

Sarcomas as a Subsequent Malignancy in Survivors of Pediatric Malignancy: The Childhood Cancer Survivor Study

T. Henderson, J. Whitton, S. Hammond, M. Stovall, A. Meadows, A. Mertens, J. Neglia, L. Robison, F. Cook, L. Diller

Author affiliations: Dana-Farber Cancer Institute, Boston, MA; Fred Hutchinson Cancer Research Center, Seattle, MA; Ohio State University of Medicine, Columbus, OH; M.D. Anderson Cancer Center, Houston, TX; Children's Hospital of Philadelphia, Philadelphia, PA; University of Minnesota, Minneapolis, MN; Harvard University, Boston, MA

Background: Subsequent sarcomas (SS) in childhood cancer survivors have not been well-studied, with prior studies limited to smaller series of bone tumors.

Methods: The Childhood Cancer Survivor Study (CCSS) is a multi-institutional cohort of 14,352 five-year survivors of childhood cancers, including leukemia, lymphoma, central nervous system tumors, neuroblastoma, kidney tumors, bone tumors and soft tissue sarcomas (STS), treated between 1970 and 1986. SS were ascertained through self-administered questionnaires and confirmed with pathology reports. The risk factors for developing second sarcomas were assessed through univariate analysis as well as multivariate Cox regression analysis.

Results: We describe a series of 91 SS [including osteosarcoma (n=27), rhabdomyosarcoma (n=3), Ewing's/PNET (n=5), non-rhabdo STS (n=36), malignant peripheral nerve sheath tumor (n=13), other (n=7)] from 28,301 person-years (py) of observation after primary cancer diagnosis (incidence rate = 3.2 cases per 10,000 py). Risk of SS was statistically associated with primary diagnosis ($p < 0.001$), history of other subsequent malignant neoplasm (SMN; $p = 0.009$), anthracycline exposure ($p = 0.009$), alkylator exposure ($p = 0.002$) and radiation therapy ($p < 0.001$) in univariate analysis. In a multivariate model, risk factors for the development of SS included anthracycline exposure and previous radiation therapy with respective rate ratios (RR) of 2.54 ($p = 0.008$) and 2.58 ($p = 0.005$), with these risks further influenced by primary diagnosis ($p < 0.001$). Subgroup analysis of Hodgkin's disease survivors revealed that alkylating agent exposure was associated with the development of SS with a RR of 4.263 ($p = 0.06$). Subgroup analysis of STS survivors revealed that younger age at primary cancer diagnosis was associated with an increased risk of developing SS ($p = 0.01$).

Conclusions: Survivors of childhood malignancy are at increased risk of developing a subsequent sarcoma. Identified risk factors include exposure to anthracyclines, alkylating agents and radiation therapy, within diagnosis-specific subgroups. Further study is planned to investigate standardized incidence ratios and absolute excess risk of SS in survivors, dose-response relationships as well as family history of cancer.