Major cardiac events for adult survivors of childhood cancer diagnosed between 1970 and 1999: report from the Childhood Cancer Survivor Study cohort

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Abstract

OBJECTIVE
To investigate the impact of modifications to contemporary cancer protocols, designed to minimize cardiotoxic exposures and preserve long term health, on serious cardiac outcomes among adult survivors of childhood cancer.

DESIGN
Retrospective cohort study.

SETTING
27 institutions participating in the Childhood Cancer Survivor Study.

PARTICIPANTS
23 462 five year survivors (6193 (26.4%) treated in the 1970s, 9363 (39.9%) treated in the 1980s, and 7906 (33.6%) treated in the 1990s) of leukemia, brain cancer, Hodgkin lymphoma, non-Hodgkin lymphoma, renal tumors, neuroblastoma, soft tissue sarcomas, and bone sarcomas diagnosed prior to age 21 years between 1 January 1970 and 31 December 1999. Median age at diagnosis was 6.1 years (range 0-20.9) and 27.7 years (8.2-58.3) at last follow-up. A comparison group of 5057 siblings of cancer survivors were also included.

MAIN OUTCOME MEASURES
Cumulative incidence and 95% confidence intervals of reported heart failure, coronary artery disease, valvular heart disease, pericardial disease, and arrhythmias by treatment decade. Events were graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events. Multivariable subdistribution hazard models were used to estimate hazard ratios by decade, and mediation analysis examined risks with and without exposure to cardiotoxic treatments.

RESULTS
The 20 year cumulative incidence of heart failure (0.69% for those treated in the 1970s, 0.74% for those treated in the 1980s, 0.54% for those treated in the 1990s) and coronary artery disease (0.38%, 0.24%, 0.19%, respectively), decreased in more recent eras (P<0.01), though not for valvular disease (0.06%, 0.06%, 0.05%), pericardial disease (0.04%, 0.02%, 0.03%), or arrhythmias (0.08%, 0.09%, 0.13%). Compared with survivors with a diagnosis in the 1970s, the risk of heart failure, coronary artery disease, and valvular heart disease decreased in the 1980s and 1990s but only significantly for coronary artery disease (hazard ratio 0.65, 95% confidence interval 0.45 to 0.92 and 0.53, 0.36 to 0.77, respectively). The overall risk of coronary artery disease was attenuated by adjustment for cardiac radiation (0.90, 0.78 to 1.05), particularly among survivors of Hodgkin lymphoma (unadjusted for radiation: 0.77, 0.66 to 0.89; adjusted for radiation: 0.87, 0.69 to 1.10).

CONCLUSIONS
Historical reductions in exposure to cardiac radiation have been associated with a reduced risk of coronary artery disease among adult survivors of childhood cancer. Additional follow-up is needed to investigate risk reductions for other cardiac outcomes.

TRIAL REGISTRATION
ClinicalTrials.gov NCT01120353.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Adult survivors of cancer in childhood have substantial morbidity related to past therapy

Cardiovascular conditions such as cardiomyopathy, cardiac arrhythmias, and coronary artery, valvular, and pericardial diseases are prominent contributors to the burden of late health outcomes

Patterns of exposure to cardiotoxic treatment have changed over time as contemporary cancer protocols have focused on advancing cure rates while attempting to minimize long term adverse effects

WHAT THIS STUDY ADDS

Efforts to modify cancer therapies in children and promote health surveillance are beginning to show benefits for survivors of childhood cancer

Reductions in cardiotoxic exposures have been associated with declines in serious cardiac outcomes, particularly for the radiation associated risk of coronary artery disease among survivors of Hodgkin lymphoma in childhood

Introduction

Progress in the treatment of children with cancer has led to an increase in the number of survivors living into adulthood. Although improved survival among children treated in the 1990s compared with the 1980s and 1970s has been shown,[1] the impact on the long term health of these individuals remains substantial, with most experiencing chronic health conditions related to previous treatment.[2-5] An array of cardiovascular conditions—a prominent contributor to the overall burden of late health outcomes—has been reported after cancer treatment, including: cardiomyopathy,

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cardiac arrhythmias, and coronary artery, valvular, and pericardial diseases.[6-8] Understanding the trajectory of these outcomes has become increasingly important as the risks for survivors of more modern, risk adapted treatments might differ from those of their predecessors.

Contemporary cancer treatment has focused on advancing cure rates while attempting to minimize long term adverse effects. Patterns of exposure to cardiotoxic treatment have changed over time, with fewer children receiving chest directed radiation, with lower doses and smaller volumes for those who do, and an increased use of anthracyclines, albeit with reduced cumulative doses as the risk for late onset heart failure became apparent.[9 10] The impact of these treatment modifications on the spectrum of late onset cardiovascular conditions in cancer survivors is understudied. The Childhood Cancer Survivor Study, which includes a diverse population of survivors with a diagnosis across three decades, provides an opportunity to examine temporal trends in cardiac outcomes and the effect of changes in treatment over time. We assessed whether changes in exposures to cancer treatment in childhood are associated with altered risks for cardiac events among adult survivors.

Methods
Population
The Childhood Cancer Survivor Study is a multi-institutional retrospective cohort study with longitudinal follow-up of five year survivors of the most common childhood cancers (leukemia, central nervous system tumors, Hodgkin lymphoma, non-Hodgkin lymphoma, renal tumors, neuroblastoma, soft tissue sarcomas, and bone sarcomas) diagnosed before age 21 years at one of 27 participating institutions in the United States and Canada. Initially inclusive of survivors with a diagnosis through 1986, the cohort was expanded to include survivors of childhood cancer with a diagnosis over three decades, from 1 January 1970 through 31 December 1999. Additionally, a random sample of siblings (n=5057) of participating survivors were recruited as a comparison group. Participants completed a baseline questionnaire and up to four follow-up surveys. Cardiac outcomes are assessed by a series of questions such as 'Have you ever been told by a doctor or healthcare professional that you have, or have had . . . congestive heart failure, a myocardial infarction/coronary heart disease, stiff/ leaky heart valves, pericarditis/pericardial constriction, or an arrhythmia?" Details of the Childhood Cancer Survivor Study design, methods, and characteristics of participants and non-participants are reported elsewhere,[11 12] and surveys can be viewed at www.ccss. stjude.org. Participants, or parents of those younger than 18 years, provided informed consent, and the protocol was reviewed and approved by the human subjects committees at each participating institution. Minor participants were re-consented at the age of majority.

Cardiac outcomes
Participants completed surveys that included personal information and medical outcomes. Outcomes were self reported and supplemented by data from the National Death Index. Using a well established algorithm, a multidisciplinary team reviewed and adjudicated all conditions graded and scored according to the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE v4.03) as previously described.[3] For this analysis, we included all reported cardiac conditions of grades 3-5, including heart failure, coronary artery disease (including myocardial infarction or coronary revascularization), heart valve replacement, pericardial disease, and arrhythmias requiring pacemakers or cardioversion, or death from any one of these five conditions (supplemental table 1). Among the 470 reported cardiac conditions, most survivors had a single condition (n=377, 80.2%). Some however, reported two (n=79, 16.8%), three (n=9, 1.4%), or four conditions (n=4, 0.85%). One survivor reported having all five conditions (supplemental figure 1).

Cardiovascular risk factors
We considered participants to have diabetes, dyslipidemia, or hypertension if they reported one of these conditions diagnosed by a physician and were taking drugs for the condition (grade 2 or higher). Smoking status was dichotomized as ever or never smoker and we used age at onset and cessation to determine years of smoking. Body mass index (BMI) was categorized as underweight (<18.5 weight (kg)/(height (m)^2), normal (18.5-24.9), overweight (25.0-29.9), or obese ($\geq$30). Sex, race/ethnicity, age, and education status at last follow-up were determined from questionnaire responses.

Treatment exposures
Details for treatment were abstracted from the medical records of those survivors who additionally authorized release of the medical record. We calculated the cumulative anthracycline dose (per square meter) in doxorubicin equivalents,[13] and the Department of Radiation Physics at MD Anderson Cancer Center estimated the mean dose of heart radiation by reconstructing individual radiation treatments on age specific computational phantoms.[14] Treatment decade (1970-79, 1980-89, 1990-99) was assigned based on diagnosis date.

Statistical analysis
Descriptive statistics compared participating and non-participating survivors across treatment decades as well as participants with the sibling comparison group, using χ^2 statistics or two sample t tests. Cumulative incidence and 95% confidence intervals were estimated for each cardiac condition, treating all cause death (except death due to the particular outcome analyzed) as a competing risk event, and stratified by cancer diagnosis and treatment decade and compared at 15 years from initial cancer diagnosis using permutation test.

To account for the variation in treatment regimens, we fitted models to clustered (institutions) data and multivariable subdistribution hazards models (Fine and Gray model[15]) with repeated measurements of time dependent covariates using years smoked, BMI (continuous), diabetes, dyslipidemia, and hypertension at each time point to estimate relative risks and 95% confidence intervals of each cardiac outcome by treatment era, adjusting for sex, race, exercise intensity, age at diagnosis (continuous), and cardiotoxic treatments (cumulative exposure to anthracycline chemotherapy and mean dose of cardiac radiation). We considered death, except for death from the particular outcome analyzed, as a competing risk. Years from diagnosis were used as the timescale, with censoring at time of grade 3-5 event or 15 years from cohort entry. Multiple imputation methods were used for the missing data on cardiotoxic treatment (11% cardiac radiation and 12% anthracycline chemotherapy), and cumulative logit models to create 20 imputed datasets under the missing at random assumption using cancer diagnosis, age at cancer diagnosis, year of diagnosis, and sex as explanatory variables.

Using mediation analysis we examined the relative risk of treatment era on each cardiac condition in models with and without cardiotoxic treatment to assess the extent of attenuation of the regression coefficient, to determine whether reduction of cardiovascular events across five year treatment eras was attributable to changes in the cardiotoxic treatment exposures over the same period. SAS version 9.4 was used for all statistical analyses and R version 3.5.0 for statistical graphics.

Patient and public involvement

Through the completion of regular surveys, the Childhood Cancer Survivor Study has included self reported patient outcomes since its inception in 1994. No patients were involved in setting the research question or the outcome measures, nor were they involved in developing plans for design or implementation of the study.

Results

Among 23 462 participants in the Childhood Cancer Survivor Study, 6193 (26.4%) were treated in the 1970s, 9363 (39.9%) in the 1980s, and 7906 (33.7%) in the 1990s (fig 1, table 1). Of the participating survivors more were women (46.3% v 39.9%, P<0.001) and slightly younger at diagnosis (6.1 years (range 0-20.9) v 6.8 years (0-20.9), P<0.001) than non-participants (supplemental table 2). However, although more non-participants than participants had died (17.4% v 12.4%, P<0.001), cardiac deaths did not differ between the two groups (2.8% v 2.6%, P=0.69). Survivors (median age at follow-up 27.7 (8.2-58.3) years) were younger than siblings (32.8 (0.3-62.6) years). Median follow-up time ranged from 11.0 years (diagnosis in the 1990s) to 29.5 years (diagnosis in the 1970s). The number of survivors exposed to chemotherapy containing anthracycline increased from 27.8% to 50.0% to 64.0% across the respective decades. However, those receiving higher doses (≥250 mg/m^2) decreased from 16.5% to 11.9% from the 1970s to the 1990s, while the number receiving <250 mg/m^2 increased substantially, from 11.3% to 52.1%. Exposure to cardiac radiation declined from more than three quarters (76.8%) of survivors treated in the 1970s to 40.3% of survivors treated in the 1990s. Nearly a quarter (24.2%) of survivors from the 1970s received a mean heart dose of 15 Gy or more, which by the 1990s had decreased by half (12.4%). Supplemental tables 3 and 4 show changes in exposure to anthracycline and cardiac radiation by diagnosis.

For the overall population, the cumulative incidence of heart failure at 15 years from cancer diagnosis was significantly lower in the 1990s (0.54%) compared with the 1970s (0.69%) (P=0.01) and the 1980s (0.74%) (P=0.01) (fig 2). For coronary artery disease the 20 year incidence decreased successively across all three decades (0.38% in the 1970s, 0.24% in the 1980s, 0.19% in the 1990s). Supplemental table 5 provides the cumulative incidence of each cardiac outcome overall and by primary cancer diagnosis. The

Survivors

ℹ 35 649
Eligible five year survivors of childhood cancer

ℹ 11 293
Non-participants
7348 Refused
3788 Lost to follow-up
65 Language barrier
92 Incomplete data

ℹ 24 356
Participants

ℹ 894
Excluded
754 Diagnosis not included*
140 Cardiac event prior to cohort entry

ℹ 23 462
Included in analysis

Siblings

ℹ 5059
Participants

ℹ 2
Cardiac event before cohort entry

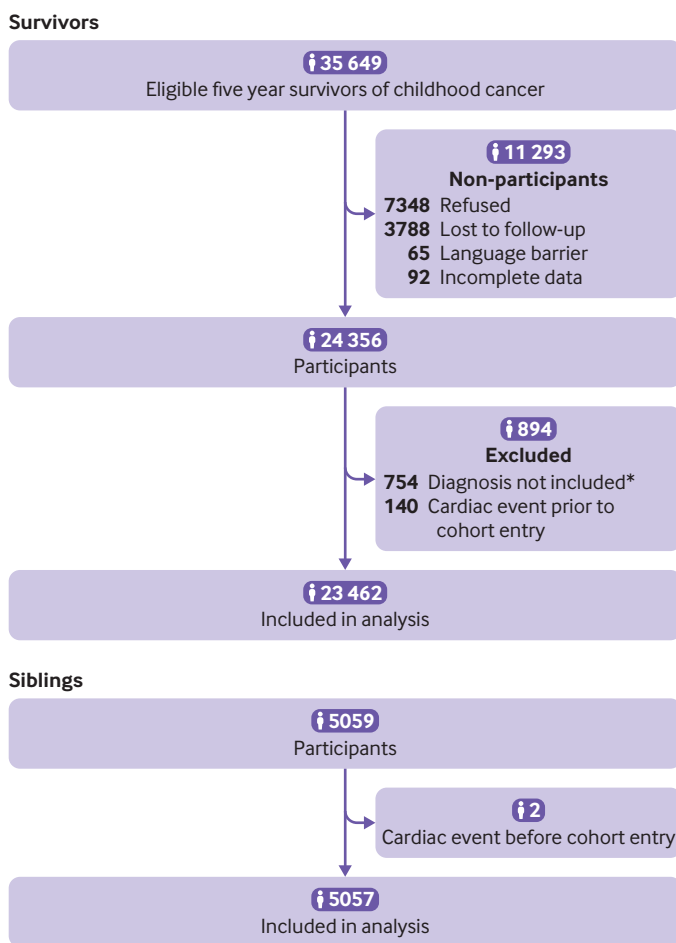**ℹ 5057**
Included in analysis

Fig 1 | Flow of participants through study. *All soft tissue sarcoma subtypes were included in the Childhood Cancer Survivor Study cohort from 1970-86. However, for the expanded cohort, 1987-99, only rhabdomyosarcoma was included. Thus, to ensure a homogeneous population across decades, non-rhabdomyosarcoma diagnoses were excluded

Table 1 | Demographic and treatment characteristics of survivors of childhood cancer overall and by decade of diagnosis and their siblings. Values are numbers (percentages) unless stated otherwise

Characteristics	Survivors				Siblings (n=5057)	P value†
	Overall cohort (n=23 462)	1970-79 (n=6193)*	1980-89 (n=9363)*	1990-99 (n=7906)*		
Sex:						
Female	10 874 (46.3)	2883 (46.6)	4292 (45.9)	3699 (46.4)	2643 (52.3)	‹0.001
Male	12 588 (53.7)	3310 (53.4)	5071 (54.1)	4207 (53.6)	2414 (47.7)	
Median (range) age at last follow-up (years)	27.7 (8.2-58.3)	36.5 (15.5-58.3)	28.3 (8.2-49.5)	22.8 (9.4-42.4)	32.8 (0.3-62.6)	‹0.001
Median (range) age at diagnosis (years)	6.1 (0.0-20.9)	7.2 (0.0-20.9)	5.9 (0.0-20.9)	5.9 (0.0-20.9)	N/A	
Median (range) time from diagnosis (years)	20.5 (7.0-39.3)	29.5 (14.4-39.3)	22.4 (7.0-29.2)	11.0 (8.4-24.3)	N/A	
Race/ethnicity:						
Non-Hispanic white	19 226 (81.2)	5503 (88.9)	7744 (82.5)	5979 (75.4)	4375 (86.5)	
Non-Hispanic black	1495 (6.5)	241 (3.9)	577 (6.1)	677 (8.4)	151 (3.0)	
Hispanic	1761 (8.1)	283 (4.6)	609 (6.7)	869 (11.4)	213 (4.2)	‹0.001
Asian/Pacific Islander	354 (1.7)	41 (0.7)	154 (1.7)	159 (2.1)	54 (1.1)	
Other/unknown	626 (2.6)	125 (2.0)	279 (3.0)	222 (2.7)	264 (5.2)	
Primary cancer diagnosis:						
Leukemia	7281 (39.5)	2023 (32.7)	3314 (40.1)	1944 (43.0)		
Acute lymphoblastic leukemia	6127 (35.2)	1818 (29.4)	2885 (35.9)	1424 (38.0)		
Acute myelogenous leukemia	852 (3.2)	131 (2.1)	324 (3.2)	397 (3.8)		
Other	302 (1.1)	74 (1.2)	105 (1.0)	123 (1.2)		
Brain tumor	4227 (15.8)	735 (11.9)	1498 (14.8)	1994 (19.1)		
Astrocytoma	2589 (9.7)	509 (8.2)	944 (9.4)	1136 (10.9)		
Medulloblastoma	994 (3.7)	147 (2.4)	348 (3.4)	499 (4.8)	N/A	
Other	644 (2.4)	79 (1.3)	206 (2.0)	359 (3.4)		
Lymphoma	4904 (18.3)	1545 (25.0)	1820 (18.0)	1539 (14.7)		
Hodgkin lymphoma	2985 (11.2)	1093 (17.7)	1053 (10.4)	839 (8.0)		
Non-Hodgkin lymphoma	1919 (7.2)	452 (7.30)	767 (7.6)	700 (6.7)		
Kidney tumor	2130 (8.0)	531 (8.6)	870 (8.6)	729 (7.0)		
Neuroblastoma	1825 (6.8)	441 (7.1)	668 (6.6)	716 (6.9)		
Soft tissue sarcoma	1153 (4.3)	364 (5.9)	443 (4.4)	346 (3.3)		
Bone cancer	1942 (7.3)	554 (9.0)	750 (7.4)	638 (6.1)	N/A	
Osteosarcoma	1187 (4.4)	354 (5.7)	467 (4.6)	366 (3.5)		
Ewing sarcoma	702 (2.6)	197 (3.2)	274 (2.7)	231 (2.2)		
Other	53 (0.2)	3 (0.1)	9 (0.1)	41 (0.4)		
Therapy type‡:						
Radiation only	81 (0.4)	24 (0.5)	33 (0.4)	24 (0.3)		
Surgery only	1867 (7.7)	274 (5.2)	627 (6.9)	966 (9.7)		
Radiation and surgery	1885 (7.8)	782 (14.8)	770 (8.5)	333 (3.3)		
Chemotherapy only	2318 (17.4)	227 (4.3)	920 (14.0)	1171 (27.4)	N/A	
Chemotherapy and radiation	2289 (11.8)	863 (16.3)	985 (13.4)	441 (7.9)		
Chemotherapy and surgery	4912 (22.0)	694 (13.1)	1969 (22.5)	2249 (26.3)		
Chemotherapy, radiation, and surgery	7804 (33.0)	2424 (45.8)	3011 (34.2)	2369 (25.1)		
Anthracycline (mg/m^2)§:						
None	11 145 (49.0)	3710 (72.2)	4248 (50.0)	3187 (36.0)		
‹250	6190 (36.0)	581 (11.3)	2360 (32.2)	3249 (52.1)	N/A	
≥250	3415 (15.0)	850 (16.5)	1511 (17.8)	1054 (11.9)		
Mean heart radiation dose (Gy):						
None	9234 (46.3)	1219 (23.2)	3631 (45.2)	4384 (59.7)		
‹15	8199 (37.8)	2764 (52.6)	3343 (39.9)	2092 (27.9)	N/A	
15 to ‹35	2376 (11.3)	675 (12.9)	866 (10.6)	835 (11.1)		
≥35	1074 (4.6)	593 (11.3)	376 (4.3)	105 (1.3)		
Education:						
Some high school	4263 (20.0)	674 (11.2)	1472 (15.7)	2103 (28.9)	398 (8.0)	
High school graduate	5173 (22.2)	1490 (24.7)	2008 (21.5)	1675 (21.4)	854 (17.2)	
Some college	5893 (25.8)	1532 (25.4)	2309 (25.4)	2052 (26.4)	1298 (26.1)	‹0.001
College graduate	5633 (23.3)	1553 (25.8)	2511 (27.4)	1569 (18.0)	1623 (32.6)	
Postgraduate	2213 (8.8)	773 (12.8)	939 (10.0)	501 (5.3)	807 (16.2)	
Median (range) body mass index	24.6 (11.0-63.2)	25.2 (11.0-63.2)	24.8 (11.2-61.2)	24.2 (11.2-62.8)	23.8 (11.2-60.8)	‹0.001
Smoking:						
Never	14 435 (68.4)	4071 (67.1)	6243 (68.9)	4121 (68.8)	3109 (65.0)	‹0.001
Ever	6654 (31.6)	1992 (32.9)	2767 (31.1)	1895 (31.2)	1674 (35.0)	
Diabetes mellitus:						
Yes	687 (2.8)	255 (4.1)	255 (2.7)	177 (2.1)	94 (1.9)	‹0.001
No	22 775 (97.2)	5938 (95.9)	9108 (97.3)	7729 (97.9)	4963 (98.1)	
Dyslipidemia:						
Yes	1578 (6.2)	715 (11.6)	579 (6.0)	284 (3.3)	271 (5.4)	0.02
No	21 884 (93.8)	5478 (88.4)	8784 (94.0)	7622 (96.7)	4786 (94.6)	

Table 1 | Continued

| Characteristics | Survivors | | | | Siblings (n=5057) | P value† |
	Overall cohort (n=23 462)	1970-79 (n=6193)*	1980-89 (n=9363)*	1990-99 (n=7906)*		
Hypertension:						
Yes	2232 (9.1)	914 (14.8)	853 (9.1)	465 (5.6)	437 (8.6)	0.35
No	21 230 (90.9)	5279 (85.2)	8510 (90.9)	7441 (94.4)	4620 (91.4)	

N/A=not applicable.
*Sampling weights were applied for all percentages, means, and medians to account for under-sampling of survivors of acute lymphoblastic leukemia (1987-99), using a weight of 1.21 for those aged 0 or 11-20 years at diagnosis and a weight of 3.63 for those aged 1-10 years at diagnosis.
†P value comparing overall cohort with siblings
‡Treatment categories are mutually exclusive. Percentages provided among those with available data on treatment exposure.
§Doxorubicin equivalents.

prevalence of each cardiac condition was relatively low but substantially raised compared with siblings (fig 2, supplemental table 6). Compared with survivors with a cancer diagnosis in the 1970s, the hazard ratio of adverse cardiac outcomes decreased in the 1990s for heart failure and coronary artery disease (table 2). However, only the decline in coronary artery disease (hazard ratios: 0.53 (95% confidence interval 0.36 to 0.77) in the 1990s and 0.65 (0.45 to 0.92) in the 1980s versus the 1970s) was statistically significant. This was primarily attributable to decreases in the rate of coronary artery disease among survivors of Hodgkin lymphoma (0.77 (0.40 to 1.45) in the 1980s to 0.44 (0.23 to 0.85) in the 1990s). Although the decline for heart failure did not reach statistical significance, the largest decrease was from the 1980s to the 1990s (0.73 (0.52 to 1.02), P=0.07, data not shown). Except for arrhythmias, the risk of each condition consistently decreased across the decades. The only population where an increase was observed was for heart failure among survivors of neuroblastoma (3.22 (0.83 to 12.53) in the 1980s and 5.72 (1.58 to 20.67) in the 1990s versus the 1970s).

The effects of therapeutic and traditional cardiac risk factors on each cardiac outcome were assessed in adjusted multivariable models (table 3). The hazard ratios for heart failure and coronary artery disease suggested a decline over the treatment eras but were attenuated by the addition of treatment variables (mean cardiac and anthracycline doses) and cardiovascular risk factors. Risk factors associated with heart failure included female sex (1.51 (1.10 to 2.06)), higher exposures to cardiac radiation and anthracycline dose, and reporting a diagnosis of diabetes, dyslipidemia, or hypertension. For coronary artery disease a dose-response was evident with increasing mean exposure to heart radiation (2.26 (1.32 to 3.84) for 15-35 Gy and 5.86 (3.69 to 9.28) for ≥35 Gy). No significant association was found with diabetes mellitus, but dyslipidemia and hypertension (3.49 (2.11 to 5.77) and 4.75 (3.37 to 6.69), respectively) were associated with a significantly increased risk for coronary artery disease. High dose (≥35 Gy) cardiac radiation and hypertension were associated with valvular heart disease (13.97 (6.01 to 32.48) and 3.12 (1.09 to 8.91), respectively). Hypertension was also significantly associated with the development of pericardial disease (6.35 (1.56 to 25.83)). Heart radiation greater than

35 Gy (2.74 (1.01 to 6.81)), high dose (≥250 mg/m^2) anthracyclines (3.81 (2.13 to 6.80)), dyslipidemia (3.54 (1.80 to 6.95)), and hypertension (2.59 (1.27 to 5.30)) were significantly associated with arrhythmias.

Table 4 presents the results of the mediation analyses. After adjustment for age at diagnosis, race, sex, BMI, smoking, exercise intensity, and modifiable risk factors (diabetes, dyslipidemia, and hypertension), the hazard ratios of heart failure and coronary artery disease declined over five year treatment eras. However, only the decline for coronary artery disease (0.80 (0.71 to 0.91)) achieved statistical significance. This finding was attenuated by adjustment for exposure to cardiac radiation (0.90 (0.78 to 1.05)), suggesting that decreases in radiation dose or changes in modalities or delivery methods might account for some portion of the treatment era risk for coronary artery disease. Adjustment for exposure to anthracyclines did not attenuate these findings. These results are consistent regardless of whether the model used time since diagnosis or attained age as its timescale adjusted for age at diagnosis. The three variables are linearly dependent and thus only two of the three can be adjusted for in the model. Stratifying the mediation analysis by diagnosis (supplemental table 7) identified that treatment era attenuation in coronary artery disease by exposure to radiation therapy is largely attributable to changes in treatment for Hodgkin lymphoma (0.77 (0.66 to 0.89) without exposure to cardiotoxic treatment and 0.87 (0.69 to 1.10) after adjustment for cardiotoxic treatments).

Discussion

Using the well characterized Childhood Cancer Survivor Study cohort, we assessed long term serious cardiovascular outcomes among survivors of cancer in childhood treated in the 1990s compared with those treated in the 1970s and 1980s, and found evidence suggesting improvements attributable to reductions or changes in exposure to therapeutic radiation. Contemporary therapeutic protocols, while modified to minimize late adverse outcomes, continue to rely heavily on anthracycline based regimens and radiation therapy to maintain successful cure rates. However, analyzing a broad spectrum of cardiovascular outcomes, we found that changes in therapies were associated with a decrease in the incidence of and risks for late cardiotoxicity among long term survivors
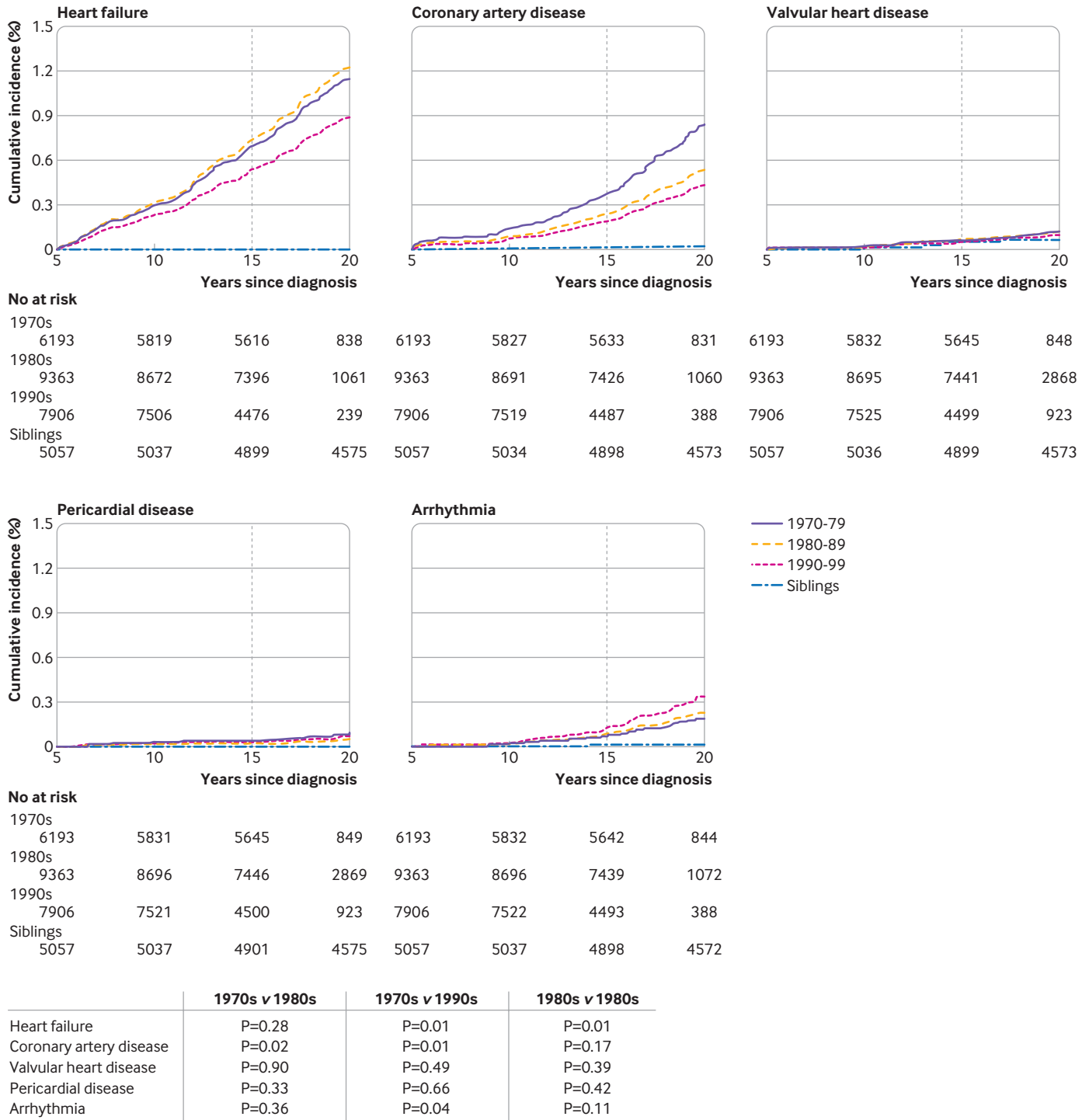
Heart failure

Coronary artery disease

Valvular heart disease

No at risk											
1970s											
	6193	5819	5616	838	6193	5827	5633	831	6193	5832	5645	848
1980s											
	9363	8672	7396	1061	9363	8691	7426	1060	9363	8695	7441	2868
1990s											
	7906	7506	4476	239	7906	7519	4487	388	7906	7525	4499	923
Siblings											
	5057	5037	4899	4575	5057	5034	4898	4573	5057	5036	4899	4573

Pericardial disease

Arrhythmia

- —— 1970-79
- – – 1980-89
- – – 1990-99
- – · – Siblings

No at risk								
1970s								
	6193	5831	5645	849	6193	5832	5642	844
1980s								
	9363	8696	7446	2869	9363	8696	7439	1072
1990s								
	7906	7521	4500	923	7906	7522	4493	388
Siblings								
	5057	5037	4901	4575	5057	5037	4898	4572

	1970s v 1980s	1970s v 1990s	1980s v 1980s
Heart failure	P=0.28	P=0.01	P=0.01
Coronary artery disease	P=0.02	P=0.01	P=0.17
Valvular heart disease	P=0.90	P=0.49	P=0.39
Pericardial disease	P=0.33	P=0.66	P=0.42
Arrhythmia	P=0.36	P=0.04	P=0.11

Fig 2 | Cumulative incidence of grades 3-5 cardiac outcomes among survivors of cancer in childhood by decade of cancer diagnosis and siblings. Vertical line represents incidence at 15 years from cancer diagnosis (10 years from cohort entry). P values of permutation tests comparing each outcome by decade. Some survivors were censored before reaching 15 years from diagnosis and thus only contributed to the estimation of cumulative incidence curves up to their censoring time

of childhood cancer. Reductions in the use and doses of radiation have resulted in statistically significant declines in serious coronary artery disease among survivors of Hodgkin lymphoma while declines in other diagnostic groups have been more modest. Notably, for survivors of neuroblastoma, for whom intensified treatments have been associated with more survivors living into adulthood, cardiotoxicity has increased. Traditional cardiovascular risk factors, previously shown to significantly augment treatment induced cardiotoxicity, were also strongly associated with an increased risk for nearly all cardiac outcomes assessed

Table 2 | Hazard ratios (95% confidence interval) of cardiac conditions 20 years from diagnosis by treatment era*

Diagnosis by decade	Hazard ratio (95% CI)				
	Heart failure	Coronary artery disease	Valvular heart disease	Pericardial disease	Arrhythmia
All survivors					
1970-79	1.0	1.0	1.0	1.0	1.0
1980-89	1.07 (0.78 to 1.45)	0.65 (0.45 to 0.92)	1.08 (0.63 to 1.85)	0.57 (0.18 to 1.81)	1.22 (0.69 to 2.17)
1990-99	0.77 (0.53 to 1.14)	0.53 (0.36 to 0.77)	0.87 (0.33 to 2.33)	0.80 (0.26 to 2.46)	1.74 (0.99 to 3.03)
Leukemia:					
1970-79	1.0	1.0	1.0	1.0	1.0
1980-89	0.80 (0.39 to 1.66)	0.69 (0.33 to 1.44)	0.64 (0.51 to 0.80)	N/E	0.64 (0.21 to 1.93)
1990-99	1.05 (0.36 to 3.12)	0.83 (0.31 to 2.22)	3.97 (0.52 to 30.34)	N/E	0.45 (0.11 to 1.85)
CNS tumors:					
1970-79	1.0	1.0	1.0	1.0	1.0
1980-89	0.58 (0.09 to 3.94)	0.80 (0.19 to 3.43)	N/E	N/E	1.47 (0.95 to 2.26)
1990-99	1.31 (0.21 to 8.39)	0.60 (0.12 to 2.88)	N/E	N/E	N/E
Hodgkin lymphoma:					
1970-79	1.0	1.0	1.0	1.0	1.0
1980-89	1.25 (0.66 to 2.35)	0.77 (0.40 to 1.45)	1.59 (0.83 to 3.06)	N/E	1.24 (0.46 to 3.39)
1990-99	0.77 (0.31 to 1.93)	0.44 (0.23 to 0.85)	0.41 (0.05 to 3.35)	N/E	1.50 (0.44 to 5.08)
Non-Hodgkin lymphoma:					
1970-79	1.0	1.0	1.0	1.0	1.0
1980-89	0.98 (0.46 to 2.12)	0.82 (0.25 to 2.75)	N/E	0.27 (0.02 to 3.52)	3.30 (0.41 to 26.60)
1990-99	0.41 (0.14 to 1.23)	0.86 (0.23 to 3.22)	N/E	0.34 (0.06 to 2.0)	3.08 (0.46 to 20.70)
Kidney tumor:					
1970-79	1.0	1.0	1.0	1.0	1.0
1980-89	1.16 (0.42 to 3.23)	N/E	0.67 (0.09 to 5.03)	N/E	1.12 (0.83 to 1.51)
1990-99	0.35 (0.10 to 1.26)	1.68 (0.11 to 24.71)	0.49 (0.04 to 6.56)	N/E	N/E
Neuroblastoma:					
1970-79	1.0	1.0	1.0	1.0	1.0
1980-89	3.22 (0.83 to 12.53)	0.64 (0.17 to 2.43)	N/E	N/E	N/E
1990-99	5.72 (1.58 to 20.67)	0.49 (0.05 to 4.46)	N/E	N/E	N/E
Soft tissue sarcoma:					
1970-79	1.0	1.0	1.0	1.0	1.0
1980-89	1.08 (0.30 to 3.85)	0.47 (0.13 to 1.68)	N/A	0.84 (0.05 to 15.44)	0.82 (0.22 to 3.06)
1990-99	0.59 (0.24 to 1.45)	N/E	N/A	N/E	N/E
Bone cancer:					
1970-79	1.0	1.0	1.0	1.0	1.0
1980-89	1.69 (0.97 to 2.97)	0.92 (0.38 to 2.24)	N/E	N/E	2.46 (0.46 to 13.12)
1990-99	0.74 (0.26 to 2.09)	0.53 (0.14 to 2.07)	N/E	N/E	1.53 (0.26 to 9.15)

CNS=central nervous system; N/E=not estimable owing to small cell size.
*Adjusted for age at diagnosis, race, and sex.

in our young adult cohort; providing a potential therapeutic target to ameliorate outcomes for cancer survivors.

Comparison with other studies

The late morbidity and mortality of therapy related cardiotoxicity, particularly in children with Hodgkin lymphoma, has been well described,[6 7 16 17] prompting the introduction of risk adapted or response adapted and immunologic therapies to better refine exposures for these patients. Early recognition of musculoskeletal toxicities associated with high dose radiation,[9] followed by increased rates of breast cancer among young women previously irradiated for a childhood cancer[18] motivated changes in dose and treatment fields as well as chemotherapy only treatment strategies. Radiation doses were reduced, and are now eliminated, for many low risk patients,[19] whereas anthracyclines were added and doses intensified. Reports of radiation induced coronary artery disease, both clinical and subclinical, and particularly among younger patients, further encouraged exposure to radiation to be minimized.[20 21] Our study shows that reduced exposure to cardiotoxic treatment modalities have been associated with a reduced risk of myocardial infarction or coronary revascularization among survivors of Hodgkin lymphoma. A reduction in the risk of heart failure was evident overall and among survivors of Hodgkin lymphoma in our cohort but did not meet statistical significance, likely the result of the intensified use of anthracyclines during the same period that radiation exposure was being reduced. Notably, the risk for heart failure was observed to further decrease from the 1980s into the 1990s, suggesting a favorable trend. In contrast, Dutch investigators recently reported that survivors from the 1970s had a lower cumulative incidence of heart failure compared with those treated in the 1980s and 1990s.[22] However, the temporal pattern of reduction in exposure to radiotherapy (defined as maximum prescribed heart dose) in Dutch survivors was of a smaller magnitude (with no chest radiotherapy ranging from 65.6% in the 1970s to 82.2% in the 1990s) than in the Childhood Cancer Survivor Study cohort (ranging from 23% to 60%) utilizing detailed heart dosimetry measurements. Additionally, we

Table 3 | Multivariable analysis of cardiac conditions by treatment era and cardiovascular risk factors 20 years from diagnosis

Risk factors by treatment era	Hazard ratio (95% CI)				
	Heart failure	Coronary artery disease	Valvular heart disease	Pericardial disease	Arrhythmia
Sex:					
Male	1.0				
Female	1.51 (1.10 to 2.06)	0.87 (0.62 to 1.23)	1.25 (0.74 to 2.12)	0.68 (0.29 to 1.58)	1.25 (0.79 to 1.99)
Treatment era:					
1970-79	1.0	1.0	1.0	1.0	1.0
1980-89	0.89 (0.67 to 1.17)	0.66 (0.42 to 1.02)	1.36 (0.77 to 2.43)	0.57 (0.16 to 1.97)	1.16 (0.65 to 2.05)
1990-99	0.70 (0.45 to 1.08)	0.63 (0.36 to 1.08)	1.33 (0.42 to 4.21)	0.96 (0.23 to 4.02)	1.71 (0.96 to 3.07)
Mean heart dose (Gy):					
None	1.0	1.0	1.0	1.0	1.0
1-15	0.74 (0.54 to 1.03)	1.31 (0.88 to 1.96)	1.12 (0.33 to 3.79)	0.64 (0.19 to 2.20)	0.97 (0.54 to 1.73)
15.1-34.99	1.56 (1.05 to 2.33)	2.26 (1.32 to 3.84)	2.03 (0.64 to 6.44)	0.88 (0.21 to 3.64)	0.89 (0.37 to 2.18)
≥35	3.95 (2.87 to 5.43)	5.86 (3.69 to 9.28)	13.97 (6.01 to 32.48)	2.77 (0.59 to 12.88)	2.74 (1.10 to 6.81)
Anthracycline dose (mg/m^2):					
None	1.0	1.0	1.0	1.0	1.0
‹250	2.76 (1.93 to 3.97)	1.42 (0.93 to 2.16)	1.67 (0.78 to 3.55)	1.38 (0.43 to 4.49)	1.38 (0.81 to 2.36)
≥250	9.29 (6.01 to 14.37)	1.77 (1.15 to 2.72)	2.04 (1.06 to 3.93)	2.81 (0.85 to 9.34)	3.81 (2.13 to 6.80)
Comorbidities:					
Diabetes	2.66 (1.67 to 4.25)	1.55 (0.67 to 3.58)	0.79 (0.10 to 6.24)	2.58 (0.26 to 25.80)	2.51 (0.82 to 7.71)
Dyslipidemia	2.32 (1.53 to 3.52)	3.49 (2.11 to 5.77)	2.43 (0.65 to 9.02)	1.49 (0.27 to 8.25)	3.54 (1.80 to 6.96)
Hypertension	4.93 (3.61 to 6.72)	4.75 (3.37 to 6.69)	3.12 (1.09 to 8.91)	6.35 (1.56 to 25.83)	2.59 (1.27 to 5.30)

Estimates adjusted for all variables in the table: race, age at diagnosis, body mass index, smoking, and exercise intensity (metabolic hours/week).

accounted for exercise intensity, reported to moderate cardiovascular outcomes in survivors of Hodgkin lymphoma,[23] as well as traditional cardiovascular risk factors such as smoking, BMI, diabetes, dyslipidemia, and hypertension. Further longitudinal follow-up will be required to determine whether these apparent reductions in risk for heart failure among survivors from the 1990s achieve statistical significance with aging of the population.

While reductions in adverse cardiac outcomes were seen across the decades, the opposite was true for survivors of neuroblastoma, with a statistically significant fivefold increased risk of heart failure for those treated in the 1990s. This corresponds with the intensification of neuroblastoma therapy during this decade with the addition of myeloablative therapy, autologous stem cell rescue, and isotretinoin, which significantly improved outcomes for children with high risk neuroblastoma.[24 25] Improved survival rates have increased the number of long term survivors at risk for adverse outcomes. Our study only included survivors with a diagnosis before 1999, thus patients with neuroblastoma treated with immunotherapy (anti-disialoganglioside antibody)[26] were not included in this analysis. Current studies focus on modifying

the acute toxicities associated with delivery of anti-disialoganglioside antibody, but successful delivery of immunotherapy, for neuroblastoma or other diagnoses, might alter the rate of heart failure for these survivors in the future.

Therapeutic interventions for cardiac toxicity induced by cancer therapy remain elusive and have largely relied on strategies used in other populations, commonly with age related cardiac declines. The pathophysiology in our relatively young population (median age 27.7 (range 8.2-58.3) years), though incompletely understood, is likely different from that of the general population. Importantly, our study supports the evidence of the contribution traditional cardiovascular risk factors have for cancer survivors. Despite adjustment for personal factors, treatment related factors, smoking, BMI, and exercise, dyslipidemia and hypertension remained strongly associated with nearly all cardiac outcomes. When stratification was by exposure to cardiac radiation or anthracycline chemotherapy, similar associations with dyslipidemia and hypertension were previously reported in the Childhood Cancer Survivor Study cohort.[27] We found that the risk persists despite adjustment for treatment era. Furthermore,

Table 4 | Hazard ratios of cardiac conditions per five year treatment era

Five year treatment era (continuous variable)	Hazard ratio (95% CI)				
	Heart failure	Coronary artery disease	Valvular heart disease	Pericardial disease	Arrhythmia
Adjusted for demographics and modifiable risk factors	0.97 (0.88 to 1.06)	0.80 (0.71 to 0.91)	0.97 (0.74 to 1.28)	0.98 (0.68 to 1.40)	1.17 (0.99 to 1.38)
Adjusted for demographics, modifiable risk factors, and cardiac radiation exposure	0.99 (0.89 to 1.10)	0.90 (0.78 to 1.05)	1.18 (0.85 to 1.63)	1.02 (0.68 to 1.53)	1.21 (1.03 to 1.43)
Adjusted for demographics, modifiable risk factors, and anthracycline exposure	0.91 (0.82 to 1.02)	0.79 (0.69 to 0.91)	0.96 (0.75 to 1.24)	0.97 (0.67 to 1.37)	1.15 (0.96 to 1.38)
Adjusted for demographics, modifiable risk factors, and cardiotoxic exposures	0.94 (0.83 to 1.05)	0.87 (0.74 to 1.03)	1.13 (0.83 to 1.53)	0.99 (0.66 to 1.50)	1.19 (0.99 to 1.43)

Demographics=age at diagnosis, sex, race, body mass index, smoking, exercise intensity (metabolic hours/week); modifiable risk factors=diabetes, dyslipidemia, and hypertension; cardiotoxic exposures=cardiac radiation and anthracycline.

a previous study identified a 2.6-fold increased risk for hypertension among survivors of childhood cancer of all diagnoses, and importantly, a high prevalence (48%) of survivors who were unaware of their hypertension.[28] Although studies are underway to ameliorate or prevent therapy induced cardiac toxicity, more aggressive surveillance or treatment of traditional cardiovascular risks, or both, combined with modifications of upfront exposures, might further mitigate the rate of adverse cardiac outcomes.

Strengths and limitations of this study

Although the large population of childhood cancer survivors followed across three decades in the Childhood Cancer Survivor Study cohort permits assessment of trends in a variety of late cardiac outcomes, several limitations need to be considered. Despite the large cohort, 31% of eligible survivors chose not to participate. It is possible that the health status of these individuals differs from those who participated, thus potentially biasing our estimates. Cardiac outcomes are self reported, and validation was not feasible. To minimize misclassification, however, we restricted the analyses to clinically symptomatic cardiac events requiring drug or surgical management (grades 3-5). Our results should be considered in the context of declining all cause mortality in survivors of childhood cancer over the past several decades (1970-99).[1] In view of this, we assessed whether the declines in risk over the treatment eras reported here differed from those in rates over the same period, the latter being unaffected by changes in competing risk. Specifically, we compared the era effect estimates from the Fine and Gray models (risk) with those from Cox regression models (rate) with the same adjustment variables. The two sets of estimates were almost identical, suggesting that although the mortality rate declined substantially over time, our findings were not appreciably influenced by it. Additionally, while we show improvement in cardiac outcomes for more recently treated survivors, caution should be exercised in the interpretation of the results, recognizing that this does not account for increased survival from childhood cancer or the enhanced awareness of cardiovascular disease after cancer therapy. Improved survival and health screening of cancer survivors could have identified more cardiac events. Our analysis included death from other causes as a competing risk, and cardiovascular screening is more likely to identify asymptomatic disease at a less severe stage, before becoming grade 3-5 and requiring medical intervention.

Conclusions

We observed that among adult survivors of childhood cancer the risk for coronary artery disease was significantly decreased. This decrease could be associated with historical reductions in exposure to cardiac radiation, particularly among survivors of Hodgkin lymphoma. This is important as childhood cancer survival rates increase and these young adults prematurely acquire cardiovascular disease. While additional longitudinal follow-up is needed to establish whether similar reductions in the cumulative incidence of heart failure can be confirmed in multivariable analysis, these results suggest that efforts to modify cancer therapies in children and promote health surveillance for survivors are beginning to show benefits not only in overall survival but also in late adverse cardiac effects. Continued follow-up is needed to determine if these positive trends persist over time.

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Supplemental information: Figure showing number of cardiac conditions reported by participants in Childhood Cancer Survivor Study

Supplemental information: additional tables 1-7