Telomere Length in Costa Rica's High Longevity Blue Zone

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Abstract

The Nicoyan Peninsula region in Costa Rica has been characterized as a "Blue Zone" with exceptionally high longevity. Traditional risk factors, however, do not appear to explain the Nicoyan advantage. In this study we examine a biomarker that has been proposed as a cellular-level marker of aging: leukocyte telomere length. We confirm that telomere length is significantly negatively related to age in Costa Rica. After controlling for age, telomere length in Nicoya is significantly greater than in other areas, equivalent to more than a 20-year advantage in cellular aging in Nicoya, providing further support to the argument that Nicoya is indeed an exceptional longevity area, and offering hints of a biological pathway to which this longevity may be related. Paradoxically, however, telomere length is not significantly related to mortality in this elderly sample, except for a *positive* relationship with mortality in the year prior to death.

Introduction

The Nicoyan Peninsula region in Costa Rica has been characterized as a "Blue Zone" with exceptionally high longevity. Our previous research has confirmed that not only are Costa Rican adult mortality rates superior to some developed nations such as the United States, but mortality rates among elderly Costa Ricans in Nicoya are even lower than in the rest of Costa Rica. The Nicoyan advantage is particularly evident in cardiovascular disease, but traditional risk factors do not easily explain the Nicoyan advantage, as smoking and hypertension are similar to other areas of Costa Rica and self-reported health actually appears worse in Nicoya. In this study we examine a biomarker that has been proposed as a cellular-level marker of aging: leukocyte telomere length (TL)(1). Examination of TL can help provide further evidence regarding dimensions in which Nicoyans are unusually healthy. Furthermore, we contribute to a small but growing literature examining the relationship between TL and elderly mortality. To our knowledge, this is the first study of telomere length and mortality outside of North America and Europe based on a well characterized population based sample with high quality mortality ascertainment. Not only does our study offer a step forward for generalizability of the role of telomere length in longevity, but the context of much weaker socioeconomic differences in mortality in Costa Rica (2) offers an opportunity to examine telomere length associations without strong socioeconomic confounding typically encountered in North American and European countries.

Background

Telomeres are repetitive canonical sequences of DNA at the ends of chromosomes that prevent the degradation of coding regions of DNA that would otherwise result from the inability of DNA

replication enzymes to copy the end of a DNA strand. A metaphor that has been used to describe their function is as the tips of shoelaces that keep them from unraveling. Although the functional importance of telomeres has been understood since the middle 1970s, the importance of their role in the human aging process has begun to emerge more recently. Telomere shortening was first found to occur with increasing age,(3) and more recent work has shown associations with chronic disease (4) and mortality independent of age.(1, 5) Beyond this, however, the social and economic determinants of telomere length are just beginning to emerge. For example, there is initial evidence that shorter telomeres are associated with chronic stress (6) and that lower SES is also associated with shorter telomere length.(7) Telomere length has also been shown to be significantly associated with unemployment.(8).

Methods

A sub-sample of 359 elderly Costa Ricans was drawn from the 2004 and 2006 waves of the nationally representative Costa Rican Study on Longevity and Healthy Aging (CRELES). The survey has been described elsewhere (2). From DNA extracted from blood draws from CRELES survey participants, we randomly selected a sample stratified on age (60-75, 76-95, >95) and oversampled the Nicoya region. To determine mortality, CRELES followed participants on the field and in computer records of the civil registration system. We further oversampled individuals who had died within three years of the first wave of visits. Quantitative PCR assay was used to determine, as indicator of telomere length, the relative ratio of telomere repeat copy number to single-copy gene copy number (t/s ratio), with the analyses using the average of two assays per sample. The two assays had a Pearson correlation of 0.99.

Results

The table below indicates our initial finding corroborating that telomere length is significantly negatively related to age in Costa Rica, as has been found elsewhere(8). After controlling for age, telomere length in Nicoya is significantly longer than in other areas, equivalent to more than a 20-year advantage in cellular aging in Nicoya (model 1), providing further support to the argument that Nicoya is indeed an exceptional longevity area. The Nicoyan advantage is robust to our initial exploratory controls for a variety of factors that could have led to higher telomere length (model 2). In addition, controlling for a number of important biological risk factors for mortality (model 3) do not decrease the strong association between Nicoya and telomere length, even as a number of these risk factors (BMI, blood pressure, C-reactive protein) are associated to telomere length. This leaves open the question as to the mechanism by which telomere length operates in this setting. The fact that traditional cardiovascular risk markers do not mediate the longer telomere length of Nicoyans may offer insight into other mechanisms explaining Nicoyan longevity. For example, in U.S. populations, telomeric aging has been associated with omega-3 fatty acid levels.(9)Future work with more detailed social exposures and stress measures will be of particular interest.

Paradoxically, telomere length is not significantly related to mortality in this elderly sample, except for a *positive* relationship with mortality in the year prior to death. This could be due to insufficient statistical power, although ours is not the first study to find this among an older population (10). Alternatively, it may be that other factors are more important determinants of mortality at older ages, leaving open the possibility that the greater telomere lengths observed in the Nicoyan population could be more strongly related to lower Nicoyan mortality at younger ages.

Table. OLS regression coefficients and standard errors of predictors of leukocyte telomere length (normalized to mean=0, s.d=1) among the Costa Rican Study on Longevity and Healthy Aging, age 60 and above.

	Model 1 (n=359)	Model 2 (n=359)	Model 3 (n=340)
Nicoyan	0.46 (0.11)***	0.45 (0.11)***	0.48 (0.11)***
Age (years)	-0.021 (0.0037)***	-0.029 (0.0046)***	-0.034 (0.0050)***
Gender (male)	0.026 (0.10)	0.0095 (0.10)	-0.020 (0.10)
Rural		0.019 (0.11)	
Education (years)		-0.023 (0.016)	-0.023 (0.017)
Death			
less than 1 year		0.50 (0.18)***	
1-2 years		0.15 (0.17)	
Greater than 2 years		0.19 (0.16)	
Potential biological mediators			
BMI			-0.042 (0.020)**
BMI squared			0.00043 (0.00020)**
Diastolic blood pressure (mm Hg)			-0.014 (0.0062)**
Systolic blood pressure (mm Hg)			0.0080 (0.0030)***
Triglycerides (mg/dl)			-0.00081 (0.003)
HbA1c (%)			-0.060 (0.043)
C-reactive protein			0.010 (0.006)*

Table notes: Death is length of time between blood draw used for telomere assay and mortality, baseline category of comparison is still alive. All errors are robust standard errors. * indicates $p<0.10$, ** indicates $p<0.05$, *** indicates $p<0.01$.

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