

Exercise and risk of major cardiovascular events in adult survivors of childhood Hodgkin lymphoma: A report from the childhood cancer survivor study (CCSS).

Lee Jones, Qi Liu, Gregory T. Armstrong, Kirsten K. Ness, Yutaka Yasui, Katie Devine, Emily Tonorezos, Luisa Soares-Miranda, Charles A. Sklar, Pamela S. Douglas, Leslie L. Robison, Kevin C. Oeffinger

Background: Adult survivors of childhood Hodgkin's lymphoma are at elevated risk of treatment-related major cardiovascular (CV) events. We investigated whether exercise modified this association in HL survivors participating in the CCSS. **Methods:** HL survivors (n=1,187), median age 31.2 (range 18.0-48.9 years) and free of CV disease at baseline completed a questionnaire evaluating vigorous-intensity exercise behavior over the past week. Subsequent CV events were collected in follow-up questionnaires and graded according to the CTCAE (v. 4.03). The primary end point was incidence of any major (grade 3 to 5) CV event. Secondary end points were incidence of grade 3 to 5 CV events [coronary artery disease (CAD), heart failure, valve replacement, arrhythmia, and CV death]. Poisson regression analyses were used to estimate the association between exercise exposure [metabolic equivalent task-hrs wk⁻¹(MET)] and risk of major CV events after adjustment for important clinical covariates (age, smoking, education, CV risk factors, and baseline grade 3-4 health conditions) and cancer treatment (anthracycline exposure and chest radiation). **Results:** A total of 135 major CV events were reported after median follow-up of 11.9 (range 1.7 - 14.3) years. In multivariable-adjusted analyses, the incidence of any CV event declined across increasing MET categories ($P_{\text{trend}}=0.002$). Compared with survivors reporting 0 METs, the adjusted RR for any CV event was 0.87 (95% CI, 0.56 to 1.34) for 3 to 6 METs, 0.45 (95% CI, 0.26 to 0.80) for 9 to 12 METs, and 0.47 (95% CI, 0.23 to 0.95) for 15 to 21 METs. A similar pattern was observed for the incidence of CAD (adjusted $P_{\text{trend}}=0.005$). The cumulative incidence of any CV event was 12.2% at 10 years for survivors reporting 0 METs, compared to 5.2% for those reporting ≥ 9 METs. Adherence to national exercise guidelines (i.e., ≥ 9 METs) was associated with a 51% reduction in the risk of any CV event, in comparison with not meeting the guidelines ($p=0.002$). **Conclusions:** Vigorous exercise reduces the incidence of CV events in a dose-dependent manner beyond CV risk profile and treatment exposure in adult survivors of childhood HL.