Title: Relationship between anthracycline dose, genetic predictors of autoimmunity, and anthracycline-associated SMNs in the Childhood Cancer Survivor Study

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Background: Childhood cancer survivors may have increased risks of anthracycline-related subsequent malignant neoplasms (SMNs). The excess risk may be related to underlying immune dysregulation. We tested whether a polygenic risk score (PRS) for autoimmune disease modified the association between anthracycline dose and anthracycline-associated SMN risk.

Methods: The study sample comprised European-ancestry survivors from the Childhood Cancer Survivor Study (diagnosed 1970-1999) who received chemotherapy, but not radiotherapy, for their childhood cancer and survived >5 years after diagnosis. As a proxy for immune dysregulation, we used a PRS for rheumatoid arthritis (Autoimmune-PRS), a well-studied trait genetically correlated with other autoimmune diseases. Competing risks models estimated the relative hazard of anthracycline-related SMNs (breast cancer or sarcoma) associated with the Autoimmune-PRS and anthracycline dose (doxorubicin-equivalent dose, mg/m^2), with other SMNs and death as competing risks. Models were adjusted for 5 genetic principal components, age at diagnosis of childhood cancer, sex, sampling weights, and receipt (yes/no) of alkylators, epipodophyllotoxins, and platinum agents. We report statistical tests of interaction for anthracycline dose×Autoimmune-PRS.

Results: There were 2,260 chemotherapy-only survivors (57% receiving any anthracycline); 43 developed a potentially anthracycline- related SMN (33 breast, 10 sarcoma). SMN risk was associated with a ≥median score on the Autoimmune-PRS (“PRS-high”; HR=2.2, 95%CI=1.1-4.4) vs <median (“PRS-low”). In the PRS-stratified model, for participants with PRS-low, a 100 mg/m^2 increase in cumulative anthracycline dose was associated with a 1.6-times increased hazard of anthracycline-associated SMNs (95%CI=1.1-2.4); for participants with PRS-high, no association was detected (HR=1.1, 95%CI 0.9-1.4; p-interaction=0.1). We then assessed risk of second breast cancer for female survivors (n=1,190). Similarly, for those with PRS-low, a 100 mg/m^2 increase in anthracycline dose was associated with second breast cancer risk (HR=1.7, 95%CI=1.2-2.6); for those with PRS-high, no association was detected (HR=1.2, 95%CI=0.8-1.4; p-interaction=0.03).

Conclusion: Anthracycline-related SMN risk may be modified by polygenic predisposition to autoimmune disease.