Telomere attrition in childhood cancer survivors

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SUMMARY:
Childhood cancer survivors experience substantial treatment-related morbidity and biomarkers of long-term survivor health are needed. Leukocyte telomere length is shortened in childhood cancer survivors and associates with the occurrence of numerous chronic health conditions. Healthy lifestyle factors can attenuate telomere attrition in young-adult survivors, implicating critical windows for intervention.
In this issue of *CLINICAL CANCER RESEARCH*, Song and colleagues measure leukocyte telomere length (LTL) in childhood cancer survivors and cancer-free control participants from the St. Jude Lifetime Cohort Study (SJLIFE) and explore associations of LTL with differing cancer treatments, diagnosis of comorbid health conditions, and variation in health behaviors among survivors (1). The population of childhood cancer survivors in the US, a growing population now estimated to exceed half a million persons, receives cancer treatment during critical developmental windows and represents a vulnerable group that experiences substantial treatment-related morbidity (2). Although approximately 1 out of every 750 individuals in the U.S. is now a childhood cancer survivor, research focusing on the biological basis for accelerated health deterioration within this population remains limited. For this reason, long-term cancer survivorship studies assessing relevant prognostic or predictive biomarkers of survivor health are urgently needed.

A significant proportion of childhood cancer survivors experience subsequent chronic health conditions, including immune dysfunction, cardiovascular disease, obesity, pulmonary deficits, and secondary malignancies following completion of therapy (3). In addition to impacting mortality, these chronic conditions reduce quality of life for survivors. While previous chemoradiotherapy treatment certainly contributes to the elevated incidence of these conditions in childhood cancer survivors, their etiology is likely multifactorial and may be modified by subsequent health behaviors, including diet, exercise, and tobacco use. Thus, future intervention research that targets health behaviors and leverages surrogate biomarker endpoints such as LTL may complement ongoing medical surveillance and enhance oncology care.

Telomeres are nucleoprotein-DNA caps found at the ends of chromosome that help to maintain genome integrity (4). Telomere length decreases with each mitotic division due to the inability of DNA polymerase to synthesize the lagging DNA strand to the end of the chromosome. In
somatic cells lacking active telomerase, telomeres can become critically short, triggering cell senescence or apoptosis. Telomere length is influenced by numerous factors, including behavior, exposure to environmental toxins and constitutive genetics. Because telomere attrition accumulates with age and because telomere length is highly correlated across cell types, LTL may be leveraged as a marker of “biological age” (4). Using whole-genome sequencing data, Song and colleagues assessed LTL in 2,427 childhood cancer survivors (median age 7 at diagnosis; age 32 at DNA sampling) and 293 cancer-free controls (median age 35 at DNA sampling).

Compared to cancer-free controls, childhood cancer survivors from the SJLIFE cohort had significantly shorter LTL overall and within all cancer subgroupings (i.e. sarcomas, central nervous system tumors, neuroblastoma, Wilm’s tumor, acute lymphoblastic leukemia, Hodgkin lymphoma, non-Hodgkin lymphoma) after adjustment for age at DNA sampling, sex, LTL-associated heritable polymorphisms, and genomic ancestry. The average LTL value across all subjects corresponded to an age of 36.8 years in survivors compared to 48.2 years among controls, suggesting an approximately eleven year acceleration in telomere attrition among childhood cancer survivors. Importantly, LTL decreased with age in survivors at a rate comparable to that in controls, indicating a critical loss of telomere reserves following treatment - but not an accelerated rate of attrition across the life-course (Figure 1).

Among childhood cancer survivors, chest radiotherapy and abdominal/pelvic radiotherapy were associated with significantly shorter LTL after adjustment for age, sex, genetic polymorphisms, ancestry, and health behaviors, but no association was observed for brain radiotherapy. Survivors exposed to glucocorticoids and vincristine also had shorter LTL, but no LTL associations were detected for exposure to alkylating agents, anthracyclines, epipodophyllotoxin, or platinum-based agents. Unfortunately, teasing out the independent effect of each specific therapy is difficult given their combined use in many treatment regimens;
however, abdominal/pelvic radiotherapy and vincristine use remained associated in a multivariable model that also included chest radiotherapy and glucocorticoid use.

Given longstanding epidemiologic associations between shortened LTL and numerous adverse health-related outcomes, LTL was assessed for association with overall mortality and 64 different chronic health conditions in the SJLIFE cohort, including risk of five different secondary neoplasms. Associations between shorter LTL and increased diagnosis of 14 chronic conditions were detected, including: cardiomyopathy, cholecystitis, chronic hepatitis C, hypercholesterolemia, hypertriglyceridemia, fibrosis/cirrhosis, gastritis/duodenitis, gastrointestinal ulcer, headaches, hypertension, lymphatic infections, obesity, obstructive pulmonary deficit and restrictive pulmonary deficit. A suggestive association between shorter LTL and higher overall mortality was also observed, but this did not reach statistical significance (P=0.08). Only one association was observed in the opposite direction, wherein longer LTL was associated with increased risk of secondary thyroid cancers. This association appears consistent with recent reports that longer genetically-predicted LTL is a risk factor for numerous cancer types, including childhood cancers (5). While analyses in the SJLIFE cohort included health conditions that may have been diagnosed either before or after date of DNA sampling, time to event analyses were also performed for health conditions diagnosed at or following DNA sampling. These separate analyses identified an association between shorter LTL and increased risk of restrictive pulmonary deficit, and suggestive associations with obstructive pulmonary deficit and hypertriglyceridemia. This indicates that in addition to its known role as a biomarker of cellular senescence, LTL may also have prognostic value in the childhood cancer survivor population.

Perhaps the most exciting finding in the data presented by Song, et al. is preliminary evidence that lifestyle or behavioral factors can modify telomere attrition rates in childhood cancer survivors. Using a composite score based on self-reported physical activity, resistance training,
tobacco use, diet, and alcohol overconsumption, those who reported more favorable health behaviors had significantly longer age-adjusted LTL among survivors age 18-35 years old at DNA collection. However, among survivors >35 years of age at DNA collection, age-adjusted LTL was comparable across survivors irrespective of health behaviors. This could imply that a critical window following childhood cancer treatment exists, during which healthy lifestyle modifications may have the greatest ability to attenuate rates of telomere attrition. This complements the observation that a critical loss of telomere reserves appeared to occur post-treatment, followed by similar rates of attrition in survivors to that of cancer-free controls.

Although tremendous progress has been made in raising childhood cancer survival rates and improving long-term outcomes for survivors, subsequent chronic health problems remain common and are frequently debilitating. Telomere reserves can act as a biomarker for numerous health-related states and has even been suggested to moderate underlying biological processes involved in senescence. Although the data of Song and colleagues is correlative and does not necessarily imply a causal relationship between LTL and chronic health conditions in childhood cancer survivors, their data do support the use of LTL as a meaningful biomarker of healthy survivorship. Additionally, these results nominate LTL as a potential surrogate biomarker with utility in health-behavior intervention studies conducted in this growing patient population, ultimately leading to reduced symptom burden and improved survivorship.
REFERENCES:


FIGURE LEGEND:

Figure 1. Hypothesized trajectories of leukocyte telomere length attrition in individuals affected by childhood cancer and in cancer-free individuals. Leukocyte telomere length is believed to be longer in childhood cancer patients than control children based on recent Mendelian randomization studies of sarcoma, neuroblastoma and acute lymphoblastic leukemia. Following treatment for childhood cancer, leukocyte telomere length becomes substantially shorter in childhood cancer survivors than in cancer-free controls based on new data from Song, et al. (1) in this issue of Clinical Cancer Research. However, subsequent to this substantial loss of telomere reserves, rates of telomere attrition normalize and are similar in childhood cancer survivors as in cancer-free controls during adulthood, as indicated by the comparable slopes in later years.
**Legend**
- Childhood cancer patients
- Cancer-free individuals
- Positive health behaviors

**Time period**

**Childhood:**
Children with cancer have modestly longer LTL at diagnosis than controls.

**Young adulthood:**
LTL attrition occurs post-treatment, but can be modified by health behaviors.

**Adulthood:**
LTL attrition rates are comparable in survivors and controls, but are not modified by health behaviors.
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