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Title: Temporal trends in chronic disease among survivors of childhood cancer diagnosed across three decades: A report from the Childhood Cancer Survivor Study (CCSS).

Authors: Todd M. Gibson, Sogol Mostoufi-Moab, Kayla Stratton, Dana Barnea, Eric J. Chow, Sarah S. Donaldson, Rebecca Howell, Melissa M. Hudson, Wendy M. Leisenring, Anita Mahajan, Paul C. Nathan, Kirsten K. Ness, Charles A. Sklar, Emily S. Tonorezos, Christopher B. Weldon, Elizabeth M. Wells, Yutaka Yasui, [Gregory T. Armstrong](#), Leslie L. Robison, [Gregory T. Armstrong](#), Kevin C. Oeffinger

Background: Modifications in childhood cancer treatments in recent decades have contributed to reductions in late mortality among 5-year survivors. We used the recently expanded CCSS cohort to investigate whether these changes have also reduced the incidence of chronic disease.

Methods: We evaluated the incidence of severe, disabling/life-threatening, or fatal chronic health conditions (CTCAE grades 3-5) among 5-year survivors diagnosed prior to age 21 years from 1970 through 1999. We calculated the 15-year cumulative incidence of chronic health conditions by decade of cancer diagnosis and compared risk across decades using Cox regression to estimate hazard ratios (HR) and 95% confidence intervals (CI).

Results: Among 23,601 survivors, median age 28 years (range 5-63), 21 years from diagnosis (5-43), the 15-year cumulative incidence of grade 3-5 conditions decreased from 12.7% in survivors diagnosed in the 1970s to 10.1% and 8.8% in those diagnosed in the 1980s and 1990s (per 10 years, HR 0.84 [95% CI=0.80-0.89]). The association with diagnosis decade was attenuated (HR 0.92 [0.85-1.00]) when detailed treatment data were included in the model, indicating that treatment [changes-reductions](#) mediated risk. Adjusted for sex and attained age, significant reduction in risk over time was found among survivors of acute lymphoblastic leukemia (HR=0.86 [0.76-0.98]), astrocytomas (HR=0.77 [0.64-0.92]), Hodgkin lymphoma (HR=0.75 [0.65-0.85]), non-Hodgkin lymphoma (HR=0.79 [0.63-0.99]), and Wilms tumor (HR=0.57 [0.46-0.70]). Decreases were largely driven by a reduced incidence of endocrine conditions (1970s: 4.0% v. 1990s:1.6%; HR 0.66 [0.59-0.73]) and subsequent malignant neoplasms (1970s: 2.4% v. 1990s: 1.6%; HR 0.85 [0.76-0.96]). Significant reductions were also found for gastrointestinal (HR 0.80 [0.66-0.97]) and neurological conditions (HR 0.77 [0.65-0.91]), but not cardiac or pulmonary conditions.

Conclusion: Changes in childhood cancer treatment protocols have not only extended lifespan for many survivors, but have also reduced the incidence of serious chronic morbidity in this population.

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