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SHORT REPORT

Mortality risk among 5-year survivors of childhood cancer in Germany—Results from the CVSS study (Cardiac and Vascular late Sequelae in long-term Survivors of childhood cancer study)

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Abstract

The growing population of long-term childhood cancer survivors is at increased risk for severe, therapy-related late effects and premature mortality. The cardiac and vascular late sequelae in long-term survivors of childhood cancer (CVSS) study is a cohort of patients from Germany diagnosed with a neoplasia prior to 15 years of age in the time period 1980 to 1990. Late mortality was evaluated in a total of 4505 individuals who survived 5 years or more after the initial diagnosis (5-year survivors). Survivors with a second primary tumor were excluded. Standardized mortality ratios (SMRs) were calculated. By December 2014, 400 patients had died. Available cause of death information from 188 individuals was used to estimate cause-specific mortality for all deceased persons. Compared to the population of (former) West Germany, we observed an excess overall mortality risk (SMR = 9.53, 95% confidence interval [CI] = 8.62-10.51). After correcting for missing cause of death information, an increased cancer mortality (SMR = 43.50, 95% CI = 25.79-73.50) in the 5-year survivors was detected. Cardiac death was ascertained in 14 individuals, resulting in an SMR of 10.85 (95% CI = 2.80-32.02) after correcting for missing values. In conclusion, childhood cancer survivors diagnosed in Germany in 1980 to 1990 have a higher mortality risk overall and an elevated risk of dying from cancer and cardiac causes in particular. The results are consistent with those of international cohort studies. However, the reported results are based on few cases and individuals with secondary cancers were excluded.

KEYWORDS
cancer treatment, cardiac, cardiovascular, childhood cancer, late effects, mortality, pediatric malignancies

Abbreviations: CCSS, Childhood Cancer Survivor Study; CI, confidence interval; CVSS, cardiac and vascular late sequelae in long-term survivors of childhood cancer; GCCR, German Childhood Cancer Registry; SMR, standardized mortality ratio.

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What's new?

Since the 1970s, significant improvements have been made in the survival of patients diagnosed with childhood malignancies. Long-term survivors of childhood cancer, however, have elevated risks for late-developing therapy-related effects, including premature mortality. The present study examined long-term survival specifically within a cohort of 5-year survivors of childhood cancer in Germany. An excess long-term overall mortality risk was observed among individuals who experienced childhood malignancies. Cancer and cardiac sequelae were the primary causes of death. Cardiac mortality was noticeably elevated in females. The findings emphasize the importance of monitoring and managing long-term health in childhood cancer survivors.

1 | INTRODUCTION

Advances in diagnosis and treatment of childhood malignancies have improved survival since the 1970s. German patients diagnosed with childhood cancer during the years 1980 to 1990 had a 5-year survival of 69%.[1] Currently, the 5-year survival of patients with childhood cancer in Germany is 86%.[1] Data from the Surveillance, Epidemiology and End Results Study (SEER) database show that 5-year survival in the United States is 83.4%.[2] The 5-year survival is used as a benchmark for cure after diagnosis. However, long-term survivors are at increased risk for severe therapy-related late effects and premature mortality. The US/Canadian Childhood Cancer Survivor Study (CCSS) found that within 30 years from diagnosis, 18% of patients who survived 5 years or more after the initial diagnosis (5-year survivors) had died.[3] Second malignant neoplasms and cardiovascular disease account for a greater proportion of premature deaths and morbidity compared to individuals from the general population.[4] Treatment for pediatric malignancies includes chemotherapy, radiation and surgery. Chemotherapy and radiation therapy account for an increased risk of cardiovascular disease among childhood cancer survivors: anthracyclines have been implicated as a principal cause of irreversible cardiomyopathy, and patients exposed to thoracic radiation can develop systolic or diastolic dysfunction.[4,5]

Currently, more than 35 000 long-term childhood cancer survivors have been registered with the German Childhood Cancer Registry (GCCR).[6] The cardiac and vascular late sequelae in long-term survivors of childhood cancer (CVSS) study considered individuals from the GCCR diagnosed with a neoplasia between 1980 and 1990. Outcomes of interest are all-cause mortality, cancer mortality and cardiac mortality of the CVSS cohort in comparison with the general population. The present study is the first to report subsequent mortality among 4505 individuals who survived 5 years or more after their initial diagnosis with cancer.

2 | METHODS

2.1 | Source population and study design

The CVSS study is a retrospective cohort study and based on patients who were registered with the GCCR.[6] Since 1980, the GCCR has registered all childhood (aged <15 years) cancer patients residing in Germany (and since 2009 all aged <18 years). The CVSS study included individuals being alive at 5 years after cancer diagnosis with (a) a neoplasia according to the International Classification of Childhood Cancer, (b) a primary cancer diagnosis 1980 to 1990, (c) age at cancer diagnosis of less than 15 years and (d) diagnosis and initial treatment at one of 34 collaborating pediatric cancer centers in (former) West Germany. We excluded individuals initially diagnosed with Hodgkin lymphoma ($n = 503$). In addition, survivors of nephroblastoma diagnosed in 1990 ($n = 73$) were excluded. Both groups of patients participated in other clinical investigations about cardiomyopathy. Furthermore, individuals with a second primary tumor (registry-based information recorded at the CCCR) were not considered. Between September 2013 and February 2016, a subset of 951 survivors was invited to a physical medical examination and cardiac screening. Detailed face-to-face interviews provided information on comorbidities and medical history. If the invited individuals indicated a second primary that was not recorded at the GCCR, they were excluded from the analysis. The final CVSS-source population comprised 4505 five-year survivors. By December 2014, a total of 400 patients had died 5 years after the initial cancer diagnosis or later.

2.2 | Ascertainment of causes of death

The GCCR performs routine follow-up assessments of the vital status of former childhood cancer patients by sending inquiries to hospitals, clinical studies and the mandatory population registry of the municipality of the last known residence. For deceased persons, death certificates were obtained from the local health authority of the place of death. Underlying causes of death were subsequently coded according to the 10th revision of the International Classification of Diseases (ICD-10). German health authorities have a limited retention period for death certificates (5-10 years on average), which limited the available information on cause of death.

2.3 | Data protection measures

The GCCR recorded identity data (name, address, date of birth) of each individual with the consent of their legal guardians or, for older

patients, with their own consent. For the CVSS study, personal identifiers (ID) were generated for all individuals of the cohort. However, identity data are necessary to conduct a mortality follow-up, where individual requests are sent to the corresponding local health authorities. To be in accordance with data protection laws, the health authorities provided anonymized death certificates labeled with the ID only, while identity data were detached. The (anonymized) cause-of-death information from the death certificates was added to the (anonymized) CVSS study database.

2.4 | Statistical analysis

Analyses were performed to investigate all-cause mortality (ICD[10]: A00-Y98) as well as the mortality of three cause-of-death categories: "cancer mortality" (ICD[10]: C00-D48), "all-cardiac deaths" according to Fidler et al[7] (ICD[10]: I01, I02.0, I05-I09, I11, I13, I20-I25, I27.1-9, I30-I52) and "all other causes of death" (ICD[10]: A00-Y98, excluding cancer mortality and all-cardiac deaths). Standardized mortality ratios (SMRs), defined as the observed number of deaths divided by the expected number of deaths, and corresponding 95% confidence intervals (CIs) were calculated. To determine the expected number of deaths for the general population of West Germany, we used the official cause-of-death statistics of the German federal government (publicly available from 1980 onward). Expected numbers were calculated by multiplying the person-years (PY) at risk of each sex-, age- (5-year categories) and calendar year- (5-year categories) specific stratum by the corresponding mortality rate for the population of West Germany and then summing across strata. Individuals with an initial cancer diagnosis between January 1, 1980 and December 31, 1990 and being alive at 5 years after cancer diagnosis were considered for follow-up. Thus, the PY were calculated starting from 5 years after diagnosis (January 1, 1986 at the earliest). The end of the individual observational period (time at risk) was defined as either date of death and, for those who were not recorded to be deceased until December 2014, the date of physical examination at the study center, the date of the last individual follow-up or the date of censoring (December 31, 2014). For deceased individuals with missing information on cause of death, a statistical imputation was performed according to the method of Rittgen and Becker,[8] which was developed to derive a maximum likelihood estimator for the true (but unknown) number observed deaths from a specific cause of death. This method uses the known number of observed deaths (O) from a specific cause of death and its proportion p among all known causes of death (stratified by sex) to calculate the corrected number of observed cases $O^b = O/p$. The standardized mortality ratio based on this estimated number is SMR = SMR/p.

The CVSS study (ClinicalTrials.gov-No.: NCT02181049) was approved by the Ethics Committee of the Rhineland-Palatinate Chamber of Physicians and was conducted in accordance with the Declaration of Helsinki.

3 | RESULTS

3.1 | Characteristics of the study population

A total of 4505 individuals included in the CVSS cohort contributed a total of 91 056.75 PY. Individuals in the cohort were, on average, 31.9 years old (range, 5.77-48.63 years) at the end of follow-up. By December 2014, 400 individuals had died. Median age at death was about 18.8 years (range, 6.15-46.40 years). The median follow-up times beginning 5-years after diagnosis and ending on the censoring date or date of death were 21.7 years and 4.9 years, respectively (Table 1). Compared to surviving individuals, the deceased had lower percentages of leukemia, lymphoma, and renal tumors and higher percentages of central nervous system and bone tumors (Table 2).

TABLE 1 Characteristics of the CVSS-population: 5-year survivors of childhood cancer (primary diagnosis 1980-1990), Germany

	5-year survivors	Deceased 5-year survivors[a]	Deceased 5-year survivors with cause of death information	Deceased 5-year survivors without cause of death information
Total No.	n = 4505	n = 400	n = 188	n = 212
Male	n = 2501 (55.5%)	n = 226 (56.5%)	n = 103 (54.8%)	n = 123 (58.0%)
Female	n = 2004 (44.5%)	n = 174 (43.5%)	n = 85 (45.2%)	n = 89 (42.0%)
Variable				
Age at primary diagnosis (y): median (range)	4.81 (0.00-14.99)	7.14 (0.04-14.99)	7.92 (0.04-14.99)	6.82 (0.20-14.90)
Age at start of follow-up[b] (y): median (range)	9.81 (5.00-19.99)	12.14 (5.04-19.99)	12.92 (5.04-19.99)	11.81 (5.20-19.89)
Length of follow-up[b], (y): median (range)	21.71 (0.00-29.97)	4.95 (0.00-28.25)	9.21 (0.09-28.25)	3.02 (0.00-24.07)
Age at death/end of follow-up[a] (y): median (range)	31.98 (5.77-48.63)	18.80 (6.15-46.40)	21.25 (6.98-46.40)	16.63 (6.15-43.57)

Abbreviation: CVSS, cardiac and vascular late sequelae in long-term survivors of childhood cancer.
[a]Death or censored: date of death or end of observational period or December 31, 2014, whichever comes first.
[b]Diagnosis + 5 years.

TABLE 2 Primary cancer diagnoses in the CVSS-population: 5-year survivors of childhood cancer (primary diagnosis 1980-1990), Germany

ICCC3 diagnosis	5-year survivors (n = 4505)	Deceased 5-year survivors[a] (n = 400)	Deceased 5-year survivors with cause of death information	Deceased 5-year-survivors without cause of death information
Total No. (%)	N = 4505 (100%)	N = 400 (100%)	N = 188 (100%)	N = 212 (100%)
Leukemia	1785 (39.6)	137 (34.3)	55 (29.3)	82 (38.7)
Lymphoma	368 (8.2)	11 (2.8)	5 (2.7)	6 (2.8)
CNS tumor	720 (16.0)	132 (33.0)	65 (34.6)	67 (31.6)
SNS tumor	299 (6.6)	22 (5.5)	10 (5.3)	12 (5.7)
Retinoblastoma	265 (5.9)	3 (0.8)	2 (1.1)	1 (0.5)
Renal tumor	306 (6.8)	9 (2.3)	5 (2.7)	4 (1.9)
Hepatic tumor	34 (0.8)	3 (0.8)	0 (0.0)	3 (1.4)
Malignant bone tumor	245 (5.4)	39 (9.8)	18 (9.6)	21 (9.9)
Soft tissue sarcoma	291 (6.5)	33 (8.3)	20 (10.6)	13 (6.1)
Germ cell tumor	152 (3.4)	8 (2.0)	6 (3.2)	2 (0.9)
Carcinoma	37 (0.8)	3 (0.8)	2 (1.1)	1 (0.5)
Other	3 (0.1)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: CNS, central nervous system; CVSS, cardiac and vascular late sequelae in long-term survivors of childhood cancer; SNS, sympathetic nervous system.
[a]Death or censored: date of death or end of observational period or December 31, 2014, whichever comes first.

TABLE 3 Five-year survivors of childhood cancer (primary diagnosis 1980–1990): standardized mortality ratios and 95% confidence intervals by broad causes of death, Germany

Causes of death[a]	Obs	Obs[b]	Exp[c]	SMR	95% CI	SMR[b]	95% CI[b]
All-cause mortality	400		41.99	9.53	8.62-10.51		
Cancer mortality	120	254.91	5.86	20.48	16.98-24.49	43.50	25.79-73.50
Cardiac mortality	14	29.83	2.75	5.09	2.78-8.54	10.85	2.80-32.02
Other causes of death	54	115.24	33.38	1.62	1.26-2.11	3.45	1.70-6.75
Missing causes of death	212						

Abbreviations: CI, confidence interval; Exp, expected number of death; Obs, observed number of death; SMR, standardized mortality ratio.
[a]Cause of death according to the 10th revision of the International Classification of Diseases (ICD). All-cause mortality: A00-Y98; Cancer mortality: C00-D48; Cardiac mortality: I01, I02.0, I05-I09, I11, I13, I20-I25, I27.1-9, I30-I52; Other causes of death: A00-Y98 excluding cancer mortality and cardiac mortality.
[b]Corrected for missing causes of death according to the method of Rittgen and Becker.[8]
[c]Expected number of deaths based on sex, age, calendar year and cause-specific mortality rates for the population during 1985 to 2014 in West Germany.

Death certificates could be obtained for 188 out of the 400 deaths (47%). A comparison between individuals with available information on cause of death and those without such information (n = 212) showed only slight differences in age at primary diagnosis and age at start of follow-up. However, we observed a difference in length of follow-up (9 vs 3 years). Among those 212 individuals without a death certificate, a total of 126 (59.4%) died in the early period of observation (1985-1995), which is associated with a shorter follow-up.

3.2 | Mortality

The all-cause mortality of survivors of pediatric malignancies was higher than the mortality of the corresponding West German population (SMR = 9.53, 95% CI = 8.62-10.51) (Table 3). The all-cause SMR was higher for females (SMR = 15.74, 95% CI = 13.48-18.25) than for males (SMR = 7.31, 95% CI = 6.39-8.32). In 120 of 188 (63.8%) deceased 5-year survivors, the underlying cause of death was cancer. After correction for missing cause of death, the SMR for cancer mortality was significantly increased (SMR = 43.50, 95% CI = 25.79-73.50). Overall, 14 of 188 deaths were attributed to cardiac causes (7.4%). Adjusted for missing information on cause of death, survivors of childhood cancer experienced at least 10 times the number of cardiac deaths expected in the general population (SMR = 10.85, 95% CI = 2.80-32.02). The SMR for cardiac mortality was higher in females than in males (females: SMR = 16.16, 95% CI = 4.28-46.44; males: SMR = 8.86, 95% CI = 2.87-22.53). A total of 54 individuals died from other causes of death (SMR = 3.45, 95% CI = 1.70-6.75) with a higher risk for females.

4 | DISCUSSION

4.1 | Principal findings

The CVSS study included 4505 German patients with childhood cancer who survived 5 years or more after the initial diagnosis in 1980 to 1990. The median follow-up time was 21.7 years. By December 2014, a total of 400 individuals in the cohort had died. The SMR was estimated by comparing the CVSS cohort with the reference population West Germany. Overall, survivors of pediatric malignancies show a significantly increased mortality ratio for all causes of death and an increased SMR for cancer mortality and cardiac mortality in particular.

4.2 | Comparison to other studies

Several other studies have assessed the mortality risk among childhood cancer survivors. A population-based Nordic cohort of 5-year survivors of childhood and adolescent cancer enrolled 37 515 incident cases diagnosed with a malignancy before 20 years of age. For 5-year survivors diagnosed in the decade 1980 to 1989, the SMR for all causes of death was 11.0 (95% CI not reported).[9] The CCSS (United States/Canada) included 34 033 five-year survivors diagnosed before age 21. During the treatment era 1980 to 1989, the overall mortality risk ratio was 12.1 (95% CI = 11.4-12.8), with 1179 deaths.[10] Within 5 to 10 years after diagnosis, the main cause of mortality is cancer.[9] A population-based cohort of 5-year survivors in Switzerland has shown that, in the first 10 years after 5-year survival, 78.9% of excess deaths were caused by recurrence of the original cancer.[11] The results of the German CVSS study regarding all-cause mortality and cancer mortality are generally consistent with previous studies on risk of death among 5-year survivors of childhood cancer, although comparisons are difficult as age of diagnosis, duration of follow-up and inclusion criteria differ between studies. The primary aim of the CVSS study was the assessment of long-term cardiovascular late effects among survivors of childhood cancer. For that reason, individuals with second neoplasms were not included, because these patients are known to have a worse prognosis. Patients with a second neoplasm received more than one cancer treatment (with a second chemo- and/or radiotherapy), and are thus at a higher risk for cancer mortality and other treatment-associated mortality. Exclusion of these persons may explain the somewhat lower overall mortality risk in the German cohort compared to the international 5-year survivor cohorts.

An increased risk for cardiac mortality among childhood cancer survivors has been described in cohorts with long observation periods. The US/Canadian CCSS observed 41 cardiac deaths in patients diagnosed between 1980 and 1989 (SMR = 11.2, 95% CI = 8.2-15.3).[10] The British Childhood Cancer Survivor Study included 34 489 five-year-survivors diagnosed between 1940 and 2006 and followed up until 2014. Among those diagnosed between 1980 and 1989, a total of 941 died, with 43 cardiac deaths, corresponding to an SMR of 9.1 (95% CI = 6.6-12.3).[7] For cardiac mortality, the German CVSS study observed a mortality ratio comparable to results of the other cohort studies mentioned above. However, the SMR for increased cardiac mortality was based on only 14 observed cardiac deaths and therefore has limited statistical power.

4.3 | Strength and limitations

The present study is the first to describe the mortality risk among German 5-year survivors of childhood cancer. Strengths of our study are the almost complete recruitment of a population cohort using a nationwide registry and the systematic follow-up of individuals. Major limitations of the CVSS study are the small cohort size and the relatively short follow-up period. Cardiac mortality increases with age. Among adult survivors of childhood cancer, 5.3% had developed severe or life-threatening coronary artery disease or had died of a myocardial infarction by the age of 45 years.[4] However, the median age of the CVSS cohort was 32 years at the end of follow-up. Thus, an even longer follow-up is necessary to assess cardiac late effects. Furthermore, patients with Hodgkin lymphoma usually receive chest-directed radiotherapy, which is associated with an elevated risk of cardiac outcomes. The exclusion of survivors with Hodgkin lymphoma in the CVSS cohort might have caused an underestimation of the cardiac mortality risk in German survivors of childhood cancer.

Cause of death information was gathered from death certificates. The validity of medical statements on death certificates is fair to moderate.[12] In addition, death certificates could be obtained for only 188 deceased individuals (47%), which indeed did not affect the results on overall mortality, but may have affected the accuracy of results for specific causes of death. Since missing death certificates were predominantly a matter of the early observational period, results for cancer mortality in particular may be underestimated in our study. Finally, the CVSS cohort did not include individuals with second primary tumors, which could also lead to an underestimation of all-cause mortality in German 5-year survivors.

4.4 | Future research and implications for clinicians

In addition to the mortality risk, more knowledge on morbidity of childhood cancer survivors would be beneficial to further plan effective prevention of late effects. Within a nested cross-sectional approach, a subsample of 951 CVSS survivors was invited to a clinical cardiovascular screening. The prevalence of cardiovascular disease and cardiovascular risk factors indicated a high premature burden of cardiovascular morbidity compared to the general population.[13] This emphasizes the need for specific cardiovascular monitoring of survivors of childhood cancer and a systematic long-term follow-up of 5-year survivors.

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CONFLICT OF INTEREST

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DATA AVAILABILITY STATEMENT

Raw data compliant with the institutional confidentiality policies are available upon request. Data requests should be sent to the corresponding author.

ETHICS STATEMENT

The CVSS study (ClinicalTrials.gov-No.: NCT02181049) was approved by the Scientific Committee of the Society for Pediatric Oncology and Hematology (GPOH). Each patient who agreed to take part in the medical examination gave written consent for the retrieval of therapy data.

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