Published in final edited form as:
Neurosci Lett. 2011 March 29; 492(1): 15–18. doi:10.1016/j.neulet.2011.01.041.

Relative Telomere Length and Cognitive Decline in the Nurses' Health Study

Elizabeth E. Devore[a], **Jennifer Prescott**[a,b,c], **Immaculata De Vivo**[a,b,c], and **Francine Grodstein**[a,b]

Jennifer Prescott: nhjxp@channing.harvard.edu; Immaculata De Vivo: devivo@channing.harvard.edu; Francine Grodstein: fgrodstein@partners.org

[a]Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, 181 Longwood Avenue, Boston, Massachusetts, 02115

[b]Department of Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, Boston, Massachusetts, 02115

[c]Program in Molecular and Genetic Epidemiology, Harvard School of Public Health, 677 Huntington Avenue, Boston Massachusetts, 02115

Abstract

Telomeres are short DNA repeats on the ends of mammalian chromosomes, which can undergo incomplete replication leading to gradual shortening with each cell cycle. Age and oxidative stress are contributors to telomere shortening; thus, telomere length may be a composite measure of biologic aging, and a potential predictor of health status in older adults. We evaluated whether relative telomere length (the proportion of telomere repeat copy number to single gene copy number, using a real-time PCR method) predicts cognitive decline measured ten years later among ~2,000 older participants in the Nurses' Health Study (NHS). Mixed linear regression was used to evaluate mean differences in cognitive decline according to telomere length. After adjustment for potential confounders, we found that decreasing telomere length was associated with more cognitive decline, although associations were modest (e.g. for a global score, averaging all six tests in our cognitive battery, mean difference=0.03 standard units per SD increase in telomere length; p=0.04). The magnitude of these estimates was similar to the differences we find in this cohort for women one year apart in age (e.g. the differences that we observe between women who

Corresponding author: Elizabeth Devore, 181 Longwood Avenue, Boston, Massachusetts, 02115; telephone: 617-525-2090; fax: 617-525-2008; nheed@channing.harvard.edu.

DISCLOSURES

Funding: This specific project was funded by a generous grant from the American Health Assistance Foundation (AHAF). On-going financial support for the Nurses' Health Study (NHS) and NHS cognitive sub-study are provided through NIH grants CA40356 and AG15424, respectively. Dr. Devore is supported by an NIH National Research Service Award Individual Postdoctoral Fellowship (F32 AG031633). The funding sources played no role in the study design; collection, analysis, and interpretation of data; writing of the manuscript; or decision to submit the paper for publication.

Role of the authors: All authors contributed materially to the original research in this article, and each author has approved the final article. Individual contributions of each author are as follows: Dr. Devore performed the data analysis and wrote and edited the manuscript; Dr. Prescott contributed to data collection and editing of the manuscript; Dr. De Vivo contributed to the concept and design of this study, data collection and analysis, and editing of the manuscript; and Dr. Grodstein contributed to the concept and design of this study, obtained grant funding, contributed to data collection and analysis, and provided substantial feedback for editing the manuscript.

are 73 versus 74 years of age); thus, our results suggest that telomere length is not a particularly powerful marker of impending cognitive decline.

Keywords

Telomeres; cognitive function; aging; epidemiology

INTRODUCTION

Telomeres are short, repetitive DNA sequences at the ends of mammalian chromosomes that prevent rearrangement and end-to-end fusion. Because DNA polymerase is unable to completely replicate them, telomeres experience replicative shortening with each cell cycle and eventually reach a critical threshold; at this point, cells stop dividing or undergo programmed cell death[6]. Oxidative stress contribute to telomere shortening[19], and the combined effects of replicative shortening and oxidative stress on telomere length may represent an important biological marker, perhaps even more relevant than chronological age, for predicting aging-related disease risk. Growing epidemiologic evidence has linked shorter telomere length with higher risk of mortality[3, 8, 10], cancer[9, 16, 18, 20, 26, 27], cardiovascular disease[1, 2, 4, 24], and dementia[8, 13, 17] – outcomes that are related to age and oxidative stress as well. Studies of telomere length and cognition have produced mixed results[7, 13, 14, 23, 28]; however, identifying predictors of subtle, early changes in cognitive function is an important public health priority, as possible interventions are likely to be most effective during the early stages of preclinical disease. In this study, we evaluated whether relative telomere length predicts cognitive decline ten years later, among older women participating in the Nurses' Health Study.

METHODS

The Nurses' Health Study (NHS) began in 1976, when 121,000 U.S. female registered nurses, aged 30–55 years old, responded to a mailed questionnaire about health and lifestyle factors. Since then, follow-up questionnaires have been mailed every two years, and participation rates have remained above 90% for all questionnaire cycles. Beginning in 1995–2000, participants who were at least 70 years of age and had no history of stroke were selected for a telephone-based study of cognitive function; 93% of eligible women participated and 7% refused. Follow-up interviews were conducted twice, at two-year intervals, and participation remained above >90% during follow up (mean time span over three interviews=4.3 years). Because the first several years were largely devoted to pilot interviews, the majority of women underwent initial cognitive assessments in 1999–2000. The institutional review board of Brigham and Women's Hospital (Boston, MA) approved this study.

Population for analysis

We obtained measurements of relative telomere length in a random sample of 239 women who were participating in the NHS cognitive sub-study. We also identified participants in the cognitive sub-study who had telomere length measured as part of previous NHS nested case-control studies of breast cancer (n=530), endometrial cancer (n=187), skin cancer (n=295), and stroke/myocardial infarction (n=841). These samples were combined, but skin cancer cases were excluded because a modest relation was found with telomere length in this cohort; no associations were found with breast and endometrial cancer, therefore we included these cases in our analyses. Although we initially excluded cases of stroke and myocardial infarction because these outcomes have been related to cognitive decline, we

include them in our analytic sample here as our results were similar regardless of their inclusion or exclusion. Thus, in total, we analyzed 2,092 participants with measured telomeres in the NHS cognitive study.

Assessment of relative telomere length

Using blood samples collected in 1989–1990, a quantitative polymerase chain reaction method was used to measure relative telomere length in genomic DNA extracted from peripheral blood leukocytes (PBL). The ratio of telomere repeat copy number to a single gene copy number (T/S) was assessed as previously described[16]. Each sample was analyzed in triplicate, and relative telomere length was calculated as the exponentiated T/S ratio. Coefficients of variation of the telomere and single-gene assay ranged from 0.46 to 3.02% and 0.29 to 2.07%, respectively. The coefficients of variation for the exponentiated T/S ratio of quality control samples ranged from 10–16%.

Assessment of cognitive function and decline

We administered a validated[22] cognitive battery consisting of six tests: the Telephone Interview for Cognitive Status (TICS), the East Boston Memory Test—immediate and delayed recall, category fluency, delayed recall of the TICS 10-word list, and digit-span backwards. Interviewers who administered the cognitive battery were blinded to telomere status, and participation rates were similar across all cognitive tests and remained stable over time. We focused on three primary outcomes: a global composite score that averaged together all six cognitive tests; a verbal composite score that averaged together four tests of verbal memory (a strong predictor of developing Alzheimer's disease[12, 21, 25]) – immediate and delayed recalls of both the East Boston Memory Test and TICS 10-word list; and TICS scores, which provide a measure of general cognition. We used z-scores to create composite scores because point values for our cognitive tests are not equivalent.

Statistical analysis

Because of batch-to-batch variation in telomere lengths over time, we created z-scores specific to each study. Multivariable-adjusted, mixed linear regression with random intercepts and slopes was used to evaluate mean differences in slopes of cognitive decline per standard deviation increase in telomere length. Ninety-five percent confidence intervals were calculated. We examined models adjusted for age and education (established risk factors for cognitive decline[11]), and models that were additionally adjusted for smoking, diabetes, and a history of cardiovascular factors: high blood pressure and use of antihypertensive medications, high cholesterol and use of cholesterol-lowering medications, and myocardial infarction. Because it is unclear when potential confounders might be most influential on the relation between telomere length and cognitive decline, we considered two approaches to statistical adjustment in our models: 1) using the status of covariates at the time of blood collection, and 2) using the status of covariates at the time of initial cognitive interview. However, our results were virtually identical despite the approach, and we therefore have chosen to present results using the status of covariates at the time of blood collection. We also assessed effect modification by age (continuous in years) and smoking status (current, former, never) because oxidative stress due to age and cigarette smoking might influence the association of telomere length and cognition.

All analyses were performed in SAS version 9 (SAS Institute Inc., Cary, NC).

RESULTS

At the time of blood draw, health and lifestyle characteristics of women in our analytic sample were similar across quartiles of telomere length (Table 1). In age- and education-

adjusted models, we observed that longer telomeres were associated with significantly slower decline in the verbal score (mean difference=0.04 standard units per SD in telomere length; p=0.03); associations for the global and TICS scores were borderline significant (Table 2). After adjusting for additional covariates, the association with telomere length became slightly more statistically significant for all three cognitive measures (p=0.02 for the verbal score, p=0.04 for the global and TICS scores). Specifically, the mean differences in decline were 0.04 standard units for the verbal score (95% CI: 0.01–0.08), 0.03 standard units for the global score (95% CI: 0.00–0.06), and 0.13 standard units for the TICS score (95% CI: 0.00–0.25). Because it can be difficult to interpret mean differences in rates of cognitive decline, we compared the effects of each SD increase in telomere length on cognitive decline to the effect of one year of age. The magnitude of the effect estimates we found for a one-SD difference in telomere length was approximately equivalent to the differences in cognitive decline that we observe for women one year apart in age (e.g. the difference observed for women who are 73 versus 74 years of age). That is, each one-SD increase in telomere length was cognitively equivalent to being approximately one year younger in age.

There was no effect modification by age (e.g. p-interaction for the verbal score=0.5) or smoking status (e.g. p-interaction for the verbal score=0.3).

DISCUSSION

We found a modest association between longer telomere length and slower cognitive decline in this cohort. The magnitude of these point estimates – a one-SD increase in telomere length being equivalent to approximately one year of chronological age – suggests that, although we identified significant relations between telomeres and cognitive decline, telomere length does not appear to be a particularly powerful marker of impending cognitive decline.

Five previous studies[7, 13, 14, 23, 28] of telomere length and cognition have produced mixed results, but four of these studies were fairly small (<355 participants)[7, 13, 14, 23] and two included cross-sectional analyses only[7, 23]; therefore, findings are somewhat difficult to interpret. Moreover, none of these studies considered the relation of telomere length at midlife to cognitive decline at older ages. However, the modest effect that we observed is generally consistent with results reported in the Health Aging and Body Composition (ABC) Study – the only other large, prospective study of telomeres and cognitive decline to date, where telomere length was associated with decline for one of two cognitive tests administered[28]. Again, a difference between our study and the Health ABC Study was the timing of telomere measurement; in the Health ABC Study, telomere length was assessed simultaneous with baseline cognitive testing (mean age of participants=74 years). In contrast, our study utilized telomere measurements that were obtained an average of ten years prior to initial cognitive testing. Thus, together, these results indicate that telomere length only modestly predicts cognitive decline, whether measured at younger or older ages.

Although previous epidemiologic data are not compelling, several mechanisms suggest a potential link between telomere length and cognitive decline. One possibility is that the shortening of telomeres and onset of cognitive decline share a common cause, either genetic (e.g. due to “aging genes”) or environmental (e.g. due to oxidative stress). Oxidative stress is known to play an important role in modulating telomere length[19] and pathology associated with cognitive impairments[15]. A second possibility is that telomere length might play a causal role in affecting cognitive decline, perhaps through a mechanism involving vascular factors. However, our analyses suggest that this mechanism is less likely, as adjustment for

cardiovascular factors made little difference in our point estimates. Alternatively, neurons are post-mitotic cells and thus PBL telomere length does not necessarily reflect brain health; yet, there does appear to be telomere shortening in microglia, which are proliferative[5]. Indeed, the association that we observed in this large cohort of older women was quite modest, indicating that PBL telomere length may not provide a particularly strong measure of brain aging.

Our study has limitations. First, we had a single measure of telomere length for each participant, and thus we were unable to evaluate rates of change in telomere length, which might be a more informative metric than a single telomere measurement. Nonetheless, the pathology underlying cognitive impairments appears to begin decades prior to onset of detectable symptoms, and thus our measurement of telomere length nearly ten years prior to initial cognitive assessments should be a clinically relevant time point for predicting cognitive decline. Second, cognitive measurements are subject to random measurement error, such that we expect a certain amount of non-differential misclassification in our outcome, which might have attenuated our results. However, we used a validated telephone-based cognitive interview and repeated measures of cognitive function; in addition, we have identified numerous associations of various exposures and cognitive decline in this cohort, clearly establishing that cognition is adequately measured.

In conclusion, we identified a modest association between longer telomeres and slower cognitive decline in this large cohort of older women. However, our modest results suggest that information on telomere length does not appear to provide a particularly powerful tool for predicting cognitive decline.

References

1. Benetos A, Gardner JP, Zureik M, Labat C, Xiaobin L, Adamopoulos C, Temmar M, Bean KE, Thomas F, Aviv A. Short telomeres are associated with increased carotid atherosclerosis in hypertensive subjects. Hypertension. 2004; 43:182–185. [PubMed: 14732735]
2. Brouilette SW, Moore JS, McMahon AD, Thompson JR, Ford I, Shepherd J, Packard CJ, Samani NJ. Telomere length, risk of coronary heart disease, and statin treatment in the West of Scotland Primary Prevention Study: a nested case-control study. Lancet. 2007; 369:107–114. [PubMed: 17223473]
3. Cawthon RM, Smith KR, O'Brien E, Sivatchenko A, Kerber RA. Association between telomere length in blood and mortality in people aged 60 years or older. Lancet. 2003; 361:393–395. [PubMed: 12573379]
4. Fitzpatrick AL, Kronmal RA, Gardner JP, Psaty BM, Jenny NS, Tracy RP, Walston J, Kimura M, Aviv A. Leukocyte telomere length and cardiovascular disease in the cardiovascular health study. Am J Epidemiol. 2007; 165:14–21. [PubMed: 17043079]
5. Flanary BE, Streit WJ. Telomeres shorten with age in rat cerebellum and cortex in vivo. J Anti Aging Med. 2003; 6:299–308. [PubMed: 15142431]
6. Harley CB. Telomere loss: mitotic clock or genetic time bomb? Mutat Res. 1991; 256:271–282. [PubMed: 1722017]
7. Harris SE, Deary IJ, MacIntyre A, Lamb KJ, Radhakrishnan K, Starr JM, Whalley LJ, Shiels PG. The association between telomere length, physical health, cognitive ageing, and mortality in non-demented older people. Neurosci Lett. 2006; 406:260–264. [PubMed: 16919874]
8. Honig LS, Schupf N, Lee JH, Tang MX, Mayeux R. Shorter telomeres are associated with mortality in those with APOE epsilon4 and dementia. Ann Neurol. 2006; 60:181–187. [PubMed: 16807921]
9. Jang JS, Choi YY, Lee WK, Choi JE, Cha SI, Kim YJ, Kim CH, Kam S, Jung TH, Park JY. Telomere length and the risk of lung cancer. Cancer Sci. 2008; 99:1385–1389. [PubMed: 18452563]
10. Kimura M, Hjelmborg JV, Gardner JP, Bathum L, Brimacombe M, Lu X, Christiansen L, Vaupel JW, Aviv A, Christensen K. Telomere length and mortality: a study of leukocytes in elderly Danish twins. Am J Epidemiol. 2008; 167:799–806. [PubMed: 18270372]

11. Lee S, Kawachi I, Berkman LF, Grodstein F. Education, other socioeconomic indicators, and cognitive function. Am J Epidemiol. 2003; 157:712–720. [PubMed: 12697575]
12. Locascio JJ, Growdon JH, Corkin S. Cognitive test performance in detecting, staging, and tracking Alzheimer's disease. Arch Neurol. 1995; 52:1087–1099. [PubMed: 7487561]
13. Martin-Ruiz C, Dickinson HO, Keys B, Rowan E, Kenny RA, Von Zglinicki T. Telomere length predicts poststroke mortality, dementia, and cognitive decline. Ann Neurol. 2006; 60:174–180. [PubMed: 16685698]
14. Mather KA, Jorm AF, Anstey KJ, Milburn PJ, Easteal S, Christensen H. Cognitive performance and leukocyte telomere length in two narrow age-range cohorts: a population study. BMC Geriatr. 10:62. [PubMed: 20843367]
15. Mattson MP. Pathways towards and away from Alzheimer's disease. Nature. 2004; 430:631–639. [PubMed: 15295589]
16. McGrath M, Wong JY, Michaud D, Hunter DJ, De Vivo I. Telomere length, cigarette smoking, and bladder cancer risk in men and women. Cancer Epidemiol Biomarkers Prev. 2007; 16:815–819. [PubMed: 17416776]
17. Panossian LA, Porter VR, Valenzuela HF, Zhu X, Reback E, Masterman D, Cummings JL, Effros RB. Telomere shortening in T cells correlates with Alzheimer's disease status. Neurobiol Aging. 2003; 24:77–84. [PubMed: 12493553]
18. Risques RA, Vaughan TL, Li X, Odze RD, Blount PL, Ayub K, Gallaher JL, Reid BJ, Rabinovitch PS. Leukocyte telomere length predicts cancer risk in Barrett's esophagus. Cancer Epidemiol Biomarkers Prev. 2007; 16:2649–2655. [PubMed: 18086770]
19. Saretzki G, Von Zglinicki T. Replicative aging, telomeres, and oxidative stress. Ann N Y Acad Sci. 2002; 959:24–29. [PubMed: 11976182]
20. Shao L, Wood CG, Zhang D, Tannir NM, Matin S, Dinney CP, Wu X. Telomere dysfunction in peripheral lymphocytes as a potential predisposition factor for renal cancer. J Urol. 2007; 178:1492–1496. [PubMed: 17707063]
21. Small BJ, Fratiglioni L, Backman L. Canaries in a coal mine: cognitive markers of preclinical Alzheimer disease. Arch Gen Psychiatry. 2001; 58:859–860. [PubMed: 11545669]
22. Stampfer MJ, Kang JH, Chen J, Cherry R, Grodstein F. Effects of moderate alcohol consumption on cognitive function in women. N Engl J Med. 2005; 352:245–253. [PubMed: 15659724]
23. Valdes AM, Deary IJ, Gardner J, Kimura M, Lu X, Spector TD, Aviv A, Cherkas LF. Leukocyte telomere length is associated with cognitive performance in healthy women. Neurobiol Aging. 2008
24. van der Harst P, van der Steege G, de Boer RA, Voors AA, Hall AS, Mulder MJ, van Gilst WH, van Veldhuisen DJ. Telomere length of circulating leukocytes is decreased in patients with chronic heart failure. J Am Coll Cardiol. 2007; 49:1459–1464. [PubMed: 17397675]
25. Welsh K, Butters N, Hughes J, Mohs R, Heyman A. Detection of abnormal memory decline in mild cases of Alzheimer's disease using CERAD neuropsychological measures. Arch Neurol. 1991; 48:278–281. [PubMed: 2001185]
26. Willeit P, Willeit J, Mayr A, Weger S, Oberhollenzer F, Brandstatter A, Kronenberg F, Kiechl S. Telomere length and risk of incident cancer and cancer mortality. JAMA. 304:69–75. [PubMed: 20606151]
27. Wu X, Amos CI, Zhu Y, Zhao H, Grossman BH, Shay JW, Luo S, Hong WK, Spitz MR. Telomere dysfunction: a potential cancer predisposition factor. J Natl Cancer Inst. 2003; 95:1211–1218. [PubMed: 12928346]
28. Yaffe K, Lindquist K, Kluse M, Cawthon R, Harris T, Hsueh WC, Simonsick EM, Kuller L, Li R, Ayonayon HN, Rubin SM, Cummings SR. Telomere length and cognitive function in community-dwelling elders: Findings from the Health ABC Study. Neurobiol Aging. 2009

RESEARCH HIGHLIGHTS

- Decreasing telomere length was associated with faster cognitive decline
- However, telomere length is not a particular powerful marker of cognitive decline

Table 1

Characteristics of women at blood draw in 1990 [a], by quartile of telomere length (n=2,092)

	Quartile 1	Quartile 2	Quartile 3	Quartile 4
Mean age, in years	65.0	64.5	64.6	64.5
Education, %				
RN	76	76	73	73
BA	16	16	21	21
Graduate degree	8	8	6	6
Alcohol intake (g/day), % [b]				
None	38	42	41	39
1–14	52	47	48	50
≥15	10	11	11	11
Smoking status, %				
None	45	42	51	49
Past	41	44	37	42
Current	14	14	12	9
Antidepressant use, %	5	7	3	4
Median physical activity, MET-hrs	10.2	10.6	11.5	10.9
Body mass index (kg/m^2), % [b]				
<22	23	21	23	22
22–24	30	33	30	34
25–29	33	32	34	31
≥30	14	14	13	13
Vitamin E supplement use, % [b]	19	19	19	21
Multivitamin use, % [b]	39	45	41	43
History of high blood pressure, %	41	35	37	38
History of high cholesterol, %	44	48	53	50
History of diabetes, %	4	6	6	5
History of myocardial infarction, %	4	3	2	1
Mean scores at initial cognitive assessment				
Global score	−0.07	−0.03	0.03	0.01
Verbal score	−0.06	−0.02	0.00	0.00
TICS	33.9	34.0	33.9	34.0

[a] Except that physical activity was reported in 1988 and antidepressant use was reported for the first time in 1996.

[b] These percentages are of non-missing values.

Table 2

Mean differences in slopes of four-year cognitive decline, per standard deviation increase in telomere length [a]

	Mean difference in cognitive decline	p-value
Global		
Age- and education-adjusted Model [b]	0.03 (0.00, 0.06)	0.06
Fully-adjusted model [c]	0.03 (0.00, 0.06)	0.04
Verbal		
Age- and education-adjusted Model [b]	0.04 (0.00, 0.08)	0.03
Fully-adjusted model [c]	0.04 (0.01, 0.08)	0.02
TICS		
Age- and education-adjusted Model [b]	0.13 (0.00, 0.25)	0.05
Fully-adjusted model [c]	0.13 (0.00, 0.25)	0.04

[a] The standard deviation is 0.95 in our analytic sample.

[b] Adjusted for age (continuous in years), education (RN, BA, graduate degree).

[c] Adjusted for age, education, smoking (none, past, current), high blood pressure (yes and treated, yes and untreated, no), high cholesterol (yes and treated, yes and untreated, no), myocardial infarction (yes, no), and diabetes (yes, no).