

Multiple subsequent neoplasms in the childhood cancer survivor study (CCSS) cohort

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Background: Childhood cancer survivors demonstrate an increased incidence of subsequent neoplasms (SNs). Those surviving the first SN remain at risk to develop multiple SNs. As SNs are a common cause of late-morbidity and mortality, characterization of risk for multiple SNs is needed.

Methods: Analysis included 14,358 ≥ 5 yr survivors of childhood cancer diagnosed 1970-86 (median age at follow-up 30.9 yrs, range 5.6-56.3; median follow-up 18.0 yrs, range 0-32.6). Among survivors with a subsequent neoplasm (SN1), the 15-yr cumulative incidence of second subsequent neoplasm (SN2) or subsequent malignant neoplasm (SMN) other than non-melanoma skin cancer (NMSC) was calculated with death as a competing risk. Hazard ratios (HR) were calculated from multivariable regression models that included age at diagnosis, age at SN1, treatment era, radiation therapy (RT) exposure, and family history of cancer.

Results: 1383 (9.6%) survivors developed SN1, of whom 384 (27.8%) developed an SN2. Of those with SN2, 153 (39.8%) developed >2 SNs. Cumulative incidence of SN2 was 38.8% (95% CI 35.1-42.5) 15 yrs after SN1. Cumulative incidence of SN2 was highest in those with a primary diagnosis of Hodgkin lymphoma (50.3%, 44.1-56.6), CNS malignancy (44.5%, 33.3-55.6), and osteosarcoma (40.9%, 21.5-60.4). Among those experiencing an SN1, multivariable analysis identified older age at SN1 (HR 2.21, $p < 0.0001$) and RT for the initial cancer (HR 1.83, $p = 0.003$) as independent risk factors for SN2. Cumulative incidence of SN2 among RT-exposed survivors was 41.3% (95% CI 37.2-45.4). For those RT-exposed with an SN1 of NMSC, the cumulative incidence of SMN (excluding NMSC) was 19.4% (95% CI 12.1-26.5). In SN1 survivors not exposed to RT for their initial cancer, the 15-yr cumulative incidence of SMN (excluding NMSC) was 18.6% (95% CI 10.6-26.5).

Conclusion: Multiple SNs are common among aging survivors of childhood cancer who experience and survive an SN1. Exposure to RT and increased age at SN1 place survivors at significantly higher risk. SN1 of NMSC identifies a population at high risk for invasive SMN. Multiple SNs among non-RT exposed patients reflect a population of interest for genetic susceptibility to neoplasia.

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