

Second primary thyroid cancer after a first childhood malignancy: A report from the Childhood Cancer Survivor Study

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Survivors of a childhood malignancy have a greater than 10-fold increased risk of developing a second primary thyroid cancer. While radiation treatment is the single most dominant risk factor, the magnitude of risk over the range of therapeutic doses has not been well established. Studies with wide dose ranges and large sample sizes are required to describe the shape of the dose-response curve, specifically for risks above 10 Gy, where the effect of cell killing may become important. We conducted the largest study of second thyroid cancer to date using the Childhood Cancer Survivor Study (CCSS). The CCSS cohort is comprised of over 14,000 five-year survivors of a childhood leukemia, lymphoma, central nervous system tumor, soft tissue and bone sarcoma, neuroblastoma, and kidney cancer diagnosed between January 1, 1970 and December 31, 1986. A nested case-control study was conducted that included 69 cases with a pathologically confirmed subsequent thyroid cancer and 277 controls without thyroid cancer. Controls were matched to cases on age at diagnosis, gender and follow-up time. For each patient, cumulative radiation doses to the right and left lobes of the thyroid gland were calculated based on individual treatment records. Conditional logistic regression was used to compute odds ratios (OR) and 95% confidence intervals (CI). The ORs peaked at 11-fold (95% CI, 3.1-38.0) for radiation doses between 20-29 Gy. At thyroid gland radiation doses above 30 Gy, a downturn in the dose-response relation, consistent with a cell-killing effect, was present. Chemotherapy for the first cancer was not associated with risk of subsequent thyroid cancer, nor did chemotherapy modify the effect of radiation treatment on thyroid cancer risk. No effect of radiation dose to the pituitary gland on the risk of thyroid cancer was observed. Among cases, 42% had a first diagnosis of Hodgkin lymphoma (HL) compared to 19% of controls. After adjusting for radiation dose and radiation sensitivity by age at diagnosis, the risk by type of first cancer remained elevated for HL and thyroid cancer (OR = 3.4; 95% CI, 0.9-12.4). Possibly due to close surveillance of HL patients, the proportion of second thyroid cancers that were less than 1 cm among HL survivors was 42%, compared to 17% among persons who had other types of childhood cancer ($p < 0.05$). Heightened clinical thyroid cancer surveillance, as in those with HL, should be as widely applied for survivors of any childhood cancer treated with radiation to the neck region. This is one of the first studies of a pediatric exposed population to demonstrate significant downward curvature in the radiation dose-response for thyroid cancer.

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