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**Comparing late mortality risks among childhood cancer survivors: A report from the Childhood Cancer Survivor Study and British Childhood Cancer Survivor Study**

## Background

It is unclear whether late-effect risks are comparable across international settings. We compared late mortality risks in the Childhood Cancer Survivor Study (CCSS) and British Childhood Cancer Survivor Study (BCCSS).

## Methods

46,474 5-year survivors of childhood cancer diagnosed from 1970-1999 and <15 years age were included: 28,248 from the CCSS and 18,226 from the BCCSS. Late mortality (death  $\geq$ 5 years from diagnosis) was assessed by linking to national vital statistics records. Adjusted ratios of the standardized mortality ratio (RSMR) and cumulative mortality probabilities were used to compare risks between cohorts. Treatment exposures were not available for the BCCSS, precluding comparison.

## Results

The cumulative all-cause mortality at 10 years from diagnosis was significantly lower in the CCSS (4.8%;95%CI:4.6%-5.0%) compared to the BCCSS (6.9%;95%CI:6.5%-7.2%); this was due to a lower probability of death from recurrence/progression of the primary cancer (CCSS=3.3% vs. BCCSS=5.8%), with significant differences observed in survivors of leukemia (7.9% vs 4.0%), Hodgkin lymphoma (2.5% vs 1.3%), CNS tumors (6.4% vs 4.4%), and sarcoma (6.5% vs 4.0%). However, with increasing time from diagnosis, risks became more similar. The CCSS ultimately had a greater

cumulative mortality at 40 years from diagnosis, attributable to a 2-fold higher mortality from subsequent neoplasms (SNs) (RSMR:2.0;95%CI:1.8-2.3), cardiac (RSMR:1.7;95%CI:1.4-2.3) and pulmonary (RSMR:1.9;95%CI:1.4-2.5) causes, and other health-related deaths (RSMR:2.4;95%CI:2.1-2.9). When assessed by follow-up interval, the differences between the CCSS and BCCSS increased significantly for deaths due to SNs, cardiac and pulmonary causes, and other health-related deaths as time increased. Among those diagnosed more recently, the gap in all-cause mortality widened, with CCSS survivors diagnosed 1990-1999 experiencing approximately half the excess (RSMR:0.5;95%CI:0.5-0.6) observed in the BCCSS; this widening was driven by declines in the RSMR for most non-recurrence/progression causes of death.

## Conclusions

Our findings suggest that North American survivors may have received more intensive regimens during this time period to achieve sustainable remission and cure. However, the cost of this approach was a higher risk of death from late-effects. Which approach confers a net survival advantage will depend critically on the magnitude of the excess risk of late-effect deaths as the cohorts age.