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ORIGINAL RESEARCH

Development and Phenotype of Heart Failure in Long-Term Survivors of Childhood Cancer: The CVSS Study

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BACKGROUND: The CVSS (Cardiac and Vascular Late Sequelae in Long-Term Survivors of Childhood Cancer) study aimed to investigate the prevalence of different stages of heart failure (HF) in childhood cancer survivors (CCSs) compared with the general population.

METHODS AND RESULTS: A total of 1002 CCSs (age range, 23–48 years) diagnosed with neoplasia before an age of 15 years underwent a comprehensive cardiovascular screening. An age- and sex-matched sample from the population-based GHS (Gutenberg Health Study) served as a comparison group. Although prevalence of HF was significantly higher in CCSs, prevalence of different HF stages varied strongly by specific tumor history. Compared with the population, the prevalence ratio was 2.6 (95% CI, 2.4–2.8) for HF stage A and 4.6 (95% CI, 4.1–5.1) for the composite of HF stage B to D in an age- and sex-adjusted Poisson regression model. Multivariable linear regression, adjusting for tumor entities, age, sex, and cardiovascular risk factors, revealed a lower left ventricular ejection fraction in patients with history of bone tumors (β, −4.30 [95% CI, −5.70 to −2.80]), soft tissue sarcoma (β, −1.60 [95% CI, −2.90 to −0.30]), and renal tumors (β, −1.60 [95% CI, −2.80 to −0.29]) compared with the population. The same model for the diastolic marker, ratio of the peak early diastolic filling velocity/lateral mitral annular early diastolic velocity, showed an association only with cardiovascular risk factors but not with tumor entities.

CONCLUSIONS: The prevalence of HF stage A to D was significantly higher among long-term CCSs compared with the population and varied strongly by tumor entity. Systolic dysfunction was primarily associated with tumor entities, whereas diastolic dysfunction was associated with a higher burden of cardiovascular risk factors in CCSs.

Key Words: cardiotoxicity ■ childhood cancer survivors ■ general population ■ heart failure

Developments in cancer therapy have resulted in a remarkable improvement of survival of patients with childhood cancer over the past decades, resulting in a 5-year survival of almost 80%.[1] However, the improved survival is associated with an increased risk for severe and life-threatening therapy-related effects[2,3] and a higher late mortality.[4–7] Although recent findings indicate a decline of late mortality attributable to reduction of cumulative doses of chemotherapeutic agents compared with older treatment regimens,[8] the impact of cardiovascular complications on mortality is still substantial, being the largest nonmalignant contributor to excess death.[5,9,10]

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CLINICAL PERSPECTIVE

What Is New?

- Childhood cancer survivors are at significantly higher risk for developing asymptomatic (ie, heart failure [HF] stage B/pre-HF) and symptomatic HF (ie, HF stages C and D) independent of their higher prevalence of cardiovascular risk factors.
- The presence of HF varied strongly with the history of tumor entity and its specific treatment.
- An increased risk of HF in childhood cancer survivors is most likely attributable to direct cardiotoxic effects, leading to systolic dysfunction, and a predisposition to cardiovascular risk factors, leading to diastolic dysfunction, especially in the long-term.

What Are the Clinical Implications?

- The current data underscore the need to monitor for early (ie, preclinical) alterations of cardiac function, to establish preventive strategies to reduce the burden of cardiovascular risk factors and consequently reduce the risk of cardiac dysfunction and to establish thorough surveillance protocols for childhood cancer survivors.

Nonstandard Abbreviations and Acronyms

CCS	childhood cancer survivor
CVRF	cardiovascular risk factor
CVSS	Cardiac and Vascular Late Sequelae in Long-Term Survivors of Childhood Cancer
GHS	Gutenberg Health Study
ICCC3	International Classification of Childhood Cancer

Childhood cancer survivors (CCSs) have a markedly increased relative risk for developing heart failure (HF) compared with matched sibling controls[2]; and among cardiovascular sequelae, HF emerged as a leading cause of morbidity and mortality.[11,12] According to the recently published Universal Definition of HF, HF is defined as a clinical syndrome with symptoms, signs, or both, caused by structural, functional, or both, cardiac abnormalities and corroborated by elevated natriuretic peptide levels, objective evidence of pulmonary congestion, or both.[13] In addition, the definition proposes a revised continuum of 4 stages of HF. Reports on prevalence of cardiac dysfunction and HF based on a standardized protocol-driven clinical and echocardiographic screening assessment in large samples of CCSs are scarce, and usually results have not been compared with those of the general population.[14]

The aim of the present analysis was to investigate the development and prevalence of HF stages (ie, stage A–D) in a sample of CCSs compared with an age- and sex-matched population sample. Tumor types, as well as the presence of systolic and diastolic functional impairment, were to be considered.

METHODS

The data and methods used to conduct the research in this study will be made available from the corresponding author upon reasonable request.

Study Sample

The CVSS (Cardiac and Vascular Late Sequelae in Long-Term Survivors of Childhood Cancer) study (NCT02181049) was designed as a prospective, single-center cohort study investigating cardiovascular sequelae of CCSs. Individuals were eligible if they (1) had been diagnosed with neoplasia according to the International Classification of Childhood Cancer (ICCC3) before 15 years of age between 1980 and 1990, (2) survived >5 years after initial cancer diagnosis, and (3) received antineoplastic treatment at 1 of 34 pediatric cancer centers participating in the study. Survivors of Hodgkin lymphoma and a negligible proportion of former patients with nephroblastoma (diagnosed in 1990) were not included as they were evaluated in other investigations. All study participants underwent a standardized 5.5-hour examination in the study center. Investigations were performed by trained and certified personnel, according to standard operating procedures, including a comprehensive echocardiographic examination, laboratory measurements, a computer-assisted personal interview, and assessment of current medication (according to Anatomical Therapeutic Chemical classification system). Written informed consent was obtained from all participants before the study investigations. The CVSS study was approved by the Ethics Committee of the Rhineland-Palatinate Chamber of the Physicians (approval number 2019-14536) and the local data safety commissioner. The study was performed according to the principles of Good Clinical Practice and the Declaration of Helsinki.

Population-Based Sample as Reference Group

A population-based sample from the GHS (Gutenberg Health Study) served as comparison group representing the general population, as it had been examined

with the identical highly standardized examination program in the same study center. The GHS was conceptualized as a population-based, prospective, observational, single-center cohort study with the primary aim of evaluating and improving individual cardiovascular risk stratification. A representative population sample was drawn randomly from the local governmental registry offices of the city of Mainz and the district of Mainz-Bingen. The sample was aged 35 to 74 years, stratified for sex, residence, and age. The study design has been published recently.[15]

Acquisition of Cancer-Related Data

Cancer- and treatment-related data were abstracted either from the GCCR (German Childhood Cancer Registry) in Mainz, on site from primary health records of former treating medical centers, the centrally documented individual therapy data of the respective study centers of the Society for Pediatric Oncology and Hematology, or both, and validated by trained medical staff.

Assessment of Cardiovascular Risk Factors, Comorbidities, and Biomarkers

Diagnosis of cardiovascular risk factors (CVRFs) was based on a medical history and a screening examination by means of clinical, medical-technical, and laboratory investigations, and a structured computer-assisted personal interview. A detailed definition of CVRFs used in the present study has been published recently.[16] Comorbidities were considered when diagnosed by a physician.

Blood samples were collected from a cubital vein after a fasting period of at least 5 hours and subsequently processed for biobanking and measurement of an ad hoc available set of laboratory markers. NT-proBNP (N-terminal pro-B-type natriuretic peptide) was measured using a commercially available Elecsys 2010 proBNP II immunoassay (Roche Diagnostics, Mannheim, Germany).

Assessment of Cardiac Function and HF Classification

A comprehensive echocardiographic examination was performed in all study participants and the population sample, according to standard operating procedures. An iE33 echocardiography system with S5-1 sector array transducer (Royal Philips Electronics, Amsterdam, the Netherlands) was used. All structural and functional measurements were made according to current American Society of Echocardiography/European Association of Cardiovascular Imaging recommendations.[17] Left ventricular ejection fraction (LVEF) was calculated according to the Simpson method from the apical 4-chamber view. Mitral inflow velocity pattern was recorded from the apical 4-chamber view with the pulse-waved Doppler sample volume positioned at the tips of the mitral valve leaflets during diastole in expiration. Peak early (*E*-wave) and late (*A*-wave) diastolic filling velocities were measured, and their ratio (*E/A*) was calculated. The lateral mitral annular early diastolic velocity (*E'*) was measured by spectral tissue Doppler imaging, and the ratio of the peak early diastolic filling velocity/lateral mitral annular early diastolic velocity (*E/E'*) was determined.

For this analysis, stages of HF were categorized as stages 0 and A to D, according to the recently proposed universal definition of HF by the Heart Failure Society of America, the Heart Failure Association of the European Society of Cardiology, and the Japanese Heart Failure Society.[13]

Statistical Analysis

Descriptive measures (mean/SD or median/interquartile range and absolute and relative frequencies) were calculated for demographic, clinical, and treatment variables according to HF stage. Prevalences of HF stages were presented with 95% CIs, according to ICCC3 classes. For comparison with the population, subsets with comparable age range (ie, 23–50 years), and in sensitivity analyses, the overlapping age range of 35 to 48 years with an age and sex matching of individuals, were analyzed. With respect to age and sex matching, for each person from the CVSS study collective, 3 people from the GHS sample with the same sex and age (±2 years tolerance) were randomly selected. No individual from the GHS sample was selected more than once, and no variable other than age and sex had an effect on matching.

Poisson regression models with a robust error variance were used to analyze the impact of "childhood cancer" (independent variable) on HF prevalence (dependent variable) compared with the GHS population sample as reference, with adjustment for age, sex, and CVRFs (ie, arterial hypertension, diabetes, dyslipidemia, family history of myocardial infarction/stroke, obesity, and smoking). Prevalence ratios were presented with 95% CIs. For an age-dependent comparison of HF prevalence, conditional density plots were generated, and nonparametric bootstrap samples (n=1000) were run to estimate 95% confidence limits. Multivariable linear regression models, including both the CCS and the population samples, were generated to assess the association of a tumor history (versus no history of tumor disease in the population sample as reference) and CVRF with systolic function (LVEF) and diastolic function (*E/E'*) as dependent variables. Linear regression was used for the analysis of LVEF and *E/E'*, and then residuals were checked by QQ plots. Statistical analyses were performed with R, version 3.4.3 (The R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

From the total sample of 1002 study participants examined between October 2013 and February 2016, individuals not being treated with chemotherapy or radiotherapy (n=76) were excluded, resulting in an analysis sample of 926 CCSs. A detailed characterization of the study sample, including tumor diagnostic and treatment characteristics and current clinical status, has been published recently.[18]

Sample Characteristics by Presence of HF in CCSs

In summary, the present analysis sample comprised 504 men and 422 women. Overall, participants with HF were ≈1.5 years older than those without HF (HF$_{Stage A-D}$ versus no HF: 35.2±5.8 versus 33.3±5.8 years; P=0.00027) and were ≈6 months older at the time of malignancy diagnosis (HF$_{Stage A-D}$ versus no HF: 6.5±4.3 versus 5.2±4.5 years; P=0.047). Stratified by stage of HF, participants with HF stage C or D were older than those with HF stage A or B (HF$_{Stage C/D}$ versus HF$_{Stage B}$ versus HF$_{Stage A}$: 39.2±5.2 versus 34.3±5.9 versus 34.4±5.3 years), and the same trend was observed with respect to age at the time of malignancy diagnosis. In contrast to participants with HF stage A or B and participants without HF, participants diagnosed with HF stage C or D were predominantly women (72.7%). Individuals across all stages of HF had a pronounced cardiovascular risk profile, particularly a higher burden of arterial hypertension and dyslipidemia, compared with participants without HF. As expected, patients in the HF stages had almost all undergone chemotherapy compared with patients without HF (no HF versus HF$_{Stage A}$, HF$_{Stage B}$, and HF$_{Stage C/D}$: 75% versus 98.3%, 97.1%, and 100%). In addition, the frequency of radiotherapy was lowest among participants without HF (no HF versus HF$_{Stage A}$, HF$_{Stage B}$, and HF$_{Stage C/D}$: 38.6% versus 65.3%, 63.9%, and 52.4%). A detailed sample characterization by presence of HF and treatment characteristics is presented in Table 1. Treatment characteristics stratified by cancer entities are also provided in Table S1.

Prevalence of HF in CCSs

Among CCSs, 530 (57.2% [95% CI, 53.9–60.5]) were categorized as having HF stage A, 291 (31.4% [95% CI, 28.5–34.7]) were categorized as having HF stage B, and 22 (2.4% [95% CI, 1.5–3.7]) were categorized as having HF stage C or D. Of those categorized as having HF stage C or D, 90.9% (95% CI, 69.3–98.5) were classified as having HF with preserved ejection fraction, and 9.1% (95% CI, 1.5–30.7) were classified as having HF with reduced ejection fraction. There was a trend for the severe stages of HF to occur more frequently in the older age groups, as illustrated by

Table S2. Stratification for left ventricular cardiac function revealed that 2% of CCSs developed reduced LVEF (ie, <50%), and almost 4% developed diastolic dysfunction. There was an age trend for the E/E'-ratio (diastolic function) with an increasing ratio at older age, whereas there was no clear relation with age for systolic function as reflected by the surrogate marker LVEF (Table S3). When exploring the association of tumor history according to ICCC3 classification with the distribution and development of HF, strong differences were found with respect to frequency (Figure 1) and severity of HF (Table S4).

Frequency of HF in CCSs Compared With the General Population

In an age- and sex-matched comparison with a population sample (N=1380), a subsample of the study cohort (N=460) was compared in a 1:3 case/control ratio and 2-year tolerance for age matching to assess the influence of cancer and cancer-specific treatment (ie, radiotherapy and chemotherapy) on the development of HF. For the clinical profile, CCSs had a higher prevalence of arterial hypertension (CCS versus population: 32.2% versus 21%; P<0.0001) and dyslipidemia (CCS versus population: 34.6% versus 27%; P=0.002) compared with the general population, as outlined in Table S5 and recently described for the whole cohort.[18] The prevalence of HF stage B to D was substantially higher in CCSs than in the population (CCS versus population: 35% versus 14%; P<0.0001; Figure 2A), which was also true considering the prevalence of HF stage A (CCS versus population: 57% versus 32%; P<0.0001).

To further investigate the prevalence of HF, Poisson regression analysis with HF as dependent variable and adjustment for age, sex, and CVRFs was applied using the whole CCS analysis sample (N=926) and a population subsample aged 35 to 50 years (N=5673). The prevalence ratios for HF stage B to D were ≈4.6 (95% CI, 4.1–5.1) after adjustment for age and sex and still 2.7 (95% CI, 2.4–3.1) after additional adjustment for CVRFs as potential mediators of the disease (Figure 2B). For systolic and diastolic dysfunction, the prevalence ratio was 2.9 (95% CI, 1.8–4.7) for diastolic dysfunction and 3.1 (95% CI, 2.3–4.1) for systolic dysfunction after full adjustment. The difference in prevalence for HF stages B to D according to age in CCSs (N=649) compared with the population (N=14 368) is displayed in Figure 3 in a conditional density plot with 95% bootstrap intervals.

Relation of History of Tumor Entity With Systolic and Diastolic Dysfunction

The association between the history of different tumor entities and their specific treatment and the phenotype of cardiac dysfunction was investigated in the whole CCS

Table 1. Clinical and Treatment Characteristics of the Study Sample, Stratified for Stages of HF (According to the Universal Definition of HF)

Characteristics	No HF (N=83)	HF stage A (N=530)	HF stage B (N=291)	HF stage C/D (N=22)	P value for trend
Age, y	33.3±5.8	34.4±5.3	34.3±5.9	39.2±5.2	0.11
Sex (women), % (n)	55.4 (46)	39.4 (209)	51.9 (151)	72.7 (16)	0.022*
BMI, kg/m^2	24.0 (22.1/26.2)	24.8 (22.2/28.1)	25.7 (22.3/30.2)	25.7 (23.7/27.7)	0.00055*
Cardiovascular risk factors, % (n)					
Diabetes	0 (0)	2.1 (11)	3.1 (9)	0 (0)	0.22
Arterial hypertension	0 (0)	24.9 (132)	29.3 (85)	45.4 (10)	<0.0001*
Dyslipidemia	19.3 (16)	30.4 (161)	31.6 (92)	36.4 (8)	0.079
Family history, % (n) Myocardial infarction/stroke	10.8 (9)	14.5 (77)	12.8 (37)	13.6 (3)	0.99
Obesity	0 (0)	16.4 (87)	25.8 (75)	18.2 (4)	<0.0001*
Smoking	19.3 (16)	22.1 (117)	21 (61)	31.8 (7)	0.66
Cardiovascular comorbidities, % (n)					
CVD	0 (0)	1.1 (6)	3.2 (6)	54.5 (12)	<0.0001*
Atrial fibrillation	0 (0)	0 (0)	0.7 (2)	4.5 (1)	0.0045*
Coronary artery disease	0 (0)	0.2 (1)	0 (0)	0 (0)	0.68
Stroke	0 (0)	0.8 (4)	1 (3)	0 (0)	0.51
Myocardial infarction	0 (0)	0 (0)	0.7 (2)	0 (0)	0.11
Peripheral artery disease	0 (0)	0.2 (1)	0.7 (2)	4.5 (1)	0.025*
Primary tumor disease, % (n)					
Leukemias	0 (0)	55.9 (273)	50 (136)	23.8 (5)	0.00094*
Lymphomas	1.3 (1)	13.7 (67)	8.8 (24)	9.5 (2)	0.87
CNS tumors	39.5 (30)	5.5 (27)	8.8 (24)	0 (0)	<0.0001*
Neuroblastoma	6.6 (5)	6.4 (31)	7.4 (20)	4.8 (1)	0.79
Renal tumors	35.5 (27)	4.1 (20)	8.5 (23)	9.5 (2)	0.00017*
Bone tumors	2.6 (2)	5.5 (27)	6.2 (17)	19 (4)	0.04
Soft tissue sarcoma	1.3 (1)	8 (39)	8.5 (23)	23.8 (5)	0.018*
Germ cell tumors	13.2 (10)	0.8 (4)	1.8 (5)	9.5 (2)	0.021*
Age at diagnosis, y	5.2±4.5	6.4±4.1	6.2±4.3	9.4±4.1	0.084
Time since diagnosis, y	28.4±3.2	28.5±3.1	28.4±3.2	30±3.1	0.66
Treatment, % (n)					
Chemotherapy	75 (48)	98.3 (511)	97.1 (272)	100 (21)	<0.0001*
Anthracyclines	0 (0)	89.8 (473)	86.5 (244)	90.5 (19)	<0.0001*
≤150 mg/m^2	0 (0)	16.3 (75)	17.2 (41)	22.2 (4)	
150 to ≤250 mg/m^2	0 (0)	45.2 (208)	33.2 (79)	22.2 (4)	
>250 mg/m^2	0 (0)	38.5 (177)	49.6 (118)	55.6 (12)	
Cyclophosphamide	8.4 (7)	75.5 (400)	68 (198)	54.5 (12)	<0.0001*
Platine derivate	9.6 (8)	10.4 (55)	12.4 (36)	18.2 (4)	0.19
Vinca alcaloids	53.4 (36)	83.6 (443)	81.1 (236)	72.7 (16)	<0.0001*
Ifosfamide	6 (5)	27 (143)	26.1 (76)	22.7 (5)	0.027*
Radiation	38.6 (22)	65.3 (335)	63.9 (172)	52.4 (11)	0.14
Cardiac directed	0 (0)	25 (83)	26.1 (43)	36.4 (4)	0.093
CDI and anthracyclines	0 (0)	13.1 (45)	17.5 (32)	33.3 (4)	<0.0001*
LV function					
LV ejection fraction, %	64.0 (61.1/66.7)	62.7 (59.6/65.7)	60.3 (54.3/64.2)	60.6 (53.4/63.9)	<0.0001*
E/E' ratio	5.3 (4.4/6.1)	5.4 (4.7/6.6)	6.0 (4.8/6.7)	7.4 (5.4/11.4)	<0.0001*
E/A ratio	1.4 (1.2/1.8)	1.4 (1.1/1.7)	1.4 (1.1/1.7)	1.6 (1.2/2.1)	0.32

(*Continued*)

Table 1. Continued

Characteristics	No HF (N=83)	HF stage A (N=530)	HF stage B (N=291)	HF stage C/D (N=22)	P value for trend
MV deceleration time, s	0.2±0.04	0.19±0.04	0.19±0.04	0.18±0.05	0.038*
NT-proBNP, pg/mL	45.1 (21.7/69.0)	48.9 (28.9/74.2)	95.4 (37.0/167.3)	333.8 (120.7/733.1)	<0.0001*
LV structure					
LV mass index, g/m$^{2.7}$	29.9±5.7	29.7±6.4	34.7±10.5	35.8±9	<0.0001*
Relative wall thickness, cm	0.36±0.07	0.36±0.07	0.37±0.07	0.35±0.08	0.071
LV end-diastolic volume, mL	96.6±20.5	98.9±23	107.1±31.2	108.7±26.7	0.0003*
Medication, % (n)					
ARA (C03DA)	0 (0)	0.2 (1)	0.7 (2)	13.6 (3)	<0.0001*
β-Blockers (C07)	0 (0)	3.6 (19)	8.3 (24)	40.9 (9)	<0.0001*
Diuretics (C03)	0 (0)	0.4 (2)	1.4 (4)	27.3 (6)	<0.0001*
Ivabradine (C01EB17)	0 (0)	0 (0)	0.3 (1)	0 (0)	0.26
Statins (C10AA)	0 (0)	0.9 (5)	1.4 (4)	0 (0)	0.42

Data are presented as relative and absolute frequencies of subjects for binary variables and median (first/third quartile) for continuous traits. Data are also presented as mean±SD. ARA indicates angiotensin receptor antagonist; BMI, body mass index; CDI, cardiac-directed irradiation; CNS, central nervous system; CVD, cardiovascular disease; E/A, ratio of the peak early diastolic filling velocity (E)/peak diastolic filling velocity based on the contraction of the left atrium (A); E/E', ratio of the peak early diastolic filling velocity/lateral mitral annular early diastolic velocity, which corresponds to the left ventricular end-diastolic filling pressure; HF, heart failure; LV, left ventricular; MV, mitral valve; and NT-proBNP, N-terminal pro-B-type natriuretic peptide.

*A P value <0.05 suggests statistical significance.

sample and a population subsample aged 23 to 50 years as reference group. The systolic marker LVEF and the diastolic marker E/E' as surrogate for left ventricular end-diastolic pressure were used as outcome variables in multivariable linear regression analyses (N=≈6400) and the presence of a tumor entity according to ICCC3 (reference: no tumor history), age, sex, and CVRFs as independent variables. LVEF was relevantly decreased in patients with previous leukemia (β: −0.99 [95% CI, −1.6 to −0.4]; P=0.00086), renal tumor (β: −1.6 [95% CI, −2.8 to −0.3]; P=0.016), bone tumor (β: −4.3 [95% CI, −5.7 to −2.8]; P<0.0001), and sarcoma (β: −1.6 [95% CI, −2.9 to −0.3]; P=0.016). These associations were independent of age, sex, and coexisting CVRFs (Table 2). In contrast, the E/E' ratio was not significantly altered in patients with history of malignancies compared with the general population after adjustment for CVRFs. However, E/E' or diastolic function was associated with the presence of CVRFs as potential mediators of the disease.

Relation of History of Tumor Entity With the Prevalence of HF Stage B to D

Finally, we investigated the association between the history of different tumor entities and their specific treatment and the prevalence ratio of the composite of HF stage B to D in the whole CCS sample and a population subsample aged 23 to 50 years as reference group. HF stage B to D was used as outcome variable in multivariable linear regression analyses, and the history of a tumor entity according to ICCC3 (reference: no tumor history), age, sex, CVRFs, and treatment modalities as independent variables. Prevalence ratios

for HF stage B to D were significantly increased in all tumor entities, independent of age and sex. However, after additional adjustment for CVRFs and treatment (ie, anthracyclines or radiation), prevalence ratios for HF stage B to D were only associated with arterial hypertension (1.5 [95% CI, 1.3–1.7]), family history of myocardial infarction, stroke, or both (1.2 [95% CI, 1.0–1.4]), smoking (1.2 [95% CI, 1.0–1.4]), obesity (1.5 [95% CI, 1.3–1.7]), history of anthracycline treatment (2.5 [95% CI, 1.2–4.7]), and history of radiation (2.3 [95% CI, 1.1–4.4]). The results are provided in Table 3.

DISCUSSION

To date, this study is the first to report prevalence estimates for all stages of HF according to the recently proposed universal definition of HF in long-term CCSs compared with a population sample. More important, both samples underwent the same highly standardized clinical investigation in 1 study center. The main findings are as follows: (1) CCSs were at significantly higher risk of developing asymptomatic (ie, HF stage B/pre-HF) and symptomatic HF (ie, HF stage C and D) independent of their higher prevalence of CVRFs, (2) the presence of HF varied strongly with the history of the tumor entity and its specific treatment, (3) systolic function, as reflected by LVEF, was significantly decreased in survivors of various tumor entities independent of CVRFs, whereas diastolic dysfunction, measured by E/E', was not associated with tumor entities, but only with presence of CVRFs, and (4) age was identified as relevant determinant with an increasing worsening in diastolic, but not systolic, function in elderly individuals.
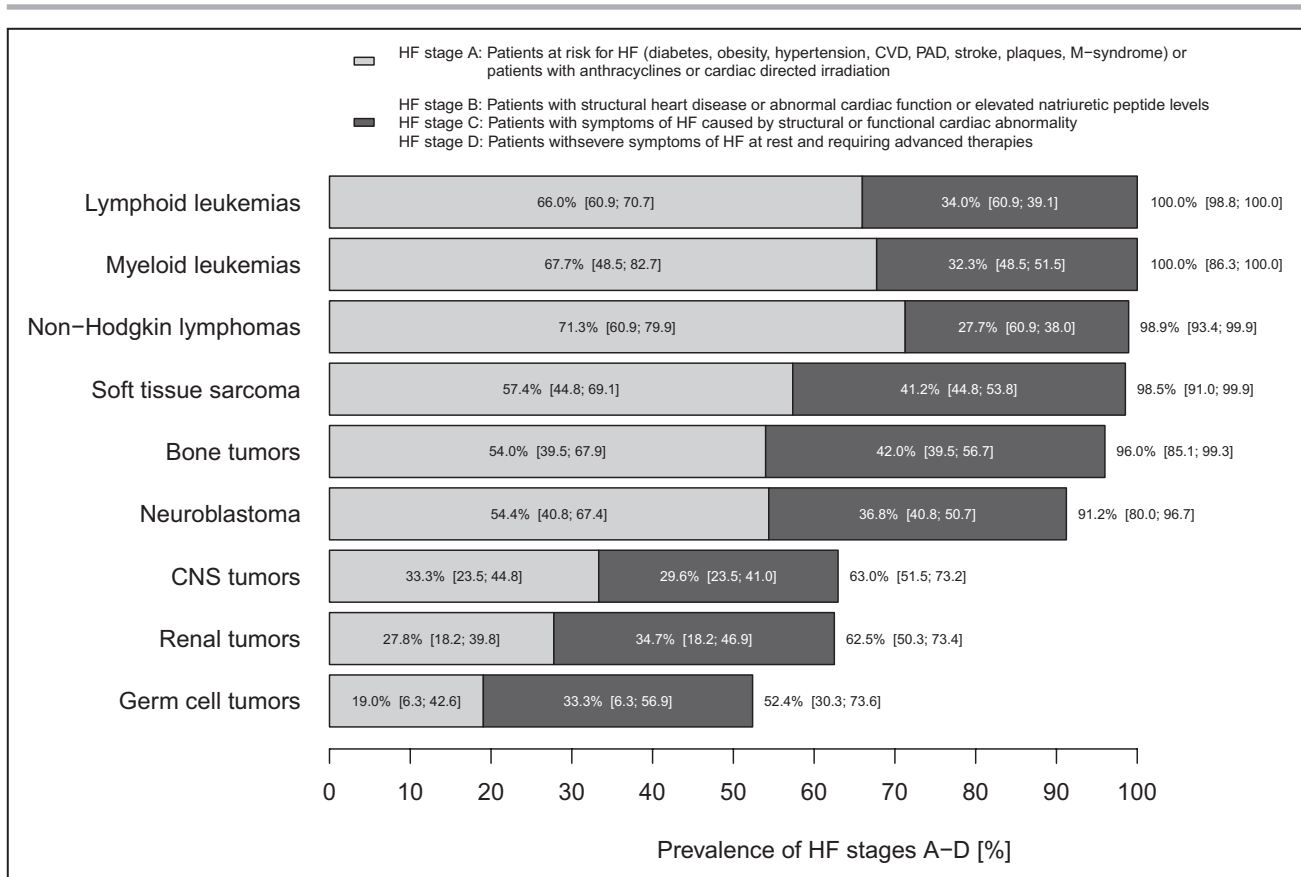
Figure 1. Prevalence for stages of HF, according to history of tumor entity.
Prevalence of HF stage A and the composite of HF stage B to D are shown for tumor entities according to International Classification of Childhood Cancer classification in the study sample (CVSS study). Prevalence is provided with 95% CIs for HF stage A, the composite of HF stage B to D (both within the columns), and the composite of HF stage A to D. CNS indicates central nervous system; CVSS, Cardiac and Vascular Late Sequelae in Long-Term Survivors of Childhood Cancer; HF, heart failure; M-syndrome, metabolic syndrome; and PAD, peripheral artery disease.

HF has emerged as the most common sequela in CCSs, with almost 5% of all CCSs developing clinical HF within 40 years after childhood cancer diagnosis.[19] However, most studies investigating prevalence and incidence of adverse outcomes relied on self-reported outcomes,[20] data from registries,[12] or death certificates.[10] In the present analysis of this CCS sample, aged 23 to 48 years, HF prevalence (HF stage B to D) was found to be 35%, with most patients being asymptomatic, consistent with other recent large-scale data.[21] The prevalence of 2.4% for symptomatic HF (ie, stage C and D) is still higher than in the general population, where it is 0.7% in people aged 45 to 54 years and 1.3% in people aged 55 to 64 years.[22] The fact that women accounted for most patients diagnosed with the composite of HF stage C/D is most likely attributable to cancer therapy-induced damage of the hypothalamic-pituitary-ovarian-uterine axis, which may subsequently lead to disturbed pubertal development, menstrual cycle disturbances, impaired fertility, and premature menopause. Furthermore, a higher

percentage of body fat in women compared with men could lead to higher concentrations of anthracyclines, in particular in non–adipose tissue, including the heart, over a longer period of time.[23,24] The nearly 4.6-fold increase in prevalence of HF stage B to D, reported for the first time compared with a population sample, is particularly notable in individuals with former bone tumors and soft tissue sarcoma, who had the highest prevalence of HF in the sample, in particular the highest prevalence of symptomatic HF (ie, HF stage C and D). Stratification by systolic and diastolic function revealed that patients with former bone tumors and soft tissue sarcoma had the highest prevalence of systolic dysfunction. The increased risk of systolic cardiomyopathy in this group is consistent with earlier findings and may be explained by the particularly high cumulative anthracycline doses administered.[20] To date, few studies have investigated the prevalence of systolic dysfunction in CCSs based on a comprehensive echocardiographic examination. Two recent studies from the SJLIFE (St. Jude Lifetime Cohort
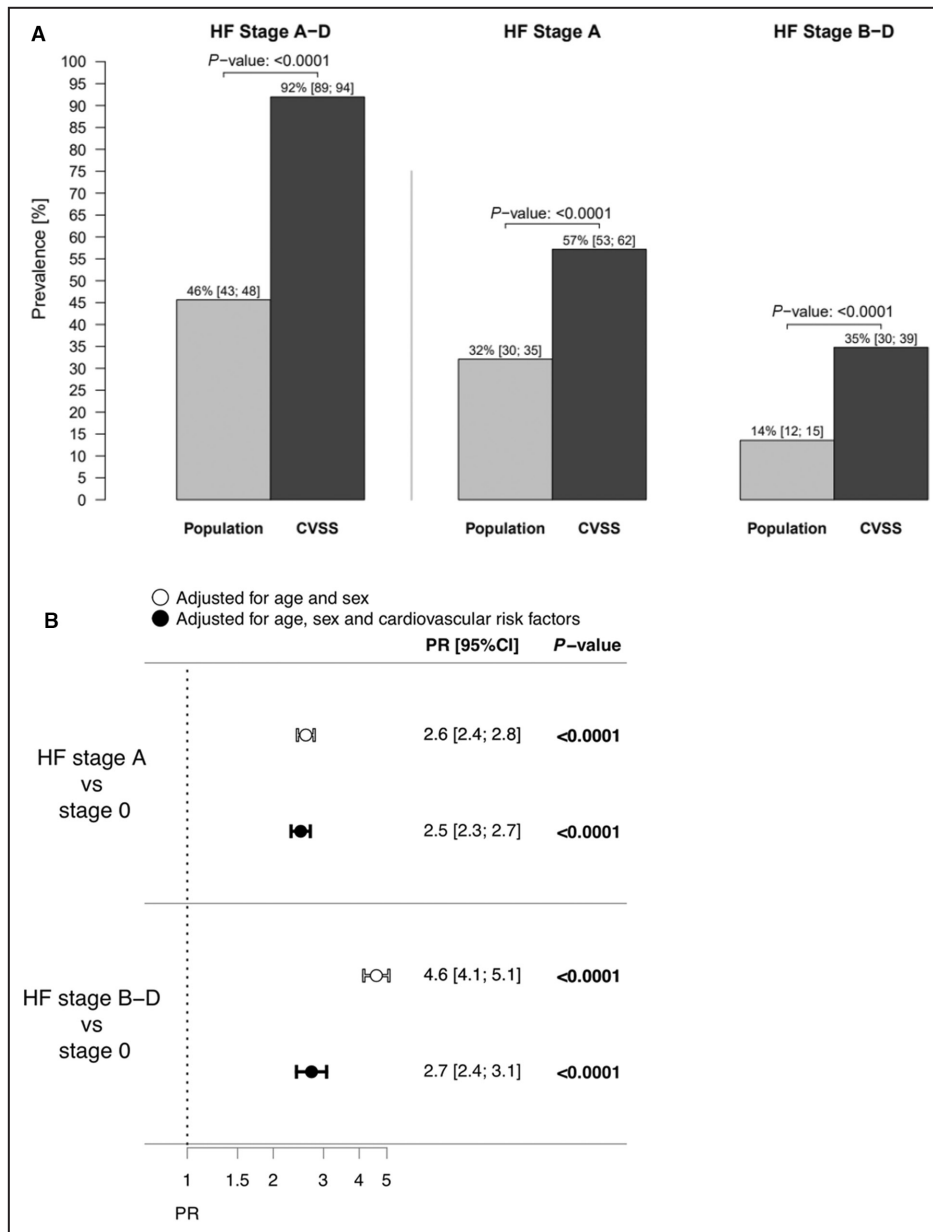
Figure 2. Crude and adjusted prevalence of stages of HF in childhood cancer survivors compared with the general population.

A, Prevalence for stages of HF in a subsample of childhood cancer survivors (N=425) compared with an age- and sex-matched sample from the general population (N=1275). A 1:3 case/control ratio and 2-year tolerance were applied for age matching. Prevalence is shown for (1) HF (all stages) and (2) HF stage A and the composite of heart failure stage B to D; *P* values were calculated by a proportion test. **B**, Poisson regression models with robust error variance were fitted to evaluate the association of former childhood cancer with prevalent HF compared with the general population (total CVSS study sample, N=929; GHS subsample, aged 35 to 50 years, N=5673). PRs are provided with 95% CIs for HF stage A and the composite of HF stage B to D with adjustment for (1) age and sex; and (2) age, sex, and cardiovascular risk factors. CVSS indicates Cardiac and Vascular Late Sequelae in Long-Term Survivors of Childhood Cancer; GHS, Gutenberg Health Study; HF, heart failure; and PR, prevalence ratio.

Study) reported prevalence rates for systolic dysfunction (defined as LVEF <50%) of 5.8%[14] and 7.4%.[21] The significantly lower prevalence of systolic dysfunction in the present study (2%) is most likely attributable to the relatively high proportion of patients with Hodgkin lymphoma included in the SJLIFE and the exclusion of these patients from the present analysis because of the study design.
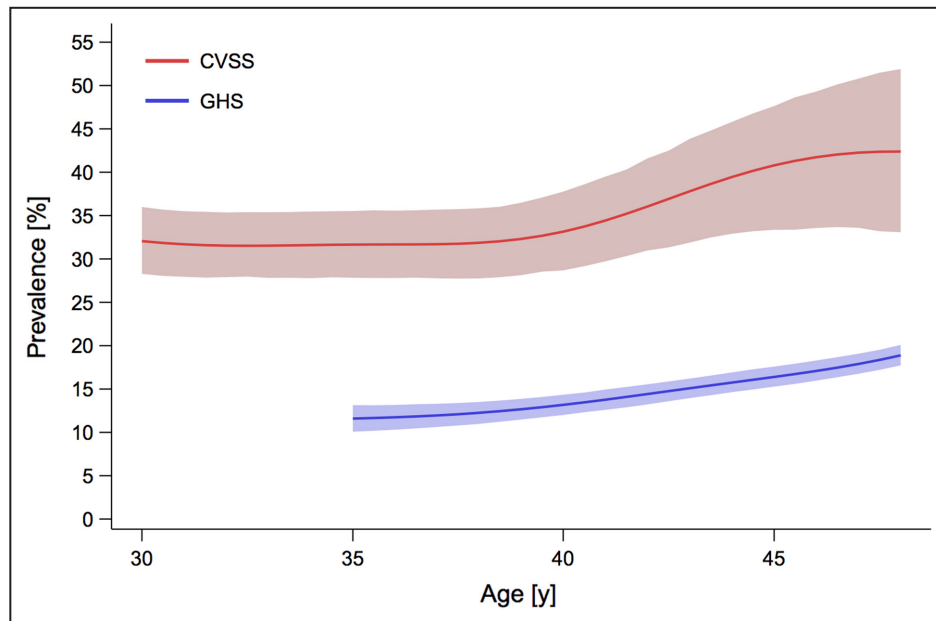
Figure 3. Age dependency of the prevalence for HF (stage B–D) in childhood cancer survivors and the general population.
Age-dependent comparison of the prevalence for the composite of HF stage B to D in childhood cancer survivors and the general population. Conditional density plots were generated, and nonparametric bootstrap samples (n=1000) were run to estimate 95% confidence limits. Data were calculated on the basis of a CVSS study subsample, aged 30 to 45 years (N=649), and the GHS sample, aged 35 to 74 years (N=14 638). For the population data, the graph is displayed for the age range 35 to 50 years only. CVSS indicates Cardiac and Vascular Late Sequelae in Long-Term Survivors of Childhood Cancer; GHS, Gutenberg Health Study; and HF, heart failure.

The effects of chemotherapy (eg, mitoxantrone, cyclophosphamide, vincristine, amsacrine, and anthracycline derivates[25]) and radiation-induced cardiotoxicity[26] on the development of HF in CCSs is well-known. Cardiotoxic effects of anthracyclines have been studied extensively, and there is evidence for a dose-dependent relation with HF.[27–31] Interindividual differences in susceptibility (eg, genetic variants[32,33] or female sex[23]) explain a fluctuating risk of cardiovascular sequelae and the need for individualized therapies for a cardiac-safe drug therapy. Notably, the present data do not support an age dependency of this therapy-related direct cardiotoxic effect on systolic function, consistent with the findings of the SJLIFE.[14]

In addition to developing systolic dysfunction, CCSs have an even greater risk of developing diastolic dysfunction and subsequently HF with preserved ejection fraction. The results of the present study underline that, in contrast to systolic dysfunction, the prevalence of diastolic dysfunction in CCSs increased with age. The risk was not related to tumor entity in regression but to the higher presence of CVRFs in CCSs. Risk factors for the development of diastolic dysfunction have been extensively studied in the general population, including obesity, arterial hypertension, and diabetes.[34,35] According to the results of a previously published

study on the CVSS study cohort, CCSs have a substantially higher burden of traditional CVRFs compared with the general population. In this context, the likelihood of developing arterial hypertension, dyslipidemia, obesity, and diabetes increases steadily with age without reaching a plateau.[18] In addition, chest-directed radiotherapy is known to induce microvascular damage, leading to myocardial fibrosis and eventually diastolic dysfunction.[36] This is also confirmed by the CVSS study cohort, in which intracranial tumors with a therapy regimen that primarily included radiotherapy (but no anthracyclines) had the highest prevalence of diastolic dysfunction. Diastolic dysfunction in patients undergoing cranial radiotherapy is likely attributable to the development of hypothalamic-pituitary insufficiency, leading to growth hormone deficiency.[37] This has been shown to be associated with structural abnormalities of the left ventricle,[38] as well as an altered cardiovascular risk profile, as indicated by higher systolic blood pressure, altered body composition, and a more unfavorable lipid profile.[39] Furthermore, diastolic dysfunction was associated with chest-directed radiotherapy, independent of age, sex, and concomitant anthracycline treatment in the SJLIFE cohort.[14] Its prevalence was 8.7%, which is explained by the larger proportion of Hodgkin lymphoma survivors (≈17%),

Table 2. Relation of History of Tumor Entity With Development of Systolic and Diastolic Dysfunction

Variable	*E/E′* (N=6421)		LVEF (N=6439)	
	Estimate (95% CI)	*P* value	Estimate (95% CI)	*P* value
History of leukemia	−0.08 (−0.26 to 0.10)	0.35	−0.99 (−1.60 to −0.41)	0.00086*
History of lymphoma	−0.25 (−0.58 to 0.10)	0.14	−0.89 (−2.00 to 0.20)	0.11
History of tumors of the CNS	0.015 (−0.34 to 0.37)	0.93	−0.41 (−1.60 to 0.76)	0.49
History of neuroblastoma	0.11 (−0.33 to 0.54)	0.63	−0.30 (−1.70 to 1.10)	0.68
History of renal tumors	−0.29 (−0.68 to 0.10)	0.14	−1.60 (−2.80 to −0.29)	0.016*
History of bone tumors	0.33 (−0.11 to 0.78)	0.14	−4.30 (−5.70 to −2.80)	<0.0001*
History of sarcoma	0.35 (−0.05 to 0.74)	0.087	−1.60 (−2.90 to −0.30)	0.016*
History of germ cell tumors	−0.03 (−0.71 to 0.66)	0.94	1.10 (−1.20 to 3.30)	0.35
Sex (women)	0.47 (0.39 to 0.55)	<0.0001*	1.20 (0.91 to 1.40)	<0.0001*
Age	0.56 (0.47 to 0.64)	<0.0001*	0.48 (0.19 to 0.76)	0.00096*
Diabetes	0.34 (0.08 to 0.60)	0.0087*	0.10 (−0.72 to 0.93)	0.8
Arterial hypertension	0.59 (0.50 to 0.68)	<0.0001*	−0.07 (−0.38 to 0.24)	0.64
Dyslipidemia	0.14 (0.04 to 0.30)	0.0031*	−0.12 (−0.43 to 0.19)	0.46
Family history of MI/stroke	0.11 (0.01 to 0.20)	0.033*	−0.14 (−0.46 to 0.18)	0.41
Smoking	0.20 (0.11 to 0.29)	<0.0001*	−0.5 (−0.8 to −0.21)	0.00091*
Obesity	0.57 (0.47 to 0.68)	<0.0001*	−0.35 (−0.60 to 0.01)	0.0044*

CNS indicates central nervous system; *E/E′*, ratio of the peak early diastolic filling velocity/lateral mitral annular early diastolic velocity, which corresponds to the left ventricular end-diastolic filling pressure; LVEF, left ventricular ejection fraction; and MI, myocardial infarction.

*A *P* value <0.05 suggests statistical significance.

who are well-known for the development of diastolic dysfunction,[40] compared with the present study (see also above).

Several limitations should be considered for this study: Dose-dependent or modality-specific effects on cardiac function could not be investigated, as detailed

Table 3. Relation of History of Tumor Entity With Development of the Composite of HF Stage B to D

Variable	HF stage B-D (N=6484)		HF stage B-D (N=6118)	
	Prevalence ratio (95% CI)	*P* value	Prevalence ratio (95% CI)	*P* value
History of leukemia	3.0 (2.4–3.6)	<0.0001*	1.2 (0.6–2.5)	0.53
History of lymphoma	2.2 (1.5–3.1)	<0.0001*	0.9 (0.4–1.9)	0.80
History of tumors of the CNS	2.5 (1.7–3.5)	<0.0001*	1.2 (0.5–2.6)	0.65
History of neuroblastoma	3.7 (2.5–5.4)	<0.0001*	1.5 (0.7–3.3)	0.29
History of renal tumors	3.2 (2.2–4.6)	<0.0001*	1.7 (0.8–3.3)	0.13
History of bone tumors	3.0 (2.0–4.2)	<0.0001*	1.3 (0.6–2.7)	0.51
History of sarcoma	3.5 (2.5–4.8)	<0.0001*	1.4 (0.7–3.0)	0.33
History of germ cell tumors	2.9 (1.6–5.3)	0.00029*	2.2 (1.0–4.8)	0.036*
Sex (women)	0.9 (0.7–1.0)	0.014*	1.0 (0.8–1.1)	0.54
Age	1.0 (1.0–1.1)	<0.0001*	1.0 (1.0–1.1)	0.0023*
Diabetes	…	…	1.3 (0.9–1.7)	0.08
Arterial hypertension	…	…	1.5 (1.3–1.7)	<0.0001
Dyslipidemia	…	…	1.1 (0.9–1.3)	0.063
Family history of MI/stroke	…	…	1.2 (1.0–1.4)	0.0043*
Smoking	…	…	1.2 (1.0–1.4)	0.0015*
Obesity	…	…	1.5 (1.3–1.7)	<0.0001*
Anthracyclines only	…	…	2.4 (1.2–4.7)	0.0094*
Radiation only	…	…	2.3 (1.1–4.4)	0.014*

Multivariable logistic regression model to investigate the association of the history of a tumor disease with the prevalence of the composite of HF stage B to D in childhood cancer survivors and a population sample free of cancer. The difference can be explained by the fact that the model presented in the left column was only adjusted for age and sex, whereas an additional adjustment for cardiovascular risk factors and therapy modalities was performed in the model presented in the right column. Based on several missings, the sample size differs. CNS indicates central nervous system; HF, heart failure; and MI, myocardial infarction.

*A *P* value <0.05 suggests statistical significance.

characterization of cancer treatment modalities was not available (ie, cumulative doses of chemotherapeutic agents or radiotherapy). The development of HF was not analyzed in a sex-specific manner, although female sex is a potential risk factor for HF in CCSs[23]; fertility and hormonal status should be included in future investigations. LVEF was calculated according to Simpson, an echocardiographic standard method but with variability of up to 10%.[41] The impact of cancer treatment on cardiac function is underscored by the fact that only survivors were considered for this analysis. For the interpretation of the results, it should be taken into account that a survival bias exists by not considering individuals who died before the study, as reported earlier by our group for the CVSS study cohort.[42] Hodgkin lymphomas were not included in the study by design. Last, prior anthracycline treatment has been shown to result in late-onset subtle changes of left ventricular strain in speckle tracking echocardiography,[14,43] which were not considered in this analysis, although their prognostic value for the development of HF remains unclear. In addition, the lack of data from the analysis of left ventricular burden may have led to a moderate underestimation of the prevalence of stage B HF.

CONCLUSIONS

In conclusion, the results of the present study demonstrated a substantially higher risk of developing all stages of HF in CCSs compared with the general population. The prevalence of HF varied widely by tumor entity, likely reflecting differences in treatment regimens. Increased HF risk in CCSs could be attributable to (1) direct cardiotoxic effects, leading to systolic dysfunction; and (2) a predisposition to CVRFs, possibly via vasculotoxic effects, leading to diastolic dysfunction, particularly in the long-term. The present data underscore the need for the following: (1) monitoring for early (preclinical) changes in systolic function by new imaging modalities (eg, strain imaging) to allow early initiation of cardioprotective therapy to prevent the development of systolic dysfunction and HF with reduced ejection fraction; (2) preventive strategies to reduce the burden of CVRFs in these high-risk patients to avoid diastolic dysfunction and HF with preserved ejection fraction; and (3) surveillance protocols even for patients at risk (ie, stage A) for developing HF.

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Acknowledgments

Sources of Funding

Disclosures

Supplemental Material

Data S1
Tables S1–S5

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