

# Lung cancer as a subsequent neoplasm: A report from the Childhood Cancer Survivor Study (CCSS).

Authors:

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**Background:** Lung cancer has been reported as a subsequent neoplasm (SN) in childhood cancer survivors. We aimed to assess the prevalence of and risk factors for lung cancer in the CCSS.

**Methods:** Among 25,654 five-year survivors participating in the CCSS, lung cancer was self-reported and then confirmed by pathologic record review. Cancer treatment exposures were evaluated including chemotherapy and chest radiation by field size (none, small, large) and in a dose group (0-10 Gy, 10-30 Gy, 30-40 Gy, and > 40 Gy). Standardized incidence ratios (SIR) were calculated using rates from the Surveillance, Epidemiology, and End Results program. Hazard ratios (HR) were estimated for demographic and treatment variables using Cox proportional-hazards models.

**Results:** Forty-two survivors developed subsequent malignant lung cancer (SIR 4.0, 95% CI 2.9-5.4), including 25 carcinomas, 7 mesotheliomas and 10 others. Two additional benign neoplasms were also identified. The cumulative incidence of lung SNs was 0.18% at 30 years (95% CI 0.10-0.25). Median time from primary diagnosis was 28 years (range 11-46); median age at diagnosis was 45 years of age (range 15-65). A multivariable model, including all covariates with a p-value < 0.2 in univariate analysis, showed significant associations between lung cancer and older age at diagnosis (HR 10.5, 95% CI 1.4-76.4, for 15-21 years vs. 0-4 years), as well as with primary diagnoses (relative to leukemia, HR 8.7, 95% CI 1.1-66.0, for Hodgkin lymphoma; HR 20.7, 95% CI 1.3-331.0 for neuroblastoma; and HR 21.4, 95% CI 2.3-202.7, for bone cancer). In a treatment model, maximum chest radiation dose (HR 4.1, 95% CI 1.4-11.7, for 30-40 Gy; and HR 8.1, 95% CI 3.0-22.2, for > 40 Gy, relative to 0-10Gy), but not sex, smoking status, or chemotherapy exposures, was associated with lung cancer. Notably, six survivors who developed lung cancer received no radiation and of these, five had a primary bone cancer. At the end of follow-up, 65.9% of survivors with lung cancer were deceased vs. 14.1% of survivors without lung cancer (p< 0.001).

**Conclusions:** Survivors of childhood cancer are at increased risk for developing lung cancer associated with exposure to high doses of chest radiotherapy. To our knowledge, this is the first study to describe associations

with neuroblastoma and bone cancer. Future studies to understand additional treatment-related risk factors beyond chest radiotherapy dose are needed.