Risk prediction of coronary artery disease in long-term survivors of childhood cancer: findings from the St. Jude Lifetime Cohort (SJLIFE) and the Childhood Cancer Survivor Study (CCSS).

Kateryna Petrykey[1], Kendrick Li[2], Lu Xie[2], Jennifer French[1], Achal Neupane[1], Cindy Im[3], Jason N. Johnson[4], John Lucas[5], Stephanie B. Dixon[1,6], Matthew J. Ehrhardt[1,6], Bonnie Ky[7], Isaac B. Rhea[8], Carmen A. Perez[5], Raja B. Khan[4], M. Monica Gramatges[9], Pradeep Natarajan[10,11], Kevin R. Krull[12], Eric J. Chow[13], Kirsten K. Ness[1], Melissa M. Hudson[1,6], Gregory T. Armstrong[1], Yutaka Yasui[1], Daniel A. Mulrooney[1,6,8*], Yadav Sapkota[1*]

[1]Department of Epidemiology and Cancer Control, St. Jude Children's Research Hospital, Memphis (TN), USA; [2]Department of Biostatistics, St. Jude Children's Research Hospital, Memphis (TN), USA; [3]Department of Pediatrics, Division of Pediatric Epidemiology & Clinical Research, University of Minnesota, Minneapolis (MN), USA; [4]Department of Pediatric Medicine, St. Jude Children's Research Hospital, Memphis (TN), USA; [5]Department of Radiation Oncology, St. Jude Children's Research Hospital, Memphis (TN), USA; [6]Department of Oncology, St. Jude Children's Research Hospital, Memphis (TN), USA; [7]Department of Cardiovascular Medicine, University of Pennsylvania School of Medicine, Philadelphia (PA), USA; [8]Department of Medicine, University of Tennessee Health Science Center, Memphis (TN), USA; [9]Baylor College of Medicine, Houston (TX), USA; [10]Cardiovascular Disease Prevention Center, Massachusetts General Hospital, Boston (MA), USA; [11]Harvard Medical School, Boston (MA), USA; [12]Department of Psychology and Biobehavioral Sciences, St. Jude Children's Research Hospital, Memphis (TN), USA; [13]Clinical Research and Public Health Sciences Divisions, Fred Hutchinson Cancer Center, Seattle (WA), USA
**Contributed equally as senior authors

Background: Childhood cancer survivors face a 10-fold increased risk for coronary artery disease (CAD) compared to the general population. Current models to estimate CAD risk in this population rely on self-reported outcomes and exclude genetic predisposition which may limit predictive ability.

Methods: Childhood cancer survivors from the St. Jude Lifetime Cohort (SJLIFE; discovery, n=4,145; median age at diagnosis: 6.3 years) and Childhood Cancer Survivor Study (CCSS; validation, n=7,065; median age at diagnosis: 7.5 years) were evaluated for demographics, treatment exposures previously associated with CAD, cardiometabolic risk factors, and the most recent multi-ancestry polygenic risk score (PRS; PGS003725) for CAD from the general population at the time of cohort entry (5-years post-cancer diagnosis). Cox proportional hazards regression-was performed to predict the risk of CAD (CTCAE grade≥3) over the next 25 years, with predictors selected by elastic net with a hyperparameter selected by 10-fold cross-validation. Time-dependent area under the receiver operating characteristic curve (AUC) evaluated model performance. Based on the predicted risk score for CAD from the final model, survivors were categorized into low (<15th percentile), moderate (15-85th percentiles), and high (≥85th percentile) risk groups. The cumulative incidence of CAD over the next 25 years from the time of cohort entry was then estimated by group.

Results: CAD was clinically diagnosed in 71 (1.7%, SJLIFE; median age at CAD diagnosis: 34.9 years) and self-reported as diagnosed by a care provider in 181 survivors (2.6%, CCSS; median age at CAD diagnosis: 40.5 years) within 25 years of cohort entry. The AUC of a clinical model including older age at childhood cancer diagnosis, male sex, cardiomyopathy (CTCAE grade≥3), dyslipidemia (CTCAE grade≥2), and exposure to cisplatin, chest irradiation, and cranial irradiation was 0.872 (95% CI=0.829-0.916) in SJLIFE and 0.761 (95% CI=0.720-0.803) in CCSS. Incorporating the PRS into the clinical model led to a modest improvement in performance, with an AUC of 0.877 (95% CI=0.834-0.920; *P*=0.094; SJLIFE) and 0.775 (95% CI=0.735-0.815; *P*=0.0013; CCSS). With the inclusion of PRS, the 25-year cumulative incidence of CAD in the high-risk group increased from 16.8% (95% CI=12.5-20.9) to 17.7% (95% CI=13.1-22.1) in SJLIFE and from 10.8% (95% CI=8.7-12.9) to 12.7% (95% CI=10.2-15.2) in CCSS. The cumulative incidences in the moderate- and low-risk groups were similar regardless of the inclusion of the PRS.

Conclusions: We developed a prediction model using clinically assessed outcomes and genetic predictors to estimate the 25-year CAD risk in 5-year childhood cancer survivors. Validated in an independent cohort, our model showed substantially improved accuracy over current models based on self-reported data. The early onset of CAD in this population highlights the need for more precise models to enable personalized screening and interventions.