Association of Longer Telomeres With Better Health in Centenarians

Dellara F. Terry, 1 Vikki G. Nolan, 2 Stacy L. Andersen, 1 Thomas T. Perls, 1 and Richard Cawthon 3

1New England Centenarian Study, Geriatrics Section of the Department of Medicine, Boston University School of Medicine and Boston Medical Center, Massachusetts.
2Boston University School of Public Health, Massachusetts.
3Eccles Institute of Human Genetics, University of Utah, Salt Lake City.

Prior animal model studies have demonstrated an association between telomere length and longevity. Our study examines telomere length in centenarians in good health versus poor health. Using DNA from blood lymphocytes, telomere length was measured by quantitative polymerase chain reaction in 38 sex- and age-matched centenarians (ages 97–108). “Healthy” centenarians (n = 19) with physical function in the independent range and the absence of hypertension, congestive heart failure, myocardial infarction, peripheral vascular disease, dementia, cancer, stroke, chronic obstructive pulmonary disease, and diabetes were compared to centenarians with physical function limitations and ≥2 of the above conditions (n = 19). Healthy centenarians had significantly longer telomeres than did unhealthy centenarians (p = .0475). Our study demonstrated that investigations of the association between telomere length and exceptional longevity must take into account the health status of the individuals. This raises the possibility that perhaps it is not exceptional longevity but one’s function and health that may be associated with telomere length.

Key Words: Telomere length—Centenarian—Longevity—Morbidity.

TELOMERES consist of hundreds to thousands of copies of a uniform double-stranded DNA sequence that caps the ends of chromosomes. Telomeres shorten with cell division in somatic cells. In 1965, Leonard Hayflick discovered that there was a limit to the number of cell divisions that a cell could give rise to (termed the “Hayflick Limit”) (1). Telomere length, in turn, appears to be a determinant of the Hayflick Limit. Consistent with this idea, previous investigations have demonstrated an association between telomere length and longevity in animal models (2–3).

Human studies examining the relationship between telomere length and mortality have demonstrated mixed results. Cawthon and colleagues (4), in their study of individuals 60 years old or older, demonstrated that the overall mortality rate of persons with short telomeres was nearly double that of individuals with long telomeres. Disease-specific mortality was also associated with shorter telomere length: Among persons with heart disease or infectious diseases, mortality was 3-fold and 8-fold greater, respectively, for persons with relatively short telomeres (4). Prior studies have demonstrated that shorter telomere length is associated with the presence of cardiovascular disease (5–8), dementia (9,10), and insulin resistance (11). Njajou and colleagues (12) demonstrated a positive correlation between life span and telomere length, although the age range of the subsample in which this was examined was not specified.

In contrast, studies of the oldest old have not demonstrated any relationship between telomere length, mortality, and/or morbidity. The Leiden 85+ Study examined baseline and follow-up telomere length measurements in individuals 85 years old or older; they demonstrated that baseline measurements were not predictive of mortality or dementia (13). Similarly, a Danish study of individuals 73–101 years old demonstrated that age-adjusted telomere length was not predictive of survival (14).

Using samples from the New England Centenarian Study (NECS), we set out to examine the role of telomere length and health in the oldest old. More specifically, we hypothesized that the centenarians in good health would have significantly longer telomeres than centenarians in poor health and that perhaps it is not exceptional longevity but one’s health and function that is associated with telomere length.

METHODS

Details of the study’s recruitment and enrollment methods have been previously published (15). Briefly, the NECS is a cross-sectional study of individuals (age 97–119), their family members, and a referent cohort for the centenarian offspring who live in the United States and Canada. The NECS protocol is approved and monitored by the Boston University Medical Center Institutional Review Board, and all participants or their proxies provided written informed consent.
Health and physical function data used in this analysis were previously collected by telephone interview and/or by mail. A family member or friend assisted with completion of the questionnaires in cases in which the participant was unable to complete the questionnaires independently. A validated health questionnaire (15) was used to determine the presence, history of, or absence of the following diseases: hypertension, congestive heart failure, myocardial infarction, peripheral vascular disease, dementia, cancer, stroke, chronic obstructive pulmonary disease (COPD), and diabetes. We used the Barthel Activities of Daily Living (ADL) Index, a validated instrument, to assess ADL (scores range from 0 to 100) (16).

“Healthy” centenarians were defined as those individuals with a Barthel score >90 (independent range) and the absence of all of the following diseases: hypertension, congestive heart failure, myocardial infarction, peripheral vascular disease, dementia, cancer, stroke, chronic obstructive pulmonary disease (COPD), and diabetes. We used the Barthel Activities of Daily Living (ADL) Index, a validated instrument, to assess ADL (scores range from 0 to 100) (16).

“Unhealthy” centenarians had Barthel scores <80 (requiring at least some assistance) and two or more of the above diseases.

Using native DNA from whole blood, we measured telomere length by quantitative polymerase chain reaction (QPCR) as described by Cawthon (17), with minor modifications. In this assay, the QPCR signal from the telomere repeats, “t”, is normalized to the QPCR signal from a nuclear single copy gene, “s”, to yield a “t/s ratio,” which is proportional to the average telomere length per cell. Telomere primers were tel1b, 5’-cggctttgcttgtttgcttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgttttgtttgtt...
shown in Figure 1. Although not statistically significant, there was a trend of female healthy centenarians having longer mean telomere length than male healthy centenarians, as shown in Table 2. There were no differences in unhealthy women versus men.

**Table 2. Mean Telomere Length Measured in Base Pairs in Female (N = 10) Versus Male (N = 9) Centenarians**

<table>
<thead>
<tr>
<th>Health Status</th>
<th>Female</th>
<th>Male</th>
<th>p Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy</td>
<td>6992.0</td>
<td>4413.9</td>
<td>.0775</td>
</tr>
<tr>
<td>Unhealthy</td>
<td>4048.3</td>
<td>3222.3</td>
<td>.4025</td>
</tr>
</tbody>
</table>

*Notes: Data compare the sex-specific, age-adjusted mean telomere lengths. *Age-adjusted p value using analysis of covariance.

**DISCUSSION**

Our results suggest that healthy centenarians have significantly longer telomeres than unhealthy centenarians have. Compared to the other studies examining telomere length in older individuals, our study was unique in that we matched pairs by both age and sex. Sex matching is important because telomere length is typically longer in women than in men of the same age (18,19). By matching pairs by age, we were able to reduce the effect of survivor bias. In addition, we were able to take into account the effect of age-related diseases and function on telomere length.

Previous studies have failed to demonstrate an association between telomere length and mortality in the oldest old. The Leiden 85+ Study of individuals 85 years old or older demonstrated that baseline measurements were not predictive of mortality or dementia (13). A Danish study of individuals 73–101 years old by Bischoff and colleagues (14) demonstrated that longer telomeres were associated with improved survival, but this association disappeared after age adjustment. In contrast to these studies, the results from this study suggest that perhaps it is not exceptional longevity but one’s health and function (e.g., frailty) that is associated with telomere length. Recently, work by Epel and colleagues (20) demonstrated that women with higher levels of perceived stress have shorter telomere length. Perceived stress was not measured in our study.

Prior research by the NECS has demonstrated three subphenotypes of centenarians: survivors (develop age-related morbidities prior to age 80), delayers (develop age-related morbidities at or after age 80 and before age 100), and escapers (survive to age 100 without any major age-related morbidities) (21). Using a larger sample of healthy and unhealthy centenarians may allow one to examine the relationship of telomere length to these three subphenotypes.

One remarkable finding is that the mean telomere length measurements for the healthy participants, 5.7 kilobasepairs (kbp), in our sample of individuals 97–108 years old are at the higher end of the range and/or above the average compared to other studies that have similarly aged as well as younger individuals. The Leiden 85+ Study demonstrated an average telomere length in their 85- to 101-year-old population ranging between 2 and 10 kbp, with most individuals having an average telomere length of about 4 kbp (13). The 2006 study by Bischoff and colleagues (14) demonstrated an average telomere length of 2.6–9.5 (subtracting 2 kb for the subtelomeric portion) for individuals 73–101 years old.

Telomeres are typically longer in women compared to similarly aged men. The results of our study were no exception. The literature suggests several explanations for this difference: Human telomerase reverse transcriptase (hTERT) may be stimulated by estrogen, resulting in increased telomerase and longer telomeres. Another possibility is that men may experience more oxidative damage, resulting in accelerated telomere erosion (22). A third explanation has been attributed to the mode of inheritance of telomere length, although this is still a source of debate (22,23).

Ultimately, using positive associations between healthy longevity and telomere length may be critical piece of the puzzle of the genetics of exceptional longevity. Phenotyping larger samples sizes as well as the increased availability and feasibility of genome-wide chips will hopefully facilitate such investigations.

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**CORRESPONDENCE**

Address correspondence to Della F. Terry, MD, MPH, Geriatrics Section, Boston Medical Center, 88 East Newton St, Robinson 2, Boston, MA 02118. E-mail: laterry@bu.edu or Richard Cawthon, MD, PhD, Eccles Institute of Human Genetics, University of Utah, Salt Lake City, UT 84112. E-mail: rcawthon@genetics.utah.edu

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The Gerontological Society of America, in collaboration with the University of Maryland, Baltimore County, is once again hosting a best paper competition in the area of Theoretical Developments in Social Gerontology.

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Papers outlining theoretical frameworks that cross disciplinary boundaries and the single disciplinary theoretical paradigm are encouraged. Papers examining the aging individual in a larger societal, economic, temporal, cultural, physical, and environmental context are welcomed.

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