

Cardiovascular Risk Factor Severity and Adverse Cardiovascular Events: a report from the Childhood Cancer Survivor Study (CCSS)

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Background: Among survivors of childhood cancer, more severe grades of CVRFs are associated with increased risk for adverse cardiovascular events (ACE). The impact of low severity CVRFs has not been defined.

Methods: Among 25,723 long-term survivors of childhood cancer, CVRF severity was graded using longitudinal self-report: Grade 1 conditions are reported but not on medications; Grade 2 are prescribed medications. Cumulative incidence of CVRFs were estimated into the 6th decade of life with death and Grade 2 CVRFs a competing risk event for Grade 1 CVRFs. Starting at 1st report of a CVRF, multivariable piecewise-exponential models were used to estimate relative rates (RR) of heart failure (HF), myocardial infarction (MI), valvular disease (VD), arrhythmia, and cardiac death relative to survivors without hypertension (HTN), diabetes (DM), and hyperlipidemia (HLD), all as time-dependent covariates.

Results: The median age of survivors was 35y (range 9-70) and 26y (range 7-52) from cancer diagnosis. Cumulative incidence by age 55 of Grade 1 HTN, DM, and HLD were 7.8% (CI 7.1-8.5%), 4.3% (CI 3.8-4.9%), and 10.8% (CI 9.9-11.6%), respectively. The cumulative incidences of Grade 2 HTN, DM, and HLD were 37.9% (CI 36.4-39.3%), 14.0% (13.0-15.0%), 31.3% (29.9-32.7%), respectively. Grade 2 CVRFs were significantly associated with an increased RR for nearly all ACE (table). Grade 1 CVRFs were also significantly associated for most ACE; often with a similar magnitude as Grade 2 CVRFs. Grade 1 vs no HTN was associated with a 2 to 5-fold significantly increased RR of HF, MI, VD, arrhythmia, and cardiac death. Grade 1 vs no DM was associated with an increased RR of HF (1.9, CI 1.1-3.4). Grade 1 vs no HLD was associated with an increased RR of MI (2.9, 1.9-4.2) and arrhythmia 2.1 (1.2-3.5).

Conclusions: Grade 1 CVRFs are associated with increased risk for ACE. These data suggest a role for more aggressive treatment of Grade 1 CVRFs among survivors.

Table: Relative rates of ACE among survivors by CVRF severity

Individual models for each CVRF vs no respective CVRF (ref)	HF	MI	VD	Arrhythmia	Cardiac death
	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
HTN Grade 1	2.9 (1.9-4.4)	3.6 (2.4-5.3)	4.7 (3.0-7.5)	2.8 (1.6-4.8)	1.9 (1.1-3.3)
HTN Grade 2	7.2 (6.1-8.6)*	7.1 (5.9-8.5)*	4.7 (3.7-6.1)	5.3 (4.2-6.7)	1.5 (1.1-2.0)
DM Grade 1	1.9 (1.1-3.4)	1.5 (0.7-3.0)	0.8 (0.3-2.5)	1.5 (0.6-3.7)	0.6 (0.1-2.2)
DM Grade 2	2.5 (1.9-3.2)	2.7 (2.2-3.5)	2.2 (1.6-3.1)	2.3 (1.6-3.2)	1.8 (1.3-2.6)
HLD Grade 1	1.5 (0.95-2.4)	2.9 (1.9-4.2)	1.5 (0.8-2.8)	2.1 (1.2-3.5)	1.2 (0.6-2.2)
HLD Grade 2	3.8 (3.2-4.7)*	6.5 (5.4-7.8)*	3.8 (2.9-4.8)*	3.1 (2.4-4.0)	1.1 (0.8-1.4)

Models adjusted for sex, race, current age, age at diagnosis, current smoking, obesity, sedentary lifestyle, anthracycline and heart radiation dose. Models fitted separately for each ACE. No respective CVRF as referent group. *Grade 2 vs Grade 1 condition above, $p < 0.05$