

**BREAST CANCER RISK BY TREATMENT ERA:
A REPORT FROM THE CHILDHOOD CANCER SURVIVOR STUDY (CCSS)**

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Background and aims:

Breast cancer (BC) is the most common invasive subsequent malignant neoplasm in childhood cancer survivors though limited data exist on BC rates over time.

Methods:

We examined treatment exposures and BC incidence rates in ≥ 5 -year female survivors in CCSS diagnosed between 1970 and 1999, using piecewise exponential modeling for rate ratio (RR) estimation with 95% confidence intervals (CI), adjusting for age at childhood cancer diagnosis and attained age.

Results:

Among 11,550 females (median age 30.5y, range 5.6-65.9), 361 females developed 428 BCs (319 invasive; 109 *in-situ*; median age 39.5y, range 19.9-58.8). The 15-yr cumulative incidence decreased from 0.6% in the 1970s to 0.2% in the 1990s ($p_{\text{trend}}=0.004$). Survivors' treatment exposures changed greatly from 1970-74 to 1995-99: overall percentage exposed to chest-directed radiation (ChestRT) decreased from 37% to 17%; ChestRT without anthracyclines decreased from 37% to 5%; low-dose anthracyclines (1-249 mg/m²) without ChestRT increased from 3% to 43%; pelvic-RT decreased from 28% to 12%; and overall alkylator exposure stayed relatively constant, increasing from 39% to 54%. Multivariable analysis revealed anthracyclines were associated with higher BC rates: relative to neither ChestRT or anthracyclines, no ChestRT+anthracyclines 1-249 mg/m² (RR=2.12, CI:0.97-4.65); no ChestRT+anthracyclines ≥ 250 mg/m² (RR=3.45, CI:1.92-6.21); ChestRT+no anthracyclines (RR=7.84, CI:4.53-13.59); ChestRT+anthracyclines 1-249 mg/m² (RR=8.81, CI:4.52-17.18); and ChestRT+anthracyclines ≥ 250 mg/m² (RR=10.18, CI:4.95-20.95).

BC rate time trend was 21% reduction every 5 years without accounting for treatment changes (RR=0.79, CI:0.70-0.90); when the decrease in ChestRT use was accounted for this declined to 12% (RR=0.88, CI:0.77-1.00); and when the increase in anthracyclines use was additionally accounted for, it increased to 16% (RR=0.84, CI:0.73-0.97)].

Conclusions:

BC rates in more recently treated survivors are lower, due largely to the decrease in ChestRT slightly tempered by the concurrent increase in anthracycline use. Future work should focus on the BC rate decline unexplained by these changes in treatment exposures.