

# ANTHRACYCLINE-ASSOCIATED RISK OF SUBSEQUENT BREAST CANCER IN FEMALE CHILDHOOD CANCER SURVIVORS: A REPORT FROM THE INTERNATIONAL CONSORTIUM FOR POOLED STUDIES ON SUBSEQUENT MALIGNANCIES

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## Background and aims

Female childhood cancer survivors have a well-established risk for developing subsequent breast cancer (SBC) associated with chest radiotherapy exposure. Growing evidence indicates that anthracycline-based chemotherapy may increase SBC risk in survivors, but the contributions of different anthracyclines and interactions with other factors are unclear. We analyzed the dose-dependent effects of individual anthracycline agents on developing SBC in an internationally pooled cohort.

## Methods

The International Consortium for Pooled Studies on Subsequent Malignancies after Childhood and Adolescent Cancer includes female 5-year survivors from six cohort studies and one case-cohort study in Europe/North-America. Cox regressions evaluated anthracycline-associated risks for SBC adjusted for chest and pelvic radiotherapy, diagnosis age, and alkylating agents. Cumulative incidences were also calculated.

## Results

After a median follow-up of 24.9 years (IQR 19.1-33.2) since primary cancer diagnosis in 17,903 women, 782 developed a first SBC. Dose-dependent increases in SBC risk were seen for doxorubicin (HR per 100 mg/m<sup>2</sup>: 1.24, 95%CI:1.18-1.31); for daunorubicin, a borderline increase in SBC risk was observed (HR per 100 mg/m<sup>2</sup> 1.13, 95%CI: 0.97-1.33). Epirubicin was also associated with SBC risk (yes vs. no HR 3.23, 95%CI 1.58-6.59). For patients treated with or without chest-exposing radiation, HRs per 100 mg/m<sup>2</sup> of doxorubicin were 1.12 (95%CI: 1.02-1.22) and 1.26 (95%CI: 1.17-1.36), respectively. Joint effects of doxorubicin and chest radiation were less than multiplicative ( $P_{multiplicative\ interaction}=0.003$ ) and compatible with additivity ( $P_{additive\ interaction}=0.93$ ). Cumulative incidences of SBC by age of 40 for women who received both doxorubicin and chest radiotherapy, chest radiotherapy only, doxorubicin only, or neither treatment were 8.7%, 7.9%, 3.1%, 0.8%, respectively.

## Conclusions

A clear dose-response relationship was observed between doxorubicin and SBC risk. Risk for women treated with both doxorubicin and chest radiotherapy was as expected if individual excess risks were summed. These results should be considered when adapting SBC surveillance guidelines.