Are Short Telomeres Hallmarks of Cancer Recurrence?

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Exposure to radiation and some chemotherapeutic agents is associated with an increased risk of developing second cancers. Short telomeres are almost universally associated with malignant cancer progression. An unanswered question is whether inherited short telomeres or therapy-related telomere shortening is a biomarker of the development of second malignant neoplasms. Clin Cancer Res; 20(4); 779–81. ©2013 AACR.

In this issue of Clinical Cancer Research, Gramatges and colleagues (1) analyzed telomere content between childhood cancer survivors with and without second malignant neoplasms. They observed that patients with short telomeres at first cancer occurrence increased the risk of developing a second cancer. By way of background, human telomeres are repetitive TTAGGG repeats of DNA at the ends of chromosomes that are essential to preserve the integrity of the genome. Telomeres progressively shorten in all dividing human cells, leading to cellular senescence (with increases in inflammatory signaling and reduced immune responses). In combination with oncogenic changes, chromosomal instability occurs and almost all human cancers have short telomeres and express the ribonucleoprotein enzyme, telomerase (2). There is an inverse relationship between telomere length in human leukocytes and both cancer incidence and mortality (3). Also, short telomeres and high levels of telomerase in tumors at the time of diagnosis are predictors of poor outcomes in a cancer-specific manner (4). In association studies in individuals without cancer, it remains unclear whether short telomeres correlate with increased risk for cancer (5, 6). In patients with pediatric cancer that undergo spontaneous remissions, such as neuroblastoma 4s (7) and low-grade gliomas (8), there is a lack of activation of telomerase. These studies demonstrate that in the absence of telomerase, short telomeres are initially protective against cancer. These studies also illustrate that telomerase is not required for the initiation of tumorigenesis, but tumor cells must engage a mechanism to maintain telomeres to continue dividing. Thus, expression of telomerase is a critical event in the progression to advanced tumors and its inhibition could be a potent, almost universal, anticancer therapeutic target. Telomere length may also be an enrichment biomarker for clinical trial enrollment as well as an independent prognostic indicator of second cancers, as is suggested in the current study (1).

Gramatges and colleagues (1) obtained specimens from the Childhood Cancer Survivor Study and performed a matched case–control analysis of telomere contents between childhood survivors with and without second malignant neoplasms. These patients were treated for their primary cancer from 1970 to 1986, and the study contains more than 14,000 survivors, including 4,000 siblings without cancer, that have been followed for long-term health outcomes. Gramatges and colleagues (1) were the first to analyze telomere content in this specific group of cancer survivors. An association was observed between shortened telomeres in buccal (mouthwash) samples at first cancer and the incidence of second cancers that was primarily driven by thyroid cancers, even though breast cancers and sarcomas were also associated with secondary cancer incidence (1). By matching controls at diagnosis and by treatments, a statistically significant increase in thyroid cancer occurred in patients with less telomere content (1). What is not known is whether these patients with a second cancer had short telomeres before first cancer therapy or afterward. Knowledge of this could separate a genetic susceptibility to second cancers versus an environmental effect of the treatment protocol. Exposure to chemotherapy (9) and ionizing radiation (10) is known to increase the risk of thyroid tumors. In addition, radiation exposure (with or without chemotherapy) in the same Childhood Cancer Survivor Study cohort led to an 83% incidence of skin basal cell carcinoma (11), but telomere content was not examined. Previously, a significant telomere length decrease was shown in Chernobyl clean-up workers compared with healthy age-matched donors 20 years after radiation exposure (12). These studies document that radiation-induced telomere loss is prolonged.

Is telomere length a molecular biomarker of recurring cancers (Fig. 1)? Approximately two thirds of all first cancers occur in the general population over the age of 65, whereas...
in patients treated for primary cancers during childhood, the incidence of second cancer increases much more quickly. Although intuitively this suggests that the treatment is leading to the increased incidence of second cancers, it is not proved, and these individuals may have a preexisting inherited susceptibility to cancer.

So what are the limitations/implications of this study and others going forward? First, these patients with pediatric cancer were treated with significantly different regimens approximately 30 years ago, so it is not certain whether the same results would occur today. Also, these studies were conducted at a specific time point after initial cancer therapy, with some of the cohort having additional rounds of therapy. It is not known whether more or fewer second cancers will occur during the next decade(s), making the association potentially more or less dramatic. Another concern is the use of buccal (mouthwash) samples from which DNA is subject to degradation and contamination artifacts. Finally, the analyses were done on average and not the shortest telomere lengths. There is increasing evidence that telomeres are heritable, and mutations in telomere regulatory genes have a causal role in human diseases, such as bone marrow failure and idiopathic pulmonary fibrosis. These have been referred to as telomeropathies or telomere syndromes. It is becoming recognized that these telomere maintenance disorders are a spectrum of diseases, and thus it is too early to draw general conclusions about the causative versus correlative role of telomere biology in most human diseases. However, there are several issues that should be addressed in future studies.

Importantly, the methods for measuring and quantifying telomere length are not standardized, and the quality of the analyses and interpretations are often not robust. There are several methods to quantitate telomere length, and most methods determine average lengths when it is actually the shortest telomeres that lead to DNA damage signaling and an increased risk for disease. Quantitating the length of chromosome ends can be done by quantitative telomere FISH with a labeled telomere-specific probe. This can be done on interphase cells, analyzed by flow cytometry or fluorescence microscopy, providing precise lengths (with about a 5%–10% variability). Although only a single or a few dysfunctional telomeres are sufficient to trigger a senescence-like response, in general, these assays have only recently become amenable to high-throughput reproducible analyses. Most, but not all, reported studies use telomere length measurement techniques such as the TRF (Telomere Restriction Fragment analysis) or PCR-based methods. Although many samples can be analyzed by these methods, determining average telomere lengths in leukocytes/buccal washings is unlikely to be as valuable as measuring individual chromosome ends. Finally, showing differences of a few percentage changes in average telomere length should be viewed with skepticism.

This study (1) and others reaffirm that radiation and chemotherapy pose significant future risks to patients. With increases in cancer survivors due to improved therapies and overall increases in human longevity, the risk of second or even third cancers is likely to increase. One possibility would be to identify nontoxic radioprotectors for normal cells that do not also protect cancer cells. There are national efforts to identify radioprotectors for first responders to nuclear disasters and to protect astronauts on long-term missions into space. Perhaps some of these identified agents can be repurposed for pretreating patients with first cancers before therapy, thus reducing the probability of second cancers. In conclusion, the study by Gramatges and colleagues (1) is important because it found an association between telomere contents and second malignant neoplasms in childhood cancer survivors using an invaluable resource provided by the cohort. In summary, measuring telomeric DNA may be a useful metric/biomarker of predicting cancer risk, recurrence, and outcomes.

**Disclosure of Potential Conflicts of Interest**

JW. Shay serves as a consultant/advisory board member for Life Length.

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