Predicting breast cancer risk among Hodgkin lymphoma survivors using radiotherapy dose distributions: A report from the Dutch Hodgkin Lymphoma Survivor Study and the Childhood Cancer Survivor Study (CCSS)

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Aim: Build and validate a prediction model for absolute breast cancer (BC) risk among female adolescent and young adult (AYA) Hodgkin lymphoma (HL) survivors using radiation dose distributions from historic treatments.

Background: Female survivors of AYA HL treated with historic chest radiotherapy (RT), i.e., before the year 2000, have a strongly increased risk of subsequent BC. Accurate BC risk prediction is important to identify high-risk subgroups and aid treatment planning. Using radiation dose distributions may allow more accurate predictions for patients treated with modern techniques.

Methods: We modeled relative risks (RRs) for BC in a case-control sample (170 cases, 456 controls), nested in a Dutch cohort of 5-year HL survivors (treated at ages 11-41 between 1965 and 2000). Dose to each of five locations in both breasts (central portion, four quadrants) was reconstructed. The linear excess relative risk (ERR) was estimated as $RR=1+\beta\ Dose$ with location-specific radiation dose. Other predictors were BC family history, parity, age at first live birth, menopausal age, age at HL, and year of HL treatment. Absolute BC risk, accounting for competing risks, was estimated by combining RRs with age-specific BC incidence from the cohort (model M1), and was compared to a model that only incorporated mean dose to the entire breast instead of multiple breast locations (model M2). Both models were validated in the US CCSS cohort. We also estimated absolute BC risks for 129 Dutch and German women treated 2006-2021, and compared their model-based risks with predicted risks in the case-control study used to develop the models to assess a change in risk over time.

Results: The ERR/Gy was 0.16 (standard deviation [sd] 0.09). Parity (RR 0.84, sd 0.23), being menopausal (RR 0.18, sd 0.09), older age at HL (RR per category 0.61, sd 0.09), and treatment in 1981 or later (RR 0.59, sd 0.12) decreased risk, whereas family history (RR 1.60, sd 0.39), older age at menopause (RR per category 2.06, sd 0.36) and older age at first live birth (RR per category 1.19, sd 0.19) increased risk. Both models significantly underestimated 20-year risk in

the external validation in 686 HL patients (1970-1986) from CCSS (observed/expected ratios of 1.54 for M1; 1.65 for M2), and there was no difference in discriminatory performance between models (AUC 0.68 for both). When compared to historic patients, recently treated patients received lower average breast location doses, and a smaller proportion of their breast volume received a dose of at least 10 Gy, resulting in a lower radiation-related BC risk.

Conclusion: We developed models for predicting breast cancer among HL survivors using doses to multiple locations in the breast. The discriminatory ability of the location-specific dose model was not better than that of a model using mean breast dose. Applications to other cancer sites are needed to judge the importance of accommodating dose distributions for risk prediction.