Overall and cardiac-specific mortality following serious cardiovascular events in survivors of childhood cancer: a report from the Childhood Cancer Survivor Study (CCSS)

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Background: The direct impact of a major cardiovascular (CV) event on mortality among childhood cancer survivors is not well described. We hypothesized that mortality following a major CV event would be higher among survivors compared with siblings and that mortality would be influenced by primary cancer treatment.

Methods: The CCSS cohort has conducted longitudinal follow-up of 25,658 survivors of childhood cancer and 5,051 siblings. All-cause and CV-cause specific mortality after a first event of heart failure (HF), coronary artery disease (CAD), or stroke occurring at least 5 years after cancer diagnosis, was estimated using the Kaplan-Meier method. The relative hazards (HR) and 95% confidence intervals (CI) between survivors and siblings as well as the influence of demographic (sex, age, race/ethnicity) and cancer treatment factors were estimated via Cox regression.

Results: In total, 1780 survivors and 91 siblings experienced a serious CV event. Total deaths included 706 survivors (271 cardiac causes, 381 non-cardiac causes, 54 unknown causes) and 14 siblings. Survivors were a median age of 31.5 years (range 6.5-61.5) and 20.0 years (range 5.0-44.6) since cancer diagnosis at time of CV event. After a CV event, estimated 10- and 20-y all-cause mortality was significantly higher among survivors than siblings (Table 1). The HR for all-cause mortality was significantly higher among survivors than siblings after HF (HR 5.2, CI 2.1-13.0), CAD (HR 4.2, CI 2.0-9.0), and stroke (HR 4.6, CI 1.5-14.6). HF and stroke-specific mortality were not significantly increased among survivors versus siblings, in contrast to CAD-specific mortality (HR 3.5, CI 1.1-11.0). Among survivors, heart dose from radiotherapy (per 10 Gy) was associated with increased all-cause and cause-specific mortality after HF (HR 1.2, CI 1.0-1.3; HR 1.3, CI 1.0-1.7), all-cause mortality after CAD (HR 1.2, CI 1.0-1.3), and cause-specific mortality after stroke (HR 2.5, CI 1.2-4.9). Brain dose from radiotherapy was associated with increased all-cause mortality (HR 1.1, CI, 1.0-1.2, per 10 Gy) after stroke. Anthracycline dose was not associated with increased overall or cause-specific mortality risk after a CV event.

Conclusions: After a CV event, mortality is higher among survivors than siblings. In survivors, mortality is primarily driven by non-cardiac causes. CAD and prior radiotherapy exposure to the heart and brain also influenced mortality.

Table 1: Kaplan-Meier estimates of all-cause mortality probability after a CV event

		HF	CI	CAD	CI	Stroke	CI
10-y mortality	Survivors	30%	0.26-0.33	36%	0.31-0.40	29%	0.25-0.33
	Siblings	14%	0.00-0.25	14%	0.02-0.25	4%	0.00-0.11
20-y mortality	Survivors	48%	0.44-0.53	63%	0.56-0.69	41%	0.35-0.45
	Siblings	14%	0.00-0.25	14%	0.02-0.25	19%	0.00-0.38

Log-rank tests comparing survivor and sibling survival curves all had $P<0.001$