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A Lens on Caregiver Stress in Cancer: Longitudinal Investigation of Cancer-Related Stress and Telomere Length Among Family Caregivers of Adult Patients with Cancer

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Abstract

Objective: Family members are typically the primary caregivers of patients with chronic illnesses. Family caregivers of adult relatives with cancer are a fast-growing population yet the physical consequences of their stress due to the cancer in the family have been poorly understood. This study examined the bidirectional relations of the perceived stress of family caregivers of individuals recently diagnosed with cancer and leukocyte cellular aging indexed by telomere length over two years.

Methods: Family caregivers (n=168; mean age=51 years old, 70% female, 46% Hispanic, 36% spouse to the patient) of patients with colorectal cancer provided psychological data and peripheral blood samples approximately 4 (T1), 12 (T2), and 21 months (T3) post-diagnosis. Time-lagged cross panel modeling was used to test the associations of perceived cancer-related stress and telomere length, controlling for age, gender, and BMI.

Results: Cancer-related stress was highest at T1 and decreased by one year. Greater cancer-related stress predicted longer telomere length at subsequent assessments over two years ($\beta \geq .911, p \leq .019$). However, telomere length did not change significantly over two years overall and did not prospectively predict cancer-related stress over this period.

Conclusions: Findings suggest the need to better understand how the perceived stress of colorectal cancer caregivers, which tends to be intense for a relatively short period compared to dementia caregiving, may impact immune cell distributions and telomere length. These findings emphasize the need for further knowledge about psycho-biological mechanisms of how cancer caregiving may impact cellular aging.

Key Words: caregiver stress, telomere length, cancer care, cross-lagged panel design, longitudinal study

Abbreviation: BMI = body mass index

ACCEPTED

Introduction

A hallmark of cellular aging is telomere shortening, which is defined as the length of telomeres that cap the ends of chromosomes and protect against damage to the DNA getting shortened as cell division cycles proceed (1-3). Shorter telomeres have been associated with aging and age-related diseases, such as coronary heart disease, diabetes, and heart failure, as well as with greater mortality, particularly among the oldest old (1, 4-7). Shorter telomere length has been observed among individuals who experienced various types of chronic or traumatic stress, including early childhood adversity (8, 9), chronic loneliness (10), lack of social support (11), and chronic stress of poverty, violence, and caregiving (8, 12, 13).

Caring for relatives with chronic illnesses is known to be stressful, often with substantial adverse health consequences (14, 15). More than 1.8 million adults were newly diagnosed with a cancer in the United States in 2020 and that number is estimated to increase to 2.6 million in 2050 (16). Family members often become primary caregivers of cancer patients. Thus, family cancer caregivers are a large population. Family cancer caregivers are primarily responsible for all aspects of cancer care, including emotional, instrumental, medical, and tangible support (17, 18). However, existing caregiver studies that examined cellular aging are mostly with caregivers of patients with dementia (9, 19, 20) and caregivers of a chronically ill child (8). These studies have found that compared with non-caregivers, the caregivers had shorter telomere length (8, 9, 19, 20).

Among caregivers, however, the relation between caregiving and telomere length has depended on individual factors, such as age of the caregiver, disease type of the care recipients.

For example, higher perceived stress in daily life was associated with shorter telomere length among healthy premenopausal maternal caregivers of children with chronic conditions (21). A subgroup of mothers of children with an autism spectrum disorder who were able to tell a more integrated story of their experiences of parenting stress that incorporated their self-identity had longer telomere length at the 18-month follow-up than mothers of children without neurological conditions (22). Among chronically stressed caregivers of patients with physical illnesses, either not being religious or being highly religious was associated with longer telomere length, whereas being moderately religious was associated with shorter telomere length (23). In response to acute laboratory-induced stressors, caregivers of patients with dementia reported greater anticipatory threat appraisals, compared with their non-caregiver counterparts. Greater anticipatory threat appraisal in turn was associated with shorter telomere length (24). On the other hand, objective measures of burden such as the numbers of years (25) or hours per week (26) spent for caregiving were not related to telomere length in large cross-sectional studies.

These existing studies with caregivers suggest that in general chronically stressed family caregivers who struggle with their caregiver role are vulnerable to premature cellular aging. However, it remains unknown whether these findings extend to family cancer caregivers. Cancer caregiving is characterized as intense for a relatively short duration with various periods of great uncertainty (27, 28), which is distinctly different from characteristics of caregiving for patients with dementia or disability. Caregivers of patients with dementia or disability had been in the caregiver role for years by the time they were studied. Typically, they would have been providing constant care for years during which time the patients would have been progressively and uniformly deteriorating. On the other hand, caregivers of patients with cancer have been

providing care for a relatively short-term in months as they have often enrolled to studies close to the time of diagnosis. In addition, cancer caregivers are often not well prepared for their new caregiver role mainly because the cancer diagnosis is often unexpected yet imposes substantial immediate challenges (27, 28).

Other unique aspects of cancer caregiving may be also important. In a national study of caregiving in the US, dementia, cancer, frailty, and diabetes were four major chronic conditions of older adults that required family caregiving. Among those four conditions, cancer required family members' involvement in the care for the shortest duration (less than 6 months) (27). However, cancer caregivers spent the longest hours for caregiving, which were associated with the greatest physical strain and emotional stress (27). Furthermore, the high demand for caregiving for patients with cancer is bimodal: it peaks around the time of diagnosis and treatment then again around the time of end-of-life care, which last days to weeks (17, 18). The different expectations for cancer caregiving also reflect the fact that cancer patients could have remissions for months to years. This unique time-course of cancer caregiving may impact telomeres differently than for the caregivers of patients with other types of chronic progressive illness. Yet, cancer caregivers remain relatively understudied regarding their physical health.

The majority of existing cellular aging studies have reported that psychological stress affect telomere shortening (e.g., (10-12)). However, severe acute psychological stressors might also mobilize cellular resources that protect against premature cellular aging. For example, in a mouse study, acute stressors over several months led to elevated telomerase, which can be protective against telomere shortening (29, 30). In a human study with a laboratory-induced

stress, greater threat/challenge appraisal of the stressor was associated with increased telomerase responsivity in both caregivers of patients with dementia and controls. This may be a stress-protective response (31). These findings hint that psychological stress may affect telomere lengthening, and support the notion that short-term stress lasting from minutes to several months could enhance adaptive biological responses, whereas long-term stress lasting years to decades suppresses adaptive responses (32). It may be that the initial period of cancer caregiving (several months after the patients' diagnosis) resembles a relatively short-term stressor.

It is also possible that low telomerase or short telomere length would lead to greater vulnerability to stress or depression. Mice with lower telomerase displayed more behavioral indicators of depression and aggression (29, 30). Two thirds of patients with dyskeratosis congenita, a genetic condition producing 50% of normal telomerase levels, were diagnosed with a psychiatric disorder, a rate double that reported in medically ill populations (33). Although psychiatric disorder or clinical depression substantively differs from caregiver stress, elevated levels of depressive symptoms and anxiety are common in family caregivers (34), which may be a manifestation of their biological susceptibility (13). However, this perspective that shorter telomere length may affect lower psychological stress remains highly speculative but suggest it is important to test bidirectional relations.

In sum, it remains unknown if the existing associations between psychological stress of caregivers and cellular aging can be generalized to caregivers of adult patients with cancer. Given the complex interplay between stress and telomere length (13) with most of our knowledge coming from cross-sectional studies, it is also unknown the extent to which telomere

length predicts subsequent caregiver stress versus caregiver stress predicts subsequent telomere length, over years. Thus, this study explored the bidirectional relations of perceived cancer-related stress with telomere length among family caregivers of adult patients who were recently diagnosed with cancer by following them with measures of perceived cancer-related stress and telomere length three times in the first two years after diagnosis.

Methods

Participants and Procedures

Cancer patients who were newly diagnosed with colon or rectal cancer (stage I-IV, > 21 years old) less than four months prior to participating in the study (T1) were recruited at the University of Miami and Northwestern University oncology clinics from April 2012 to April 2017. Patients identified family members or individuals considered family who were providing unpaid help during their cancer experience (e.g., providing emotional support or medical information, paying for groceries, transportation to clinic). Eligibility criteria for family caregivers were: 21 years of age or older, self-identified as Black, Non-Hispanic White, or Hispanic, and able to speak and read in English or Spanish at the 5th grade level. Exclusion criteria included active/untreated psychosis, substance abuse/dependence, and suicidal ideation within the past year; and for blood sample, HIV seropositive status. A total of 168 caregivers enrolled and provided study data (166 for questionnaire data; 131 for blood data; 128 for both questionnaire and blood data) at T1 ($M = 3.83$ months post diagnosis, $SD = 2.29$ months) and at two follow-ups: one-year (T2: $M = 11.6$ months post diagnosis, $SD = 1.34$ months) or two-year post diagnosis of the patient (T3: $M = 20.6$ months post diagnosis, $SD = 1.84$ months).

This study was approved by the University of Miami and Northwestern University Institutional Review Boards. Caregivers who provided signed informed consent were sent an introductory letter and received calls to schedule assessments that could be done alone at their home or at a clinic. Participants completed a questionnaire assessing cancer-related stress, and demographic and biobehavioral factors; and non-fasting blood samples were drawn by the study phlebotomist at each assessment time point. Participating caregivers were provided a \$40 incentive at each assessment.

Measures

Cancer-related Stress. The extent to which caregivers felt the cancer in the family had caused stress to themselves and their family since the cancer diagnosis of their relatives (T1) and over the past 12 months (for T2 and T3) was measured by the 7-item Appraisal of Cancer Experience Scale (35). Example items are “Cancer has been a stressful life event” and “Cancer has distressed my family”. The Appraisal of Cancer Experience Scale underwent standard translation and back-translation processes for the Spanish version. Each item was rated for the extent of agreement on a four-point Likert-type scale (0=*not at all*; 3=*very much*). Seven items were averaged, with higher scores reflecting a greater perceived level of cancer-related stress. This measure had good internal consistency across three assessment time points ($.737 \leq \alpha \leq .817$).

Telomere Length. Venous blood was drawn to either EDTA Lavender-Top vacutainer tubes for whole blood or CPT Blue/Black-Top vacutainer tubes. Whole blood was stored at -80°C until DNA extraction. For the blood collected using CPT Blue/Black-Top tubes, peripheral

blood mononuclear cells (PBMCs) were purified according to the manufacturer's instructions. PBMCs were stored at -80°C until DNA extraction. Whole blood was collected from 28 caregivers only in the Miami site at T1, 6 of them remained with whole blood collection at T2 or T3, whereas 8 of them were switched to CPT Blue/Black-Top tubes at T2 or T3. Blood was drawn using CPT Blue/Black-Top tubes for all caregivers at the Northwestern site at all three assessment time points. Assay procedures and telomere length values between the CPT and the EDTA tubes were equivalent.

Total genomic DNA was purified using QIAamp® DNA Blood Mini kit (QIAGEN, cat # 51106) from whole blood. DNA was quantified by measuring OD₂₆₀. The Quality control criterion was the ratio of absorbance at 260 nm and 280 nm between 1.7-2.0. All samples passed quality control. Leukocyte telomere length was measured by qPCR using a modified version of the method first described by Cawthon et al. (36) and reported as T/S, the ratio of telomere signal (T) and single copy gene signal (S), relative to a reference standard DNA. Details of the method can be found in Lin et al. (37). The average coefficient of variation for this study was 2.3%. All DNA samples over time from each participant were extracted using the same reagent lots and assayed as one batch on the same assay plate.

Demographic and Biometric Covariates. Demographic and biometric factors that have been known to be associated with perceived stress of cancer in the family or telomere length were considered to be included in the statistical analyses as covariates (1, 18). Those were age, gender, and body mass index (BMI) that was calculated (kg/m^2) from self-reported height and weight. These variables were measured at T1. We considered ethnicity (Hispanic, 46.3% vs non-

Hispanic) and spousal caregiver (spouse/partner, 35.8% vs no-spouse) as additional covariates because our sample had substantial proportions of these sub-groups.

Statistical Analysis

Means and standard deviations or percentages of study variables are reported in Table 1. We found Hispanic ethnicity and spousal status had multicollinearity problems with other selected covariates (both with age and gender, $.003 \leq p \leq .075$) that have shown to be consistently and significantly correlated with cancer-related stress and telomere length. In addition, ethnicity and spousal status were not significantly correlated with the primary study variables in our data, except that Hispanics had longer telomere length at T1 (1.153 vs 1.021, $t = 1.889$, $p = .038$), which became marginally significant at T2 (1.126 vs 1.015, $t = 0.084$, $p = .076$). Thus, we decided not to include ethnicity and spousal status as covariates in subsequent analyses. Group differences of ethnicity or spousal status in demographics and study variables are reported in Table S1, Supplemental Digital Content, <http://links.lww.com/PSYMED/A944>. Pearson or Spearman correlations among continuous or dichotomous variables, respectively, are reported in Table 2. The time lagged associations of cancer-related stress with telomere length across three assessment time points were tested using cross-lagged panel design analysis (38, 39) in a structural equation modeling framework using Mplus 8 (40) (Mplus code available upon request). Mplus utilizes the full information maximum likelihood (FIML) estimation method to estimate population parameters that include missing data from all observed data.

The cross-lagged panel model (CLPM) was set to cancer-related stress at T1 predicting cancer-related stress at T2, which was then used to predict cancer-related stress at T3. In parallel,

telomere length at T1 was used to predict telomere length at T2, which was then used to predict telomere length at T3 (time lagged, auto regression effects). In addition, the model was set to test cancer-related stress at T1 as a predictor of telomere length at T2, and cancer-related stress at T2 in predicting telomere length at T3; telomere length at T1 was used to predict cancer-related stress at T2, and telomere length at T2 was used to predict cancer-related stress at T3 (time lagged cross association, cross-lagged effects: Table 3, Figure 1). The auto regression effects and cross-lagged effects were constrained to be equal across timepoints. Three covariates (age, gender, and BMI) that were measured at T1 were controlled for their variance in cancer-related stress and telomere length at T1 (Table 3). Four indices were used to evaluate the model fit to the data. Chi-squared (χ^2) values less than two times of degree of freedom, the comparative fit index (CFI) > .95, the root mean squared error of approximation (RMSEA) < .06, and the standardized root mean squared residual (SRMR) < .08, indicate adequate fit of a specified model to the data (41). Statistical significance was set at a 2-tailed p -value < .05.

Results

Sample Characteristics

Caregivers were primarily middle-aged, female, Hispanic, relatively well educated, middle income, spouses of the index patient, providing care to patients whose cancer was diagnosed at an advanced stage, and on average overweight (Table 1). A total of 17 patients passed away by T3 and 50.6% of patients were off treatment at T3. Overall, caregivers reported mild levels of feeling stressed by the cancer in the family on the Appraisal of Cancer Experience Scale and displayed comparable levels of leukocyte telomere length to those observed in other older caregiver samples assayed by the same lab with the same method (22, 24). Cancer-related

stress at T2 significantly decreased from T1 ($t = 2.899, p = .005$), which was not significantly changed at T3 from T2 ($t = 0.251, p = .803$). Telomere length did not significantly change across T1 to T3 ($t < 1.503, p > .143$).

Associations of Cancer-related Stress and Telomere Length Across Three Assessments

As shown in Table 2, zero-order concurrent correlation coefficients between cancer-related stress and telomere length at T2 were positive and significant ($r = .367, p = .005$). The cross-lagged panel effects between cancer-related stress and telomere length across three assessment time points were tested using the CLPM. The model fit to the data was acceptable, $\chi^2_{(15)} = 22.052$, CFI = .941, RMSEA = .053, and SRMR = .062. As shown in Table 3 and Figure 1, caregivers' cancer-related stress ($\beta \geq .449, p \leq .003$) and telomere length ($\beta \geq .983, p \leq .001$) were in general stable across time, illustrating time lagged effects within each variable during the two years.

In addition, cross lagged association effects of cancer-related stress on telomere length were also significant. Caregivers with greater cancer-related stress at T1 (vs sample's average level of stress) had longer telomere length at T2 (vs the sample's average telomere length) ($\beta = .911, p = .006$). A similar association was found between greater cancer-related stress at T2 and longer telomere length at T3 ($\beta = 1.205, p = .019$). The cross lagged effects of telomere length on cancer-related stress at later assessment timepoints were not significant ($p \geq .870$). These cross-lagged effects were above and beyond the effects of three covariates included in the model.

Discussion

This study investigated the time lagged cross associations between family caregivers' perceived stress due to the cancer in the family and their telomere lengths across the first two years since their patients' cancer diagnosis. Results revealed that cancer-related stress predicted longer telomere length at subsequent assessments but not vice versa, supporting the perspective that psychological stress may play a role in protecting against telomere shortening. These findings are, however, contradictory to existing studies that report inverse relations between stress and telomere length (13). We speculate the differences in types of sample (caregivers as opposed to non-caregiving adults), the patients' medical characteristics, and the time of initial assessment may be attributable in part to the inconsistent findings.

Specifically, the current study sample differs from other existing caregiver studies in the anticipation about the subsequent trajectories of the patients' illness and the extent to which caregivers are involved in the patients' medical care upon the diagnosis. For example, caregivers of patients with dementia expect that they would be involved in years long caregiving for the patients whose functioning uniformly and progressively deteriorates, whereas caregivers of patients with cancer expect providing care for days to weeks that can be followed by the patients' remission for months or years. Cancer caregivers' expectation to be involved in caregiving for a relatively shorter period of time may promote more active coping, which may help not yet leading to biological depletion and increased allostatic load.

Furthermore, existing caregiver studies are mostly with family members who have been in the caregiver role for years as their care recipients are primarily patients with dementia or

disability (19-22, 24, 26). The long-term caregivers' telomeres by the time they enrolled to a study may reflect their chronically imbalanced, dysregulated stress physiology. In contrast, our cancer caregivers were in the newly assumed role only for a couple of months at the initial assessment time point. Supporting this speculation, greater threat appraisal of a laboratory-induced stress was associated with higher telomerase responsivity in both caregivers of patients with dementia and controls (31), showing the protective role of acute stress on telomerase, which sustained levels can lengthen telomeres. It is possibly that short-term stress of several months could lead to telomerase related lengthening.

The distress of family caregivers of cancer patients who have been recently diagnosed may be higher due in part to the high fatality of cancer. For example, the 5-year overall survival rate of cancer is 68% (42), whereas patients with any form of dementia survive from onset for an average 7.3 years (43) with a lifetime death rate of 64.5% (44). Cancer caregivers' heightened threat perception that reflects accurate understanding about the impact of cancer, requires an intensive care for relatively short period that is intermittent during the course of patients' illness (27), may energize them to engage in carrying out various caregiving tasks for the relatives with cancer. Such perception may also promote their post-traumatic growth and healthy lifestyle behaviors, which could have been protective to telomeres.

Another explanation for telomere lengthening is a change in cell distribution due to acute stress. In response to a relatively acute stressor, B cell reactivity may be larger than T cell reactivity which is manifested in longer telomere length (31, 37). We might have sampled more B cells in circulation, which we unfortunately did not assess to control for differential cell

populations. In other words, the longer telomere length may be a manifestation of larger B cell to T cell ratio due to the acutely stressful period (37). The observation of telomere lengthening due to change in circulating cell types has been called “pseudo-lengthening” (45). The putative beneficial effects of changing mutation rates in response to stress on survival, although mainly grounded in animal studies, have been hypothesized in recent years (46), with calls for empirical testing with human adults.

Together, our findings reveal cancer-related stress in the family influences telomere length at subsequent assessments but not vice versa, suggesting cancer-related stress during the first couple of years since the relative’s diagnosis may reflect psychological adaptation with no signs of telomere shortening on average across the sample. The mechanistic investigation of such potential protective role of psychological stress from telomere shortening is warranted. For example, the roles of social support, engaging in healthy lifestyle behaviors after the relative’s cancer diagnosis as a “wake-up call” (47), and finding meaning and purpose through a newly acquired role of cancer caregiver, need to be investigated as they may stimulate telomerase activity to be manifested in telomere lengthening.

This study has several limitations. Three assessment timepoints are insufficient to establish sound causal relations between cancer-related stress and telomere length. With more assessment timepoints and larger sample size, our current research inquiry should also be validated by alternate statistical approaches (48). For example, the random intercept cross-lagged panel model allows to examine the degree to which individual caregivers change around their own mean in study variables over time (38, 49). The autoregressive latent trajectory model with

structured residuals enables testing individual differences in the initial assessment and change patterns of the two study domains across times (50). The dual change score model takes into consideration of prior and future changes in either the same or another domain (51). These alternate models would be particularly relevant if large individual differences of changes in cancer-related stress and telomere length during study duration are expected.

Caregivers in the current study reported only mild levels of cancer-related stress during the study duration, which may not adequately represent intense stress expected for family caregivers of cancer patients. Furthermore, caregivers' perception of cancer and related stress may vary by the patients' illness trajectory, particularly those who bereaved and whose patients' cancer recur. In addition, the impact of elevated cancer-related stress at the two-year mark (final assessment of the current study) on subsequent cellular aging, when allostatic overload may start to emerge, may differ from that at an earlier phase of caregiving. Thus, expanding the assessments beyond the first two years and sub-group analysis by patients' illness trajectory are needed. Furthermore, although we had relatively large proportion of sample representing Hispanic ethnicity or spousal vs non-spousal familial relationship with the patient, the sample size for each group was insufficient for testing their moderation effects. Hispanics had longer telomere length only at T1, which was not controlled for in the study model due to multicollinearity problems with two primary covariates (age and gender). Thus, the generalizability of our findings to cancer caregivers of other types of cancer, to various familial relationship groups, and to ethnically and sexually diverse populations is also limited. Similarly, testing the effects of multiple aspects of caregiving burden, as opposed to general stress from having cancer in the family, including both subjective (e.g., specific caregiving stress) and

objective (e.g., hours and types of caregiving) is warranted in future studies with a larger sample. The clinical significance of cancer-related stress associating with subsequently measured telomere length and their impact on care recipients' health are also unknown.

Examining the associations of telomere length with other psychosocial, behavioral, and protective factors involved in cancer caregiving experience, such as anxiety, depression, PTSD-like symptoms, and loneliness as well as resilience, finding meaning and personal growth, social support, and healthy lifestyle behaviors is warranted. We provided simple correlations of social support and benefit finding at T1 with cancer-related stress and telomere length at T1 through T3 as a supplemental information to be considered for future studies (Table S2, Supplemental Digital Content, <http://links.lww.com/PSYMED/A944>). Long-term follow-up of these caregivers is necessary to adequately evaluate the biological cost of perceived stress of cancer in the family. Such biological cost also needs to be examined with other biological aging markers. Investigating the application of various stress management interventions for cancer caregivers that have shown to be effective (52, 53), now in relation to cancer-related stress perception and telomere length is also warranted in future studies.

Despite these limitations, this study also has several strengths. This is the first study to our knowledge, reporting cellular aging indexed by telomere length among family caregivers of adult cancer patients. Cancer caregiving is characterized as intense for a relatively short period, particularly around the time of diagnosis and around the end-of-life phase. Employing a prospective longitudinal study design and an advanced statistical approach, our findings suggest that the perception of newly acquired caregiving role being overwhelmed affects subsequent

cellular aging marker, but not cellular aging affects subsequent stress. The initial assessment of the majority of cellular aging research with caregivers is typically many years after the patients' diagnosis (e.g., (19, 26)), thus those assessments may reflect the caregivers' already well established psychological and biological reactions to the illness in the family, whereas ours reflects the initial, volatile psychological and biological reactions.

Our findings linking high initial stress to longer telomeres was surprising and conflicts with studies of caregivers of other chronic conditions. It points to the possibility that the typically shorter and more intense caregiving for loved ones with cancer may be different experientially and have less detrimental effects. Our findings suggest further investigation of the complex underlying pathways of cancer caregiving links to cellular aging. Clinically, the experience of cancer caregiving is an important area to understand to guide the development of new interventions targeted to improve caregivers' effective stress regulation strategies during the early phase of caregivership.

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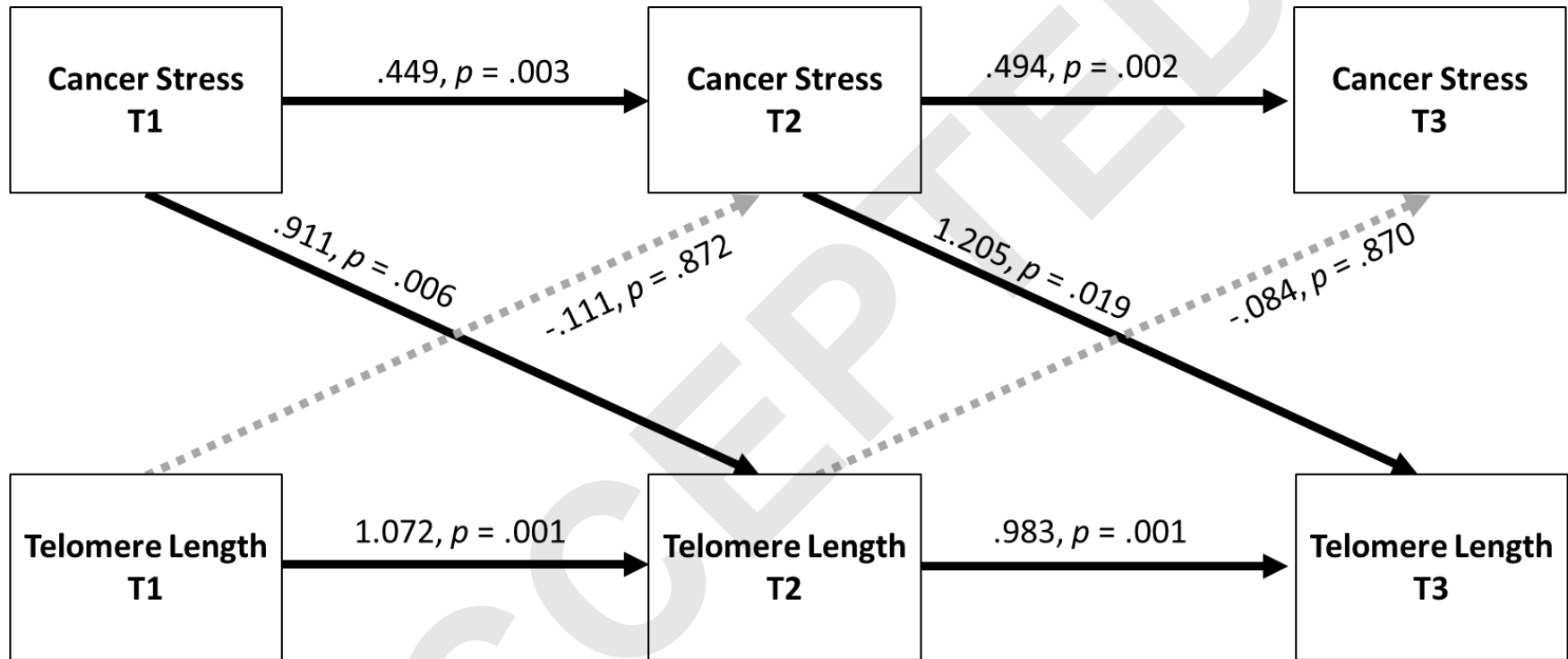
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Figure 1. Associations of Cancer-related Stress and Telomere Length Across Two Years



$N = 168$; solid paths indicate significant paths; dotted paths indicate non-significant paths; age, gender, and BMI at T1 were included in the model as covariates but not presented here.

Table 1. Sample Characteristics

	Mean (SD) or %		
Age	51.08 (14.75)		
Gender (Female)	70.2%		
Ethnicity			
Hispanic	46.3%		
Non-Hispanic White	30.2%		
African American	17.3%		
Education			
< High School	33.7%		
College	49.1%		
> Post-graduate	17.2%		
Income			
<\$19,999	22.0%		
\$20,000 - \$39,999	22.0%		
\$40,000 - \$75,000	18.9%		
> \$75,000	21.4%		
Prefer not to answer	15.7%		
Relationship to Patient			
Spouse/Partner	35.8%		
Offspring	20.3%		
Friend	13.6%		
Sibling	12.3%		
Parent	9.9%		
Other	8.0%		
Patients' Cancer Stage			
Stage I or II (Early)	20.2%		
Stage III or IV (Advanced)	53.2%		
Unknown	26.6%		
BMI	29.14 (7.90)		
	T1	T2	T3
Cancer-related stress (scale range 1-3)	1.29 (0.64)	1.12 (0.71)	1.26 (0.69)
Telomere length	1.09 (0.32)	1.07 (0.25)	1.06 (0.20)

N = 168

Table 2. Zero-order Correlation Coefficients among Study Variables

	Gender	BMI	Cancer stage	Stress T1	Stress T2	Stress T3	TL T1	TL T2	TL
T3									
Age	-.004	.085	-.010	.028	-.225*	-.051	-.411***	-.581***	-.493***
Gender	-	-.008	.143	-.033	-.143	-.058	.047	.266*	.261+
BMI		-	.066	.198*	-.049	.149	-.076	-.209	-.332*
Patient Cancer stage (Cancer Stage)			-	.078	.092	.162	.190+	.187	.124
Cancer-related Stress at T1 (Stress T1)				-	.484***	.530***	-.099	.181	.157
Cancer-related Stress at T2 (Stress T2)					-	.567***	.219	.367**	.266
Cancer-related Stress at T3 (Stress T3)						-	.034	-.101	.052
Telomere Length at T1 (TL T1)							-	.516***	.387*
Telomere Length at T2 (TL T2)								-	.685***
Telomere Length at T3 (TL T3)									-

+ $p < .06$ * $p < .05$ ** $p < .01$ *** $p < .001$

Correlations with continuous variables are Pearson r coefficients and with non-continuous variables are Spearman ρ coefficients; Gender:

female=1, male=0; Patient cancer stage: advanced = 1, non-advanced = 0.

Table 3. Estimates of Associations of Cancer-related Stress and Telomere Length

	Cross-Lagged Panel Model (CLPM)				Random Intercept CLPM		
	β	SE	<i>t</i>	<i>p</i>	β	SE	<i>t</i>
				<i>p</i>			
<u>Auto-Regression Effects:</u>							
Cancer-related Stress at T1 -> Cancer-related Stress at T2	0.449	.152	2.959	.003	0.079	.194	0.408 .683
Cancer-related Stress at T2 -> Cancer-related Stress at T3	0.494	.158	3.131	.002	0.093	.245	0.381 .703
Telomere Length at T1 -> Telomere Length at T2	1.072	.200	5.368	.001	0.280	.171	1.641 .101
Telomere Length at T2 -> Telomere Length at T3	0.983	.191	5.154	.001	0.220	.129	1.706 .088
<u>Cross-Lagged Effects of Cancer-related Stress and Telomere Length:</u>							
Cancer-related Stress at T1 -> Telomere Length at T2	0.911	.329	2.766	.006	0.193	.143	1.346 .178
Cancer-related Stress at T2 -> Telomere Length at T3	1.205	.516	2.336	.019	0.288	.171	1.689 .091
Telomere Length at T1 -> Cancer-related Stress at T2	-0.111	.688	-0.161	.872	0.274	.139	1.968 .049
Telomere Length at T2 -> Cancer-related Stress at T3	-0.084	.517	-0.163	.870	0.170	.104	1.630 .103
<u>Covariate Effects:</u>							
Age -> Cancer-related Stress at T1	1.059	.253	4.187	.001	0.036	.057	0.622 .534
Gender -> Cancer-related Stress at T1	0.066	.016	4.217	.001	0.002	.003	0.616 .538
BMI -> Cancer-related Stress at T1	0.061	.014	4.217	.001	0.002	.003	0.616 .538
Age -> Telomere Length at T1	2.108	.482	4.370	.001	0.055	.086	0.643 .520
Gender -> Telomere Length at T1	0.132	.029	4.501	.001	0.003	.005	0.637 .524
BMI -> Telomere Length at T1	0.121	.027	4.501	.001	0.003	.005	0.637 .524

$N = 168$; β = standardized coefficient; Gender: female =1, male=0.

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