Germline Genetic Risk Factors for Cardiac Toxicity in Childhood Cancer Survivors Exposed to Heart Radiotherapy

Carson Gehl, BS; Lauren Pedersen, PhD; Gopika SenthilKumar, PhD; Gordon Watt, PhD; Monica Gramatges, MD PhD; Yadav Sapkota, PhD; Smita Bhatia, MD, MPH; Eric Chow, MD MPH; Rebecca Howell, PhD; Wendy Leisenring, ScD; Lindsay Morton, PhD; Daniel Mulrooney, MD, MS; Kevin Oeffinger, MD; Yutaka Yasui, PhD; Greg Armstrong, MD, MSCE; Carmen Bergom, MD PhD*; Sarah Kerns, PhD MPH*
*equal contribution as last authors

Introduction:
Survivors of childhood cancer who received chest radiation as a part of their treatment experience high rates of cardiovascular events at earlier ages relative to the general population. Genetic biomarkers may help identify patients at high risk of late cardiac toxicity and allow for tailored treatment plans and survivorship care.

Methods:
This was a retrospective observational cohort study that included patients enrolled in the Childhood Cancer Survivor Study. The primary outcome was time to development of any self-reported grade 3+ heart toxicity (coronary artery disease, arrhythmia, valve disease, heart failure). A genome-wide association study (GWAS) tested single nucleotide variants (SNVs) using a Cox proportional hazards model adjusted for sex, age at diagnosis, and principal components (PCs) capturing ancestry. SNVs showing genome-wide significance were analyzed separately using Cox models to identify interactions with radiation exposure. All analyses were performed in R using the gwasurvivr and survival packages.

Results:
5,074 survivors were included; 49.5% were female, 94.2% were White, 58.7% had heart exposure to radiation, 33.9% received cardiotoxic chemotherapy, and average age at diagnosis was 7.6yrs. At a median age of 40 and 26.5 years since diagnosis, 322 patients (6.3%) experienced a grade 3+ heart toxicity. GWAS controlling for age at diagnosis, sex, and the first three PCs revealed two genomic regions significantly associated with grade 3+ heart toxicity. The top two SNVs from these regions (chr12:92449688:C:A; chr14:84559356:G:T) were further analyzed using Cox models controlling for three PCs, sex, age at diagnosis, radiation dose to the heart, and cardiotoxic chemotherapy. Patients carrying these SNVs were at increased risk of heart toxicity when exposed to heart radiation, and this effect was exacerbated by higher doses (>= 20Gy) to a large volume (>80%) of the heart (Table 1).

Conclusions:
We found two SNVs associated with the development of cardiovascular events, and the effect of each was modified by the dose and volume of heart irradiated. Such biomarkers, if validated, may be incorporated into treatment planning, particularly in pediatric cancers where survivors are at increased risk of treatment-related morbidity and mortality throughout the rest of their life.

Table 1

SNV	Minor Allele Frequency (%)	Overall p-value	HR (0 Gy to heart)	HR (<20 Gy to heart)	HR (>= 20 Gy to < 80% of heart)	HR (>= 20 Gy to > 80% of heart)
Chr12:92449688:C:A	1.98	1.18×10^{-8}	1.79 [0.63, 7.49]	3.67 [1.80, 7.49]	2.09 [1.11, 3.92]	5.73 [1.74, 18.8]
Chr14:84559356:G:T	5.83	2.61×10^{-8}	1.50 [0.79, 2.83]	1.93 [1.16, 3.19]	2.09 [1.34, 3.26]	6.05 [2.17, 16.9]