

## Modifiable risk factors for late mortality among five-year survivors of childhood cancer: a report from the Childhood Cancer Survivor Study

**Background:** The impact of modifiable lifestyle and cardiovascular risk factors (CVRFs) on risk for late mortality in adult survivors of childhood cancer is not well established.

**Methods:** All-cause and health-related late (>5 years from cancer diagnosis) mortality (HRM; excludes death from primary cancer and external causes) were evaluated in five-year survivors diagnosed <21 years of age using the National Death Index through 2017. Modifiable lifestyle (smoking status, alcohol use, physical activity, body mass index [BMI]; combined to create a score [0-4] and categorized as unhealthy [0-2], moderate [2.5 or 3], healthy [3.5 or 4]) and CVRFs (hypertension [HTN], diabetes [DM], dyslipidemia) were assessed as time-varying covariates. Standardized mortality ratios (SMRs) and absolute excess risk of death per 1000 person-years (AER) with 95% confidence intervals (CIs) were estimated. Multivariable models estimated the relative risk (RR) of death adjusted for demographic and socioeconomic variables.

**Results:** Among 20,051 adult survivors (median age 40.0 years, range 18.7 – 67.7), 19% reported  $\geq 1$  CVRF (13% HTN, 9% dyslipidemia, 5% DM) and few reported a healthy lifestyle (29% healthy, 40% moderate, 31% unhealthy). There were 1476 deaths due to health-related causes. While all survivors experienced an increased risk of HRM compared to the US population, risk was lower among those with a healthy vs. unhealthy lifestyle (SMR 3.5, 95% CI 3.1-3.9 vs. 6.2, 5.7-6.7) and very high among underweight survivors (11.1, 9.3-13.3) and those with both HTN and DM (13.0, 9.2-18.0).

Stratified by lifestyle score, the excess risk of HRM was lowest in those with a healthy lifestyle across survival time (Table). Similar trends were seen when stratified by 0, 1 and 2 CVRFs.

In multivariable models, compared to survivors with no CVRFs and healthy lifestyle, no CVRFs and unhealthy lifestyle was associated with a 50% increased risk of HRM (RR 1.5, 95% CI 1.2-1.8) and unhealthy lifestyle plus HTN a 2-fold increased risk of HRM (2.2, 1.6-2.8). Regardless of lifestyle group,  $\geq 2$  CVRF increased risk for HRM at least 2-fold (p-values <0.001).

**Conclusions:** A reduction in excess deaths is observed among adult survivors of childhood cancer with a healthy lifestyle and no CVRFs as they age. Interventions that target improved lifestyle choices and prevention or aggressive treatment of modifiable CVRFs may reduce risk for late mortality.

AER (95% CI) of health-related death

	Survival Time (yrs)			
	6-14	15-24	25-34	$\geq 35$
Lifestyle				
Healthy	0.6 (0.0-1.9)	1.4 (1.0-1.9)	3.2 (2.5-4.0)	6.5 (4.5-9.0)
Moderate	2.0	2.3	4.9	12.1

	(0.8-3.7)	(1.8-2.8)	(4.2-5.7)	(10.1-14.4)
Unhealthy	1.6 (0.3-3.9)	2.9 (2.3-3.7)	6.4 (5.5-7.4)	15.7 (13.3-18.3)
<b>CVRF</b>				
0	1.3 (0.7-2.2)	1.9 (1.6-2.2)	4.1 (3.6-4.6)	9.7 (8.3-11.3)
1	0.7 (0.0-5.6)	3.8 (2.6-5.2)	7.2 (5.8-8.8)	15.4 (12.2-19.2)
≥2	8.8 (0.0-50.5)	5.1 (2.6-8.6)	10.8 (8.2-13.9)	20.5 (15.8-26.0)

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