Shorter naïve T cell telomere length is associated with thyroid subsequent malignant neoplasm: A report from the Childhood Cancer Survivor Study (CCSS)

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Introduction: Reduced blood telomere content has been associated with an increased risk for subsequent malignant neoplasms of the thyroid (thyroid SMN) in survivors of childhood cancer. Here, we further investigate this association by examining telomere length (TL) in leukocyte subsets.

Methods: Survivors were enrolled to the CCSS, a multicenter, retrospective cohort of 5-year + survivors of childhood cancer. Cases were survivors with thyroid SMN, and matched (1:1) to survivor controls without SMN by primary diagnosis, year of primary diagnosis (decade), chemotherapy (yes/no), radiation field, and follow-up time (exceeding time to SMN for the case). Stem cell transplant recipients were excluded. Absolute TL was determined from viably frozen leukocytes (lymphocytes, naïve T, memory T, B, and NK cells) by telomere flow cytometry fluorescence in situ hybridization (telomere flow FISH, Repeat Diagnostics), and transformed to age-adjusted percentiles based on age at sample collection. For each leukocyte subset, we used McNemar's test to compare frequency of very low (VL, ≤1st age-adjusted percentile) or low (L, >1st to ≤10th percentile), and a paired t-test to compare age-adjusted TL between cases and controls. Odds ratios were determined by conditional logistic regression.

Results: Of the 52 matched pairs identified, 46 pairs (92 survivors) had sufficient cell recovery for flow FISH: primary diagnoses included Hodgkin lymphoma (20 pairs), acute lymphoblastic leukemia (13 pairs), CNS tumors (7 pairs), neuroblastoma (2 pairs), non-Hodgkin lymphoma (3 pairs), and kidney tumor (1 pair). All survivors had age-adjusted TL below the population median. Cases had shorter age-adjusted TL than controls in 4/5 leukocyte subsets: lymphocytes (p=0.04), naïve T cells (p=0.02), B cells (p=0.01), and NK cells (p=0.01). Naïve T cell TL was VL in 9 cases/46 pairs vs. 2 controls/46 pairs, p=0.04). The odds of L or VL naïve T cell TL was greater in cases compared with controls (OR=2.8, 1.11-7.19, p=0.03), even after adjusting for age at diagnosis.

Conclusions: Survivors of childhood cancer had shorter age-adjusted leukocyte TL than the general population. This negative deviation was more pronounced among survivors with thyroid SMN than among those without SMN, which may reflect a differential risk among survivors for excess premature aging in the hematopoietic compartment. SMN treatment effect on TL is unlikely, as treatment for thyroid SMN is primarily surgical. In cancer-naïve populations, VL lymphocyte TL is a sensitive and specific indicator of underlying defects in telomere maintenance. In survivors of childhood cancer, VL TL in naïve T cells may defects in T cell-mediated cancer surveillance and augmented risk for thyroid SMN.