

The Paradoxical Lengthening of Telomeres in Somatic Tissues of the Very Old: Aging Effect Meets Birth-Cohort Effect

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Correspondence re: Lapham K, Kvale MN, Lin J, et al. 2015. Automated assay of telomere length measurement and informatics for 100,000 subjects in the Genetic Epidemiology Research on Adult Health and Aging (GERA) Cohort. *Genetics* 200: 1061–1072.

Last year, a large cross-sectional study with interesting findings on telomere dynamics during human aging appeared in the journal *Genetics* (Lapham et al., 2015). Telomere length of saliva DNA samples showed a negative correlation with age up to 75 years; unexpectedly, age was correlated positively with longer telomeres in those older than 75 years. If, as proposed by the authors, this phenomenon might simply reflect a survival advantage at old age for those with longer telomeres (Lapham et al., 2015), one would expect to see a slow-rise pattern starting at age 60 years, when age-associated diseases begin to take their toll, but this is not the case (see Fig. 7 of (Lapham et al., 2015)). The reversal of telomere dynamics in both sexes occurs in participants aged ≥ 80 years. Most interestingly, in cross-sectional cancer data sets from the U.S. National Cancer Institute, after a sharp rise starting at middle age, cancer incidence patterns also reverse in participants aged ≥ 80 years (Stindl, 2008). (Replicative telomere erosion in somatic tissues during aging is causally involved in the genesis of carcinoma (Stindl, 2008) and other age-associated diseases.)

Here, I propose that a progressive telomere loss between human generations—a model that was introduced 12 years ago (Stindl, 2004, 2014) and which was confirmed by a large study in 2015 (Holohan et al., 2015)—results in a birth-cohort effect that “compensates” for the telomere loss in somatic tissues during aging in the very old. Very old individuals (≥ 80 years) are members of previous generations and, on average, have bypassed the intergenerational telomere loss of at least two generations compared to young individuals (Fig. 1). Thus, I conclude that at very advanced ages, the cumulative birth-cohort effect results in a reversal of telomere dynamics in a cross-sectional data set, corresponding to ~ 20 years of aging in somatic tissues in this

age group. The possible underlying biological mechanism is outlined elsewhere (Stindl, 2004, 2011, 2014, 2016).

The cumulative loss of telomere length between human generations (Stindl, 2004, 2014; Holohan et al., 2015) could explain the sudden appearance of the reversal at a certain advanced age, when tissue regeneration and therefore replicative telomere erosion in somatic tissues is slowing. The reason why the age-associated telomere-length-reversal in saliva samples is not seen in standard studies using blood samples is that very few mammalian blood cells contain DNA; i.e. white blood cells, and this highly variable population of immune cells responds to all sorts of stimuli, including hormones, stress, and infection.

To summarize, the findings of Lapham and colleagues reported as a cross-sectional data set are proposed to result from the interference of two independent mechanisms, intergenerational telomere loss in the germline and replicative telomere erosion in somatic tissues during aging. Accordingly, a theoretical model of stable sperm telomeres and telomere erosion in oocytes has been introduced (Stindl, 2011, 2014, 2016). Longitudinal studies on human oocytes and sperms are required to test the hypothesis of transgenerational telomere erosion in the female germline (Stindl, 2016).

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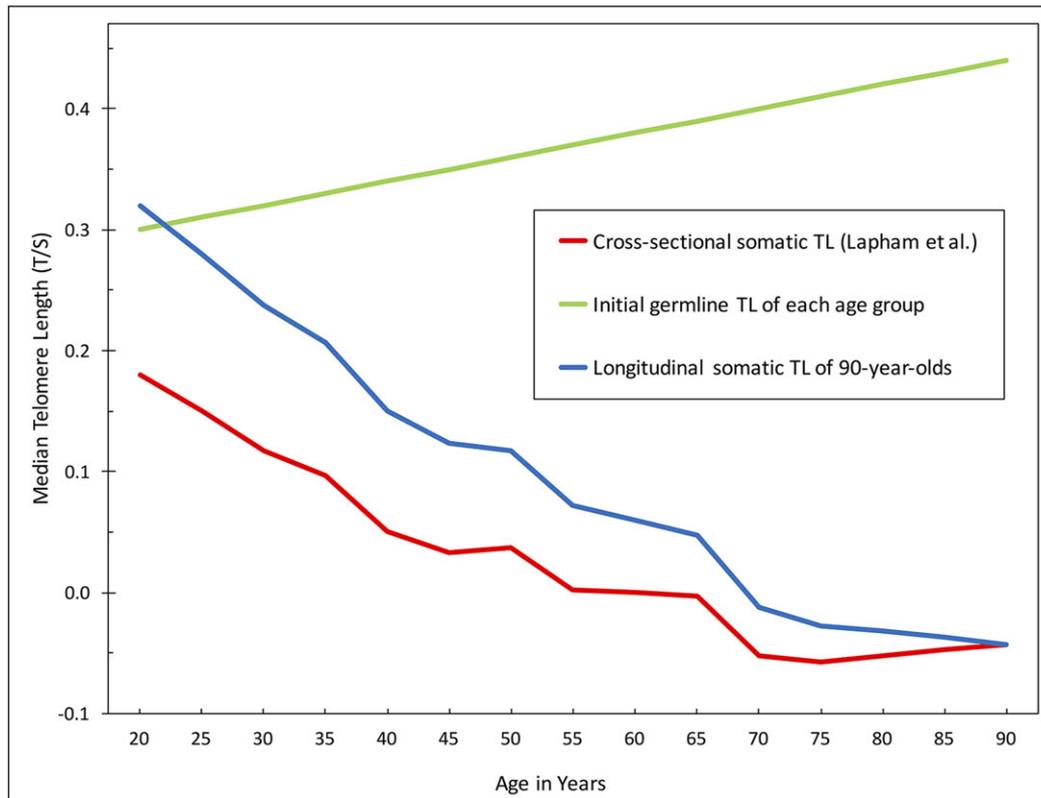


Figure 1. Paradoxical telomere lengthening in somatic tissues of the very old (Lapham et al., 2015) is an artifact of the cross-sectional study design and is caused by transgenerational telomere erosion (Stindl, 2004, 2014, 2016). *Red line*: original Lapham et al findings for both sexes; *green line*: proposed intergenerational telomere erosion, which results in reduced initial germline telomere lengths of each subsequent generation (corresponds to younger age groups in this cross-sectional data set); *blue line*: corrected version of the supposedly longitudinal somatic tissue trend by Lapham et al (red line) for 90-years-old participants. This is the sum of the intergenerational telomere loss in the germline of each age group (green line) and the telomere length value of each age group measured by Lapham et al. (red line). *Abbreviations*: T/S, the ratio of the telomeric product versus the single copy gene product obtained using quantitative PCR; TL, telomere length.

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