

## TELOMERE LENGTH AND RISK OF SECOND MALIGNANT NEOPLASMS (SMNs) IN SURVIVORS OF CHILDHOOD CANCER: A CHILDHOOD CANCER SURVIVOR STUDY (CCSS)

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**PURPOSE:** Shorter constitutional telomere length (TL) has been associated with an increased risk of *de novo* cancers. Furthermore, exposure to chemotherapy and ionizing radiation leads to telomere shortening and subsequent genomic instability. Thus, cancer therapy-induced telomere dysfunction may predispose cancer survivors to development of additional cancers. In this study, we tested the hypothesis that shorter TL would be associated with treatment-related SMNs in childhood cancer survivors.

**PATIENTS AND METHODS:** Using the CCSS study population and a nested case-control design, 147 cancer survivors with SMNs (breast cancer [n=68], thyroid cancer [n=48], or sarcoma [n=31]) developing after treatment for childhood cancer (cases) were matched (1:1) with childhood cancer survivors without SMN (controls). Cases and controls were matched by primary cancer diagnosis, age at sample collection, years of follow up from childhood cancer diagnosis, and exposure to specific chemotherapeutic agents and radiation fields. Quantitative PCR was used to measure relative TL in buccal cell DNA. Conditional logistic regression analysis was performed to determine the association between TL and SMNs, estimated as odds ratios (OR) with corresponding 95% confidence intervals (CI), first for all SMNs and then by SMN type.

**RESULTS:** In cases with samples collected prior to SMN diagnosis (thereby removing the potential effect of additional treatment upon TL) there was an inverse relation between mean TL and SMN (OR=0.08, 95% CI 0.01-1.11, p=0.06). For all cases, including those with samples collected after SMN diagnosis, the adjusted OR was 0.3 per unit length (95% CI, 0.09-1.02, p=0.05). Shorter TL was associated with thyroid cancer (OR=0.04, 95% CI, 0.00-0.55, p=0.01), but statistically significant associations could not be demonstrated for breast cancer or sarcoma.

**CONCLUSIONS:** This matched-pair study suggests a relation between shorter TL and treatment-related SMNs, particularly radiation-related thyroid cancers, indicating that shorter telomeres may contribute to SMN in cancer survivors.