Risk Factors for Heart Failure Among Pan-European Childhood Cancer Survivors: A PanCareSurFup and ProCardio Cohort and Nested Case-Control Study

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PURPOSE Heart failure (HF) is a potentially life-threatening complication of treatment for childhood cancer. We evaluated the risk and risk factors for HF in a large European study of long-term survivors. Little is known of the effects of low doses of treatment, which is needed to improve current treatment protocols and surveillance guidelines.

METHODS This study includes the PanCareSurFup and ProCardio cohort of ≈ 5-year childhood cancer survivors diagnosed between 1940 and 2009 in seven European countries (N = 42,361). We calculated the cumulative incidence of HF and conducted a nested case-control study to evaluate detailed treatment-related risk factors.

RESULTS The cumulative incidence of HF was 2% (95% CI, 1.7 to 2.2) by age 50 years. The case-control study (n = 1,000) showed that survivors who received a mean heart radiation therapy (RT) dose of 5 to ≤ 15 Gy have an increased risk of HF (odds ratio, 5.5; 95% CI, 2.5 to 12.3), when compared with no heart RT. The risk associated with doses 5 to < 15 Gy increased with exposure of a larger heart volume. In addition, the HF risk increased in a linear fashion with higher mean heart RT doses. Regarding total cumulative anthracycline dose, survivors who received ≥ 100 mg/m² had a substantially increased risk of HF and survivors treated with a lower dose showed no significantly increased risk of HF. The dose-response relationship appeared quadratic with higher anthracycline doses.

CONCLUSION Survivors who received a mean heart RT dose of ≥ 5 Gy have an increased risk of HF. The risk associated with RT increases with larger volumes exposed. Survivors treated with < 100 mg/m² total cumulative anthracycline dose have no significantly increased risk of HF. These new findings might have consequences for new treatment protocols for children with cancer and for cardiomyopathy surveillance guidelines.

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BACKGROUND Developments in the treatment for children with cancer have improved survival considerably over recent decades.1 However, long-term survivors are at risk of adverse effects induced by cancer and its treatment. One of the most severe effects is cardiotoxicity. This may occur as asymptomatic myocardial dysfunction and can progress to symptomatic heart failure (HF), which is related to increased morbidity and mortality.2,7 Previous studies among childhood cancer survivors (hereafter survivors) identified treatment-related risk factors for HF, including anthracyclines, mitoxantrone, and radiation therapy (RT) where the heart was in the radiation field.4,8,12 Anthracycline analogs that have been linked to cardiotoxicity comprise doxorubicin, daunorubicin, epirubicin, and idarubicin. Mitoxantrone is an anthraquinone and structurally comparable with doxorubicin.13 Of these chemotherapeutic agents, mitoxantrone has the greatest cardiotoxic potential, which may be related to differences in underlying pathophysiology.14,15 Other potential risk factors for HF are cyclophosphamide, sex, age at cancer diagnosis, and presence of traditional cardiovascular risk factors.2,4,7,16-18
Surveillance of myocardial function after cardiotoxic treatment is of great importance to detect treatable abnormalities at an early stage.\textsuperscript{19} The International Guideline Harmonization Group (IGHG) formulated cardiomyopathy surveillance recommendations in 2015 for survivors treated with anthracyclines (all doses) and survivors treated with radiotherapy involving the heart region of \( \geq 15 \text{ Gy} \). Furthmore, this group highlighted future directions for research including the risk of symptomatic HF in survivors treated with \(< 15 \text{ Gy} \) chest RT as little was known about the effects.\textsuperscript{19} New evidence for low doses of cardiotoxic treatments is needed to guide both updates of cardiomyopathy surveillance strategies and designs of treatment regimes.

Pooling data from two EU-funded consortia, the PanCareSurFup (PCSF) cardiac study\textsuperscript{20} and ProCardio,\textsuperscript{21} created a large cohort of survivors (\( N = 42,361 \)) to investigate low treatment doses of anthracyclines and cardiac RT and the nature of dose responses, by using phantom-based radiation dosimetry including dose-volume histogram indicators. The latter technique calculates the estimated dose received by the organ at risk.

**METHODS**

In 2011, collaborative efforts initiated the PCSF cardiac study\textsuperscript{22} and ProCardio and designed them to be complementary with a view of pooling data. We conducted a cohort study and a nested case-control study using these data. We described the exact process below and show it by a flowchart in the Data Supplement (online only).

**Study Population**

We included \( \geq 5 \)-year survivors in whom cancer was diagnosed at age \(< 20 \) years between 1940 and 2009. The PCSF cardiac study comprised eight European subcohorts from France, Hungary, Italy (two subcohorts), the Netherlands, Slovenia, Switzerland, and the United Kingdom. The ProCardio project comprised survivors from France and the United Kingdom. The inclusion criteria, which are listed in the Data Supplement, differed slightly between the subcohorts. The study was performed after approval by a local Human Investigations Committee. Depending on the regulations in each country, informed consent was obtained from all individual participants included in the corresponding subcohort or the data were collected under national law.

**Identification of Survivors With Heart Failure**

We identified survivors with HF (hereafter case) as a first event by using multiple strategies, for example, linkage to population-based databases and patient-based questionnaires. A case was defined as having symptomatic HF graded according to the Common Terminology and Criteria for Adverse Events\textsuperscript{23} as grades 3, 4, and 5 (Data Supplement). The exact methods are described by Feijen et al.\textsuperscript{22}

**Case-Control Study: Control Selection**

We randomly selected controls by density sampling and matched them with cases with HF (ratio 1:1) on subcohort, sex, age at first cancer diagnosis (\( \pm 1 \) year), and calendar year of first cancer diagnosis (\( \pm 3 \) year). The length of follow-up after first cancer diagnosis of controls was at least as long as the interval between cancer diagnosis and HF in the matched case, but controls had to be HF-free. When no suitable control could be found, the calendar period criterion was relaxed (maximum 10 years). If still no eligible control was available, then age at cancer diagnosis was relaxed (maximum 3 years).

**Data Collection**

For the cohort study, we collected baseline characteristics for all survivors included in the analysis. These data included sex, month and year of birth, month and year of first cancer diagnosis, morphology code, type of treatment, and the month
and year of the start of treatment. For the case-control study, we collected details of treatment for all cases and controls from medical records by using a standardized extraction form. We collected data for each cycle of each cytotoxic agent to enable calculation of cumulative dose (or equivalent). We performed radiation dosimetry for the whole body including seven parts of the heart for all cases and controls who received RT, as previously described. With dosimetry, we calculated the estimated average of the maximum dose that was given to different parts of the whole heart, and this measure is reflected by mean heart RT dose. In addition, we created dose volume variables by calculating the percentage of heart volume that received at least 5 (V5), 10 (V10), 15 (V15), 20 (V20), or 30 (V30) Gy. The variable V5-15 reflects the percentage of the cardiac volume that received a maximum dose of 5-15 Gy, and the variable V15 reflects the percentage of the cardiac volume that received at least 15 Gy. We collected all treatment data until the date of the cardiac event for cases and for the same period of follow-up from childhood cancer diagnosis for the matched controls.

**Statistical Analysis**

For the cohort study, the main outcome of interest was the first occurrence of symptomatic HF. Time at risk started 5 years after the first primary cancer diagnosis. Cardiac follow-up ended at the first occurrence of HF, death for deceased individuals, or at last date of exit from cardiac follow-up. To limit follow-up bias, we fixed the final end of follow-up date separately for each subcohort as the last date on which cardiac follow-up was available for ≥ 80% of subcohort members (Data Supplement). We calculated the cumulative incidence of symptomatic HF with attained age as the time scale and taking death into account as a competing risk. We analyzed cumulative incidence for the overall cohort, by subcohort and by treatment period until the number at risk was < 100. We performed Gray’s test to test for unadjusted significant differences between the cumulative incidences in the case-control study, we included all cases identified in the cohort study (100% of all subcohort members) and used a conditional logistic regression model to estimate odds ratios (ORs). The model included treatment-related exposures on the basis of the literature and clinical knowledge. See the Data Supplement for the complete list of chemotherapy agents that were tested. We started with a baseline model including total cumulative anthracycline dose and mean heart RT dose since these are well-established risk factors for HF. Thereafter, we expanded the baseline model by adding each potential covariate to the model and compared it with the baseline model with a likelihood ratio test. For the final model, we evaluated evidence of interaction between treatment variables and age at diagnosis. In addition, we analyzed heart RT dose-volume variables by including them instead of mean dose. We used R-studio (version 6.1.1) to analyze noncontinuous treatment exposures, and we used Epicure software to evaluate continuous exposures by fitting a linear model for the excess odds ratio (EOR) and to evaluate departures from linearity. For all analyses, we defined statistical significance as a two-sided P value of < .05.

**RESULTS**

The characteristics of survivors included in the cohort study are presented in the Data Supplement. The cohort included a total of 36,205 survivors (45% were female). The UK subcohort contributed 46%. The median age of the survivors was 5.8 years at the time of diagnosis and was 29.7 years at the end of follow-up. The most frequent cancer diagnoses were leukemia (27%), lymphoma (15%), central nervous system tumors (18%), and sarcoma (12%). Figure 1 shows the cumulative incidence of HF by attained age. By 50 years of attained age, the cumulative incidence of HF was 2.0% (95% CI, 1.7 to 2.2). The Data Supplement illustrates the variation in cumulative incidence of HF between the subcohorts. The latest time point where we could analyze all different subcohorts was age 30 years at which the cumulative incidence ranged between 0.2% and 2.6%. For France, the United Kingdom, and the Netherlands, the risk by age 50 years was available and the cumulative incidence ranged from 1.0% to 5.2%. See the Data Supplement for the characteristic of the survivors by subcohort. The cumulative incidence of HF was greater among those with cancer diagnosed from 1980 onward than among those diagnosed before (Figure 2A). Figure 2B shows that the cumulative incidence of cardiac mortality because of HF was lower in the treatment period 1990-2008 compared with that in 1980-1990.

The case-control study included 500 cases and 500 controls, and their characteristics are demonstrated in Table 1. Of all survivors, 366 had not received any RT and the RT exposure was unknown for one case and two controls. Among the 631 survivors who received RT, dosimetry was impossible for seven (1.1%) cases and five (0.8%) controls. The median of the mean heart RT dose in

![Graph showing cumulative incidence of heart failure for all survivors (including all types of treatment) with attained age as the time scale. Shaded: 95% CI.](image-url)
Risk Factors for Heart Failure Among Childhood Cancer Survivors

The median cumulative anthracycline dose (including mitoxantrone) was 362 mg/m² in cases and 218 mg/m² in controls. Analyzing mitoxantrone as separate exposure would have led to underpowered results because only 29 survivors (nine of them with missing dose) received this agent. Dexrazoxane treatment was equal between cases and controls. Analyzing mitoxantrone as separate exposure (adjusted for anthracyclines or heart RT in the risk of HF) did not reach statistical significance (2.3; 95% CI, 0.7 to 7.1), the OR for 100 to < 250 mg/m² was 5.8 (95% CI, 2.9 to 11.3), and the OR for ≥ 250 mg/m² was 21.2 (95% CI, 11.4 to 39.2). When compared with survivors who received anthracyclines, the OR associated with total cumulative anthracycline doses < 100 mg/m² did not reach statistical significance (2.3). 95% CI, 0.7 to 7.1), the OR for 100 to < 250 mg/m² was 5.8 (95% CI, 2.9 to 11.3), and the OR for ≥ 250 mg/m² was 21.2 (95% CI, 11.4 to 39.2). When compared with survivors who received anthracyclines, the OR associated with total cumulative anthracycline doses < 100 mg/m² did not reach statistical significance (2.3).

The final model included cumulative anthracycline dose and mean heart RT dose (Table 2). See the Data Supplement for the likelihood ratio tests for all analyzed covariates. The ORs of HF significantly increased with both the total cumulative anthracycline dose (P_trend = < .0001) and mean heart RT dose (P_trend = < .0001). When compared with survivors who did not receive anthracyclines, the OR associated with total cumulative anthracycline doses < 100 mg/m² did not reach statistical significance (2.3). 95% CI, 0.7 to 7.1), the OR for 100 to < 250 mg/m² was 5.8 (95% CI, 2.9 to 11.3), and the OR for ≥ 250 mg/m² was 21.2 (95% CI, 11.4 to 39.2). When compared with survivors who received anthracyclines, the OR associated with total cumulative anthracycline doses < 100 mg/m² did not reach statistical significance (2.3). 95% CI, 0.7 to 7.1), the OR for 100 to < 250 mg/m² was 5.8 (95% CI, 2.9 to 11.3), and the OR for ≥ 250 mg/m² was 21.2 (95% CI, 11.4 to 39.2). When compared with survivors who received anthracyclines, the OR associated with total cumulative anthracycline doses < 100 mg/m² did not reach statistical significance (2.3). 95% CI, 0.7 to 7.1), the OR for 100 to < 250 mg/m² was 5.8 (95% CI, 2.9 to 11.3), and the OR for ≥ 250 mg/m² was 21.2 (95% CI, 11.4 to 39.2). When compared with survivors who received anthracyclines, the OR associated with total cumulative anthracycline doses < 100 mg/m² did not reach statistical significance (2.3).

When fitting the continuous total cumulative anthracycline dose as a linear term (adjusted for heart RT), there was a significant departure from linearity (Data Supplement). The EOR per 100 mg/m² total cumulative anthracycline dose is expressed by the following equation: EOR = −0.3 (dose/100) + 1.6 (dose/100²) (Fig 3A). For mean heart RT dose, the dose-response relationship (adjusted for anthracyclines) was linear and yielded an EOR of 5.1 per 10 Gy (Fig 3B).

DISCUSSION
Insight into the risk factors for HF in survivors of childhood cancer is relevant for both the treatment of new children and survivors.
| Characteristic                                                                 | Cases = 500 (100%) | Controls = 500 (100%) |
|-------------------------------------------------------------------------------|--------------------|-----------------------|
| **Sex,** No. (%)                                                             |                    |                       |
| Female                                                                        | 219 (43.8)         | 219 (43.8)            |
| **Subcohort,** No. (%)                                                       |                    |                       |
| United Kingdom                                                                | 129 (25.8)         | 129 (25.8)            |
| France                                                                        | 195 (39)           | 195 (39)              |
| The Netherlands                                                               | 105 (21)           | 105 (21)              |
| Italy                                                                         | 18 (3.6)           | 18 (3.6)              |
| Switzerland                                                                   | 11 (2.2)           | 11 (2.2)              |
| Hungary                                                                       | 37 (7.4)           | 37 (7.4)              |
| Slovenia                                                                      | 5 (1)              | 5 (1)                 |
| **Type of childhood cancer, No. (%)**                                         |                    |                       |
| Leukemias, myeloproliferative diseases, and myelodysplastic diseases          | 85 (17)            | 73 (14.6)             |
| Lymphomas and reticuloendothelial neoplasms                                   | 136 (27.2)         | 107 (21.4)            |
| CNS and miscellaneous intracranial and intraspinal neoplasms                 | 15 (3.0)           | 78 (15.6)             |
| Neuroblastoma and other peripheral nervous cell tumors                        | 42 (8.4)           | 37 (7.4)              |
| Retinoblastoma                                                                | 2 (0.4)            | 21 (4.2)              |
| Renal tumors                                                                  | 64 (12.8)          | 81 (16.2)             |
| Hepatic tumors                                                                | 8 (1.6)            | 3 (0.6)               |
| Bone tumors                                                                   | 57 (11.4)          | 23 (4.6)              |
| Soft tissue and other extraosseous sarcomas                                   | 68 (13.6)          | 46 (9.2)              |
| Germ cell tumors, trophoblastic tumors, and neoplasms of gonads               | 13 (2.6)           | 18 (3.6)              |
| Other malignant epithelial neoplasms and malignant melanomas                  | 8 (1.6)            | 13 (2.6)              |
| Other and unspecified malignant neoplasms                                     | 2 (0.4)            | 0 (0)                 |
| **Age at childhood cancer diagnosis, years**                                  |                    |                       |
| Median (IQR)                                                                  | 5.8 (2.7-10.9)     | 5.6 (2.6-10.4)        |
| 0 to < 5, No. (%)                                                             | 222 (44.4)         | 228 (45.6)            |
| 5 to < 10, No. (%)                                                            | 135 (27)           | 118 (23.6)            |
| 10 to < 15, No. (%)                                                           | 119 (23.8)         | 126 (25.2)            |
| ≥ 15, No. (%)                                                                 | 24 (4.8)           | 28 (5.6)              |
| **Calendar year of diagnosis,** No. (%)                                       |                    |                       |
| < 1980                                                                        | 202 (40.4)         | 208 (41.6)            |
| 1980 to < 1990                                                                | 212 (42.4)         | 212 (42.4)            |
| 1990-2008                                                                     | 86 (17.2)          | 80 (16)               |
| **Attained age, years**                                                       |                    |                       |
| Median (min-max)                                                              | 27.0 (5.3-73.2)    | 26.4 (5.3-73.0)       |
| < 15, No. (%)                                                                 | 68 (13.6)          | 74 (14.8)             |
| 15 to < 25, No. (%)                                                           | 155 (31.0)         | 155 (31.0)            |
| 25 to < 35, No. (%)                                                           | 142 (28.4)         | 142 (28.4)            |
| 35 to < 45, No. (%)                                                           | 93 (18.6)          | 89 (17.8)             |
| 45 to < 55, No. (%)                                                           | 29 (5.8)           | 27 (5.4)              |
| ≥ 55, No. (%)                                                                 | 13 (2.6)           | 13 (2.6)              |
| **Follow-up duration, years**                                                 |                    |                       |
| Median (min-max)                                                              | 20.3 (5.0-62.5)    | 20.0 (5.0-62.0)       |

(continued on following page)
TABLE 1. Characteristics of the Survivors Included in the Case-Control Study (continued)

| Characteristic | Cases = 500 (100%) | Controls = 500 (100%) |
|----------------|-------------------|-----------------------|
| > 5 to < 10, No. (%) | 79 (15.8) | 85 (17.0) |
| 10 to < 20, No. (%) | 167 (33.4) | 161 (32.2) |
| 20 to < 30, No. (%) | 155 (31.0) | 159 (31.8) |
| 30 to < 40, No. (%) | 75 (15.0) | 72 (14.4) |
| ≥ 40, No. (%) | 24 (4.8) | 23 (4.6) |
| Cardiotoxic treatment, No. (%) | | |
| No cardiotoxic treatment | 23 (4.6) | 125 (25) |
| Anthracyclines only | 140 (28) | 89 (17.8) |
| Heart RT only | 108 (21.6) | 189 (37.8) |
| Anthracyclines and heart RT | 241 (44.1) | 88 (17.6) |
| Unknown | 15 (3.0) | 9 (1.8) |
| Total cumulative anthracycline dose, mg/m² | | |
| Median (IQR) | 362 (248-476) | 218 (125-331) |
| No, No. (%) | 135 (27.0) | 321 (64.2) |
| > 0 to < 100, No. (%) | 9 (1.8) | 22 (4.4) |
| 100 to < 200, No. (%) | 36 (7.2) | 49 (9.8) |
| 200 to < 300, No. (%) | 55 (11) | 38 (7.6) |
| 300 to < 400, No. (%) | 73 (14.6) | 37 (7.4) |
| ≥ 400, No. (%) | 125 (25) | 19 (3.8) |
| Unknown, No. (%) | 67 (13.4) | 14 (2.8) |
| Mitoxantrone, No. (%) | | |
| No | 465 (93) | 495 (99) |
| Yes | 26 (5.2) | 3 (0.6) |
| Unknown | 9 (1.8) | 2 (0.4) |
| Mean heart RT dose, Gy | | |
| Median (IQR) | 18.1 (9.4-28.3) | 16.5 (5.5-23.3) |
| No, No. (%) | 166 (33.2) | 215 (43) |
| > 0 to < 5, No. (%) | 138 (27.6) | 195 (39) |
| 5 to < 15, No. (%) | 55 (11) | 25 (5) |
| 15 to < 35, No. (%) | 111 (22.2) | 53 (10.6) |
| ≥ 35, No. (%) | 22 (4.4) | 5 (5) |
| Unknown, No. (%) | 8 (1.6) | 7 (1.4) |
| Grade of validated heart failure, No. (%) | | |
| 3 | 231 (46.2) | NA |
| 4 | 112 (22.4) | NA |
| 5 | 157 (31.4) | NA |
| Vital status, No. (%) | | |
| Alive | 301 (60.2) | 450 (90.0) |
| Deceased | 199 (39.8) | 50 (10.0) |

Abbreviations: IQR, interquartile range; max, maximum; min, minimum; NA, not applicable; RT, radiotherapy.

*Matching variable to select controls (ratio 1:1): on subcohort, sex, age at first cancer diagnosis (± 1 year), calendar year of first cancer diagnosis (± 3 year), and length of follow-up.

Cardiotoxic treatment = anthracyclines including mitoxantrone and/or mean heart RT dose > 0 Gy.

Total cumulative anthracycline dose (mg/m²) = doxorubicin + (daunorubicin × 0.5) + (epirubicin × 0.8) + (idarubicin × 3) + (mitoxantrone × 10.5).
TABLE 2. Multivariable Conditional Logistic Regression Model of Grade 3-5 Heart Failure by Cancer Treatment Variables

| Variable                        | Dose | Cases, a No. | Controls, No. | OR (95% CI) | P*       |
|--------------------------------|------|--------------|---------------|-------------|----------|
| Total cumulative anthracycline dose, mg/m² | 0    | 135          | 321           | Ref         | —        |
|                                 | > 0 to < 100 | 9            | 22            | 2.3 (0.7 to 7.1) | .2       |
|                                 | 100 to < 250 | 66           | 68            | 5.8 (2.9 to 11.3) | < .0001  |
|                                 | ≥ 250  | 223          | 75            | 21.2 (11.4 to 39.2) | < .0001  |
| Missingc                        | 67    | 14           |               | F_{trend} = < .0001 |         |
| Mean heart RT dose, Gy          | 0     | 166          | 215           | Ref         | —        |
|                                 | > 0 to < 5 | 138          | 195           | 1.3 (0.8 to 2.0) | .4       |
|                                 | 5 to < 15  | 55           | 25            | 5.5 (2.5 to 12.3) | < .0001  |
|                                 | 15 to < 35 | 111          | 53            | 9.0 (4.6 to 17.6) | < .0001  |
|                                 | ≥ 35     | 22           | 5             | 22.6 (4.9 to 102.8) | < .0001  |
| Missingd                        | 8     | 7            |               | F_{trend} = < .0001 |         |

Abbreviations: OR, odds ratio; Ref, reference group; RT, radiotherapy.

aMatching variables: subcohort, sex, age at first cancer diagnosis (±1 year), calendar year of first cancer diagnosis (±3 year), and length of follow-up after first cancer diagnosis.

bCalculated with the clogit function in R-studio.

cn = 9 cases and n = 2 controls unknown whether received anthracyclines versus n = 58 cases and n = 12 controls received anthracyclines but dose unknown.

dn = 1 cases and n = 2 controls unknown whether received radiotherapy versus n = 7 cases and n = 5 controls exposed but dose on heart unknown.

with cancer and cardiac surveillance in survivors after cardiotoxic treatment. This large pan-European nested case-control study shows important new findings. We show that survivors who received a comparatively low mean heart RT dose of 5 to < 15 Gy had a five times higher risk of HF compared with survivors who did not receive RT in the heart region, especially when more than half of the heart was exposed to low RT doses. Furthermore, we did not identify a significantly increased risk of HF for survivors treated with < 100 mg/m² total cumulative anthracycline dose.

As emphasized by the IGHG cardiomyopathy surveillance guideline,19 little was known about the risk of HF for survivors exposed to lower doses of RT. Consequently, no recommendations could be made for survivors treated with chest RT < 15 Gy and a moderate recommendation (on the basis of weak quality evidence) could be made for 15-35 Gy.19 Previous studies in childhood cancer survivors have not found evidence that heart RT doses < 15 Gy calculated with dosimetry were associated with HF.2,12,16,35,36 This could be the result of insufficient statistical power. Recently, Bates et al11 demonstrated that phantom-based mean heart RT doses of 10-20 Gy are associated with a higher risk for HF in 24,214 survivors from the Childhood Cancer Survivor Study (CCSS; n = 371 HF events); however, they could not demonstrate a dose-volume relationship in this dose range. Within our large case-control study derived from an underlying cohort exceeding 50,000 survivors, we found that survivors treated with a mean heart RT dose 5–< 15 Gy are at risk of HF. Our results could be of great clinical importance because, on the basis of our data, a part of the survivors who are at risk will be labeled as low risk by current cardiomyopathy surveillance strategies19 (see the Data Supplement). We recognize that this concerns a small absolute number of cases; however, the proportion of survivors exposed to low mean heart RT doses is likely growing as a result of developments in radiotherapy techniques.37

Mean heart RT dose will be more and more available as it is part of current treatment planning in many institutions. Therefore, we propose to include this measure in the current cardiomyopathy surveillance guideline and recommend echocardiographic follow-up for survivors treated with a mean heart RT dose of ≥ 5 Gy. However, mean heart RT dose is not available for survivors who received radiotherapy before the introduction of advanced RT planning systems.38 For these survivors, the prescribed chest RT dose can be used as a surrogate for the maximum heart RT dose (calculated by dosimetry) in our dose-volume analysis. This analysis showed that in survivors treated with a maximum heart RT dose of 5 to < 15 Gy, the risk increased when larger cardiac volumes were exposed (≥ 50% of the total volume). Accordingly, one could consider monitoring survivors who were exposed to a prescribed chest RT dose of 5 to < 15 Gy when an experienced member of the pediatric radiotherapy planning team estimates that at least 50% of the heart was included in the original treatment field.

Regarding mean heart RT dose and the risk of HF, we show a linear dose-response relationship when adjusted for anthracyclines. By contrast, a case-control study by van Nimwegen et al,39 who included 369 adolescent or adult 5-year survivors of Hodgkin Lymphoma, demonstrated a nonlinear dose-response relationship. However, this was not adjusted for anthracycline dose, and the HF cases were older and exposed to higher doses of mean heart RT, which might have influenced their results.
Currently, the IGHG cardiomyopathy surveillance guideline includes a moderate (on the basis of weak-quality evidence) recommendation for cardiac surveillance for survivors treated with a 100 mg/m² anthracyclines.19 Our study did not identify a significantly increased risk of HF for survivors treated with a 100 mg/m² total cumulative anthracycline dose, in line with previous studies.16,36,40 Nevertheless, there were some cases with HF in this treatment group; possible

| Variable | Volume of the Heart, % | Cases, No. | Controls, No. | OR (95% CI) | P |
|----------|------------------------|------------|---------------|-------------|---|
| 5 to < 15 Gy<sup>a</sup> | No RT | 166 | 215 | Ref | — |
| 0 to < 10 | 117 | 179 | 1.3 (0.7 to 2.2) | .4 |
| 10 to < 50 | 7 | 5 | 1.9 (0.4 to 8.9) | .4 |
| ≥ 50 | 27 | 5 | 5.6 (1.5 to 20.6) | .01 |
| Missing<sup>b</sup> | 8 | 7 | — | — |
| ≥ 15 Gy | No RT | 166 | 215 | Ref | — |
| 0 to < 10 | 176 | 213 | 1.9 (1.1 to 3.1) | .01 |
| 10 to < 50 | 21 | 18 | 3.4 (1.1 to 9.0) | .01 |
| 50 to < 90 | 68 | 39 | 9.4 (4.4 to 20.1) | <.0001 |
| ≥ 90 | 61 | 8 | 14.6 (6.0 to 35.5) | <.0001 |
| Missing<sup>b</sup> | 8 | 7 | — | — |

Abbreviations: OR, odds ratio; Ref, reference group; RT, radiotherapy.

<sup>a</sup>All models were adjusted for total cumulative anthracycline dose.

<sup>b</sup>Matching variables: subcohort, sex, age at first cancer diagnosis (± 1 year), calendar year of first cancer diagnosis (± 3 year), and length of follow-up after first cancer diagnosis.

<sup>c</sup>All the patients are included in the model; the factor variable also included n = 175 cases and n = 89 controls who received ≥ 15 Gy to any volume of the heart (OR, 8.3; 95% CI, 4.5 to 15.5).

<sup>d</sup>n = 1 cases and n = 2 controls unknown whether received radiotherapy versus n = 7 cases and n = 5 controls exposed but dose on heart unknown.

Currently, the IGHG cardiomyopathy surveillance guideline includes a moderate (on the basis of weak-quality evidence) recommendation for cardiac surveillance for survivors treated with < 100 mg/m² anthracyclines.19 Our study did not identify a significantly increased risk of HF for survivors treated with < 100 mg/m² total cumulative anthracycline dose, in line with previous studies.16,36,40 Nevertheless, there were some cases with HF in this treatment group; possible

**FIG 3.** (A) The ORs and corresponding 95% CIs (red dots and bars) of developing heart failure by the received total cumulative anthracycline dose and the fitted linear EOR and corresponding 95% CIs per 100 mg/m² anthracyclines (solid blue and gray line), both of which were adjusted for mean heart RT dose. ORs were calculated relative to survivors treated without anthracyclines and are plotted at the mean cumulative anthracyclines dose of the controls within each relevant dose category. (B) The ORs and corresponding 95% CIs (red dots and bars) of developing heart failure by the received mean heart RT dose and the fitted linear EOR and corresponding 95% CIs per 10 Gy mean heart RT (solid blue and gray line), both of which were adjusted for cumulative anthracycline dose. ORs were calculated relative to survivors treated without heart RT and are plotted at the mean cumulative radiation dose of the controls within each relevant dose category. EOR, excess odds ratio; OR, odds ratio; RT, radiation therapy.
reasons for this include the presence of cardiovascular risk factors and genetic susceptibility to anthracycline-induced cardiomyopathy. We calculated the total cumulative anthracycline dose on the basis of the results in the study by Feijen et al and included the mitoxantrone dose. Previous studies used different doxorubicin equivalent ratios, so a comparison with our study can be limited. Previous literature suggested that the dose response of HF and cardiac events more generally might increase substantially with higher anthracycline doses, which is confirmed by our study. On the basis of our data, the dose-response relationship appeared quadratic and Figure 3 reflects that the risk of HF increases exponentially with higher cumulative anthracycline doses. The results of our study and the cost-effectiveness study by Ehrhardt et al strengthen the need to reconsider the current recommendation for cardiac screening of low-risk survivors.

In the cohort study, we evaluated the trend in cumulative incidence of both HF (grade ≥ 3) and HF-related mortality (grade 5). An important finding is that the cumulative incidence of HF increases more steeply with attained age in survivors treated ≥ 1980. In contrast to our results, in the CCSS, the cumulative incidence of HF was lower in the 1990s compared with earlier decades. Although detailed treatment information is not available for our cohort, we postulate that the difference in the degree of changes in treatment intensity and the difference in era grouping could play a role. In addition, the introduction of survivorship care in the 1990s potentially resulted in more survivors being monitored and being aware of cardiac diseases, and thus, they are more likely to visit the GP or late effects clinic in Europe. This could have led to more HF diagnoses after 1990. Furthermore, we showed that the cumulative incidence of HF-related mortality is lower for survivors who are diagnosed ≥ 1990 when compared with 1980-1989. As in the general population, this may be related to improvement in early diagnosis and treatment. As demonstrated in the Data Supplement, the cumulative incidence of HF varies between the subcohorts. This is most likely caused by different proportions of survivors exposed to cardiotoxic treatment as a result of the subcohort-specific inclusion criteria. Also, the differences in health care systems might have influenced the detection of grade 3 HF.

Beside the strengths of our study where we were able to provide precise estimates of HF risk in the low doses for heart RT and anthracycline, some limitations need to be considered. A potential limitation of the case-control study is that traditional cardiovascular risk factors could not be analyzed because data on, for example, hypertension, diabetes mellitus, and smoking status were missing for > 50% of cases and controls. However, such risk factors are unlikely to be strong confounding factors in the relationship between the investigated treatment factors and risk of HF. In Tables 8 and 9 of the Data Supplement, the actual risk might be underestimated for some cases as a result of missing anthracycline dose. Furthermore, the cumulative incidence of HF may be underestimated because of the methods of HF ascertainment in the cohort study. Despite the advantages of linkage, it is possible that some cases were missed. In the United Kingdom, most of the period at risk was covered by a questionnaire completed by the survivor followed by medical record validation; only a minority of follow-up was covered by linkage alone.

In conclusion, this study provides new evidence that survivors who received a mean heart RT dose of 5 to < 15 Gy have an increased risk for HF, especially when more than half of the heart was exposed to RT. Furthermore, this study did not identify a significantly increased risk of HF for survivors treated with < 100 mg/m² total cumulative anthracycline dose. These new findings might have consequences for new treatment protocols for children with cancer and for cardiomyopathy surveillance guidelines.

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