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Polygenic risk of anthracycline-related cardiomyopathy in childhood cancer survivors: report from Children's Oncology Group and Childhood Cancer Survivor Study

Background: Considerable inter-patient variability in anthracycline-related cardiomyopathy (aCM) risk exists among childhood cancer survivors (CCS). A polygenic risk score (PRS) that accounts for combined effects of multiple genetic variants is established in other clinical situations, but remains understudied in anthracycline-exposed CCS.

Methods: For discovery, a case-control set of 278 anthracycline-exposed non-Hispanic White (NHW) CCS (129 aCM cases; 149 controls) matched on primary cancer diagnosis, year of diagnosis and duration of follow-up was included from a Children's Oncology Group study (COG-ALTE03N1). Genomic DNA underwent whole exome sequencing (100X depth). We searched Medline and Embase databases between 2005 and 2022 to curate evidence for published single nucleotide polymorphisms (SNPs) associated with CM. We identified 1,156 SNPs on 343 genes with minor allele frequency [MAF] ≥0.05 in white populations. We constructed a weighted PRS using sequenced SNPs that were linkage disequilibrium pruned, yielding a final list of 279 independent SNPs. Conditional logistic regression models adjusted for anthracycline dose, age at diagnosis, sex, chest radiation and cardiovascular risk factors (CVRFs; diabetes, hypertension, dyslipidemia) were used to estimate PRS-aCM associations. An independent population of 475 anthracycline-exposed NHW CCS from the Childhood Cancer Survivor Study (CCSS: 96 cases; 379 matched controls) was used to replicate the PRS-aCM association. Area under the receiver operating characteristic curve (AUC) was used to evaluate the performance of a model including the PRS.

Results: Median age at primary cancer diagnosis was 7y for cases and controls in the Discovery and 11y in the Replication set. Mean anthracycline dose was higher for cases (Discovery: 312 *v* 186 mg/m^2; Replication: 333 *v* 289 mg/m^2). Cases were more likely to have received chest radiation (Discovery: 35.7% *v* 24.8%; Replication: 34.3% *v* 23.2%); and were more likely to have a CVRF (Discovery: 37.2% *v* 8.7%; Replication: 55.2% *v* 31.9%). $PRS_{continuous}$ was significantly associated with aCM (aOR = 2.09, 95%CI: 1.1-4.0, p=0.024) in the Discovery set. Compared to a model with clinical variables only, a model including the PRS had significant predictive performance: AUC_{clin}=0.72, 95% CI: 0.65-0.79. *v* $AUC_{clin+PRS}$=0.91, 95% CI: 0.87-0.95, p<0.001. In the Replication set, the top PRS quartile (top 25%) was significantly associated with aCM (aOR = 2.14, 95%CI: 1.05-4.37, p=0.036; reference: lowest PRS quartile).

Conclusions: The significant association between this comprehensively curated PRS and aCM in CCS could serve as an important tool to identify survivors at increased risk for CM and inform targeted interventions.