

Gonadal Hormone Exposure and Radiation-Associated Breast Cancer Risk: A Report from the Childhood Cancer Survivor Study

Chaya S. Moskowitz, Joanne F. Chou, Dana Barnea, Charles A. Sklar, Wendy M. Leisenring, Joseph P. Neglia, Lucie Turcott, Rebecca M. Howell, , Danielle Novetsky Friedman, Tara O. Henderson, Cécile M. Ronckers, Flora van Leeuwen, Malcolm C. Pike, Gregory T. Armstrong, Kevin C. Oeffinger

Background: Women treated with chest radiation for a childhood cancer have a high risk of breast cancer. We sought to explore the relationship between hormonal factors and the risk of radiation-associated breast cancer.

Methods: We studied 1,108 female participants in the Childhood Cancer Survivor Study who were diagnosed before age 21 years between 1970 and 1986, treated with chest radiation, and had survived to age 20 years or beyond. We estimated cause-specific hazard ratios (HRs) using Cox models with time-dependent covariates and adjusted for treatment factors: age at diagnosis and chest radiation field and delivered dose.

Results: With a median follow-up of 26 years, 195 women were diagnosed with breast cancer, 112 at ages <40 years, 83 at ages ≥40 years, and 102 tumors were estrogen-receptor positive (ER+). Chest radiation within one year of menarche was significantly associated with an increased risk of breast cancer diagnosed prior to age 40 (HR=1.78, 95% CI 1.07-2.97, p=0.026), but not with the risk of breast cancer diagnosed ≥40 years (HR=1.56, 95% CI 0.76-3.24, p=0.226). Results were similar when studying risk of ER+ breast cancer. In postmenopausal women (n=261, 38 with breast cancer), breast cancer risk was higher in women treated with combined estrogen-progestin replacement therapy, although this increase was not significant (HR=1.62, 95% CI 0.74-3.55, p=0.225, adjusted for treatment factors and age at menopause).

Conclusions: The risk of breast cancer diagnosed at a young age is significantly elevated when treated with chest radiation near menarche. While lack of ovarian function significantly decreases risk, the relationship between estrogen-progestin replacement therapy and breast cancer risk in postmenopausal childhood cancer survivors warrants further study.

Ovarian radiation (HR=0.33, 95% CI 0.17-0.66, p=0.001), treatment with high doses of alkylators (HR=0.44 relative to no alkylating agent exposure, 95% CI 0.23-0.85, p=0.046), and never experiencing menarche (HR=0.11, 95% CI 0.02-0.80, p=0.029) were significantly associated with reduced breast cancer risk, while older age at menarche was associated with a significantly increased risk (relative to menarche between 11-12 years, HR=

