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Commentary

# Leukocyte Telomere Length and Cancer Risk: A Dynamic Problem

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Telomeres are the protective structure at both ends of each chromosome. Telomere length is widely considered a marker of biological aging. For convenience, telomere lengths in human population studies have been predominately measured in peripheral blood leukocytes. Although leukocyte telomere length (LTL) is generally inversely correlated with age, there is considerable inter-individual variation of LTL among people of the same ages (Aubert and Lansdorp, 2008). An individual's LTL at any given age is determined by a combination of genetic, environmental, and lifestyle factors (Lin et al., 2012). The inter-individual variation of LTL has been proposed to contribute to an individual's susceptibility to age-related diseases, including cancer.

Since the first epidemiologic study linking short LTL with increase risks of several cancers in 2003 (Wu et al., 2003), there have been numerous studies assessing the association of LTL with the risks of cancer (Weischer et al., 2013; Wentzensen et al., 2011), but the results were inconsistent. The inconsistent results are often attributed to technical variations in LTL measurement methods, "reverse causation" limitation in retrospective case control studies, small sample size of cancer cases in prospective cohort studies, and heterogeneous populations. Furthermore, all the published studies relating LTL to cancer risks have used a single time measurement of LTL without consideration of longitudinal changes of LTL. In this issue of *EBioMedicine*, Hou et al. (2015), for the first time, reported a dynamic change of LTL in the context of cancer risks. This study included 792 Normative Aging Study participants with one to four LTL measurements during a follow-up of 12-years. The authors observed that age-related LTL attrition was accelerated among participants who ultimately developed cancer. Strikingly, this trend reversed when age-adjusted LTL was examined relative to time to diagnosis. This divergence of age-adjusted LTL attrition began seven years pre-diagnosis and culminated in significantly longer LTL 3–4 years pre-diagnosis among cancer cases compared to cancer-free participants, resulting in a positive association between longer LTL measured within 4 years of diagnosis and increased risks of prostate cancer and all cancers combined. This provocative observation provides important biological insight into the role of the telomeres in cancer etiology and adds another possible explanation to the prior inconsistencies in reporting the association of LTL with cancer risks.

The decelerating age-adjusted LTL attrition in cancer cases as they approach diagnosis suggests that telomere elongation mechanisms may be activated in the blood due to cancer initiation. Telomere integrity is primarily maintained by telomerase, which catalyzes the synthesis of telomere repeats and adds telomere sequences onto chromosome ends. It is well known that telomere shortening is an early event in carcinogenesis. Critically shortened telomeres may trigger cellular senescence and apoptosis. Activation of telomerase occurs in the majority of cancers to counter-balance the critical shortening of telomeres in tumor cells, which can stabilize and elongate telomeres, overcome senescence and apoptosis, and increase cellular lifespan of malignant cells. Prior studies have also reported telomerase activity in normal and leukocytes (Broccoli et al., 1995). Biologically, it is fathomable that individuals with higher telomere erosion rate over their early lifetime have increased cancer risks; however, as their LTL reaches a threshold and cancer is well on its trajectory of development, their telomere elongation mechanisms are hijacked to stabilize and elongate telomeres even in blood leukocytes, thus, providing better survival. Normal leukocytes benefit from telomere elongation mechanisms, resulting in longer LTL for cancer patients near their diagnosis.

This divergence of LTL at some point before cancer diagnosis has important implications in assessing the relationship of LTL with the cancer risks. Current literature in this regard all measured LTL at a single time point. The timing of blood collection was not strictly controlled. The above observation by Hou et al. (2015) indicates that the differences in sample collection time relative to cancer development and diagnosis will have a significant impact on assessing the association of LTL with cancer risks, which at least partially contributes to the inconsistency in literature. Future association studies of single time measurement of LTL should carefully control the timing of blood collection. More importantly, studies with multiple blood collection are warranted to establish the temporal associations between LTL and cancer risks, and to assess the dynamic changes of LTL in relation to cancer development.

Due to the small sample size, this study of Hou et al. (2015) could only evaluate prostate cancer and the odds ratio is likely inflated. Whether a similar phenomenon occurs to other cancer types is unclear. Recent large cross-sectional studies and prospective studies have shown that both long LTL and short LTL can predispose individuals to increased cancer risks and the direction of association is not only cancer type-dependent, but also histology-dependent (Weischer et al., 2013; Gu and Wu, 2013; Sanchez-Espiridion et al., 2014; Seow et al., 2014). For example, long LTL was associated with an increased risk of lung adenocarcinoma, whereas short LTL was associated with a reduced risk of

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lung squamous cell carcinoma (Sanchez-Espiridion et al., 2014; Seow et al., 2014). The study of Hou et al. (2015) adds additional complexity to the link of LTL to cancer risks. The cancer type- and histology-dependent association between LTL and cancer risks, accelerated age-related LTL shortening in cancer cases, and decelerating age-adjusted LTL attrition in cancer cases as they approach diagnosis, all point to a complex and dynamic relationship between LTL and cancer development. Future large, prospective, longitudinal studies are needed to confirm and extend the intriguing observations of Hou et al. (2015). A full understanding of LTL epidemiology and cancer association will facilitate intervention efforts to prevent cancer and improve our lives through modulating telomere dynamics.

## Conflicts of Interest

The author declares no conflict of interest.

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