

Authors: Cindy Im, PhD,¹ Hasibul Hasan, PhD,¹ Emily Stene, BSN,¹ Aaron J. McDonald, PhD,² Chaya S. Moskowitz, PhD,³ Tara O. Henderson, MD,⁴ Gregory T. Armstrong, MD,² Yutaka Yasui, PhD,² Rita Nanda, MD,⁵ Kevin C. Oeffinger, MD,⁶ Joseph P. Neglia, MD,¹ Anne Blaes, MD,⁷ Lucie M. Turcotte, MD^{1*}

Affiliations:

1. Department of Pediatrics, University of Minnesota, Minneapolis, MN, 55455, USA
2. Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis, TN, 38105, USA
3. Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, NY, 10017, USA
4. Department of Pediatrics, University of Chicago, Chicago, IL, 60637, USA
5. Department of Medicine, University of Chicago, Chicago, IL 60637, USA
6. Department of Medicine, Duke University, Durham, NC, 27705, USA
7. Department of Medicine, University of Minnesota, Minneapolis, MN, 55455, USA

Breast cancer recurrence and mortality among survivors of childhood cancer: a report from the Childhood Cancer Survivor Study (CCSS)

Background: Survivors of childhood cancer are at high risk for developing subsequent breast cancer (BC) and face excess mortality despite receiving therapeutic tradeoffs intended to lessen risk for long-term toxicities. Recurrence among women with first primary BC is well-studied, but knowledge surrounding survivors' risks for and survival after BC recurrence is limited.

Methods: Analyses included female 5-year survivors participating in CCSS with pathology-ascertained breast carcinomas (in situ or invasive) diagnosed from 1981-2016 at age ≥ 18 y. BC treatment was evaluated against chronological period-specific National Comprehensive Cancer Network guidelines for primary BC. Recurrent BC cumulative incidence curves were estimated treating death as a competing risk among survivors and females with first primary BC (controls) matched one-to-one by demographics and first BC clinical characteristics including diagnosis age/year, histology and race/ethnicity. All-cause mortality rates among survivors and controls with recurrent BC were compared in multivariable Cox regression models adjusted for race/ethnicity, first BC diagnosis age and year, histology, and receipt of guideline-concordant treatment.

Results: Among the 431 childhood cancer survivors with subsequent BC (median diagnosis age: 40 years, IQR: 35-44), 68 developed recurrent BC. Compared with matched controls (N=206 pairs), survivors had similar 10-year BC recurrence risk (survivors: 14%, 95% CI: 9-20% versus controls: 12%, 95% CI: 9-18%; $P=0.52$). Among survivors with BC recurrence, Hodgkin lymphoma was the predominant primary cancer diagnosis (63%) and first subsequent BCs were largely early stage (stage 0: 8%; stage I/II: 69%) and estrogen (71%) or progesterone (80%) receptor positive. Most (84%) received first BC treatment following national guidelines for primary BC. However, nearly half (47%) underwent bilateral mastectomies (81% occurring before recurrence) and most received chest radiotherapy (86%) or anthracycline chemotherapy (69%) for either their primary childhood cancer or first subsequent BC. A total of 48 survivors died after BC recurrence, mostly related to BC (83%) or cardiovascular causes (11%). Following recurrence, the 10-year overall mortality probability was significantly higher among survivors (89%, 95% CI: 61-97%) than controls (42%, 95% CI: 18-58%; $P=0.0025$) and survivors had an adjusted 3.1-fold (95% CI: 1.24-7.94) greater risk of death.

Conclusions: Although the risk for BC recurrence among childhood cancer survivors with subsequent BC is similar to females with primary BC, this vulnerable population faces diminished treatment options and substantially greater mortality risk after recurrence. Future studies to identify early predictors of subsequent BC and BC recurrence among survivors are needed to reduce mortality risk.