Mortality among 5-year survivors of childhood cancer: results over five decades of follow-up in the Childhood Cancer Survivor Study

Background: Adult survivors of childhood cancer are at greater risk for late mortality compared to the general population due to cancer and its treatment. Risk factors, patterns and specific causes of late mortality across the lifespan are not well established.

Methods: All-cause, cause-specific, and health-related late mortality (HRM; excludes death from primary cancer and external causes) >5 years from diagnosis were evaluated in survivors diagnosed <21 years of age between 1970-1999. Cause of death was based on ICD codes from the National Death Index through December 2017. Cumulative mortality, mortality rates and standardized mortality ratios (SMRs) with 95% confidence intervals (CIs) were estimated, overall and in 5- and 10-year survival periods.

Results: Among 34,230 survivors (median time from diagnosis 29.1 years, range 5.0 - 48.0) the 40-year cumulative mortality was 23.3% (95% CI 22.7 – 24.0). Of 5,916 deaths, 3,061 (51.2%) were attributable to health-related causes including subsequent neoplasm (n=1,458), cardiac (n=504), and pulmonary causes (n=238). All-cause mortality by time from diagnosis demonstrated a U-shaped distribution: 10.1 deaths/1000 person-years at 5-9 years, largely due to recurrence of the primary cancer, decreasing to 4.1 at 15-19 years before increasing to 18.5 at 40-48 years, attributable to an increasing mortality rate from HRM (2.3 at 5-9 years; 17.0 at 40-48 years).

For the interval 5-9 years from diagnosis, survivors had an 18.1-fold (95% CI 17.3-18.9) higher risk of death from any cause, and a 13.1-fold (11.9-13.4) higher risk for HRM when compared to the general population. Although the SMRs declined with duration of follow-up, survivors had a 4-fold higher risk of death overall, attributable to a more than 4-fold increased risk of HRM. HRM 40-48 years from diagnosis was largely attributable to an increased risk of death due to subsequent neoplasm (SMR 6.0, 95% CI 4.9-7.2), cardiac (3.9, 2.9-5.0) and pulmonary (5.6, 3.6-8.4) causes.

Cause-specific mortality remained markedly elevated at 40-48 years from diagnosis: CNS malignancy (SMR 11.7, 95% CI 5.4-22.3), benign meningioma (171.3, 34.4-500.5), valvular heart disease (39.8, 21.2-68.1), cardiomyopathy (10.4, 4.5-20.5), stroke (7.9, 4.6-12.6), and renal failure (5.6, 1.8-13.2). HRM was significantly higher among the youngest group of survivors (0-4 years at diagnosis), non-Hispanic blacks and those who received radiation to the brain, chest or total body, or who were exposed to anthracycline, alkylating or platinum chemotherapy.

Conclusions: After five decades, aging survivors consistently remain at higher risk of all-cause mortality compared to the general, aging population, primarily due to a persistent 4-fold increased risk of HRM. Continued late-effects surveillance and reduction of therapies associated with long-term morbidity and increased mortality is essential.

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