

Mortality and the burden of subsequent malignant neoplasms in survivors of childhood cancer beyond age 50: a report from the Childhood Cancer Survivor Study (CCSS)

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Background: The first generation of survivors of childhood cancer is now older than 50 years (y) of age. There is a paucity of information on the risk for late mortality and the evolving burden of subsequent malignant neoplasms (SMNs) in these aging survivors.

Methods: We assessed cause-specific mortality (National Death Index) and self-reported SMNs (excluding nonmelanoma skin cancers) among CCSS participants diagnosed between 1970-1999, conditional on having survived to 50y by 12/31/2017. There were 4,772 survivors alive at 50y eligible for mortality analyses. Of the 3,355 who completed a baseline CCSS questionnaire, 2,273 also completed a follow-up questionnaire at ≥ 50 y and were included in the SMN analyses. Cumulative mortality, standardized mortality ratios (SMRs), and, for SMNs, cumulative burden, standardized incidence ratios (SIRs), and relative rate (RR) with 95% confidence intervals (CIs) were calculated, compared with the general US population and by survivor subgroups. Piecewise-exponential multivariable regression was used to identify risk factors associated with the development of SMNs after 50y.

Results: Mean age at diagnosis was 14y (standard deviation 4.2y). **Mortality:** Among survivors who attained 50y of age, the subsequent 5y, 10y, and 15y incidences of all-cause mortality were 9%, 19%, and 35%, respectively, (overall SMR 3.7 [95% CI 3.4-4.1]). SMRs were highest for SMN (SMR 5.1 [95% CI 4.4-5.9]), pulmonary (SMR 4.7 [95% CI 3.3-6.5]) and cardiovascular (SMR 3.9 [95% CI 3.2-4.8]) causes of death. The highest SMR (SMR 9.2 [95% CI 7.7-10.8]) was seen in female survivors of Hodgkin lymphoma. **SMN:** By age 50y, 14% of CCSS participants reported ≥ 1 SMN. History of SMN < 50 y was independently associated with the rate of developing another SMN at ≥ 50 y (RR 1.6 [95% CI 1.1-2.3]). The most frequent SMNs ≥ 50 y were breast (41%) in females and prostate (21%) in males, followed by gastrointestinal cancers in both (14% [females], 19% [males]). The cumulative burden of SMNs in survivors treated with radiation therapy (RT) increased sharply with age and exceeded 50 per 100 survivors by 65y (SIR 3.3 95%CI 2.0-5.2). Survivors who did not receive RT had a SMN rate comparable to the general population (**Table**).

Conclusion: This sentinel population of survivors of childhood cancer is at high risk for poor outcomes as they enter older adulthood. RT exposure and history of SMN <50y are associated with increased risk for developing SMNs after 50y. The evolving burden of late morbidity attributed to SMNs may be lower for contemporary survivors projected to have less RT exposure.

At age (y)	Cumulative burden of SMN per 100 survivors (95%CI)		SIR for SMN (95%CI)	
	RT	No RT	RT	RT No
55	26.8 (23.7-29.8)	15.0 (11.9-18.5)	2.7 (2.1-3.4)	1.2 (0.7-2.0)
60	34.3 (30.0-38.5)	20.5 (15.8-26.0)	1.9 (1.3-2.7)	1.4 (0.7-2.5)
65	53.4 (42.5-66.0)	21.7 (16.4-27.4)	3.3 (2.0-5.2)	0.4 (0.0-2.3)