Race/ethnicity and telomere length in the Multi-Ethnic Study of Atherosclerosis

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Summary

Telomere length has emerged as a marker of exposure to oxidative stress and aging. Race/ethnic differences in telomere length have been infrequently investigated. Leucocyte telomere length (LTL) was assessed 981 white, black and Hispanic men and women aged 45-84 years participating in the Multi-Ethnic Study of Atherosclerosis. Direct measurement and questionnaire were used to assess covariates. Linear regression was used to estimate associations of LTL with race/ethnicity and age after adjustment for sex, income, education, smoking, physical activity, diet, and body mass index. On average blacks and Hispanics had shorter telomeres than whites (adjusted mean differences (standard error) in T/S ratio compared to whites: -0.041 (0.018) for blacks and -0.044 (0.018) for Hispanics). Blacks and Hispanics showed greater differences in telomere length associated with age than whites (adjusted mean differences in T/S ratio per one year increase in age -0.0018, -0.0047, and -0.0055 in whites, blacks, and Hispanics respectively). Differences in age associations were more pronounced and only statistically significant in women. Race/ethnic differences in LTL may reflect the cumulative burden of differential exposure to oxidative stress (and its predictors) over the lifecourse.

Keywords

Telomeres; race/ethnicity; aging

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Introduction

Telomeres are protein/DNA structures that cap the ends of linear chromosomes of eukaryotes and support chromosomal stability by protecting against DNA degradation(von Zglinicki and Martin-Ruiz, 2005). In cells with low levels of telomerase, a cellular enzyme with telomere-protecting properties, telomeres shorten during DNA replication. Shortened telomeres eventually result in cellular senescence. Most adult somatic cells have low or absent telomerase and experience telomere attrition with each mitotic cycle (Serrano and Andres, 2004). Oxidative stress increases the loss of telomere repeats per cell division (Saretzki and Von Zglinicki, 2002; Tchirkov and Lansdorp, 2003). For these reasons telomere length has emerged as a potential biomarker of replicative history and cumulative history of oxidative stress (von Zglinicki and Martin-Ruiz, 2005).

The study of telomere length is of interest in human health because telomere loss and cellular senescence may have implications for the functionality of tissues of special relevance to particular disease processes such as immune response and infection (Cawthon et al., 2003; von Zglinicki and Martin-Ruiz, 2005), atherosclerosis (Serrano and Andres, 2004), and osteoporosis and osteoarthritis (von Zglinicki and Martin-Ruiz, 2005). It has also been posited that leukocyte telomere length (LTL) may serve as a general marker of aging and the cumulative effects of oxidative stress on the organism as a whole (von Zglinicki and Martin-Ruiz, 2005). Although there are variations in the dynamics of telomere length across different tissues(Prowse and Greider, 1995; Serrano and Andres, 2004), there is some evidence that telomere lengths for different tissues within an individual are correlated (Takubo et al., 2002; von Zglinicki et al., 2000). Shorter leukocyte telomere length has been linked to subclinical atherosclerosis(Fitzpatrick et al., 2007) cardiovascular risk factors associated with aging (Benetos et al., 2001; Fitzpatrick et al., 2007) and mortality (Bakaysa et al., 2007; Cawthon et al., 2003; Honig et al., 2006; Kimura et al., 2008), although mortality associations have not always been replicated (Bischoff et al., 2006; Harris et al., 2006; Martin-Ruiz et al., 2005). These associations appear to be independent of chronological age suggesting an added value of telomere length as a marker of biological or cellular aging.

Little is known about the association of LTL with race/ethnicity. Membership in certain race/ethnic groups may be associated with a range of exposures that could result in accelerated aging and telomere shortening. For example, recent work has suggested that life stress is associated with shorter telomeres and greater levels of oxidative stress(Epel et al., 2004). The presence of telomere differences would suggest that long term exposure to oxidative stress (and its behavioral and psychosocial antecedents) could contribute to persistent differences in health and mortality by race/ethnicity which are often unexplained by traditional risk factors. The study of differences in telomere shortening by race/ethnicity could also yield insights into paradoxical mortality differences between race/ethnic groups, such as the hypothesized mortality advantage of US Hispanics suggested by some research (Palloni and Arias, 2004). Using cross-sectional data from a subsample of the Multi-Ethnic Study of Atherosclerosis (MESA), we examined race/ethnic differences in telomere length in a large multi-ethnic population-based study of adults aged 45 to 84 years.

Results

LTL was available for 981 participants, including 182 whites, 279 blacks, and 520 Hispanics (Table 1). The mean age was 62.6 years in whites, 60.8 years in blacks, and 61.3 years in Hispanics. Age ranged from 45 to 84 years in each race/ethnic group. Hispanics and blacks were more likely than whites to be in the lower income and educational categories. Median telomere length (T/S ratio) was lower in blacks and Hispanics than in whites but differences

in means were not statistically significant. Telomere length was inversely associated with age with stronger associations observed in women than in men (mean difference (SE) in T/S ratio per 10 year age increase 0.064 (0.007) and 0.042 (0.007) in women and men respectively, P for heterogeneity 0.03).

Table 2 shows mean differences in T/S ratio by race/ethnicity and covariates. Blacks and Hispanics had slightly shorter telomeres than whites after adjustment for age and sex, although differences were not statistically significant (Table 2). These differences persisted and became statistically significant after additional adjustment for income, education, smoking, physical activity, diet and BMI (mean differences in T/S ratio (SE) compared to whites: -0.041 (0.018) for blacks and -0.044 (0.018) for Hispanics). In the fully adjusted model, women had significantly longer telomeres than men (at the mean age) but age was more strongly associated with shorter telomeres in women than in men. Income was not associated with telomere length but an inverse association was observed for education (mean difference per year of education -0.004 (SE 0.001)). Higher pack years of smoking and higher intake of processed meats were significantly associated with shorter telomeres, and marginally significant associations were observed between greater inactive leisure activity and shorter telomeres (Table 2).

The association of age with telomere length differed by race/ethnicity with blacks and Hispanics showing greater differences in telomere length associated with age after adjustment for sex, income, and education (Table 3). These differences persisted after additional adjustment for smoking, physical activity, diet, and BMI (mean adjusted differences in T/S ratio per one year increase in age -0.0018, -0.0047, and -0.0055 in whites, blacks, and Hispanics respectively). Stratified analyses showed that stronger associations of age with telomere shortening in blacks and Hispanics compared to whites were present in both genders but race/ethnic differences were greater (and only statistically significant) in women (Table 3). Adjusted mean differences in T/S ratio per one year increase in age – were 0.0012, -0.0062, and -0.0071 in white, black, and Hispanic women respectively, and -0.0012, -0.0030, and -0.0038 in whites, black, and Hispanic men respectively. This heterogeneity by sex was not statistically significant (P>0.1 in all three models).

Figure 1 shows mean predicted telomere length by race/ethnicity and age in men and women adjusted to the mean covariate distribution of the full sample. In men, whites had longer telomeres than blacks and Hispanics across the full age range, and age slopes were slightly stronger in blacks and Hispanics than in whites, although these differences were not statistically significant. In women, the stronger age slope in black and Hispanic women (P=0.03 for Blacks and 0.01 for Hispanics) resulted in widening race/ethnic differences across the age span, and shorter telomeres in blacks and Hispanics than in whites in the older age groups.

Discussion

The central finding of our analyses is that in a population-based sample of adults 45-84 years of age, cross –sectional associations of age with shorter telomeres were stronger in black and Hispanics than in whites. In women, associations of age with telomere length were nearly six times greater in black and Hispanic women than white women, whereas in men associations were three times stronger in blacks and Hispanics than in whites. These associations were independent of socioeconomic factors, BMI, and behaviors. In analyses pooling across ages (and ignoring the age by race/ethnicity interaction) telomeres were shorter in blacks and Hispanics than in whites after adjustment for socioeconomic factors, BMI, and behavioral covariates. These differences were equivalent to aging 6-10 years. Given the presence of age by race/ethnicity interactions, overall comparisons across race/

ethnic groups are less meaningful than comparisons of age effects because they will depend on the age distribution of the samples compared

Few studies have investigated race/ethnic differences in telomere length. Recently, Hunt el al(Hunt et al., 2008) reported longer telomeres in blacks than in whites in cross-sectional analyses of sub-samples of the Family Heart Study (n=1968) and the Bogalusa Heart Study (n=573). Black-white differences were substantially smaller in the older Family Heart Study sample (mean age 57 years) than in the younger Bogalusa Heart Study sample (mean age 31 years): 63% smaller in men and 53% smaller in women. Hunt et al also report a steeper decline in telomere length with age in blacks than in whites, although in their analyses Blacks had on average longer telomeres than whites across most of the age range. Differences in age composition may have contributed to the differences between our results and those obtained by Hunt et al in analyses pooling across ages. Sampling differences may also have contributed: the FHS sample included participants from high and low CVD risk families and the Bogalusa Heart Study recruited children from a single semirural community in Louisiana. Ours is a population –based sample of individuals free of cardiovascular disease living in two large metropolitan areas. Additional replications are needed to understand heterogeneity in race/ethnic differences in telomere length across samples.

Telomere length did not differ between blacks, whites and Hispanics in a small sample of newborns(Okuda et al., 2002). Our results suggest that race differences in telomere length may emerge and grow with age. No studies of which we are aware have investigated telomere differences in adults from race/ethnic groups other than blacks and whites. We show that similar to blacks, Hispanics in our sample show stronger associations of telomere length with age than whites. To the extent that telomere length predicts mortality, our findings are not consistent with a protective effect of Hispanic ethnicity on mortality. The implications for health of the telomere differences we observed and their correspondence (or absence of correspondence) with mortality differentials by race/ethnicity and age need to be further investigated.

As many other biological parameters, telomere length is likely to be a product of the combined effect of genetic and environmental factors. Although telomere length at birth may be partly heritable(Andrew et al., 2006) the strong differences in the associations of age with telomere length by race/ethnicity (and consequent changing race differences in telomere length with age) suggest that environmental factors are likely to play an important role in race/ethnic differences. These environmental factors may include factors that increase the turnover of leucocytes (such as inflammation) as well as factors that increase oxidative stress. Both behavioral and psychosocial factors have been linked to inflammation and oxidative stress (Irie et al., 2003; Irie et al., 2001; Laufs et al., 2005; Steptoe et al., 2007). Long term exposures to these factors over the lifecourse may contribute to stronger associations of age with telomere length in blacks than in whites, and shorter telomeres in blacks than in whites at older ages. In our analyses, race/ethnic differences persisted after adjustment for available behavioral measures (smoking, diet, physical activity) and BMI, but limitations in the behavioral measures as well as the absence of measures of these behaviors over the lifecourse may have limited our ability to adjust for these factors.

The other covariates investigated (pack-years of smoking, BMI, processed meat intake, and physical activity) were generally related to telomere length in the expected direction. An important exception was socioeconomic position. Education was inversely related to telomere length and no associations were observed for income. Few studies have investigated socioeconomic differences in telomere length: one study of 1552 Caucasian female twins found shorter telomeres in manual compared to nonmanual workers but no consistent trend across occupational categories and no differences by income or education

(Cherkas et al., 2006). Another study of 318 men and women aged 50 years found no differences in telomere length by adult or lifecourse occupational class(Adams et al., 2007). The socioeconomic composition of our sample (which included a large number of Hispanics with low education) as well as the specific measures available may have limited our ability to detect socioeconomic differences. Our results were robust to alternative categorizations of income and education. Moreover, our main findings which relate to race/ethnic differences in age effects were largely unaffected by adjustment for socioeconomic factors.

Strengths of our study include the large sample size, the population-based nature and broad age range, and the triethnic composition. The MESA sample was not designed to be representative of each race/ethnic group in the United States. Although race/ethnic differences in major cardiovascular risk factors have generally been consistent with those reported in nationally representative samples, the contribution of selection factors to our results cannot be categorically ruled out. MESA participants were free of clinical cardiovascular disease at baseline. If telomere length is associated with cardiovascular disease prevalence and prevalence varies by race/ethnicity, this exclusion may have resulted in underestimates of race/ethnic differences in telomere length. Differences in mean telomere length measured in whole leukocyte pools may be influenced by the proportions of different kinds of leukocytes(Weng, 2001). It is unclear whether differential cell counts could be patterned by age and race/ethnicity in such a way that they would explain the patterns we observed. Hunt et al.reported no relationship between leucocyte differential counts and mean telomere length in whites or Blacks (Hunt et al., 2008). However the data available did not allow us to rule out this factor as a contributor.

Our analyses are cross-sectional and therefore we were not able to examine race/ethnic differences in the effects of aging within an individual. Nevertheless the presence of important cross-sectional race/ethnic differences in telomere length in adulthood is still informative as it reflects cumulative exposures operating over the lifecourse. These long-term cumulative effects are difficult to capture in short term studies of longitudinal change. Cross-sectional analyses of the effects of aging may yield biased estimates of the longitudinal effect of aging when there are important cohort or period effects(Jacobs et al., 1999). If early life exposures are related to telomere length and vary substantially by birth cohort and race/ethnicity, they may result in cohort effects and contribute to the race/ethnic differences in cross-sectional age associations that we report. This may occur for example if elderly blacks and Hispanics were more likely than elderly whites to be exposed to childhood environments associated with premature aging and shorter telomeres. In addition, cross-sectional associations of age with telomere length among "survivors" (like our study) will underestimate true race/ethnic differences in the effects of aging when there is differential mortality by age for the different race/ethnic groups. Only lifecourse studies of the dynamics of telomeres can provide definitive answers to questions regarding effects of aging. Age effects may also be non-linear but there was no clear evidence of nonlinearity in the data we had available so the simpler linear model was used.

Our data provide evidence of substantially stronger cross-sectional associations of age with telomere shortening in blacks and Hispanics than in whites, resulting in shorter telomeres in Blacks and Hispanics compared to whites at older ages. These differences were not explained by BMI and behavioral risks factors. The complexities of interpreting results of race/ethnic comparisons of biological parameters have been noted(Kaufman and Cooper, 2008). The determinants of differences in the rate of telomere shortening with age remain to be identified but could involve greater exposure to a range of environmental stressors over the lifecourse in blacks and Hispanics compared to in whites. Additional multiethnic studies are needed to confirm these findings. If these differences are confirmed in other samples, understanding the reasons for differential rates of aging (and its biological consequences)

could have implications for understanding disparities by race/ethnicity in multiple health outcomes.

Experimental Procedures

MESA is a longitudinal study supported by NHLBI with the goal of identifying risk factors for subclinical atherosclerosis(Bild et al., 2002). Between July 2000 and August 2002, 6814 men and women who identified themselves as white, black, Hispanic, or Chinese were 45 to 84 years old and free of clinically apparent CVD, were recruited from 6 US communities, including New York City New York, and Los Angeles County, California. Each field site recruited from locally available sources, which included lists of residents, lists of dwellings, and telephone exchanges.

Telomeres were assessed on a random subsample of approximately 1000 white, black, and Hispanic participants aged 45 to 84 years from the New York and Los Angeles sites of MESA who agreed to participate in an ancillary study to MESA examining the effects of stress on cardiovascular outcomes (the MESA Stress Study). Only white, black, and Hispanic participants were eligible to participate.

LTL was measured at the baseline examination by quantitative PCR (Q-PCR).(Cawthon, 2002) Each sample was amplified for telomeric DNA and for 36B4, a single-copy control gene that provided an internal control to normalize the starting amount of DNA. A four-point standard curve (2-fold serial dilutions from 10 to 1.25 ng DNA) was used to transform cycle threshold into nanograms of DNA. Baseline background subtraction was performed by aligning amplification plots to a baseline height of 2% in the first 5 cycles. The cycle threshold was set at 20% of maximum product. All samples were run in triplicate and the median was used for calculations. The amount of telomeric DNA (T) was divided by the amount of single-copy control gene DNA (S), producing a relative measurement of the telomere length (T/S ratio). Two control samples were run in each experiment to allow for normalization between experiments and periodical reproducibility experiments were performed to guarantee correct measurements. The intra- and inter-assay variability (coefficient of variation) for Q-PCR was 6 and 7%, respectively.

Race and ethnicity were characterized based on participants' responses to questions modeled on the Year 2000 US census. Family income and education were each collected inn several categories an treated as continuous variables or collapsed into three groups (<$20,000,; $20,000-$49,999; and $50,000 or more; and less than high school; complete high school, technical school certificate or associate degree; and complete college or more). Smoking was characterized based on participant responses to standardized questions. Physical activity was assessed via questionnaire. Inactive leisure activities (MET-min/wk) was the main measure investigated because leisure activity was found to be associated with telomere length in prior analyses(Cherkas et al., 2008; Nettleton et al., 2008). Usual dietary intake was assessed using a validated food frequency questionnaire (Mayer-Davis et al., 1999; Nettleton et al., 2006). Processed meat intake (including ham/hot dogs/lunch meats, sausage, organ meats, ham hocks) in servings per day was selected because it was the only dietary variable shown to be related to telomere length in prior analyses of the MESA sample (Nettleton et al., 2008).

Linear regression was used to estimate mean differences in telomere length associated with race/ethnicity after adjustment for age and sex, socioeconomic factors, and after additional adjustment for body mass index, and the behavioral factors of smoking, diet and physical activity. Body mass index and the behavioral factors were investigated because they have been hypothesized to be associated with telomere length (possibly through their effects on

oxidative stress) and could confound or mediate any observed differences in telomere length by race/ethnicity (Cherkas et al., 2008; Nettleton et al., 2008; Valdes et al., 2005). An age by sex interaction term was included in all models because there was evidence of significant heterogeneity in associations of age with telomere length by gender. In order to investigate differences in the effects of aging on telomere length by race/ethnicity we also fit models that included interaction terms between race/ethnicity and age. Interactions between other risk factors and age were also included to allow investigation of whether these factors accounted for any race/ethnic differences in age effects observed. These models were used to predict slopes by age, sex and race/ethnicity after adjustment for covariates.

All P values reported correspond to two-tailed tests. The study was approved by Institutional Review Boards at UCLA, Columbia University, and the University of Michigan. All subjects gave written informed consent.

Acknowledgments

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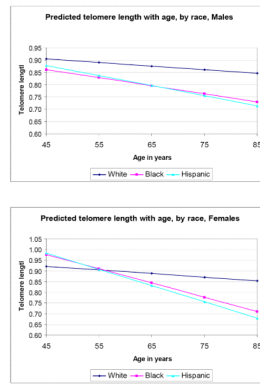
Figure 1. Predicted telomere length by age, sex, and race/ethnicity*
*Predictions based on sex-stratified full models shown in Table 3. All predictions are at the mean levels of risk factors. In men, P values for differences in slopes (compared to whites) are 0.5 for Blacks and 0.3 for Hispanics; in women they are 0.03 for Blacks and 0.01 for Hispanics.

Table 1

Selected characteristics of study sample by race/ethnicity, the Multiethnic Study of Atherosclerosis (n=981)

	Whites (n=182)	Blacks (n=279)	Hispanics (n=520)	P value[*]
Mean age (SD) in years	62.6 (10.3)	60.8 (10.1)	61.3 (9.7)	*0.1692*
Percent male	48.9%	44.8%	48.6%	*0.5406*
Income (% distribution)				
<20,000	7.9	22.6	40.3	
20-37,499	36.5	48.9	33.5	
>=37,500	55.6	28.5	15.2	*<.0001*
Education (%distribution)				
Less HS	5.0	10.0	44.0	
Complete HS	34.6	67.0	46.5	
4yr college / tech cert	60.4	22.9	9.4	*<.0001*
Pack-years of smoking (Mean, SD)	9.2 (14.9)	10.1 (15.9)	6.8 (15.8)	*0.0117*
Inactive Leisure MET-min/wk	1928 (1208)	1869 (1146)	1463 (945)	*<.0001*
Processed Meats (servings/day)	0.111 (0.19)	0.196 (0.34)	0.114 (0.20)	*<.0001*
Body Mass Index (kg/m^2)	26.7 (4.9)	29.9 (6.2)	29.3 (5.2)	*<.0001*
Telomere length (T/S ratio)				
10th percentile	0.66	0.63	0.63	
25th percentile	0.76	0.70	0.72	
50th percentile	0.85	0.82	0.83	
75th percentile	0.94	0.94	0.96	
90th percentile	1.08	1.09	1.10	
Mean (SD)	0.85 (.14)	0.84 (.18)	0.85 (.18)	*0.6206*

[*] P value for comparison across race/ethnic groups are based on F-tests for continuous variables and chi-square tests for categorical variables.

Table 2

Mean differences in telomere length (T/S ratio) by race/ethnicity after adjustment for sets of covariates

	Adjusted for age and sex		Adjusted for age, sex, income, and education		Age, sex, race, SEP, smoking, BMI, leisure time minutes, Diet	
	Mean diff. (SE)	P value	Mean diff. (SE)	P value	Mean diff. (SE)	P value
Whites	Reference		Reference		Reference	
Blacks	-0.025 (0.016)	0.1095	-0.030 (0.017)	0.0713	-0.041 (0.018)	0.0248
Hispanics	-0.010 (0.014)	0.4773	-0.028 (0.017)	0.1043	-0.044 (0.018)	0.0152
Sex (at mean age)						
Male	Reference		Reference		Reference	
Female	0.052 (0.011)	<.0001	0.05 (0.011)	<.0001	0.041 (0.012)	0.0005
Age (per year)						
Male	-0.004 (0.001)	<.0001	-0.004 (0.001)	<.0001	-0.003 (0.001)	0.0002
Female	-0.007 (0.001)	<.0001	-0.007 (0.001)	<.0001	-0.007 (0.001)	<.0001
Education (per year)			-0.004 (0.001)	0.0056	-0.004 (0.001)	0.0052
Income (per $10K increase)			0.002 (0.002)	0.2762	0.001 (0.002)	0.5873
Pack-years (in 10s)					-0.007 (0.004)	0.0537
BMI					0.001 (0.001)	0.5789
Leisure MET-mins (in 1000s)					-0.009 (0.006)	0.1273
Processed Meats (servings/day)					-0.047 (0.023)	0.0426

All models include an interaction between age and sex (P<0.05 in all models). Sex differences are estimated at the mean age. Interactions between sex and race/ethnicity were not statistically significant in any of the models (all P>0.1) and were not included.

Table 3

Mean differences in telomere length associated with a one year difference in age by race/ethnicity after adjustment for sets of covariates[*]

	Adjusted for sex	Adjusted for sex, income, and education†	Adjusted for sex, income, education, smoking, BMI, and leisure activity, and diet‡
Full Sample			
Whites	-0.0031 (0.0012)	-0.0029 (0.0013)	-0.0018 (0.0015)
Blacks	-0.006 (0.001)	-0.0059 (0.001)	-0.0047 (0.0011)
Hispanics	-0.0057 (0.0007)	-0.0059 (0.0008)	-0.0055 (0.0009)
P value (whites-blacks)†	*0.0604*	*0.0562*	*0.0864*
P value (whites-hispanics)†	*0.069*	*0.0594*	*0.0301*
Men			
Whites	-0.0039 (0.0018)	-0.0042 (0.0021)	-0.0012 (0.0024)
Blacks	-0.0047 (0.0014)	-0.0048 (0.0015)	-0.0030 (0.0017)
Hispanics	-0.0041 (0.001)	-0.0041 (0.0011)	-0.0038 (0.0012)
P value (whites-blacks)†	*0.718*	*0.8098*	*0.4988*
P value (whites-hispanics)†	*0.9273*	*0.9867*	*0.317*
Women			
Whites	-0.0031 (0.0016)	-0.0026 (0.0017)	-0.0012 (0.002)
Blacks	-0.0074 (0.0013)	-0.0072 (0.0014)	-0.0062 (0.0016)
Hispanics	-0.0074 (0.0011)	-0.0075 (0.0012)	-0.0071 (0.0013)
P value (whites-blacks)†	*0.0372*	*0.0307*	*0.0299*
P value (whites-hispanics)†	*0.025*	*0.0215*	*0.0128*

[*] All models (except sex stratified models) include interactions between age and sex, and between age and each of the other risk factors. Mean differences per 1 year of age in the full sample are adjusted to the overall sex composition of the full sample. Risk factor adjusted estimates are also adjusted to the mean risk factor distribution of the full sample.