

## **Breast cancer in childhood cancer survivors not treated with chest-directed radiation in the childhood cancer survivor study (CCSS).**

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**Background:** While chest radiation (CRT) is strongly associated with risk of breast cancer (BC) in childhood cancer survivors (CCS), there are BC cases among survivors not exposed to CRT. We sought to examine if BC risk is elevated in non-CRT exposed women to inform surveillance recommendations. **Methods:** Using the CCSS cohort, BC risk was assessed among 3,768 female 5-yr CCS (median follow-up 25.5 yr, range 8-39) not treated with CRT. Cumulative incidence was examined treating death as a competing risk. BC risk was assessed using standardized incidence ratios (SIR) and 95% confidence intervals (CI) using incidence from the Surveillance, Epidemiology, and End Results Program, and by calculation of absolute excess risk (AER) per  $10^4$  person-yrs (py). **Results:** 47 CCS developed BC at a median age of 38 yrs (range 22-47) and median of 24 yrs (range 9.6-34.3) from primary diagnosis. Primary cancers included: 14 leukemia; 10 bone tumor; 10 soft tissue sarcoma; 6 Ewing's sarcoma (EWS); 2 CNS; and, 1 each of neuroblastoma, Wilms, Hodgkin, NHL. Among non-CRT exposed survivors, the cumulative incidence of BC was 2.5% (CI 1.6-8.8) at 35 yrs from diagnosis and 1.6% (CI 1.0-2.3) by age 40 yrs. Non-CRT survivors had a 3.8-fold increased risk of BC (SIR=3.8, CI 2.8-5.0) with an AER of  $4.8/10^4$  py, CI 2.9-6.2. Survivors with potential Li-Fraumeni (LF)-associated malignancy (leukemia, CNS, sarcoma except EWS) had an SIR of 3.8 (CI 2.7-5.2) and AER of  $5.1/10^4$  py (CI 3.0-7.4). Leukemia and sarcoma survivors were at highest risk (SIR=3.9, CI 2.3-6.6 and AER= $3.5/10^4$  py, CI 1.0-5.9 and SIR 5.3, CI 3.6-7.8; AER= $14.2/10^4$  py, CI 7.5-20.9, respectively). Among sarcomas, EWS survivors had a significant risk (SIR=9.5, CI 4.3-21.7; AER= $29.3/10^4$  py, CI 3.2-55.3). Survivors of all other cancers (excluding EWS and LF cancer) did not have an elevated BC risk (SIR=2.2, CI 0.9-5.3; AER  $1.5/10^4$  py, CI 0.8 – 2.3). **Conclusions:** Although overall incidence is low, CCS not treated with chest-directed radiation are at increased risk for BC. The elevated BC risk is predominantly among leukemia and sarcoma survivors, potentially due to a genetic risk, and support consideration of early BC surveillance and genetic risk assessment.