dysfunction/heart failure in adolescent and young adult childhood cancer survivors, even decades after initial treatment.
- Other treatment possibilities, if available, should be considered in childhood cancer treatment protocols, and cardiotoxic doses should be limited because heart failure also develops after low doses of anthracyclines and/or mitoxantrone.

is known that 75% of CCS will develop at least a chronic health condition,<sup>4</sup> and among those aged 45 years, 80.5% of survivors will have a serious/disabling or life-threatening health condition.<sup>5</sup>

Heart failure is one of the most frequent late effects in CCS, contributing to significant morbidity and mortality.<sup>3–9</sup> Previous reports show that the cumulative incidence of symptomatic heart failure among CCS 30 years after diagnosis ranges between 2.7% and 4.1%.<sup>10,11</sup> The prevalence of asymptomatic heart failure, defined as a left ventricular shortening fraction <30%, has been found to be 27% in CCS treated with cardiotoxic treatment at a median of 15 years after diagnosis.<sup>12</sup>

A higher dose of anthracyclines and radiotherapy involving the heart region are associated with asymptomatic and symptomatic heart failure.<sup>10,11,13–18</sup> So far, the role of other types of chemotherapy such as mitoxantrone and cyclophosphamide on heart failure risk is not clear.<sup>11,19</sup>

The risk of cardiotoxicity after childhood cancer treatment has already been known for several decades. Studies that investigate the temporal changes of heart failure by treatment periods are lacking. Recent studies did show a reduction in cardiac mortality of CCS in later periods of treatment compared with earlier treatment periods.<sup>8,9</sup>

We aimed to determine the cumulative incidence, the temporal changes by treatment period, and factors that are

associated with the cause-specific incidence of systematically ascertained and validated symptomatic heart failure in CCS within a Dutch nationwide cohort. This knowledge will guide future treatment and surveillance protocols for children with cancer.

## Methods

The data, analytic methods, and study materials will not be made available to other researchers for purposes of reproducing the results or replicating the procedure.

## Study Population

We obtained our study population from the national DCOG-LATER (Dutch Childhood Oncology Group—Long-Term Effects After Childhood Cancer) nationwide cohort (n=6165), a collaborative effort of all Dutch pediatric oncology/hematology centers. Eligible survivors included 5-year CCS diagnosed before the age of 18 years between January 1, 1963 and December 31, 2001 with a malignancy according to the third edition of the International Classification of Childhood Cancer.<sup>20</sup> We only included CCS who were living in the Netherlands at the time of childhood cancer diagnosis and who were treated in 1 of the Dutch pediatric oncology/hematology centers (Academic Medical Center Amsterdam, VU University Medical Center, Leiden University Medical Center, Erasmus Medical Center, University Medical Center Groningen, Radboudumc, and University Medical Center Utrecht).

## Data Collection on Chemotherapy Treatment

Data on childhood cancer diagnosis and treatment (including treatment for recurrences) were extracted from the medical records for all eligible CCS. The total cumulative anthracycline dose was calculated by summing the doxorubicin-equivalent doses (daunorubicin [ $\times 0.45$ ]<sup>21</sup>, epirubicin [ $\times 0.67$ ], idarubicin [ $\times 3$ ]) based on the previously published equivalence ratio.<sup>22</sup> This cumulative anthracycline dose (the sum of all types of anthracyclines) was based directly on risk for heart failure and not on those doses that produce equivalent hematological toxicity with the assumption that hematological and cardiac toxicities are correlated.<sup>21</sup>

## Data Collection on Radiotherapy Treatment

Detailed radiotherapy involving the heart was classified as follows: no radiotherapy involving the heart; radiotherapy potentially involving the heart (abdomen, para-aortal, spleen, inverted Y, spine not otherwise specified, scapula,

vertebrae, ribs/sternum/clavicle, kidney, liver, total abdominal radiation); radiotherapy involving the heart (total body radiation, thorax, mediastinum, total node, mantle field, spine [whole and thoracic], lung, parasternal). We used the maximum prescribed dose of the largest field involving the heart and added the dose of total body radiation. For the latter group, we used a cutoff point of 20 Gy, which is the median of the cumulative prescribed dose. Validation of radiotherapy data was performed by experts in radiotherapy.

## Cardiac Outcome Data Collection and Cardiac Follow-Up

The outcome of interest was heart failure, graded according to the Common Terminology Criteria for Adverse Events as grade 3 (severe), 4 (life-threatening), or 5 (death).<sup>23</sup> The incidence date of heart failure was defined as the date of an abnormal diagnostic test combined with symptoms.

Information on potential heart failure was collected from 3 different data sources: the DCOG-LATER questionnaire, GP (primary physician) DCOG-LATER questionnaire, and medical records (Figure S1). Cohort members resident in the Netherlands received a DCOG-LATER questionnaire between 2012 and 2014. The DCOG-LATER questionnaire is a general health and risk factor questionnaire including diseases of the circulatory system. To optimize response, CCS initially not willing to participate were offered the option of completing a brief telephone survey addressing sociodemographic characteristics and health status. CCS were considered nonresponders to the DCOG-LATER questionnaire if they had not responded after a written invitation, a written reminder, and at least 2 telephone reminders. For nonresponders, we obtained data on heart failure from the GP DCOG-LATER questionnaire, a short questionnaire on major health outcomes and risk factors sent to the GP of the CCS. The GP was considered a “GP nonresponder” if he or she had not responded after a written invitation, a written reminder, and at least 2 telephone reminders. For “GP nonresponders,” we extracted heart failure data from the DCOG-LATER outpatient clinics where available. Finally, for known deceased CCS, the main cause of death and underlying diseases were extracted from the medical records. Potential heart failure was subsequently validated following a standardized method described previously (Figure S2 and Data S1 for more detailed information).<sup>24</sup>

For the DCOG-LATER questionnaire data, written informed consent was obtained from the participating survivors. Informed consent was also sought from the parents of underage (<18 years of age) CCS. Data collection from the GP DCOG-LATER questionnaire and medical records was exempt from institutional review board review.

## Statistical Analyses

The following dates were assigned as the end of cardiac follow-up: the date of death for decedents; the date of DCOG-LATER (or GP DCOG-LATER) questionnaire completion for responders; the date of the last recorded patient contact for nonresponders or for CCS lost to follow-up. If a cohort member died from a cause other than heart failure, death was considered a competing event.<sup>25</sup> Heart failure was evaluated if it started more than 5 years after childhood cancer diagnosis or if it started within 5 years of childhood cancer diagnosis and was still present after 5 years from diagnosis. The time at risk started 5 years after childhood cancer diagnosis, and it ended on the incidence date of heart failure diagnosis or at the end date of cardiac follow-up, whichever occurred first.

## Cumulative Incidence

We estimated the cumulative incidence overall and for different mutually exclusive treatment groups using the nonparametric Aalen-Johansen estimator. Both follow-up time since childhood cancer diagnosis and age at follow-up were used as time scales. Additionally, we examined the cumulative incidence of heart failure (grades 3, 4, and 5) in relation to the period of treatment (1970–1979, 1980–1989, and 1990–2001). The differences between the groups were evaluated with Gray log-rank tests.<sup>26</sup> We also tested the differences between the period of treatment and the use of anthracyclines (yes versus no), anthracycline dose, mitoxantrone (yes versus no), mitoxantrone dose, and radiotherapy to the chest.

## Risk Factor Analyses

We assessed risk factors for heart failure using a multivariable Cox proportional hazards model with attained age as the time scale. The model was adjusted for age at childhood cancer diagnosis, sex, and calendar year of childhood cancer diagnosis. We examined possible risk factors for heart failure based on the literature and clinical knowledge. We evaluated the effects of age at diagnosis, sex, and year of cancer diagnosis as well as the effect of treatment: anthracycline (per 1 mg/m<sup>2</sup>), mitoxantrone (per 1 mg/m<sup>2</sup>), cyclophosphamide (per 100 mg/m<sup>2</sup>), cisplatin (per 1 mg/m<sup>2</sup>), ifosfamide (per 1 mg/m<sup>2</sup>), vincristine (per 1 mg/m<sup>2</sup>), and radiotherapy involving the heart (no radiotherapy involving the heart; radiotherapy potentially involving the heart; radiotherapy involving the heart <20 Gy; radiotherapy involving the heart ≥20 Gy). We examined the dose-response relationship between anthracyclines, mitoxantrone, and cyclophosphamide and the development of heart failure by modeling via restricted cubic splines using 3 knots (10%, 50%, 90%

quantiles). In order to avoid overadjusting the model, we did not include treatment and diagnosis variables in the same model.

Two-sided *P*-values were reported, and those of less than 0.05 were considered statistically significant. Analyses were performed using R (version 3.1.1; R Foundation, Vienna, Austria) and SPSS (version 24; IBM SPSS Statistics, Armonk, NY).

## Results

### Study Population, Cardiac Follow-Up, and Cardiac Events

The nationwide cohort included 6165 CCS. For 5845 CCS (94.8%), cardiac follow-up information was retrieved. Of those 5845 CCS, cardiac follow-up was complete for 84.7% in 2013. Data S2 and Figure S1 provide an extensive overview of the cardiac follow-up. Table 1 presents demographic information, tumor characteristics, and follow-up information on the cohort with cardiac follow-up and CCS with heart failure. At the end of follow-up 5278 (90.3%) CCS were alive, and 567 (9.7%) were deceased. Median follow-up time since childhood cancer diagnosis was 19.9 years (range 5.0–50.4 years), and median attained age was 27.3 years (range 5.1–65.2 years).

Among the 5845 eligible CCS with cardiac follow-up, 116 CCS (2.0%) developed heart failure, 61 CCS were grade 3, 33 CCS grade 4, and 22 CCS grade 5. Among all cases, 35 (30.2%) had received both cardiotoxic chemotherapy and radiotherapy involving the heart, 75 (64.7%) had received cardiotoxic chemotherapy only, 2 cases (1.7%) had received radiotherapy involving the heart only, and the 4 remaining cases (3.4%) had received no known potential cardiotoxic treatment, or their treatment was unknown.

The 3 cases without known potential cardiotoxic treatment had conditions known to predispose to heart failure: Duchenne muscular dystrophy, noncompaction cardiomyopathy, and Tetralogy of Fallot. The details of the CCS with heart failure are presented in Table 1.

### Cumulative Incidence by Treatment Groups

Table S1 presents the cumulative incidence of developing heart failure by time since childhood cancer diagnosis and for mutually exclusive treatment groups. The cumulative incidence of developing heart failure 40 years after childhood cancer diagnosis was 4.4% (95% CI 3.4% to 5.5%). The cumulative incidence of heart failure 40 years after diagnosis was much higher among CCS who received had 1 or more types of cardiotoxic treatment (10.6%, 95% CI 7.4% to 13.9%) than among CCS treated without cardiotoxic treatment

(0.3%, 95% CI 0.0% to 0.7%) (Gray test of cardiotoxic treatment versus no cardiotoxic treatment,  $P < 0.0001$ ) (Table S1 and Figure 1). The cumulative incidence of heart failure 40 years after diagnosis was 27.8% (95% CI 5.1% to 50.6%) for CCS who had received both cardiotoxic chemotherapy and radiotherapy involving the heart, 10.5% (95% CI 6.4% to 14.4%) for CCS who had received only cardiotoxic chemotherapy, and 3.0% (95% CI 0.0% to 5.9%) for CCS treated with only radiotherapy involving the heart (Table S1, Figure S3).

The cumulative incidence of heart failure 20 years after diagnosis for CCS treated with mitoxantrone ( $\pm$ anthracyclines) was 11.4% (95% CI 3.6% to 19.1%). The cumulative incidence increased significantly in the CCS treated with higher anthracycline doses (Table S1 and Figure 2).

The cumulative incidence of developing heart failure by attained age is presented in Table S2 and Figure S4. At age 50 years, the cumulative incidence of developing heart failure in the whole cohort was 5.3% (95% CI 3.7% to 6.9%).

### Cumulative Incidence by Treatment Era

Table 2 shows the cardiotoxic treatment survivors received for the different treatment periods (1960–1979, 1980–1989, and 1990–2001). We observed a statistically significant difference between survivors treated in the oldest treatment era (1960–1979) and in more recent treatment eras (1980–1989 and 1990–2001), especially for those survivors treated with anthracyclines (compared with those not treated with anthracyclines), and for those survivors treated with radiotherapy to the chest.

The cumulative incidence of heart failure (grades 3, 4, and 5) increased for CCS treated in more recent years (Figure 3A). The cumulative risks at 20 years after diagnosis for CCS treated during 1970–1979, 1980–1989, and 1990–2001 were 0.5% (95% CI 0.01% to 0.9%), 1.6% (95% CI 1.0% to 2.2%), 1.5% (95% CI 0.9% to 2.0%), respectively. The risks of heart failure 20 years after diagnosis for CCS treated during 1990–2001 and between 1980 and 1989 were significantly higher than the risk of heart failure for CCS treated during 1970–1979 (Gray test 1970–1979 versus 1980–1989,  $P = 0.01$ ; 1970–1979 versus 1990–2001,  $P = 0.03$ ). Figure 3B displays the cumulative incidence per treatment period for fatal heart failure (grade 5). The risks of a fatal event 20 years after diagnosis for CCS treated during 1970–1979 and 1980–1989 were significantly higher than the risk of CCS treated during 1990–2001 (Gray test 1970–1979 versus 1990–2001,  $P = 0.04$ ; 1980–1989 versus 1990–2001,  $P = 0.02$ ). Because most childhood cancer treatment centers started in 1970 in the Netherlands, there is a possibility that children had been treated in adult cancer centers before that time; thus, we excluded children

**Table 1.** Patient, Cancer, and Treatment Characteristics of the 5-Year Survivors of the DCOG-LATER Cohort With Complete Cardiac Follow-Up

Characteristics	Cohort With Cardiac Follow-Up (n=5845) (94.8%)*	CCS With Heart Failure (n=116)
	n (%)	n (%)
<b>Patient characteristics</b>		
<b>Sex</b>		
Female	2588 (44.3)	44 (37.9)
Male	3257 (55.7)	72 (62.1)
<b>Cancer characteristics</b>		
<b>Primary childhood cancer (ICCC)</b>		
Leukemias, myeloproliferative diseases, and myelodysplastic diseases	2034 (34.8)	30 (25.9)
Lymphomas and reticuloendothelial neoplasms	1019 (17.4)	26 (22.4)
CNS and miscellaneous intracranial and intraspinal neoplasms	749 (12.8)	3 (2.6)
Neuroblastoma and other peripheral nervous cell tumors	306 (5.2)	2 (1.7)
Retinoblastoma	29 (0.5)	0 (0)
Renal tumors	571 (9.8)	11 (9.5)
Hepatic tumors	46 (0.8)	0 (0)
Bone tumors	355 (6.1)	25 (21.6)
Soft tissue and other extrasosseous sarcomas	422 (7.2)	18 (15.5)
Germ cell tumors, trophoblastic tumors, and neoplasms of gonads	219 (3.7)	0 (0)
Other malignant epithelial neoplasms and malignant melanomas	88 (1.5)	1 (0.9)
Other and unspecified malignant neoplasms	7 (0.1)	0 (0)
<b>Age at diagnosis (y), median (IQR)</b>		
0 to 4	2692 (46.1)	49 (42.2)
5 to 9	1567 (26.8)	35 (30.2)
10 to 14	1233 (21.1)	28 (24.1)
15 to 17	353 (6.0)	4 (3.4)
<b>Treatment period</b>		
1963 to 1979	990 (16.9)	22 (19.0)
1980 to 1989	1853 (31.7)	58 (50.0)
1990 to 2001	3002 (51.4)	36 (31.0)
<b>Overall treatment modality</b>		
Surgery only	587 (10.0)	0 (0)
Chemotherapy±Surgery	2882 (49.3)	60 (51.7)
Radiotherapy±Surgery	445 (7.6)	0 (0)
Chemotherapy and Radiotherapy±Surgery	1854 (31.7)	55 (47.4)
No therapy/unknown	77 (1.3)	1 (0.9)
<b>Cardiotoxic treatment</b>		
No cardiotoxic treatment	2845 (48.7)	3 (2.6)
Cardiotoxic CT only	2304 (39.4)	83 (71.6)
RT involving the heart only	211 (3.6)	4 (3.4)
Cardiotoxic CT and chest RT	434 (7.4)	25 (21.6)
Unknown	51 (0.9)	1 (0.9)

Continued

Table 1. Continued

Characteristics	Cohort With Cardiac Follow-Up (n=5845) (94.8%)*	CCS With Heart Failure (n=116)
	n (%)	n (%)
<b>Anthracyclines median dose (IQR)</b>	175 (114–272)	360 (201–450)
No anthracyclines	3099 (53.0)	13 (11.2)
1 to 100 mg/m <sup>2</sup>	491 (8.4)	21 (18.1)
100 to 250 mg/m <sup>2</sup>	1402 (24.0)	33 (28.4)
>250 mg/m <sup>2</sup>	720 (12.3)	42 (36.2)
Missing	133 (2.3) <sup>†</sup>	7 (6.0)
<b>Mitoxantrone median dose (IQR)</b>	40 (20–60)	45 (20–120)
No mitoxantrone	5660 (96.8)	103 (88.8)
<40 mg/m <sup>2</sup>	81 (1.4)	6 (5.2)
>40 mg/m <sup>2</sup>	58 (1.0)	6 (5.2)
Missing	46 (0.7) <sup>‡</sup>	1 (0.9)
<b>Cyclophosphamide (intravenous)</b>		
None	3674 (62.8)	34 (29.3)
Any	2132 (36.5)	81 (69.8)
Unknown	39 (0.7)	1 (0.9)
<b>Cisplatin</b>		
None	5363 (91.8)	103 (88.8)
Any	443 (7.6)	12 (10.3)
Unknown	39 (0.7)	1 (0.9)
<b>Ifosfamide</b>		
None	5107 (87.4)	98 (84.5)
Any	699 (12.0)	17 (14.7)
Unknown	39 (0.7)	1 (0.9)
<b>Vincristine</b>		
None	1642 (28.1)	16 (13.8)
Any	4164 (71.2)	99 (85.3)
Unknown	39 (0.7)	1 (0.9)
<b>Radiotherapy field involving the heart</b>		
No chest radiotherapy	4575 (78.3)	78 (67.2)
Radiotherapy potentially involving the heart	588 (10.1)	9 (7.8)
Radiotherapy involving the heart <20 Gy	275 (4.7)	15 (12.9)
Radiotherapy involving the heart ≥20 Gy	363 (6.2)	14 (12.1)
Unknown	44 (0.7)	0 (0)
<b>Recurrence</b>		
No	4836 (82.7)	87 (75.0)
Yes	1009 (17.3)	29 (25.0)
<b>Follow-up</b>		
<b>Vital status</b>		
Alive	5278 (90.3)	87 (75.0)
Deceased	567 (9.7)	29 (25.0)

Continued

Table 1. Continued

Characteristics	Cohort With Cardiac Follow-Up (n=5845) (94.8%)*	CCS With Heart Failure (n=116)
	n (%)	n (%)
Attained age (y), median (min-max)	27.3 (5.1–65.2)	23.8 (6.2–48.8)
≤14	463 (7.9)	15 (12.9)
15 to 24	1949 (33.4)	45 (38.8)
25 to 34	2000 (34.2)	38 (32.8)
35 to 44	1129 (19.3)	16 (13.8)
45 to 54	267 (4.6)	2 (1.7)
≥55	37 (0.6)	0 (0)
Follow-up duration from primary cancer diagnosis (y), median (min-max)	19.9 (5.0–50.4)	16.8 (5.0–36.8)
>5 to 9	480 (8.2)	21 (18.1)
19 to 10	2459 (42.1)	48 (41.4)
20 to 29	1791 (30.6)	34 (29.3)
30 to 39	965 (16.5)	13 (11.2)
≥40	150 (2.6)	0 (0)
Source		
LATER questionnaire	3056 (52.3)	58 (50.0)
General practitioner questionnaire	773 (13.2)	6 (5.2)
Medical chart	2016 (34.5)	52 (44.8)
Cardiac events		
Type of validated symptomatic heart failure		
Grade 3	61 (52.5)	61 (52.5)
Grade 4	33 (28.5)	33 (28.5)
Grade 5	22 (19.0)	22 (19.0)
Other cardiac events		
Cardiac ischemia	21 (0.4)	2 (1.7) <sup>§</sup>
Pericarditis	13 (0.2)	1 (0.9) <sup>§</sup>
Valvular disease	22 (0.4)	3 (2.6) <sup>§</sup>
Arrhythmia	41 (0.7)	3 (2.6) <sup>§</sup>

CCS indicates childhood cancer survivor; CNS, central nervous system; CT, chemotherapy; DCOG-LATER, Dutch Childhood Oncology Group Long-term outcomes after cancer treatment; ICCC, International Classification of Childhood Cancer; IQR, interquartile range; RT, radiotherapy.

\*Percentage of the total DCOG-LATER cohort.

<sup>†</sup>n=94 anthracycline=yes, but dose missing.

<sup>‡</sup>n=7 mitoxantrone=yes, but dose missing.

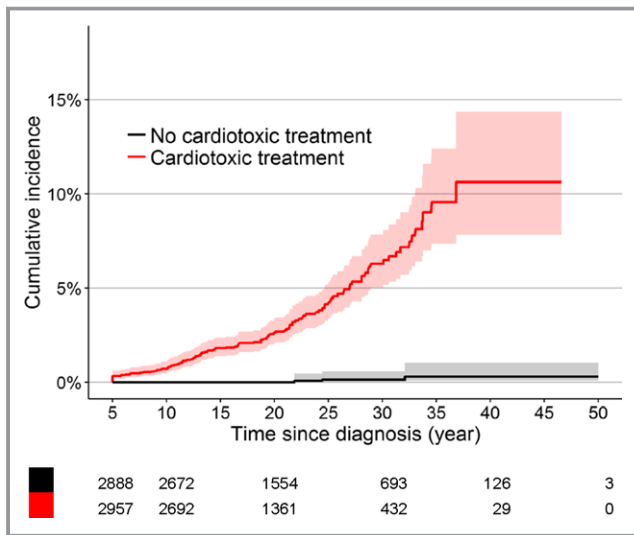
<sup>§</sup>Cardiac event before the onset of heart failure.

diagnosed with cancer before 1970 (n=90, 1.5%; n=2 children treated with anthracyclines).

## Risk Factor Analyses

Table 3 presents the results of the multivariable model for the analysis of risk factors for heart failure (grade 3, 4, and 5). We found that younger age at childhood cancer diagnosis (per-year hazard ratio [HR]=0.8, 95% CI 0.8–0.9), more recent year of childhood cancer diagnosis (HR=1.0, 95% CI 1.0–1.1),

anthracyclines (per 1 mg/m<sup>2</sup>), mitoxantrone (per 1 mg/m<sup>2</sup>), cyclophosphamide (per 100 mg/m<sup>2</sup>) (the dose-response curves and the actual HRs for anthracyclines, mitoxantrone, and cyclophosphamide are presented in Figure 4), and radiotherapy involving the heart (HR=2.0, 95% CI 1.1–3.6; HR=2.1, 95% CI 1.1–4.0) were significantly associated with heart failure risk. There was no influence of sex on the risk of developing heart failure. We did not find any statistically significant interaction between radiotherapy to the chest and cardiotoxic chemotherapy or among the different chemotherapy treatments.



**Figure 1.** Cumulative incidence of heart failure for cardiotoxic treatment (anthracyclines, mitoxantrone, and radiotherapy involving the heart) with time since childhood cancer diagnosis as time scale. *P*-value for Gray test is  $P<0.0001$ . Shaded areas indicate 95% CI.

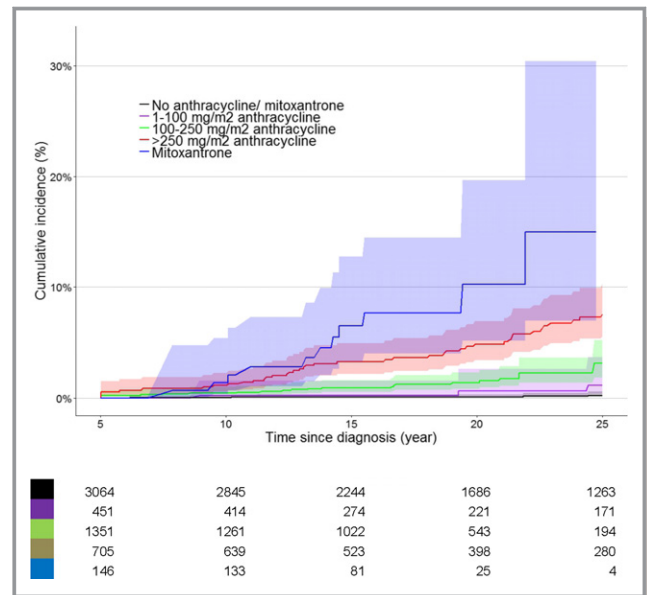
## Discussion

CCS are at a high risk of developing heart failure in young adulthood after cardiotoxic treatment. Important findings of this study are the increase in cumulative incidence of severe or life-threatening heart failure in more recent treatment periods and the association of mitoxantrone and cyclophosphamide with symptomatic heart failure.

The current cohort study demonstrates that CCS treated with cardiotoxic treatment have a high risk of developing heart failure even at a relatively young age.

Previous research showed a reduction in (cardiac) mortality among CCS in recent periods of treatment, and the authors attributed this to a reduction in anthracycline dose in treatment regimens.<sup>8,9</sup> In line with this finding, our study identified a decreased risk of mortality due to heart failure in more recent treatment eras.

In our study we also identified an increased risk of heart failure with a broader definition (severe, life threatening, and death due to heart failure) and a decreased risk of heart failure (fatal) for CCS treated in more recent treatment years compared with survivors treated earlier. We identified this higher risk in the comparisons of the cumulative risk estimates as well as in the Cox proportional hazards model analysis. The cumulative incidence of heart failure remained low with anthracyclines at doses below 100 mg/m<sup>2</sup>, or at least below 250 mg/m<sup>2</sup>. However, most importantly, our results showed no safe dose for anthracyclines. This finding and the statistically significant association and dose-response relationship of mitoxantrone with symptomatic heart failure underscore the



**Figure 2.** Cumulative incidence of heart failure (grades 3, 4, and 5) for 2 specific treatment groups: anthracyclines only ( $n=2598$  cohort members, 96 cases) and mitoxantrone (with/without anthracyclines) ( $n=146$  cohort members, 12 cases). All childhood cancer survivors who had radiotherapy involving the heart region were excluded from these analyses. Pairwise comparisons found these degrees of significance: no anthracycline/mitoxantrone vs anthracycline 1 to 100 mg/m<sup>2</sup>,  $P=0.17$ ; no anthracycline/mitoxantrone vs anthracycline 100 to 250 mg/m<sup>2</sup>,  $P<0.00001$ ; no anthracycline/mitoxantrone vs anthracycline >250 mg/m<sup>2</sup>,  $P<0.00001$ ; no anthracycline/mitoxantrone vs mitoxantrone,  $P<0.00001$ ; anthracycline 1 to 100 mg/m<sup>2</sup> vs anthracycline 100 to 250 mg/m<sup>2</sup>,  $P=0.007$ ; anthracycline 1 to 100 mg/m<sup>2</sup> vs anthracycline >250 mg/m<sup>2</sup>,  $P<0.00001$ ; anthracycline 1 to 100 mg/m<sup>2</sup> vs mitoxantrone,  $P<0.00001$ ; anthracycline 100 to 250 mg/m<sup>2</sup> vs anthracycline >250 mg/m<sup>2</sup>,  $P<0.00001$ ; anthracycline 100 to 250 mg/m<sup>2</sup> vs mitoxantrone,  $P<0.00001$ ; anthracycline >250 mg/m<sup>2</sup> vs mitoxantrone,  $P=0.02$ . Shaded areas indicate 95% CI.

need for primary prevention (such as avoiding cardiotoxic treatment), the use of lower doses of cardiotoxic treatments in children with cancer, and considering alternatives to mitoxantrone in new treatment protocols for children with cancer.

Several explanations for the increased risk of heart failure in more recent treatment periods can be considered. A first explanation could be the more frequent use of cardiotoxic treatment. The number of CCS treated with anthracyclines and mitoxantrone increased over the decades (Table 2).

Another possible explanation for the increased risk of heart failure among CCS treated more recently could be that CCS with heart failure in recent eras were diagnosed more precisely. Specialized outpatient late-effects clinics were first established during the decade from 1990 to 2000, and among physicians, awareness of anthracycline-induced heart failure increased. A third reason for the increased risk of heart failure over time could be a decrease in cardiac mortality. Individuals with



**Table 2.** Description of Cardiotoxic Treatment for Different Cancer Treatment Periods

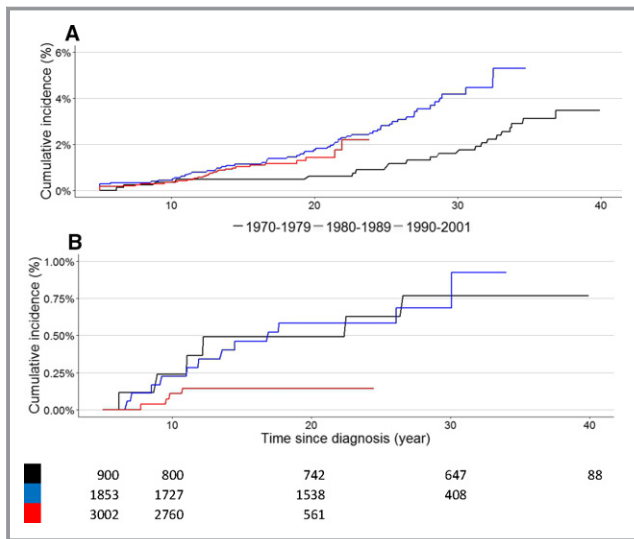
	Treatment Between 1960 and 1979 (n=990 CCS)	Treatment Between 1980 and 1989 (n=1853 CCS)	Treatment Between 1990 and 2001 (n=3002 CCS)
<b>Anthracycline</b>			
Median dose (IQR)	180 (22.5–740)	200 (18.0–1950)	160 (6.89–668)
	n (%)	n (%)	n (%)
No anthracyclines	745 (75.2)	970 (52.3)	1384 (46.1)
Anthracyclines any dose	233 (23.6)	867 (46.8)	1607 (53.5)
Missing	12 (1.2)	16 (0.9)	11 (0.4)
1 to 100 mg/m <sup>2</sup>	75 (7.6)	174 (9.4)	212 (7.1)
100 to 250 mg/m <sup>2</sup>	40 (4.0)	324 (17.5)	1059 (35.3)
>250 mg/m <sup>2</sup>	85 (8.6)	342 (18.5)	302 (10.1)
Missing	33 (3.3)	27 (1.5)	34 (1.1)
<b>Mitoxantrone</b>			
Median dose (IQR)	50 (20–40)	38 (22–46)	39 (20–70)
	n (%)	n (%)	n (%)
No mitoxantrone	976 (98.5)	1822 (98.3)	2863 (95.4)
Mitoxantrone any dose	3 (0.3)	15 (0.8)	128 (4.3)
Missing	12 (1.2)	16 (0.9)	11 (0.4)
1 to 40 mg/m <sup>2</sup>	1 (33.4)	9 (60.0)	71 (55.5)
>40 mg/m <sup>2</sup>	2 (66.6)	3 (20.0)	53 (41.4)
Missing		3 (20.0)	4 (3.9)
<b>Radiotherapy</b>			
No chest radiotherapy	650 (65.6)	1447 (78.1)	2478 (82.5)
Radiotherapy potentially involving the heart	192 (19.4)	190 (10.3)	206 (6.9)
Radiotherapy involving the heart	142 (14.3)	204 (11.0)	301 (10.0)
Missing	7 (0.7)	11 (0.6)	17 (0.6)

CCS indicates childhood cancer survivor; IQR, interquartile range.

cardiac dysfunction are expected to be referred more often to the cardiologist and are perhaps treated in an earlier phase. Similarly, treatment of heart failure has improved considerably over the past few decades.<sup>27</sup> With the introduction of angiotensin-converting enzyme inhibitors by the end of the 1980s<sup>28</sup> into heart failure treatment and the addition of  $\beta$ -blockers by the end of the 1990s,<sup>29</sup> the mortality due to heart failure significantly decreased in the overall population of patients with heart failure.<sup>30</sup>

Despite the small number of CCS treated with mitoxantrone in our study, our results showed a statistically significant association of mitoxantrone with symptomatic heart failure in our cohort of CCS with a dose-response relationship. We showed this both in the comparisons of the cumulative risk estimates—by time since treatment—as well as in the Cox proportional hazards model analysis (with attained age on the time scale and adjusted for follow-up time). Our findings are in line with previous studies that have

described a mitoxantrone association with cardiac dysfunction and symptomatic heart failure in CCS.<sup>19,31</sup> It has been suggested that mitoxantrone has different cardiotoxic mechanisms from the anthracyclines.<sup>32,33</sup> In the current study we showed that timing of presentation for mitoxantrone-associated heart failure seems different from that of anthracycline-associated heart failure, and that there are differences with respect to dose-response relationship. CCS treated with mitoxantrone have a high risk for heart failure, and targeted follow-up is needed.<sup>34</sup> Further data on (childhood cancer) patients treated with mitoxantrone need to be replicated in studies with larger study populations. We found a significant association between cyclophosphamide and heart failure. Acute cardiac damage from cyclophosphamide has been suggested by other studies,<sup>35,36</sup> but, to our knowledge, late cardiac damage has not been previously reported. Further and more extensive research into the role of cyclophosphamide in the development of heart failure is needed.



**Figure 3.** **A**, Cumulative incidence of heart failure (grades 3, 4, and 5) per treatment period, with time since childhood cancer diagnosis. *P*-value for Gray test: 1970–1979 vs 1980–1989, *P*=0.011; 1970–1979 vs 1990–2001, *P*=0.03; 1980–1989 vs 1990–2001, *P*=0.81 **B**, Cumulative incidence of heart failure grade 5, fatal events, per treatment period with time since childhood cancer diagnosis. *P*-value for Gray test: 1970–1979 vs 1980–1989, *P*=0.99; 1970–1979 vs 1990–2001, *P*=0.04; 1980–1989 vs 1990–2001, *P*=0.02. All childhood cancer survivors diagnosed between 1970 and 2001 were included in this figure.

The findings of this study need to be considered subject to the limitation of not having information on the absorbed radiation dose to the heart. However, based on the current results and

those reported previously,<sup>11</sup> the association between radiotherapy involving the heart and heart failure is less strong than the association between chemotherapy and heart failure.

The strengths of the current study include the near complete follow-up (94.8%, 84.7% until 2013) of our entire nationwide cohort of CCS, the nearly complete collection of treatment data, and the validation of all cases of heart failure by extracting information from the medical charts or from the treating physicians using an extraction-flowchart method.<sup>24</sup> These strengths will increase the validity of the study.

Our study findings can inform new treatment protocols for children with cancer. In addition, other treatment options—if available—should be considered in current childhood cancer treatment protocols, and cardiotoxic doses should be limited because heart failure also develops after low doses of anthracyclines and/or mitoxantrone.

It is also important to realize that the risk of heart failure is high even at a young attained age, and therefore, CCS at risk of heart failure might benefit from early intervention. Previous literature suggests that early treatment can lead to better survival in comparable study populations.<sup>37</sup> Thus, our results also warrant the need for appropriate cardiac surveillance of CCS and can therefore inform the current recommendations<sup>34</sup> for cardiomyopathy surveillance by suggesting the need to provide separate recommendations for survivors treated with mitoxantrone and anthracyclines.

In addition, future studies are needed to evaluate risk factors models for heart failure that include variables that

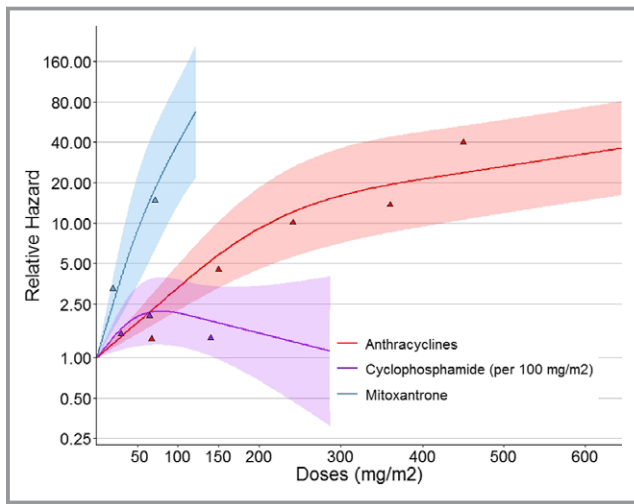
**Table 3.** Multivariable Cox Proportional Hazard Regression Model for the Analysis of Potential Determinants for Heart Failure (Grades 3, 4, 5): Age at Diagnosis, Sex, Period of Treatment, and Cancer Treatment

Covariates*	REF (n)/Total (n)	Hazard Ratio, Median (IQR)	<i>P</i> Value	REF (n)/Events (n)
Age at primary childhood diagnosis (per y)		0.8 (0.8–0.9)	<0.001	
Sex (REF=male)	3257/5845	0.9 (0.6–1.3)	0.64	
Year of childhood cancer diagnosis (per y)		1.0 (1.01–1.1)	0.04	
Anthracycline (per 1 mg/m <sup>2</sup> , splines)		See Figure 4	<0.001	
Mitoxantrone (per 1 mg/m <sup>2</sup> , splines)		See Figure 4	<0.001	
Cyclophosphamide (per 100 mg/m <sup>2</sup> , splines)		See Figure 4	0.04	
<b>Chest radiotherapy</b>				
No chest radiotherapy	4575/5845	REF		78/116
Radiotherapy potentially involving the heart	588/5845	1.0 (0.4–2.0)	0.96	9/116
Radiotherapy involving the heart <20 Gy	275/5845	2.0 (1.1–3.6)	0.02	15/116
Radiotherapy involving the heart ≥20 Gy	363/5845	2.1 (1.1–4.0)	0.02	14/116
Cisplatin (per 1 mg/m <sup>2</sup> )		1.0 (1.0–1.0)	0.61	
Ifosfamide (per 1 mg/m <sup>2</sup> )		1.0 (1.0–1.0)	0.28	
Vincristine (per 1 mg/m <sup>2</sup> )		1.0 (1.0–1.0)	0.20	

REF indicates reference category.

\*We did not find a significant interaction term between anthracycline and radiotherapy involving the heart.

The bold values indicate the significant risk factors.



**Figure 4.** Dose-response curves of the development of heart failure with anthracyclines, mitoxantrone, and cyclophosphamide. The colored triangles are the hazard ratios (HRs) from the model presented on a logarithmic scale to show the actual HRs. The model is also corrected for sex, age at diagnosis, year of childhood cancer diagnosis, and radiotherapy where the heart was in the field yes/no. Shaded areas indicate 95% CI.

change value over time, such as smoking history, current BMI, and presence of other heart diseases.

In conclusion, CCS are at high risk of developing severe life-threatening or fatal heart failure even 40 years after their diagnosis at a relatively young age, and CCS treated with anthracyclines and mitoxantrone are most at risk. Although mortality due to heart failure decreases in more recent treatment periods, the incidence of severe or life-threatening heart failure increases. Primary prevention to diminish the risk of heart failure for CCS is needed.<sup>38</sup>

## Appendix

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## Disclosures

None.

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# **Supplemental Material**

## **Data S1.**

### **Supplemental Methods**

#### **Definition of Cardiac Event**

Childhood cancer survivor (CCS) had potentially heart failure if “yes” was answered to one of the following questions of the DCOG-LATER (Dutch Childhood Oncology Group - Long term Effects after Childhood Cancer) questionnaire: “Do you have now or did you ever have one of the following conditions, if yes please estimate at what age it started and if you use medications at this moment: heart attack, chest pain, valvular disease, inflammation of the sac around your heart (pericarditis), weak heart muscle (cardiomyopathy), heart failure, arrhythmias/ palpitations, other heart disease?”; “Did you ever have one of the following surgeries: replacement of the heart valve, other surgery to the heart (including stenting), did you ever have a pacemaker or ICD?”.

When using the GP (general practitioner) DCOG-LATER questionnaire, we considered CCS to have potentially heart failure when “yes” was answered to one of the following questions: “Did the CCS develop one of the following conditions since the diagnosis of the primary childhood cancer: arrhythmia, valvular disease, cardiac conduction disorders, angina, ischemia or infarction, heart failure, pericarditis or other cardiovascular disorder?, If “yes”, information on diagnosis year and treatment institute were established with the following question: “in what year was it diagnosed and what and where was the treatment?”. In order to validate the self-reported heart failure data, we extracted heart failure information from the medical records for all CCS with potentially heart failure. We used an extraction-flowchart method especially developed for consistent and valid grading (see Figure S2).<sup>1</sup> This method consists of an extraction form and a set of flowcharts for specific cardiac conditions which allows grading of the heart failure according to the CTCAEv3.0 and v4.0.1

We defined grading of heart failure as follows: grade 3 (severe), grade 4 (life-threatening or disabling) or grade 5 (fatal).<sup>1</sup> We considered the date on which a symptomatic heart failure was first confirmed by diagnostic testing as the cardiac incidence date. We included heart failures occurring after the 5-year survival date and heart failures that started within 5 years after primary childhood cancer diagnosis

and were still on-going after 5-year survival: the incidence date is then set on 5 years + 1 day.

## Data S2.

### Supplemental Results

#### CE origins

Around 17% of the CCS reported potential heart failure (n=484) in the DCOG-LATER questionnaire. We were able to validate almost all of them (n=474; 97.9%) and we graded by extracting relevant data on the potential heart failure from their DCOG-LATER hospital medical chart, from their GP or other hospital records. However, 10 (2.1%) CCS did not give permission to request information from their GP or other hospital and we were unable to extract sufficient information from their medical notes at the DCOG-LATER hospital. Nevertheless, we were able to establish the nature and grade of the potential CE for these CCS, by the information they provided on the DCOG-LATER questionnaire. Of the 484 CCS who reported a cardiac event (CE) in the DCOG-LATER questionnaire, 58 (11.8%) CCS had a symptomatic heart failure and were therefore included in the study as a cardiac case. Six percent (n=46) of the GPs reported a potential CE in the GP DCOG-LATER questionnaire. All of them could be validated and graded by extracting relevant data from their medical chart. Of the GPs who reported a potential CE in the GP DCOG-LATER questionnaire, we found that 6 (13.0%) CCS had a symptomatic heart failure and were therefore included in the study as a cardiac case. From the DCOG-LATER outpatient clinics we found 7.9% (n=161) CCS who had a potential CE. All of the potential CEs could be validated and graded by extracting relevant data about the potential CE from their cardiology medical chart. In 52 (32.3%) CCS the heart failure was symptomatic and these patients were therefore included in the study as a cardiac case. In order to assess completeness of reporting, we randomly collected 20 CCS who did not report a potential CE and validated this by extracting data from their medical records, none of the CCS had a CE.



**Table S1. Cumulative incidence of heart failure ( $\geq$  grade 3) over time since diagnosis (follow-up) in childhood cancer survivors according to the nonparametric estimator of cause-specific cumulative incidence, with death from any cause as competing risk.**

<i>Treatment groups</i>	<i>follow-up 10 yr</i>	<i>95% CI</i>	<i>follow-up 20 yr</i>	<i>95% CI</i>	<i>follow-up 30 yr</i>	<i>95% CI</i>	<i>follow-up 40 yr</i>	<i>95% CI</i>	
Overall	0.4%	0.2-0.5	1.3%	1.0-1.7	3.0%	2.3-3.6	4.4%	3.4-5.5	
<i>Cardiotoxic treatment yes/no</i>									
No cardiotoxic treatment*	0.0%	0.0-0.0	0.0%	0.0-0.0	0.1%	0.0-0.3	0.3%	0.0-0.7	
Cardiotoxic treatment†	0.7%	0.41-1.0	2.6%	2.0-3.3	6.3%	4.9-7.7	10.6%	7.4-13.9	
<i>Types of cardiotoxic treatment</i>									
Cardotoxic CT only	0.8%	0.4-1.1	2.8%	2.1-3.6	6.4%	4.7-8.1	10.5%	6.6-14.4	
Chest RT only	0.5%	0.0-1.4	0.5%	0.0-1.5	1.2%	0.00-3.0	3.0%	0.0-5.9	
Cardiotox CT and chest RT	0.5%	0.0-1.1	2.5%	0.8-4.2	9.6%	5.13-14.12	27.8%	5.1-50.6	
<i>Types of cardiotoxic chemotherapy</i>									
Mitoxantrone (+/-anthracyclines)	1.5%	0.1-3.5	11.4%	3.6-19.1	16.9%	4.1-29.7	16.9%	4.1-29.7	
1-100 mg/m <sup>2</sup> anthracycline‡	0.2%	0.1-0.7	0.7%	0.0-1.7	1.2%	0.0-2.7	1.2%	0.0-2.7	
100-250 mg/m <sup>2</sup> anthracycline‡	0.5%	0.1-0.8	1.4%	0.7-2.2	4.0%	1.8-6.2	37.3%	0.0-87.5	
>250 mg/m <sup>2</sup> anthracycline‡	1.2%	0.4-2.0	5.2%	3.4-7.1	13.0%	9.4-16.6	24.3%	15.3-33.3	
<i>Period of treatment</i>									
1970-1979	0.2%	0.0-0.5	0.5%	0.0-0.9	1.4%	0.6-2.2	2.9%	1.7-4.2	
1980-1989	0.4%	0.1-0.7	1.6%	1.0-2.2	3.9%	2.8-4.9	xx	xx	
1990-2001	0.4%	0.2-0.6	1.5%	0.9-2.0	xx	xx	xx	xx	

\* No cardiotoxic treatment defined as treated without anthracyclines, mitoxantrone and radiotherapy involving the heart

† Cardiotoxic treatment defined as treated with anthracyclines, mitoxantrone and/ or radiotherapy involving the heart

‡ Without mitoxantrone

**Table S2. Cumulative incidence of heart failure (≥ grade 3) at attained age in childhood cancer survivors according to the nonparametric estimator of the cause-specific cumulative incidence, with death from any other cause as competing risk.**

<i>Treatment groups</i>	<i>10</i>		<i>20</i>		<i>30</i>		<i>40</i>		<i>50</i>	
	<i>years of age</i>	<i>95% CI</i>	<i>years of age</i>	<i>95% CI</i>	<i>years of age</i>	<i>95% CI</i>	<i>years of age</i>	<i>95% CI</i>	<i>years of age</i>	<i>95% CI</i>
Overall	0.2%	0.0-0.4	0.8%	0.5-1.1	2.0%	1.6-2.5	3.7%	2.9-4.4	5.3%	3.7-6.9
<i>Cardiotoxic treatment yes/no</i>										
No cardiotoxic treatment†	0.0%	0.0-0.0	0.0%	0.0-0.0	0.1%	0.0-0.1	0.3%	0.0-0.6	0.3%	0.06-0.6
Cardiotoxic treatment◇	0.5%	0.0-0.9	1.7%	1.1-2.3	4.0%	3.1-4.9	7.3%	5.6-8.9	11.6%	7.4-15.8
<i>Types of cardiotoxic treatment</i>										
Cardotoxic CT only	0.3%	0.0-0.6	1.5%	0.9-2.1	3.9%	2.9-4.9	6.4%	4.7-8.2	11.6%	7.1-16.1
Chest RT only	0.0%	0.0-0.0	0.0%	0.0-0.0	0.5%	0.0-1.5	2.6%	0.0-5.1	2.6%	0.0-5.1
Cardiotox CT and chest RT	2.9%	0.0-7.4	4.7%	0.0-9.3	7.4%	2.5-12.2	14.6%	7.4-21.7	33.2%	2.8-63.7
<i>Types of cardiotoxic chemotherapy</i>										
Mitoxantrone (+/anthracyclines)	0.0%	0.0-0.0	0.3%	0.2-0.7	0.6%	0.0-1.4	1.2%	0.0-2.7	1.2%	0.0-2.7
1-100 mg/m2 anthracycline*	0.3%	0.0-0.6	0.8%	0.3-1.4	2.3%	1.3-3.4	4.5%	1.9-7.0	18.3%	0.0-43.3
100-250 mg/m2 anthracycline*	0.4%	0.0-1.1	3.0%	1.5-4.6	7.0%	4.8-9.2	13.0%	9.3-16.7	19.2%	12.7-25.8
>250 mg/m2 anthracycline*	0.0%	0.0-0.0	4.1%	0.6-7.7	12.9%	5.5-20.3	12.9%	5.5-20.3	12.9%	5.5-20.3

† No cardiotoxic treatment defined as treated without anthracyclines, mitox heart

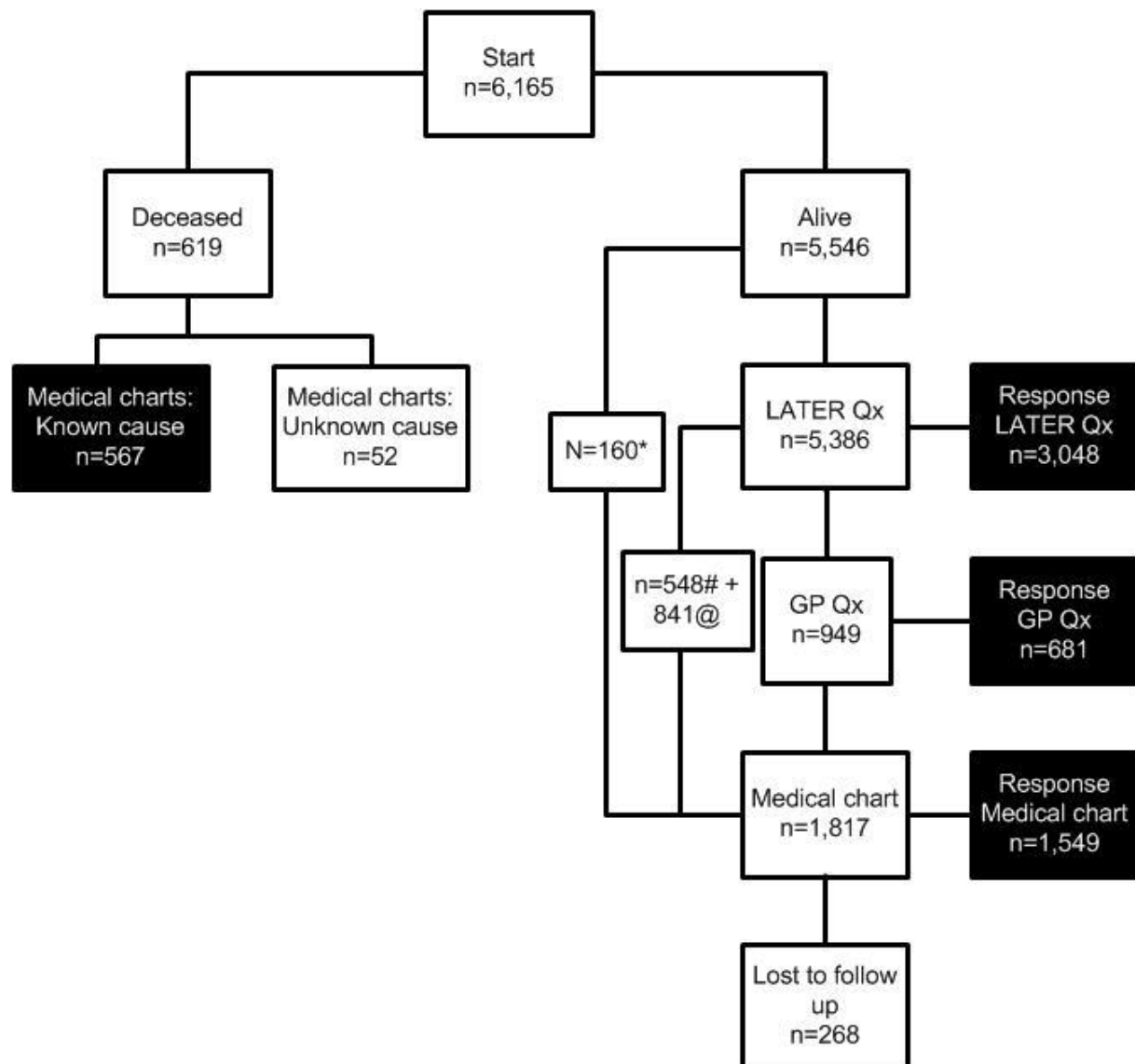
◇ Cardiotoxic treatment defined as treated with anthracyclines, mitoxantror heart

\* Without mitoxantrone

CT= chemotherapy (anthracyclines and mitoxantrone)

Chest RT =radiotherapy involving the heart

**Figure S1. Flowchart of the cardiac data collection.**



Qx= Questionnaire, LATER= Long term Effects after Childhood Cancer

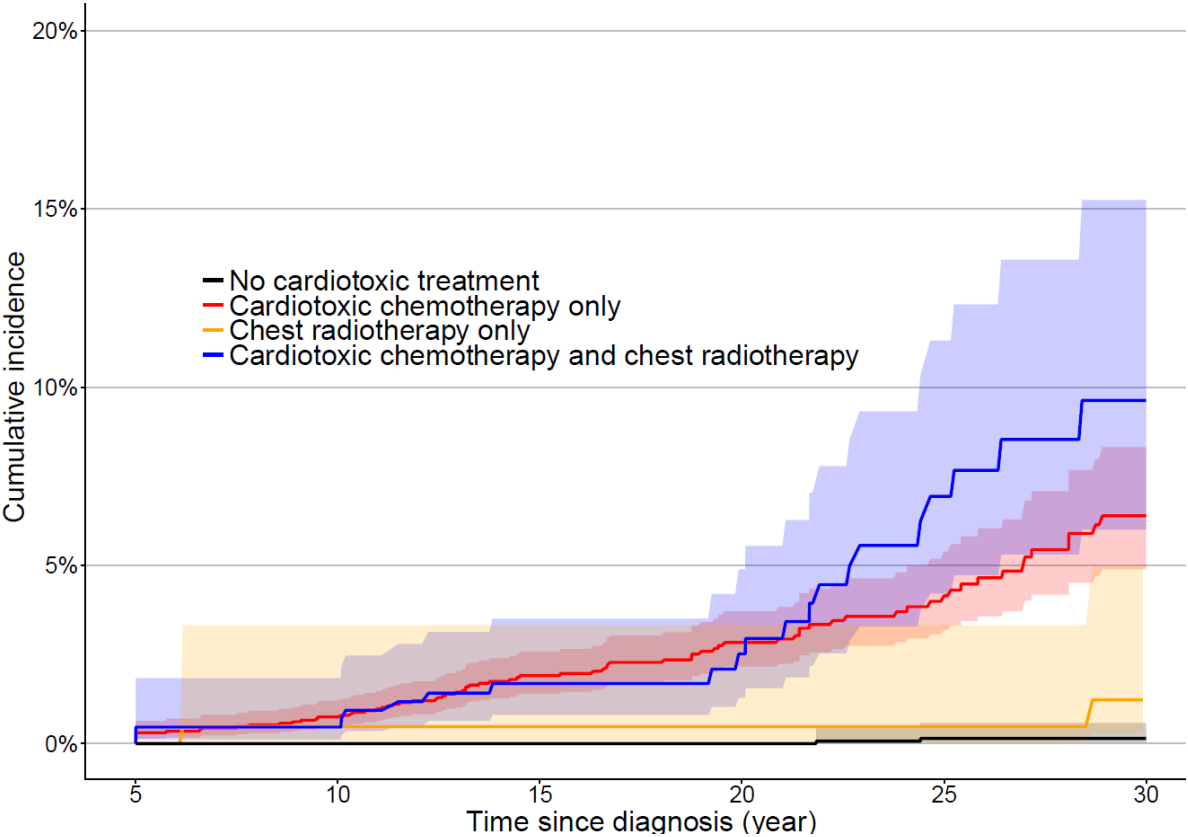
\* CCS were who living abroad, were in active cancer treatment or could not be traced at the time of follow-up

# CCS who did not participate in the LATER questionnaire, and did not give permission for GP questionnaire

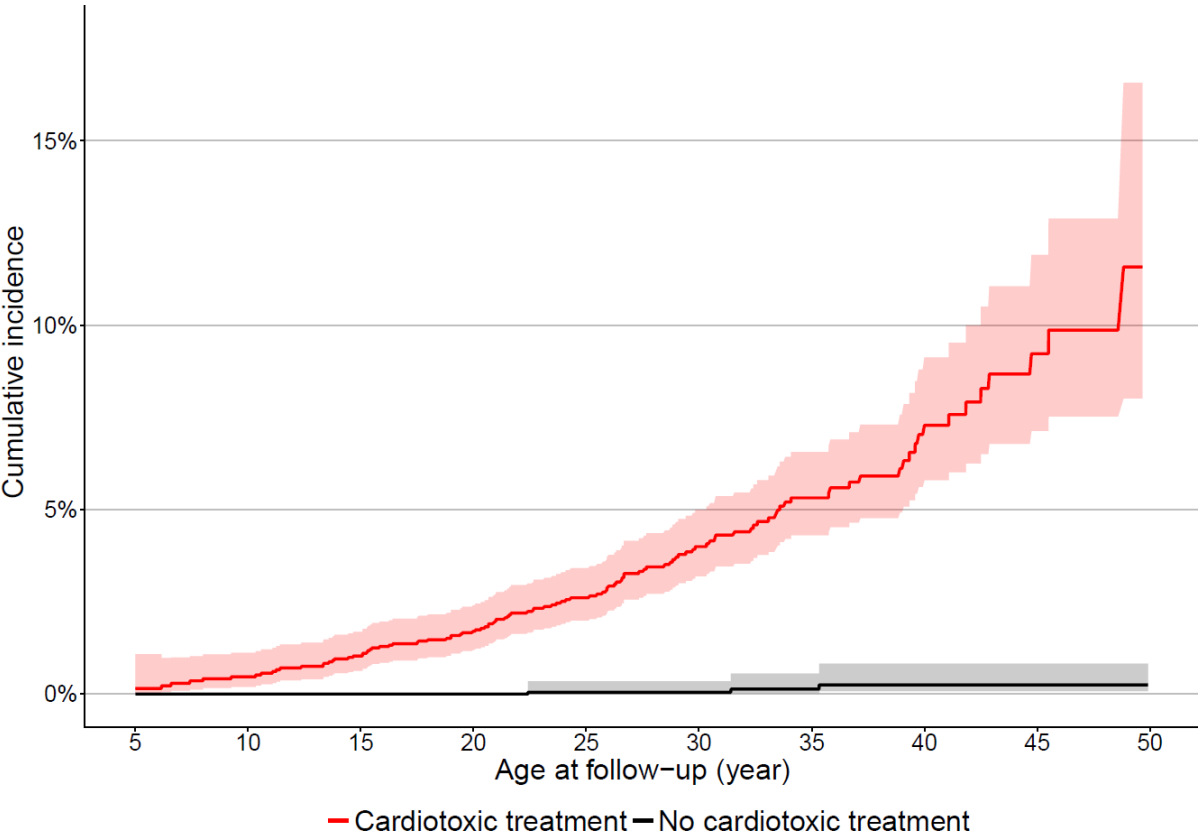
@ CCS who were seen within the last 2 years of follow-up in the LATER outpatient clinic



**Figure S3. Cumulative incidence of heart failure at time since childhood cancer diagnosis for four mutually exclusive treatment groups.**



**Figure S4. Cumulative incidence of heart failure at attained age for cardiotoxic treatment and no cardiotoxic treatment.**



**Supplemental Reference:**

1. Feijen EAM, van der Pal HJ, van Dalen EC, Mulder RL, Bardi E, Kuehni C, Tissing WJ, Kremer LC. A new method to facilitate valid and consistent grading cardiac events in childhood cancer survivors using medical records. *PloS one*. 2014;9:e100432.