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Risk Prediction of Anthracycline-related Cardiomyopathy (AC) in Childhood Cancer Survivors (CCS): A COG-ALTE03N1 and CCSS Report

Background: CCS treated with anthracyclines are at risk for AC. While risk increases with dose, significant inter-patient variability in AC risk suggests a role for genetic predisposition in moderating the risk and provides an opportunity to identify patients at high or low risk.

Methods: We curated candidate single nucleotide polymorphisms (SNPs) associated with AC from previous publications and used these to develop a risk prediction model, drawing upon COG-ALTE03N1 (CCS with AC [155 cases] matched with CCS without AC [256 controls]). Final Model (clinical + genetic) was obtained using backward variable selection guided by effect on area under receiver operating characteristic curve (AUC). Bootstrapping corrected for optimism of AUC. Regression coefficient estimates from Final Model were used to calculate risk scores, which were used to create risk groups. We validated the model in an independent sample from CCSS (229 cases; 5,360 controls).

Results: Previously-published SNPs (rs1786814 [*CELF4*], rs11864374 [*ABCC1*], rs1800566 [*NQO1*], rs4673 [*CYBA*], rs2232228 [*HAS3*]) were verified in COG-ALTE03N1 and were included, along with GxE interaction of rs1786814, rs4673, rs2232228 in a Final Model containing age at cancer, sex, race, cumulative anthracyclines (mg/m^2), chest radiation, diabetes, hypertension, dyslipidemia. This yielded an optimism-corrected AUC = 0.8138, which was superior (*P*=0.0002) to the Clinical Model (corrected AUC=0.7677). The sensitivity/specificity of the prediction model were 73.7%/ 81.3%. The prediction model was successfully replicated in CCSS (Final Model performed significantly better than the Clinical Model, *P*=0.02).

Conclusion: It is possible to identify CCS at high or low risk for AC on the basis of genetic and clinical information. This information can be used to inform interventions in CCS.

Table - Characteristics	COG-ALTE03N1 Cases (n=155)	COG-ALTE03N1 Controls (n=256)	CCSS Cases (n=229)	CCSS Controls (n=5360)
Median age at cancer dx	7.2 (0-21)	7.6 (0-2)	13 (0-20)	6 (0-20)
Cumulative anthracyclines (mg/m^2) Median (range)	340 (0-760)	175 (0-825)	230 (0-918)	0 (0-1120)
Radiation to heart (n, %)	35 (23)	33 (13)	115 (50)	1248 (23)