

Germline Genetic Risk Factors are Independently Associated with Cardiac Dysfunction Among Childhood Cancer Survivors: A Report from the Childhood Cancer Survivor Study (CCSS) and St. Jude Lifetime Cohort Study (SJLIFE)

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Objectives: Survivors of childhood cancer are at increased risk of treatment-related cardiovascular (CV) events. While polygenic risk scores (PRS) characterizing multiple germline genetic variants are established as risk factors for CV disease in the general population, there are limited data on their role in survivors, particularly those who received chest-directed radiation.

Methods: This retrospective cohort study included participants from the CCSS and SJLIFE cohorts of 5-year survivors of childhood cancer who received radiation therapy (RT) that included heart exposure. The primary outcome was development of any grade 3+ CV event (coronary artery disease (CAD), heart failure, arrhythmia, and valve disease). An established PRS for CAD trained in multi-ancestry general populations (PGP000466) was calculated for each survivor using germline genetic data. The CAD PRS was tested for association with CV events in each cohort using Cox proportional hazards regression adjusting for principal components capturing ancestry, sex, age at cancer diagnosis, co-morbidities (hypertension, diabetes, dyslipidemia), mean heart RT dose, and cumulative lifetime anthracycline dose. Effect sizes are reported as the hazard ratio (HR) per standard deviation of the PRS as well as comparing those in the highest vs lowest quartile of the standardized PRS further stratified by mean heart dose $\geq 10\text{Gy}$ vs $< 10\text{Gy}$.

Results: The CCSS cohort included 3,386 survivors (median age at diagnosis 6 years, median of the mean heart dose = 5.4 Gy) among whom 46.9% received anthracycline-based chemotherapy (mean 85.3 mg/m²). The SJLIFE cohort included 2,148 survivors (median age at diagnosis 6 years, median of the mean heart dose = 5.1 Gy) among whom 53.4% received anthracyclines (mean 95.6 mg/m²). The 40-yr cumulative incidence of cardiac dysfunction in CCSS was 24.0% (median age 40 years) and in SJLIFE was 22.2% (median age 35 years). After adjustment, the CAD PRS was independently associated with increased risk of CV event in both cohorts (CCSS HR 1.21 [1.06, 1.39]; SJLIFE HR 1.24 [1.07, 1.45]). The combination of the PRS and mean heart RT dose was able to separate participants into risk groups: participants with a PRS in the highest quartile and receiving $\geq 10\text{Gy}$ mean heart dose had a 40-year cumulative risk of CV event of 34.9% in CCSS and 51.7% in SJLIFE, while those with a PRS in the lowest quartile and receiving $< 10\text{Gy}$ mean heart dose had a cumulative risk of 4.9% in CCSS and 11.4% in SJLIFE.

Conclusions: Germline genetic risk factors are associated with CV events in childhood cancer survivors exposed to heart irradiation, with contribution to risk independent of mean heart dose. A PRS might be incorporated into survivorship care to identify high-risk individuals who may benefit from early intervention aimed at CV risk reduction.