Study title: COMPARISON OF EXCESS RISK OF LATE MORTALITY AND SUBSEQUENT MALIGNANT NEOPLASMS (SMNs) AFTER HODGKIN LYMPHOMA (HL): A CHILDHOOD CANCER SURVIVOR STUDY (CCSS) AND DUTCH HODGKIN LYMPHOMA SURVIVOR STUDY COLLABORATION

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Background-Aim: HL survivors are at increased risk for late cancer treatment associated morbidity and mortality. Few studies have compared outcomes across countries with differing treatment pattern and population health, and none, to our knowledge, have included treatment exposures. We compared rates of late mortality and SMNs among survivors of HL in the United States and Netherlands, including associations with HL treatment exposures.

Methods: This retrospective analysis used the CCSS and registry-based Dutch Late-Effects HL Study. We included 5-year survivors of HL diagnosed at ages 15-20 years between 1970-1999. Age, diagnosis year, and sex were used to create inverse probability weighting with robust standard error estimates for the CCSS cohort to account for non-participation among potentially eligible cases. Crude, standardized rates of mortality and SMNs as well as absolute excess risks (AER) were estimated relative to the age- and sex-matched general population in each country. Adjusted rate ratios (ARR) for cohort-specific standardized mortality and SMNs were estimated using multivariable piecewise-exponential models adjusting for attained age, year of diagnosis, and sex.

Results: 2,116 eligible CCSS (1,488 participants) and 720 Dutch survivors were included, with respective median (IQR) follow-up times of 26.9 (20.8-35.1) and 25.3 (19.4-29.7) years from HL diagnosis. Crude all-cause late mortality rates were comparable between cohorts (death per 1000 person-years [95% confidence interval (95%CI)]: CCSS=15.1 [95%CI:14.1-16.1]; Dutch=13.2 [95%CI:11.5-15.1]). The standardized all-cause mortality ratio was lower among CCSS (6.1 [95%CI:5.7-6.5]) compared with Dutch survivors (12.1 [95%CI:10.5-13.8]). AER of death per 1000 person-years was comparable (CCSS=12.6 [95%CI:11.6-13.7]; Dutch=12.1 [95%CI:10.4-14.0]). The crude incidence rate of SMNs was comparable between cohorts (rate per 10,000 person-years: CCSS=111.8 [95%CI:103.2-120.9]; Dutch=122.6 [95%CI:104.8-142.6]), while the standardized SMN incidence ratio was lower among CCSS (5.9 [95%CI:5.4-6.4]) compared with Dutch survivors (8.6 [95%CI:7.3-9.9]). AER of SMN was comparable between cohorts (rate per 10,000 person-years: CCSS=92.8 [95%CI:84.1-101.9]; Dutch=108.3 [95%CI:90.4-128.3]). In multivariable analyses, CCSS (vs. Dutch) survivors had a 25% lower standardized rate of SMNs (ARR=0.74 [95%CI:0.61-0.89]) and a 50% lower standardized rate of mortality (ARR=0.49 [95%CI:0.41-0.58]). After adjusting for treatment exposures, ARRs decreased for both SMN (ARR=0.66 [95%CI:0.55-0.80]) and mortality (ARR=0.40 [95%CI:0.33-0.48]) in CCSS (vs. Dutch) survivors.

Conclusion: Despite comparable crude rates, standardized rates for mortality and SMNs differed between cohorts, reflecting variation in background population risk. These findings suggest that excess risk of death and SMNs due to HL treatment may be similar for HL survivors despite differences in country-level population health, supporting ongoing global initiatives to improve survivor health and lifespan.