

Title: Treatment and treatment-related toxicity *following* subsequent breast cancer: a report from the Childhood Cancer Survivor Study (CCSS).

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Background: Long-term survivors of childhood cancer are at high risk for treatment-related breast cancer and have higher mortality risk after a breast cancer diagnosis than the general population. There is no standard of care for women with treatment-related breast cancer, and treatment patterns and risk for toxicity are not known.

Methods: Female survivors in CCSS diagnosed and treated for childhood cancer between 1970-1999 who developed a subsequent breast cancer (N=344) were matched with females with sporadic breast cancer (multi-institution sampling; 1:1 matching ratio) on age at breast cancer diagnosis, breast cancer treatment decade, race/ethnicity, histology, and hormone receptor status. Conditional logistic regression evaluated univariate associations with treatments, toxicities, and synchronous breast cancer (≤ 12 months from diagnosis). Hazard ratios (HR) for metachronous disease risk (> 12 months from diagnosis) were estimated using proportional hazard models with robust variance estimation.

Results: Among survivors, the median time between the primary cancer and initial breast cancer diagnosis at median age 40 years (IQR 35-45) was 26 years (IQR 21-30). Two-thirds received chest radiation therapy (RT) and 44% were treated with anthracyclines for their childhood cancer. In the matched sample, breast cancer clinical features were similar between survivors vs. controls, but the odds of synchronous bilateral disease at diagnosis was 4.8-fold greater (95% CI 2.2-10.2) among survivors. Surgical interventions (99% vs. 98%, $P=0.22$) and treatment with chemotherapy (46% vs. 45%, $P=0.43$) were similar between groups. However, women with sporadic breast cancers were more likely to receive RT (OR 4.4, 95% CI 2.9-6.8) or anthracyclines (OR 2.4, 95% CI 1.5-3.8). Survivors were more likely to undergo mastectomy (OR 3.0, 95% CI 2.1-4.2) and experience surgical complications (OR 2.2, 95% CI 1.4-3.4), and had 1.4-fold greater odds (95% CI 1.01-1.98) of experiencing any treatment-related toxicity compared to controls. The 15-year cumulative incidence of developing a metachronous breast cancer was 20% (95% CI 13-25%) in survivors versus 9% (95% CI 5-13%) in controls ($P<0.001$). Risk of metachronous disease remained higher among survivors (HR 2.4, 95% CI 1.5-4.0) after adjusting for breast cancer treatments (mastectomy, RT, and anthracyclines).

Conclusions: Female survivors of childhood cancer who develop subsequent treatment-related breast cancer are more likely to develop synchronous and metachronous breast cancer compared to controls. Despite similar biologic characteristics, survivors are treated differently from females with sporadic breast cancer and are more likely to experience treatment-related toxicities. Further study of how treatment of subsequent breast cancers and corresponding toxicities impact prognosis and survival is needed.