Title: Treatment modifications and mortality among females with subsequent breast cancer: a report from the Childhood Cancer Survivor Study (CCSS).

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Background: Childhood cancer survivors are at high risk for developing subsequent breast cancer with higher mortality than females in the general population with primary breast cancer. Whether therapeutic tradeoffs in treating primary versus subsequent breast cancer alter survival is unknown.

Methods: Breast cancer treatment data were abstracted from medical records for female survivors from the CCSS and a multi-institutional sample of females with primary breast cancer matched one-to-one by demographics, diagnosis age/year, and breast cancer characteristics. Survivors' excess mortality risk was evaluated as hazard ratios (HRs), adjusting for receipt of historically-appropriate guideline-concordant treatment established for primary breast cancer.

Results: Subsequent breast cancers were diagnosed between 1981-2016 among 431 survivors, with a median diagnosis age of 40 years (IQR: 35-44). Most subsequent breast cancers were invasive (77%), with hormone receptor profiles similar to the general population (78% ER-positive; 26% HER2-positive). Guideline-concordant breast cancer treatment did not differ between survivors and controls (N=688; 94% versus 93%), but treatment selection differed, reflecting survivors' complex clinical history and guidelines' multiple treatment options. Anthracyclines were used in 47% of survivors (controls 66%), mastectomy in 81% of survivors (controls 60%), and radiotherapy in 18% of survivors (controls 61%). In the subgroup treated with surgery and chemotherapy (survivors 31%, controls 26%), survivors did not have greater likelihood of dose reductions or omissions, treatment delays, or hospitalization for fever and neutropenia, but they were more likely to experience hematological toxicities (21% vs. 9%, p=0.033) and other organ system-specific toxicities (36% vs. 11%, p<0.001). Over one-third (38%) of survivors died during follow-up (median follow-up 9 years, IQR 6-14) after breast cancer. Strikingly higher all-cause mortality was observed among survivors than controls (HR=3.5, 95% CI 2.2-5.6), especially after in situ disease (HR=9.9, 95% CI 2.2-44.2). Among survivors with invasive disease, breast cancer accounted for most deaths (51%), followed by other subsequent malignancies (15%) and cardiovascular diseases (15%). Other health conditions accounted for 67% of deaths following in situ disease.

Conclusions: Childhood cancer survivors with subsequent breast cancer generally receive guideline-concordant breast cancer treatment. While the treatments survivors receive differ from females with primary breast cancer, they do not experience higher rates of on-therapy treatment modifications. Despite this, they face excess mortality, primarily driven by other health conditions. Managing comorbidities is critical to enhancing long-term survival for this high-risk population.