

# NAÏVE T CELL IMMUNOSENESCENCE ASSOCIATED WITH THYROID SUBSEQUENT MALIGNANT NEOPLASM IN SURVIVORS OF CHILDHOOD CANCER: A REPORT FROM THE CHILDHOOD CANCER SURVIVOR STUDY

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**Background:** Reduced blood telomere content is associated with increased risk for subsequent malignant neoplasms of the thyroid (thyroid SMN) in survivors of childhood cancer. Here, we further investigated this association within leukocyte subsets.

**Methods:** Survivors were enrolled to CCSS, a multicenter, retrospective cohort of 5-year+ survivors of childhood cancer. Survivors with thyroid SMN were matched to survivor controls without SMN by primary diagnosis, diagnosis year, chemotherapy, radiation field, and follow-up time. Telomere length (TL) was determined from viably frozen leukocytes by flow cytometry fluorescence in situ hybridization (Repeat Diagnostics), and transformed to age-adjusted percentiles based on age at collection. We compared frequency of very low (VL) and low (L) TL ( $\leq 1^{\text{st}}$  and  $>1^{\text{st}}-\leq 10^{\text{th}}$  age-adjusted percentile), age-adjusted TL, and leukocyte subset proportions between cases and controls using McNemar's test, paired t-test, and Wilcoxon matched pairs signed rank test. Odds ratios were determined by conditional logistic regression.

**Results:** 46 out of 52 pairs had sufficient cell recovery for analysis. All survivors had age-adjusted TL below the population median. Cases had shorter age-adjusted TL than controls in lymphocytes ( $p=0.04$ ), naïve T cells ( $p=0.02$ ), B cells ( $p=0.01$ ), and NK cells ( $p=0.01$ ). Naïve T cell VL TL was observed in 9 cases vs. 2 controls,  $p=0.04$  (OR for L/VL TL 2.8, 1.11-7.19,  $p=0.03$ ). Naïve T cells also comprised a smaller proportion of all lymphocytes in cases vs. controls with high confidence immunophenotype data (median CD45RA+CD20- lymphocyte percentage: 24%, interquartile(IQ) range 19-32% vs. 39%, IQ range 30-50%,  $n=40$ ,  $p=0.002$ ).

**Conclusions:** Survivors of childhood cancer have shorter age-adjusted TL than population controls. This difference was most pronounced for survivors with thyroid SMN and particularly significant in naïve T cells, corresponding with lower cell frequency relative to total lymphocytes. Risk for SMN may be related to defects in T cell-mediated cancer surveillance due to premature naïve T cell exhaustion.