

RADIATION-ASSOCIATED BREAST CANCER AND HORMONE EXPOSURE: A REPORT FROM THE CHILDHOOD CANCER SURVIVOR STUDY (CCSS)

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Background: Women treated with chest radiation for childhood cancer have a high risk of subsequent breast cancer. We sought to explore relationships between hormonal factors and risk of radiation-associated breast cancer (BC).

Methods: We studied 1,108 female participants in CCSS who were diagnosed 1970-1986, treated with chest radiation, and had survived to ages ≥ 20 . Hazard ratios (HR) and 95% confidence intervals (CI) from Cox models adjusted for treatment factors (age at diagnosis, chest radiation field and delivered dose, anthracycline exposure) estimated risk.

Results: Median follow-up was 26 years (range 5-38). Among 195 women diagnosed with BC, 80% were estrogen-receptor positive (ER+), and 112 were diagnosed prior to age 40. Risk of ER+ BC and BC diagnosed before age 40 were significantly increased with 10+ years of ovarian function relative to <10 years (ER+: HR=5.32, 95% CI 1.88-15.06, $p=0.002$; <age 40: HR=3.30, 95% CI 1.50-7.25, $p=0.003$); risk was increased but to a lesser degree for BC diagnosed at ages ≥ 40 (HR=2.57, 95% CI 0.91-7.23, $p=0.074$). A similar pattern was observed for chest radiation given within one year of menarche vs. >1 year from menarche (ER+: HR=1.76, 95% CI 1.01-3.09, $p=0.047$; <age 40: HR=1.84, 95% CI 1.10-3.07, $p=0.008$; age ≥ 40 : HR=1.72, 95% CI 0.84-3.49, $p=0.137$). Among 259 postmenopausal women, 38 with BC, risk was modestly higher in women treated with estrogen+progestin therapy (E+P) compared to those untreated although this was not statistically significant (HR=1.54, 95% CI 0.70-3.40, $p=0.282$). Survivors with an age at menopause <20 years treated with E+P had a lower BC risk than premenopausal women (HR=0.47, 95% CI 0.23-0.94, $p=0.033$).

Conclusions: Endogenous hormones are key contributors to the risk of radiation-associated BC observed among childhood cancer survivors. Hormone therapy given for premature ovarian insufficiency does not appear to fully replace the function that endogenous hormones have in radiation-related BC development.