

Combined effect of radiotherapy and anthracyclines on risk of breast cancer risk among female childhood cancer survivors: a report from the Childhood Cancer Survivor Study (CCSS)

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Background: Breast cancer is a common late-effect for female childhood cancer survivors and chest radiotherapy is an established risk factor. Recent findings showed that treatment with anthracyclines also increases breast cancer risk. The risk from the combined effect of radiotherapy and anthracyclines is unknown.

Methods: We conducted a matched case-control study of 271 subsequent breast cancer and 1044 controls nested within the CCSS - a North-American cohort of five-year survivors of childhood cancer, diagnosed from 1970-1986 and followed-up through 2016. Detailed treatment records were abstracted to estimate radiation dose (Gy) to the breast cancer location and ovaries and calculate cumulative chemotherapy doses (mg/m²). Multivariable conditional logistic regression was used to estimate Odds ratios (OR) and 95% confidence intervals (CI).

Results: Breast cancer risk increased linearly with radiation dose to the breast (OR per 10Gy=3.9, 95%CI:2.5-6.5) and decreased with increasing ovarian dose (p<0.01). Adjusted for radiation dose, the highest quartile of dose (455+mg/m²) of anthracyclines was associated with a 3.8-fold increased risk of breast cancer (95%CI:1.8-8.2) compared to no anthracyclines. This risk increased with cumulative anthracycline dose (p-trend<0.01) and was non-significantly higher for ER+ than ER- breast cancers. For a breast dose of 10+Gy, the OR was 19.1 (95%CI:7.6-48.0) with anthracyclines versus 9.6 (95%CI:4.4-20.7) without anthracyclines, compared to 0-<1Gy breast dose and no anthracyclines (p-additive interaction=0.04).

Conclusions: The combination of anthracyclines and radiotherapy doses to the breast can markedly increase breast cancer risk compared to those who receive neither treatment. Our results can be used to inform risk management for childhood cancer patients treated in the past, as well as project potential breast cancer risk from current treatment protocols.