Obesity is Associated with Shorter Telomere Length in Prostate Stromal Cells in Men with Aggressive Prostate Cancer

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ABSTRACT

In our prior studies, obesity was associated with shorter telomeres in prostate cancer-associated stromal (CAS) cells, and shorter CAS telomeres were associated with an increased risk of prostate cancer death. To determine whether the association between obesity and shorter CAS telomeres is replicable, we conducted a pooled analysis of 790 men who were surgically treated for prostate cancer, whose tissue samples were arrayed on five tissue microarray (TMA) sets. Telomere signal was measured using a quantitative telomere-specific FISH assay and normalized to 4′,6-diamidino-2-phenylindole for 351 CAS cells (mean) per man; men were assigned their median value. Weight and height at surgery, collected via questionnaire or medical record, were used to calculate body mass index (BMI; kg/m^2) and categorize men as normal (<25), overweight (25 ≤ BMI < 30), or obese (≥30). Analyses were stratified by grade and stage. Men were divided into tertiles of TMA- (overall) or TMA- and disease aggressiveness- (stratified) specific distributions; short CAS telomere status was defined by the bottom two tertiles. We used generalized linear mixed models to estimate the association between obesity and short CAS telomeres, adjusting for age, race, TMA set, pathologic stage, and grade. Obesity was not associated with short CAS telomeres overall, or among men with nonaggressive disease. Among men with aggressive disease (Gleason≥4+3 and stage>T2), obese men had a 3-fold increased odds of short CAS telomeres (OR: 3.06; 95% confidence interval: 1.07–8.75; $P_{trend} = 0.045$) when compared with normal weight men. Telomere shortening in prostate stromal cells may be one mechanism through which lifestyle influences lethal prostate carcinogenesis.

Prevention Relevance: This study investigates a potential mechanism underlying the association between obesity and prostate cancer death. Among men with aggressive prostate cancer, obesity was associated with shorter telomeres prostate cancer associated stromal cells, and shorter CAS telomeres have been associated with an increased risk of prostate cancer death.

Introduction

Obesity is associated with the development of advanced prostate cancer at diagnosis and prostate cancer death (1–3). Telomere shortening in prostate cell populations is a possible biological alteration underlying the association between obesity and lethal prostate carcinogenesis. Telomeres, repetitive DNA sequences that protect chromosome ends from degradation and recombination, can shorten and become dysfunctional. We previously reported that men with shorter telomeres in prostate cancer-associated stromal (CAS) cells had a significantly increased risk of lethal prostate cancer and prostate cancer death after surgical treatment (4). In the same cohort, we also found that prediagnostic obesity was associated with significantly shorter telomeres in prostate CAS cells (5). These findings were novel, because we evaluated the association between obesity and telomere length in cells in the prostate, the target tissue. Our findings were consistent with prior studies linking obesity to shorter telomeres in circulating leukocytes (6, 7). Given the potential of telomere shortening as a mechanism underlying the association between obesity and lethal prostate carcinogenesis, additional studies are needed to further explore the link between obesity and telomere length in prostate cells.

The purpose of this study was to determine whether the association between obesity and shorter prostate CAS cell telomere length observed in a prior epidemiologic cohort study (5) is replicable in an independent study population of

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Note: Supplementary data for this article are available at Cancer Prevention Research Online (http://cancerprevres.aacrjournals.org/).

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Cancer Prev Res 2021;14:463–70

doi: 10.1158/1940-6207.CAPR-20-0250

men who underwent surgical treatment for prostate cancer. We hypothesized that obesity would be positively associated with short CAS cell telomere length. We evaluated the association between obesity and prostate CAS cell telomere length, measured using a quantitative telomere-specific FISH assay that provides single-cell resolution of telomere length, in a pooled analysis of 790 men surgically treated for prostate cancer at Johns Hopkins Hospital (Baltimore, MD).

Materials and Methods

Study population

We conducted a pooled cross-sectional analysis of five tissue microarray (TMA) sets of prostate cancer tissues from men who underwent radical prostatectomy at Johns Hopkins Hospital (Baltimore, MD). The construction of TMA set 1, which has 16 TMAs, has been described previously (8). Briefly, this set is a case–control study nested within a cohort of men surgically treated between 1993 and 2004, who had not had hormonal therapy or radiotherapy before radical prostatectomy or as adjuvant therapy before biochemical recurrence. For this set, we included only men selected as controls in the pooled analysis because they are representative of the men in the underlying cohort that gave rise to the cases in this set. We did not use the cases because cases and controls were 1:1 matched and the cases would have been overrepresented relative to the underlying cohort. Telomere biomarker data were available for 238 controls; we excluded 30 men without height or weight at surgery, leaving 208 men for the analysis. The construction of TMA set 2, which has nine TMAs, has been described previously (9). Briefly, this set is a case-cohort study of men surgically treated between 1992 and 2010 for intermediate or high-risk prostate cancer, and who had undetectable PSA after surgery and sufficient tissue and clinical data for analysis. Telomere biomarker data were available for 252 men in the subcohort; we excluded 46 men without height and weight at the time of surgery, leaving 206 men for analysis. TMA set 3, a cross-sectional study that has eight TMAs, was designed specifically to evaluate the association of obesity and weight change with prostate tissue biomarkers. Men were sampled from a retrospective cohort study of 1,337 men with clinically localized prostate cancer surgically treated between 1993 and 2006 who returned a lifestyle questionnaire (10). A total of 291 men were jointly categorized by weight change (gain>5 lbs, loss<5 lbs, maintain±5 lbs) from 5 years before prostatectomy to 1 year after and BMI category (<25, 25 to < 30 kg/m^2, ≥30 kg/m^2) at 1 year after prostatectomy and frequency matched by age, race, and pathologic stage and grade. As a result of computer hardware failure, data for three of the TMAs were irretrievably lost; therefore, only five TMAs or 162 men were included in the analysis. TMA set 4, a cross-sectional study that has four TMAs, included 75 white men and 75 black men surgically treated between 2000 and 2010, and matched on age within 3 years, pathologic stage and grade enriched for low-grade disease. Telomere data were available for 145 men (11); we excluded 16 men without height and weight at the time of surgery, leaving 129 men for analysis. TMA set 5, a cross-sectional study that has three TMAs, included 60 white men and 60 black men surgically treated between 2014 and 2016, and frequency matched on pathologic grade, enriched for high-grade disease. Telomere data were available for 108 men (11); we excluded 21 men without height and weight at the time surgery ($n = 21$), and 2 men included on a prior TMA set, leaving 85 men for analysis. All TMA sets were constructed under a waiver of consent by the Institutional Review Board at the Johns Hopkins University School of Medicine (Baltimore, MD). The measurement of telomere length, and all analyses were approved by the Institutional Review Board at the Johns Hopkins Bloomberg School of Public Health (Baltimore, SD) and Johns Hopkins University School of Medicine (Baltimore, SD).

For TMA set 3, height and weight at 1 year after surgery were collected via questionnaire as described previously (10). For all other TMA sets, height and weight at the time of radical prostatectomy were abstracted from the medical record as described previously (12). BMI (kg/m^2) was calculated and used to categorize men on all TMA sets as normal weight (<25), overweight (25 to <30), or obese (≥30). Men were also categorized by disease aggressiveness. To maximize the sensitivity of the nonaggressive disease category (definition 1), men were categorized as having nonaggressive (pathologic Gleason sum≤3+4 AND pathologic stage = T2) or aggressive (pathologic Gleason sum≥4+3 OR pathologic stage>T2) disease. To maximize the sensitivity of the aggressive disease category (definition 2), men were categorized as having nonaggressive (pathologic Gleason sum≤3+4 OR pathologic stage = T2) or aggressive (pathologic Gleason sum≥4+3 AND pathologic stage>T2) disease.

Measurement of telomere length

Telomere length was previously measured for TMA sets 1 and 2, and for TMA sets 4 and 5 (11), and newly measured for TMA set 3 using TMA sections containing areas of adenocarcinoma and benign tissue using a telomere-specific FISH probe and 4′,6-diamidino-2-phenylindole (DAPI) for labeling total nuclear DNA as described previously (4, 11). In addition, simultaneous colabeling of prostate epithelial cells was performed using an anti-NKX3.1 primary antibody (Athena; 1:1,000 dilution) followed by detection with an anti-rabbit IgG fraction Alexa Fluor 647 secondary antibody. Each individual TMA spot on the TMA slides was imaged using the TissueFAXS Plus (Tissue Gnostics) automated fluorescence microscopy workstation and Zeiss Z2 Axioimager microscope. Cells in stromal regions in the same TMA spot as cancer (i.e., CAS cells) were identified by exclusion of cancer and benign epithelial cells based on positive immunolabeling for the epithelial cell marker NKX3.1, and their digitized fluorescent telomere FISH signals were then quantified using the TissueQuest software module. Benign glands and other cell types (e.g., infiltrating lymphocytes) were excluded from the digital image analysis based on their unique morphologic features. Relative

telomere lengths in individual prostate CAS cells and prostate cancer cells were determined by calculating the ratio of the total telomere FISH intensity by the total DAPI intensity for each nucleus, thereby compensating for differences in nuclear cutting planes. An average of 351 individual CAS cells per man were analyzed.

Statistical analysis

Means and proportions for demographic and pathologic characteristics were calculate by TMA set. The median telomere length (i.e., telomere signal normalized to DAPI) among each man's CAS cells was determined. Men were then categorized into (i) tertiles of CAS telomere length within TMA set (TMA-specific tertile), and (ii) tertiles of CAS telomere length within TMA set and category of disease aggressiveness (TMA-specific and aggressiveness-specific tertiles). Because falling within the bottom two tertiles of CAS telomere length was associated with an increased risk of metastatic and fatal disease in our prior study (4), we then categorized men as having short telomeres if they fell within the bottom two tertiles of their TMA-specific (overall analysis) or TMA- and aggressiveness-specific (stratified analyses) cut-off points.

Because falling within the top tertile of prostate cancer cell telomere length variability was also associated with an increased risk of metastatic and fatal disease in our prior study (4), we also calculated SD (telomere length variability) for prostate cancer cells. Men with prostate cell telomere variability in the top tertile of TMA- (overall) or TMA- and disease aggressiveness-specific distributions (stratified) were categorized as having variable telomeres; men in the bottom two tertiles were categorized as having not variable telomeres. In contrast to our hypothesis for CAS cells, we hypothesized that there would be no association between obesity and telomere length variability in prostate cancer cells. In prostatectomy specimens, telomere length and variability may be a consequence of the dynamic carcinogenesis process and we would not expect obesity to be a predominant factor in length. Furthermore, obesity was not associated with cancer cell telomere length or telomere variability in our prior analysis (5).

For all analyses, we used a generalized linear mixed model for binomial data with a logit link to estimate the OR and 95% confidence interval (CI) of short telomeres in CAS or variable telomere length in prostate cancer cells for each BMI category; the reference group was men classified as normal weight. All analyses were adjusted for potential confounders: age at diagnosis (continuous), race (white/non-white), prostatectomy Gleason sum (categorical: ≤6, 3+4, 4+3, 8, 9), pathologic tumor–node–metastasis (TNM) stage (categorical T2, T3a, T3b, or N1, overall and aggressive disease models only), and a random term for TMA set. We tested for trend in the associations by entering into the models a continuous variable for each BMI category, the coefficient for which was evaluated by the Wald test. All analyses were conducted overall (primary analysis) and stratified by disease aggressiveness (secondary analyses). All analyses were performed using SAS v 9.4 (SAS Institute). All statistical tests were two sided, with $P < 0.05$ considered to be statistically significant.

Results

In total, 790 men were included in the analysis. **Table 1** provides demographic and pathologic characteristics of men in

Table 1. Demographic and pathologic characteristics of men surgically treated for prostate cancer at Johns Hopkins Hospital (Baltimore, MD), 1992 to 2016, by TMA set.

		TMA set				
	All sets ***N* = 790**	**Set 1** ***N* = 208**	**Set 2** ***N* = 206**	**Set 3** ***N* = 162**	**Set 4** ***N* = 129**	**Set 5** ***N* = 85**
Mean age, years	58	59	59	56	57	61
White (%)	80.4	86.5	90.3	100	49.6	50.6
Median year of surgery	1999	1995	1997	1999	2002	2015
Body mass index (kg/m^2, %)						
<25	25.3	29.3	27.2	27.2	17.1	20.0
25 to <30	53.5	55.3	56.8	43.2	61.2	49.4
≥30	21.1	15.4	16.0	29.6	21.7	30.6
Pathologic stage (%)						
T2	44.4	14.6	28.2	71.6	74.4	60
T3a	23.9	17.3	51	10.5	13.2	16.5
T3b	20.6	29.8	20.9	14.2	11.6	23.5
LN+	11.0	38.5	0	3.7	0.8	0
Pathologic Gleason sum (%)						
≤6 (Grade Group[a] 1)	31.1	19.3	0.5	69.7	59.7	17.7
3+4 (Grade Group 2)	35.4	41.4	43.7	22.2	35.7	25.9
4+3 (Grade Group 3)	12.7	12.5	21.4	8.0	4.7	12.9
8 (Grade Group 4)	10.9	26.9	12.1	0	0	5.9
9 (Grade Group 5)	9.9	0	22.3	0	0	37.7

[a]Grade groups from reference 23.

Table 2. ORs[a] and 95% CIs for the association between BMI category and short telomeres[b] in prostate CAS cells overall and stratified by prostate cancer aggressiveness at surgery among men surgically treated for prostate cancer at Johns Hopkins Hospital (Baltimore, MD), 1992 to 2016.

	Normal, <25 kg/m²	**Overweight, 25 to <30 kg/m²**	**Obese, ≥30 kg/m²**	P_{trend}[c]
		Overall		
N_{short}/N_{long}	132/68	276/147	118/49	
OR	1.00	0.95	1.23	0.41
95% CI	Reference	0.67–1.36	0.78–1.93	
		Nonaggressive prostate cancer—definition 1		
		Gleason sum<4+3 **AND** pathologic stage = T2		
N_{short}/N_{long}	53/22	91/58	45/22	
OR	1.00	0.62	0.83	0.59
95% CI	Reference	0.34–1.16	0.40–1.74	
		Nonaggressive prostate cancer—definition 2		
		Gleason sum<4+3 **OR** pathologic stage = T2		
N_{short}/N_{long}	103/50	195/108	89/42	
OR	1.00	0.86	0.98	0.1
95% CI	Reference	0.57–1.31	0.59–1.63	
		Aggressive prostate cancer—definition 1		
		Gleason sum ≥4+3 **OR** pathologic stage>T2		
N_{short}/N_{long}	80/46	188/89	74/27	
OR	1.00	1.21	1.57	0.13
95% CI	Reference	0.77–1.91	0.88–2.82	
		Aggressive prostate cancer—definition 2		
		Gleason sum≥4+3 **AND** pathologic stage>T2		
N_{short}/N_{long}	29/18	81/39	29/7	
OR	1.00	1.31	3.06	0.045
95% CI	Reference	0.64–2.71	1.07–8.75	

[a]All analyses were adjusted for potential confounders: age at diagnosis (continuous), race (white/non-white), prostatectomy Gleason sum (categorical: ≤6, 3+4, 4+3, 8, 9), pathologic TNM stage (categorical T2, T3a, T3b, or N1, overall and aggressive disease models only), and a random term for TMA set.
[b]Men with a median prostate CAS cell telomere length in the bottom two tertiles of TMA- (overall) or TMA- and disease aggressiveness-specific distributions (stratified) were categorized as having short telomeres; men in the top tertile were categorized as having long telomeres.
[c]Wald test.

each TMA set. The majority of men were white and overweight at diagnosis. As expected, due to their differing study criteria, pathologic stage and grade varied by TMA set.

Overall, there was no statistically significant association between obesity and short telomere length in prostate CAS cells; although obese men had a nonsignificant higher odds of having short telomeres in CAS cells compared with normal weight men (**Table 2**). When stratified by disease aggressiveness, obesity was not significantly associated with telomere length in CAS cells among men with nonaggressive prostate cancer at diagnosis, irrespective of definition. Overweight and/or obese men had nonsignificant lower odds of short telomeres in CAS cells compared with normal weight men using both definitions. In contrast, when using the more sensitive definition of aggressive disease (definition 2), obese men were significantly more likely (OR: 3.06; 95% CI: 1.07–8.75) to have short telomeres in CAS cells as compared with normal weight men ($P_{trend} = 0.045$). When using the less sensitive definition of aggressive disease (definition 1), obesity was positively associated with short telomeres in CAS cells, but the association was attenuated and not statistically significant. Overweight men had nonsignificant higher odds of short telomeres in CAS cells compared with normal weight men using both definitions.

There were no statistically significant associations between obesity and variability in telomere length in prostate cancer cells, overall or by disease aggressiveness (Supplementary Table S1).

Discussion

In this pooled analysis of 790 men who were surgically treated for prostate cancer, obesity was not significantly associated with short telomeres in prostate CAS cells overall or among men with nonaggressive disease at diagnosis. However, among men with aggressive disease, Gleason ≥4+3 and stage>T2, obese men had three times higher odds of shorter telomeres in prostate CAS cells as compared with normal weight men. These findings build on those of our prior study in which men who were overweight or obese prior to diagnosis had significantly shorter telomeres in prostate CAS cells than men who were normal weight (5).

To our knowledge, this is only the second study to investigate the association between obesity and telomere length in prostate

cells. In our prior study conducted in an epidemiologic cohort independent of this study (5), prediagnostic overweight/obesity was associated with 7.4% shorter telomeres in prostate CAS cells. Men with large waist circumferences and greater weight gain since the age of 21 also had shorter CAS cell telomere length. Unlike in this study, these differences were observed in the overall study population. Differences in the proportion of aggressive disease in the overall study population could have contributed to the some of the differences in findings. In our prior study population, approximately 43% of men had Gleason 4+3 or higher, whereas in our current study population only 33.5% of men had Gleason 4+3 or higher. Furthermore, in our prior study, our findings were stronger among overweight and obese men who were also inactive. However, we were unable to evaluate physical activity levels among men in this study (no data). Because the measurement of the telomere signal is optimized for each TMA set when analyzed, values of telomere length are not directly comparable across TMA sets. Thus, we were unable to determine whether measured telomere length differed by BMI category across all men in the pooled study population. However, we were able to categorize men as having short telomeres, and this categorization was previously associated with an increased risk of metastatic and fatal disease in our prior study (4). Using this categorization, we found obesity was associated with short CAS cell telomeres among men with aggressive disease, providing further support for the role of telomere shortening in the association between obesity and lethal prostate carcinogenesis.

We previously found shorter telomeres in CAS cells was associated with a significantly increased risk of lethal prostate cancer and prostate cancer death after surgical treatment (4). Additional studies have also reported telomere shortening in CAS cells (13, 14). The exact mechanism by which shortened telomere length in CAS cells influences carcinogenesis is not fully understood. However, it may lead to replicative senescence (15), and senescent fibroblasts that promote the senescence-associated secretory phenotype or SASP (16). The resulting secretion of proinflammatory cytokines, growth factors, and matrix remodeling enzymes may remodel the microenvironment to promote prostate cancer initiation and progression (11).

Several mechanisms can lead to telomere shortening, including incomplete replication during DNA synthesis, alterations of telomere-binding proteins involved in telomere maintenance, and by oxidative stress leading to DNA damage (17–19). Obesity induces proinflammatory cytokine production, which can lead to increased oxidative stress and increased production of more growth factors (20). Increased DNA damage induced by oxidative stress, and increased cell proliferation due to increased growth factors are two ways in which obesity could influence telomere shortening. Obesity has been inversely associated with telomere length in peripheral blood leukocytes in several, but not all, studies (6, 7). A small intervention study reported telomere lengthening in leukocytes after comprehensive lifestyle change (21). Taken together, existing evidence indicates that obesity could influence telomere length through several biologically plausible mechanisms.

Some aspects of our study warrant discussion. We evaluated the association between obesity and prostate CAS cell telomere length for 790 men with prostate cancer. Weight measures were collected for men with prostate cancer at or near the time of surgery. We cannot comment on the association between prediagnostic obesity and CAS cell telomere length, though our findings are consistent with our prior study, which used prediagnostic anthropometric measures. We used a validated, state-of-the-art method to measure telomere length that provided single-cell resolution (22), allowing us to identify CAS cells and estimate length in an average of 351 cells per man. We were able to evaluate the association between obesity and telomere length in CAS cells overall and stratified by disease aggressiveness at diagnosis, though smaller subgroup sample sizes resulted in wide confidence intervals. It should be noted that our findings for a positive association between obesity and short telomere length in CAS cells was observed only among a subset of 203 men with aggressive disease, 36 of whom were obese. These findings would not be considered to be statistically significant using a Bonferroni-corrected P value of 0.01. Furthermore, our sample size was not large enough to obtain stable estimates separately by race/ethnicity. The telomere length measures were for CAS cells in TMA spots that included cancer; it is unknown whether observations would be similar in prostate stromal cells located further from the cancer or in prostate stromal cells in men without prostate cancer. More work is needed to determine whether the association between obesity and telomere length would be similar for men at risk for prostate cancer.

Obesity is associated with advanced prostate cancer at diagnosis and prostate cancer death. Investigating the mechanisms that underlie this association could potentially inform our understanding of the etiology of lethal prostate carcinogenesis and help identify potential interventions to reduce the incidence of metastatic disease and prostate cancer death. We previously found that short telomeres in prostate CAS cells were associated with a significantly increased risk of lethal prostate cancer and prostate cancer death among men surgically treated for the disease (4). In the same cohort, we also found that prediagnostic obesity was associated with significantly shorter telomeres in prostate CAS cells (5), suggesting telomere shortening may be one mechanism by which obesity influences prostate carcinogenesis. Thus, we sought to determine whether our observations for obesity and CAS cell telomere length were replicable in another study population. In this study, we found that obesity appears to be associated with short telomeres in prostate CAS cells among men with aggressive disease at the time of surgery. These findings provide further evidence that telomere shortening may be one mechanism by which obesity influences lethal prostate carcinogenesis. More studies are needed to evaluate the association between obesity and telomere length in prostate CAS cells, particularly those able to assess the association separately by

disease aggressiveness and race/ethnicity and those able to account for physical activity, diet, and other factors that could influence telomere length.

Authors' Disclosures

C.M. Heaphy reports grants from NCI, Department of Defense, and-Prostate Cancer Foundation during the conduct of the study.R. Zarinshenas reports grants from NCI and Department of Defense during the c-onduct of the study. T.L. Lotan reports grants from Roche and DeepBio, and nonfinancial support from Myriad Genetics outside the submitted work. A.M. De Marzo reports grants from U.S. NCI and U.S. Department of Defense during the conduct of the study; grants from Janssen R&D and Myriad Genetics, and personal fees from Cepheid outside the submitted work. E.A. Platz reports grants from NCI and DOD during the conduct of the study; personal fees from Kaiser Permanente Northern California, Division of Research and AACR, EIC CEBP outside the submitted work. No disclosures were reported by the other authors.

Authors' Contributions

C.E. Joshu: Conceptualization, supervision, methodology, writing–original draft, writing–review and editing. **C.M. Heaphy:** Conceptualization, formal analysis, supervision, methodology, writing–review and editing. **J.R. Barber:** Formal analysis, writing–review and editing. **J. Lu:** Formal analysis, writing–review and editing. **R. Zarinshenas:** Formal analysis, writing–review and editing. **C. Davis:** Formal analysis, writing–review and editing. **M. Han:** Resources, writing–review and editing. **T.L. Lotan:** Resources, writing–review and editing. **K.S. Sfanos:** Resources, writing–review and editing. **A.M. De Marzo:** Conceptualization, resources, writing–review and editing. **A.K. Meeker:** Conceptualization, resources, supervision, funding acquisition, methodology, project administration, writing–review and editing. **E.A. Platz:** Conceptualization, resources, supervision, funding acquisition, methodology, project administration, writing–review and editing.

Acknowledgments

This study was supported by grant numbers W81XWH-12-1-0545, P50 CA05823, P30 CA006973 and W81XWH-14-2-0182. C.E. Joshu and C.M. Heaphy supported by the Prostate Cancer Foundation. Some TMAs were provided by the Prostate Cancer Biorepository Network (PCBN), which is supported by the Department of Defense Prostate Cancer Research Program Award (W81XWH-15-2-0062).

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Received May 18, 2020; revised September 17, 2020; accepted December 9, 2020; published first December 22, 2020.

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