Short Communication

Obesity and Weight Gain in Adulthood and Telomere Length

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Abstract

Obesity and weight gain in adulthood are associated with an increased risk of several cancers. Telomeres play a critical role in maintaining genomic integrity and may be involved in carcinogenesis. Using data from 647 women ages 35 to 74 years in the United States and Puerto Rico (2003-2004), we examined the association between current and past anthropometric characteristics and telomere length in blood. In a multivariate linear regression model, higher current body mass index (BMI) and hip circumference were inversely associated with telomere length. Higher BMI in the 30s was associated with shorter telomere length among women ages ≥40 years ($P_{trend} < 0.01$). Weight gain since the age 30s ($P_{trend} = 0.07$) and weight cycling ($P_{trend} = 0.04$) were also inversely associated with telomere length. When current BMI and BMI at ages 30 to 39 years were considered together, the most marked decrease in telomere length was found for women who had overweight or obese BMI at both time points (mean telomere repeat copy number to single-copy gene copy number ratio = 1.26; 95% confidence interval, 1.21-1.30) compared with women who had normal BMI at both times (mean telomere repeat copy number to single-copy gene copy number ratio = 1.33; 95% confidence interval, 1.30-1.36). These findings support the hypothesis that obesity may accelerate aging, and highlight the importance of maintaining a desirable weight in adulthood. (Cancer Epidemiol Biomarkers Prev 2009;18(3):816–20)

Introduction

Telomeres, noncoding double-stranded repeats (TTAGGG in humans) at the ends of chromosomes, become shortened with each cell division due to incomplete replication of the lagging strand (1). This process is further accelerated by oxidative stress and inflammation (2, 3). Although the findings are not completely consistent, short telomeres have been associated with an increased risk of insulin resistance (4, 5), cardiovascular disease (6, 7), and several cancers (8-11).

Obesity is implicated in many age-related disorders (12) and has been recognized as a state of increased oxidative stress (13) and inflammation (14). Shorter telomeres have been associated with increasing body mass index (BMI; refs. 2, 3) and more recently with increasing waist and hip circumferences in women (15).

The present study investigated the relationship between various measures of current body size and telomere length in 647 women ages 35 to 74 years. Changes in weight and obesity status since women were in their 30s were also examined in relation to telomere length among 608 women ages ≥40 years.

Materials and Methods

Study Population. The National Institute of Environmental Health Sciences Sister Study[3] is a prospective cohort study of environmental and genetic risk factors for breast cancer and other endpoints in ~50,000 women ages 35 to 74 years who do not have breast cancer themselves but have a sister who was diagnosed with the disease. Details of the study design have been described elsewhere (16). The study was approved by the Institutional Review Board of the National Institute of Environmental Health Sciences, NIH and the Copernicus Group Institutional Review Board. Selection criteria were developed for another study (17). Briefly, women who enrolled during the vanguard phase of the Sister Study were included in the first annual health update follow-up mailing in June 2005 and were not known to have developed breast cancer at the time of follow-up were eligible for the study. Of 2,086 eligible women, 295 were excluded for one or more of the following reasons: missing or inadequate blood or urine sample, urine

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Note: S. Kim, C.G. Parks, and D.P. Sandler conceptualized the study. R.M. Cawthon did laboratory analysis. S. Kim analyzed and interpreted the data and drafted the article. D.P. Sandler, L.A. DeRoo, and J.A. Taylor contributed to the interpretation of the data and provided editorial and scientific review. C.G. Parks and D.P. Sandler obtained funding. All authors contributed to discussion of the findings and revision of the article.

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sample that was not a first morning void, major dental procedure or surgery within the past week, current shift work, chemotherapy or radiation treatment for cancer, or missing value for race or smoking status. A further 18 women were excluded due to known breast cancer diagnosis before follow-up. Of 1,773 women left, we selected all women with high or very high perceived stress [score = 6-16 based on the four-item version of perceived stress scale developed by Cohen et al. (18)], non-White race, and current smoking and a random sample of the remaining women for a final weighted random sample of 740 women. Duplicate measurements were available for 647 women because 54 were run in pilot assays without adequate plate controls, 29 had failed PCRs, and 10 samples were run only in a single plate. For methodologic consistency among samples, only women with duplicate measurements were included in the present analysis. However, the distributions of telomere length were similar in those with and without duplicate measurements, and the relationship between obesity and telomere length did not change by further inclusion of women with a single measurement.

Anthropometric Measurement. Current height, weight, and hip and waist circumferences were measured during a home visit and were used to derive current BMI and waist-to-hip ratio. BMI was categorized based on WHO definitions (12) as normal or underweight (<25.0 kg/m^2), overweight (25-29.9 kg/m^2), or obese (≥30.0 kg/m^2). Waist circumference was classified based on the American Diabetes Association criteria for abdominal obesity as normal (<80 cm), action level 1 (80-87.9 cm), or action level 2 (≥88 cm; ref. 19). Other body size variables without known standard classification criteria were categorized into quartiles (for height and weight) or tertiles (for hip circumference and waist-to-hip ratio) based on distributions of the entire study population.

In a computer-assisted telephone interview, women ages ≥40 years were asked the following question: ''Thinking back to your 30s (when you were not pregnant, breastfeeding, or in the 6 months after pregnancy), what was your average weight?'' The self-reported average weight at ages 30 to 39 years (hereafter called past weight) was used to assess changes in weight and obesity status during adulthood. Weight change since their 30s was calculated as the difference between current and past weights. Cut points for weight change categories were chosen in consideration of those used in previous literature on weight change (20). Change in obesity status from the 30s was classified based on BMI in the 30s (hereafter called past BMI) and current BMI as follows: (*a*) having a normal BMI at both time points if both past and current BMI fall in the normal range, (*b*) gaining weight from normal past BMI to currently overweight BMI, (*c*) gaining weight from normal past BMI to currently obese BMI, (*d*) having an overweight or obese BMI at both time points if both past and current BMI fall in overweight or obese categories, and (*e*) losing weight from overweight past BMI to currently normal BMI or from obese past BMI to currently normal or overweight BMI. Additionally, women were asked the following question about lifetime episodes of weight cycling: ''How many times in your life have you lost ≥20 pounds (9 kg) and then later gained all of the weight back? [Do not count weight changes related to pregnancy.]'' The response to this question was categorized as never, once, two to three times, or four times or more.

Assessment of Telomere Length. DNA was extracted from whole blood stored at −80°C. Telomere length was quantified using the real-time quantitative PCR assay described previously (21), with some modifications. Briefly, each sample was amplified for telomeric DNA and a single-copy control gene in 1 μL aliquots containing 100 to 200 ng template DNA. Based on a standard curve with serial dilutions, cycle threshold was transformed into nanograms of DNA. A total of 647 specimens were run in triplicate on duplicate plates. The ratio of telomere repeat copy number to single-copy gene copy number (T/S ratio) was calculated from the average telomeric DNA and single-copy control gene of triplicate measurements in a single plate. Additionally, three controls with known T/S ratio (one each at high, medium, and low T/S ratio) were included in all assay batches to adjust for interbatch variation. After the adjustment, the coefficient of variation of the adjusted replicates was 8.5%. Data are the average of the adjusted replicates of T/S ratio. The average T/S ratio is an indicator of telomere length; a lower T/S ratio reflects shorter telomere length.

Statistical Analysis. Overall, relative telomere length was normally distributed (kurtosis = 3.1, skewness = 0.3). Therefore, we used a linear regression model to estimate mean relative telomere length and 95% confidence interval (95% CI) according to current and past anthropometric characteristics controlling for the following variables: race, smoking status (never, past, or current), perceived level of stress (five categories), age in years (continuous), education level (high school or less, some college or associate degree, or college graduate or more), regular use of nonsteroidal anti-inflammatory drugs (NSAIDs; yes/no), regular use of vitamin supplement (yes/no), medical history of hypertension (yes/no), and cardiovascular disease (yes/no). Other covariates considered in multivariate models included menopausal status (premenopause or postmenopause), dietary intakes of calories and total fat (quartiles based on distributions of the entire sample), physical activity in the past 12 months (total metabolic equivalents-hours per week from sports and exercise activities as well as activities of daily living and domestic chores, quartiles based on distributions of the entire sample), and diagnosis of diabetes mellitus (yes/no); however, adding these variables did not change the association between body size variables and telomere length. Menopausal status and regular use of NSAIDs and vitamin supplements were investigated as potential effect modifiers. Strong correlations existed between past and current body size variables with correlation coefficients of 0.74 ($P < 0.01$) for current and past weights and 0.67 ($P < 0.01$) for current and past BMI.

Therefore, past body size variables were evaluated with additional adjustment for current body size variables by fitting a simple linear regression model for current body size variables given past body size variables and entering the residuals into the model. Tests for linear trend were done by treating an ordered categorical variable as a continuous variable. Analyses were done using Stata 10.0, and all statistical tests were two-sided, with an α level of 0.05.

Results

Selected characteristics of the study population by BMI are presented in Table 1. Mean ages were similar across three BMI categories. However, women in higher BMI categories tended to be physically inactive and have higher intakes of energy and fat compared with women with normal BMI. BMI was also positively associated with non-White race, regular use of NSAIDs, menopause, and comorbidity but inversely associated with regular use of vitamin supplement.

There was a linear decrease in mean relative telomere length with increasing BMI (P_{trend} = 0.03; Fig. 1). The respective mean T/S ratios were 1.34 (95% CI, 1.31-1.37) for BMI < 25 kg/m^2, 1.31 (95% CI, 1.27-1.35) for BMI 25 to 29.9 kg/m^2, and 1.29 (95% CI, 1.25-1.32) for BMI ≥ 30 kg/m^2. Increase in weight was also associated with shorter mean relative telomere length, although the association did not appear to be strictly linear. Reduced telomere length was found with increasing hip and, to a lesser extent, waist circumferences, but no association was observed with waist-to-hip ratio. Women who were shorter than 1.6 m had the shortest telomere length (mean relative T/S ratio = 1.28; 95% CI, 1.24-1.32), but telomere length did not increase with increasing height (P_{trend} = 0.38).

The association between BMI and telomere length was similar among premenopausal and postmenopausal women. NSAIDs and vitamin supplements, which are known to have antioxidant properties (22, 23), were also examined as a potential effect modifier of the association between BMI and telomere length; however, there was little evidence for effect modification by these factors (data not shown).

After adjustment for current BMI, past BMI was inversely associated with relative telomere length (Fig. 2). The mean T/S ratios were 1.33 (95% CI, 1.30-1.36), 1.29 (95% CI, 1.26-1.33), and 1.26 (95% CI, 1.21-1.30)

Table 1. Characteristics of study population by current BMI

	BMI (kg/m^2)		
	<25 (*n* = 260)	25-29.9 (*n* = 183)	≥30 (*n* = 201)
Mean (SD)			
Age at enrollment (y)	53.1 (9.8)	53.6 (9.4)	54.0 (9.5)
Physical activity (metabolic equivalents-h/wk)	13.8 (14.3)	11.2 (17.0)	7.3 (9.7)
Calories (kcal/d)*	1,450.3 (540.4)	1,546.1 (580.0)	1,603.7 (593.8)
Total fat (g/d)*	63.9 (29.4)	70.4 (32.7)	71.4 (31.9)
n (%)			
Non-White race †	31 (11.9)	27 (14.8)	50 (24.9)
High or very high perceived stress	98 (37.7)	66 (36.1)	84 (41.8)
Education level			
High school graduate or less	34 (13.1)	36 (19.7)	32 (15.9)
Some college/ associate degree	96 (36.9)	84 (45.9)	81 (40.3)
College graduate or more	130 (50.0)	63 (34.4)	88 (43.8)
Smoking			
Never smoker	123 (47.3)	89 (48.6)	92 (45.8)
Past smoker	73 (28.1)	52 (28.4)	61 (30.3)
Current smoker	64 (24.6)	42 (23.0)	48 (23.9)
Postmenopause	166 (63.8)	127 (69.4)	143 (71.1)
Regular use of NSAIDs	113 (43.5)	79 (43.2)	122 (60.7)
Regular use of vitamin supplement*	180 (69.2)	120 (65.6)	129 (64.2)
Medical history			
Hypertension	34 (13.1)	39 (21.3)	85 (42.3)
Cardiovascular disease	28 (10.8)	29 (15.8)	46 (22.9)
Diabetes mellitus	2 (0.8)	10 (5.5)	23 (11.4)

NOTE: Of 647 subjects, 3 with missing values for BMI were not included.
*21 subjects (7 in BMI < 25 kg/m^2, 5 in BMI 25-29.9 kg/m^2, and 9 in BMI ≥ 30 kg/m^2) with missing dietary data and 18 subjects (7 in BMI < 25 kg/m^2, 4 in BMI 25-29.9 kg/m^2, and 7 in BMI ≥ 30 kg/m^2) with missing vitamin supplement use.
† Includes Blacks, Hispanic Whites, and others.

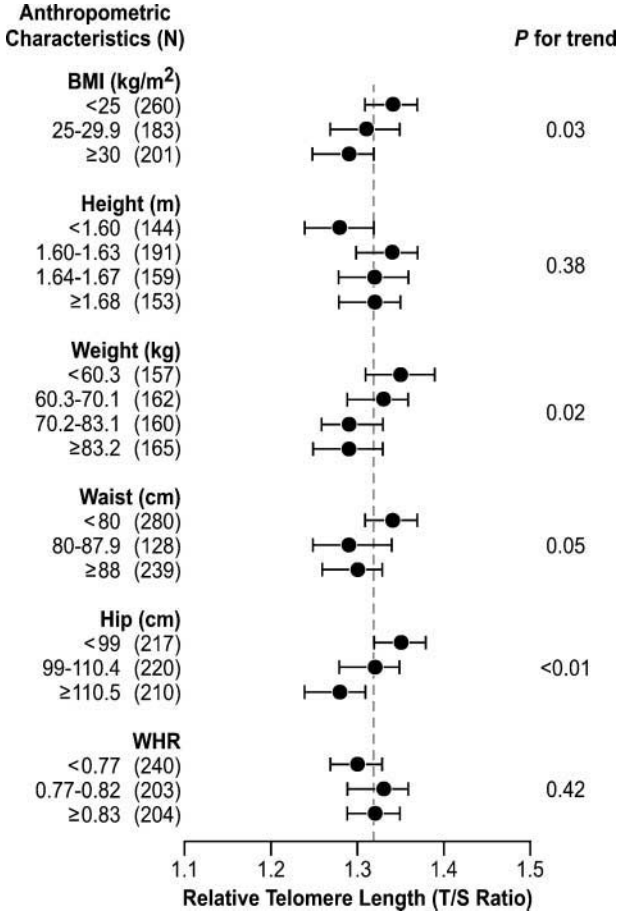

Figure 1. Adjusted mean of relative telomere length (T/S ratio) according to anthropometric characteristics among 647 women ages 35 to 74 y in the Sister Study, 2003 to 2004. Mean values (●) were adjusted for age, race, smoking status, perceived level of stress, regular use of NSAIDs, regular use of vitamin supplement, diagnosis of hypertension, and history of cardiovascular diseases. *Bars,* 95% confidence intervals. A reference line (-----) indicates the overall mean of relative T/S ratio in the study sample.

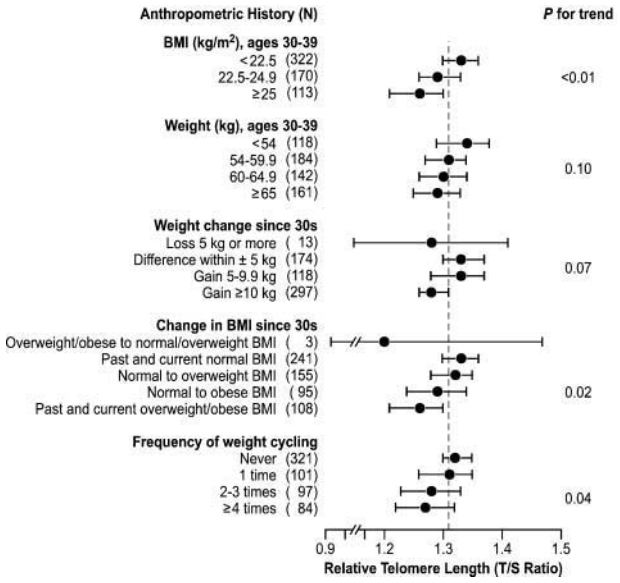

Figure 2. Adjusted mean of relative telomere length (T/S ratio) according to anthropometric history variables among 608 women ages ≥40 y in the Sister Study, 2003 to 2004. Mean values (●) were adjusted for age, race, smoking status, perceived level of stress, regular use of NSAIDs, regular use of vitamin supplement, diagnosis of hypertension, history of cardiovascular diseases, and residuals of current weight or BMI. *Bars,* 95% confidence intervals. A reference line (-----) indicates the overall mean of relative T/S ratio among all women ages ≥40 y.

for past BMI of <22.5, 22.5 to 24.9, and ≥25 kg/m^2, respectively. Weight gain since the 30s (P_{trend} = 0.07) and frequent weight cycling (P_{trend} = 0.03) were also associated with shorter telomere length. Further assessment of change in obesity status confirmed shorter telomere length associated with adult weight change, but the most marked reduction in telomere length was found among women who had overweight or obese BMI at both time points with mean T/S ratio 1.26 (95% CI, 1.21-1.30). Those who were overweight or obese in their 30s but currently normal weight also had short telomeres, but they were too few to be reliably examined also had short telomeres, but they were too few to be reliably examined.

Discussion

Consistent with previous studies particularly among women (2, 3, 15), we found an inverse association between current BMI and telomere length. Shorter telomeres were also associated with higher hip and, to a lesser extent, waist circumferences. Additionally, higher BMI at ages 30 to 39 years, adult weight gain, and frequent weight cycling were inversely associated with telomere length.

Women with higher BMI at baseline tend to have experienced more frequent intentional weight loss and weight cycling than those with lower BMI; therefore, it is not easy to sort out whether the reduction in telomere length is due to higher BMI at baseline, weight change, or both. However, our finding that women who maintained an overweight or obese BMI since their 30s had shorter telomeres than those who became overweight or obese since their 30s suggests that duration of obesity may be more important than weight change *per se*.

One previous study has reported an inverse association between telomere length and insulin resistance only in premenopausal women (5). Estrogens (24) as well as vitamins (23) and NSAIDs (22) are known to have antioxidant properties. In our exploratory analyses, however, the relationship between current BMI and telomere length was not modified by these factors.

Oxidative stress and inflammation have been suggested as an underlying mechanism for the association between obesity and short telomeres (3). Accumulating adiposity increases oxidative stress and causes deregulation of inflammatory cytokines (13). Oxidative stress is a direct and indirect source of single strand breaks in DNA (24). Compared with genomic DNA, the G-rich telomeric sequence is an ideal target for acute oxidative damage, and telomeric DNA is relatively less capable of DNA repair, allowing acceleration of telomere loss during cell cycle and subsequent replicative senescence (24).

Limitations of the present study should be acknowledged. First, we had insufficient data to comment on the influence of weight loss on telomere length: only a few women were obese in their 30s; thus, very few had lost ≥5 kg. Additionally, weight at ages 30 to 39 years was recalled in our study. Although a strong correlation between recalled and previously measured weight has been reported, accuracy of self-reported past body weight appears to be influenced by race and current body weight (25). Lastly, there was a one-time measurement of telomere length in this cross-sectional study. Although evidence suggests that oxidative stress, possibly promoted by obesity, accelerates telomere shortening (24), we could not directly evaluate whether shorter telomeres in obese individuals relative to the nonobese are attributed to rapid telomere attrition rate or some other reasons such as genetic differences (26).

In summary, the present study showed reduced telomere length associated with higher BMI at ages 30 to 39 years, weight gain in adulthood, and current BMI. These findings support the hypothesis that obesity accelerates aging (3) and provide further evidence of the advantages of maintaining a healthy weight. Further investigations are warranted to characterize the role of obesity-driven aging in the development of degenerative diseases and cancer.

Disclosure of Potential Conflicts of Interest

R.M. Cawthon has submitted a patent application for the method of telomere length measurement by quantitative PCR. No other actual or potential conflict of interest is declared.

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